Published in final edited form as:
Cancer. 2012 October 15; 118(20): 5124–5131. doi:10.1002/cncr.27497.

Prospective Analysis of Association Between Use of Statins and Melanoma Risk in the Women's Health Initiative

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Abstract

BACKGROUND—Melanoma is the most lethal form of skin cancer, with an estimated 68,130 new cases and 8700 deaths in the United States in 2010. The increasing incidence and high death rate associated with metastatic disease support the need to focus on prevention. The authors used data from the Women's Health Initiative (WHI) to assess whether 3-hydroxy-3 methylglutaryl coenzyme A inhibitors (statins) are associated with a decreased risk of melanoma.

METHODS—The study population consisted of 119,726 postmenopausal white women, in which 1099 cases of malignant melanoma were identified over an average (istandard deviation) of 11.6 ±3.2 years. All diagnoses were confirmed by medical record review and pathology reports. Information on statin use was collected at baseline and during follow-up. Self-administered and interview-administered questionnaires were used to collect information on other risk factors. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses investigated the association of any statin use, type, potency, lipophilic status, and duration of use with melanoma.

RESULTS—Statins were used by 8824 women (7.4%) at baseline. The annualized rate of melanoma was 0.09% among statin users and 0.09% among nonusers The multivariable adjusted HR for statin users compared with nonusers was 1.14 (95% CI, 0.91–1.43). There were no significant differences in risk based on statin type, potency, category, duration, or in time-dependent models.

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For a list of all the investigators who have contributed to WHI science, please visit: http://www.whiscience.org/publications/WHI_investigators_longlist.pdf

CONFLICT OF INTEREST DISCLOSURES
The authors made no disclosures.

CONCLUSIONS—There was no significant association between statin use and melanoma risk among postmenopausal women in the WHI.

Keywords

statins; melanoma; cohort study; epidemiology; cancer risk

INTRODUCTION

Melanoma is the most lethal form of skin cancer,[1] with an estimated 68,130 new cases and 8700 deaths in the United States in 2010.[2] Melanoma incidence continues to rise, with an average annual increase of 3.1% per year, making it the most rapidly increasing cancer in the United States.[3] Up to 65% of melanomas are related to exposure to ultraviolet (UV) radiation, especially UVB radiation,[4,5] and an increased risk is associated with childhood/adolescent sun exposure, sun exposure during later decades of life,[6] sun beds,[6–8] a tendency to burn, and the presence of multiple nevi.[6,9] Other risk factors include family history,[10] mutations in the *P16* gene,[11] and smoking.[12] The rapidly increasing incidence and the high death rate associated with advanced or metastatic disease[13–15] support the need to focus on prevention.

Educational strategies devoted to protecting individuals against UV radiation have had a modest impact on melanoma incidence. Statins are known to have anticancer properties because of their antiangiogenic, proapoptotic,[16–18] and growth-inhibiting effects.[19] Preclinical studies in a mouse melanoma cell line have demonstrated inhibition of cell migration, invasion, adhesion, and metastasis.[20] With an estimated 45 million Americans using statins for their cardioprotective effects,[21] statins may provide an easy way in which to reduce the burden of melanoma.

Randomized controlled trials of statins in the setting of heart disease risk have yielded mixed results, and the majority of studies have identified no significant impact on melanoma risk,[22,23] although 1 trial of lovastatin resulted in a significant risk reduction.[24] In contrast, 3 nested case-control studies have revealed no significant effect of statins on melanoma risk.[25–27] To our knowledge, there are no previously published cohort studies evaluating the relation between statins and melanoma risk.

We used the Women's Health Initiative (WHI) cohort to assess the hypothesis that statins are associated with a lower risk of melanoma. The WHI is the largest cohort of postmenopausal women in the United States and provides a unique opportunity to study outcomes for relatively uncommon cancers like melanomas.

MATERIALS AND METHODS

Study Population

The WHI includes an observational study (OS) (n = 93,676) and a randomized controlled clinical trial (CT) (n = 68,132), which were described previously in detail. Recruitment was conducted between October 1, 1993 and December 31, 1998 at 40 clinical centers in the United States. Women were eligible if they were ages 50 to 79 years, postmenopausal, planned to remain in the area where they lived at recruitment, and had an estimated survival of at least 3 years.[29,30]

The current analysis is based on 133,541 white women who were enrolled in the OS and CT, excluding those who had a previous cancer diagnosis except nonmelanomatous skin cancer (NMSC) and those with missing information on cancer history (n= 13,815). One woman was

excluded with unknown information on statin use. The final sample included 67,032 women enrolled in the OS and 52,694 women enrolled in the CT (n = 119,726). Institutional review boards at the participating institutions approved all protocols and procedures, and informed consent forms were signed by all participants. Follow-up for this report is through September 30, 2010, for a mean ± standard deviation follow-up of 11.6 ± 3.2 years.

Statin Exposure

Participants were asked to bring all current prescription medication containers to their first screening interview (baseline), and interviewers entered each medication name directly into the database assigning drug codes using Medispan software (Frist DataBank, Inc., San Bruno, Calif), including duration of use. Mediation use was updated using the same methodology at the years 1, 3, 6, and 9 in the CT and at year 3 in the OS.

Statins were defined as any 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and were classified based on solubility in octanol (lipophilicity) or water (hydrophilicity).[32,32] Lipophilic statins (lovastatin, simvastatin, fluvastatin, and cerivastatin) penetrate the plasma membrane, whereas hydrophilic statins (pravastatin, atorvastatin, and rosuvastatin) do not.[33–35] Statins were classified according to their potency based on lipid-lowering efficacy as low (fluvastatin and lovastatin), medium (pravastatin), and high (simavastatin, atorvastatin, cerivastatin, and rosuvastatin).[34–36]

Melanoma Diagnosis

Cancer diagnoses were updated annually in the OS or semiannually in the CT by mail and/or telephone questionnaires. Self-reports or next-of-kin reports of melanoma were verified by centrally trained physician adjudicators after review of medical records and pathology reports using the Surveillance, Epidemiology, and End Results (SEER) coding system.[37] Only 1099 centrally adjudicated and SEER-coded cases of cutaneous melanoma were included. We excluded 27 cases (2.40%) that were not centrally confirmed and 40 cases of uveal melanomas that were not SEER coded.

Covariates

Information on age, race and ethnicity, geographic region by latitude, education, current and past smoking status, current and past alcohol intake, total energy expenditure in metabolic equivalent hours per week, current health provider, and history of NMSC were ascertained by baseline questionnaires. Other medication use included nonsteroidal anti-inflammatory drugs (NSAIDS) and aspirin. Body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Current and previous use of menopausal hormone therapy and oral contraceptives was ascertained by using a detailed questionnaire, including type, route of administration, the number of pills per day or week, and the duration of use for each hormone preparation. Hormone therapy users were defined as those who used estrogen (with or without progestin) after menopause for at least 3 months.

We included information on geographic region, education, income, and exercise as a proxy for solar UV exposure. Current health care provider was included as an additional proxy for quality of health care and medical surveillance. Tobacco use is linked to skin cancers of all types,[12] and hormone therapy use may be linked to melanoma development, because melanocytes have hormone receptors.[38]

Statistical Methods

The characteristics of statin users at baseline were compared with those of nonusers by using chi-square tests. Annualized melanoma rates were calculated as the percentage of women with an event divided by total follow-up time in years by statin use categories at baseline. Subgroup analyses were performed by statin use duration (< 1 year vs 1 to <3 years and ≥3 years as well as <5 years vs ≥5 years), type, potency, and lipophilic status. Use of 2 or more statins was included in analyses that compared statin use with none and were excluded from analyses that examined details of statin use according to type, potency, or lipophilic status.

Cox proportional hazards analyses were used to assess associations between statin use and melanoma risk. Age-adjusted and multivariable-adjusted models were developed, and both were stratified by age decade, assignment to active hormone or placebo in the 2 WHI hormone trials (estrogen plus progestin and estrogen alone), assignment to intervention or control in the dietary modification trial, enrollment in the OS, and extension study participation. To control for confounding, the multivariable model also was adjusted for linear age, education, smoking, alcohol use, physical activity, body mass index, report of a current health care provider, geographic region by latitude (based on the clinical center where the participant enrolled), current hormone therapy use, history of NMSC, and NSAID use. To evaluate the effects of change in statin use over time, models were rerun by entering statin use as a time-dependent exposure and using updated information on statins gathered at follow-up clinic visits. Comparisons of risk of melanoma by tumor characteristics between statin users and nonusers were based on Cox models and competing-risk, partial-likelihood methods.

Tests for the proportional hazards assumptions were conducted by using a Cox model that included statin use and the interaction of statin use with follow-up time and that tested for a zero coefficient on the interaction term. Results of these analyses indicated that the assumptions were not violated. All analyses were conducted using SAS software (version 9.2; SAS Institute, Inc., Cary, NC). All statistical tests were 2-sided with a significance level of $P = .05$.

RESULTS

There were 8824 statin users (7.4%) in a cohort of 119,726 women at baseline. Table 1 lists baseline characteristics according to statin use. Although most of the absolute differences between statin users and nonusers were small, many were statistically significant because of the large number of women. Statin users were more likely than nonusers to be older (mean age ± standard deviation, 65.8 ± 6.4 years and 63.2 ±7.2 years, respectively), to have a higher body mass index (28.7 ± 5.4 kg/m^2 and 27.6 ± 5.8 kg/m^2, respectively), to have smoked, to have a current health care provider, to have 1 or more comorbid medical conditions, to have used aspirin, and to have a diagnosis of NMSC. Statin users were less likely to have higher education, high family income, drink alcohol, and use hormone therapy. No difference was noted by geographic region.

Table 2 provides the distribution of statin users at baseline other characteristics. Simvastatin was the most common followed closely by lovastatin. Of 8824 statin users, 3390 women (38.4%) used a low-potency statin, 1895 (21.5%) used a medium-potency statin, and 3318 (37.6%) used a high-potency statin (Table 2). In total, 6033 women (68.4%) who used statins reported at least 1 lipophlic statin. Among statin users, 1479 participants (16.8%) took statins for ≥5 years, 2940 (33.3%) took statins for ≥3 years, 2966 (33.6%) took statins for 1 to 3 years, and 2918 (33.1%) took statins for <1 year.

Table 3 lists the incidence of melanoma and HRs according to statin use among WHI participants. There were 89 women with melanoma among statin users for a yearly incidence of 0.09% (9 cases per 10,000 person-years of follow-up) compared with 0.09% for nonusers. There were no significant differences in the risk of melanoma in the age-adjusted and WHI trial-adjusted model (HR, 1.07; 95% CI, 0.86–1.33) or in the multivariable-adjusted model (HR, 1.14; 95% CI, 0.91–1.43; P=.25) There were no significant differences in risk for type of statin, potency, category, or duration. When statin use reported at years 1, 3, 6, and 9 was incorporated into a time-dependent model, there was no significant effect of statins on the risk of melanoma (HR, 0.98; 95% CI, 0.820–1.16; data not shown). Regional, distant, and unknown tumor stages were twice as common among nonstatin users (6.2% vs 3.4%) than among users; however, there was no overall significant effect according to tumor stage (Table 4). Most melanomas were local stage followed by in situ and regional or distant stage.

DISCUSSION

We hypothesized that statins are associated with a lower risk of melanoma based on preclinical data suggesting that simvastatin decreased the ability of melanoma cells to adhere to laminin and collagen type IV, thereby decreasing proliferation, cell migration, invasion, and melanoma-induced angiogenesis,[39] as well as findings from 1 randomized control trial.[24] Our results, however, demonstrated no protective effect of statins when statins were considered as a class of drugs or for individual types of statins, potency, or duration of use. In addition, we observed no significant relation according to tumor stage; however, advanced tumors were slightly more common among nonstatin users compared with statin users (6.2% vs 3.4%), suggesting that statin users may have more opportunity for diagnosis at an earlier stage. It should be noted, however, that this observation was based on only 3 cases among statin users. It is also noteworthy that statin users in the WHI were more likely to have a current health care provider than nonusers, supporting the observation of an earlier stage at diagnosis among users. Thus, statin use may not be associated with a protective effect but, rather, may serve as a proxy indicator for factors that reflect greater medical surveillance.[40]

The results presented here represent the first report to our knowledge of the effect of statins on the incidence of melanoma from a cohort analysis and include a larger number of cases of melanoma and person-years of follow-up than were reported in either of the 2 previously published meta-analyses.[22,23] Our results confirm those of others, including 9 randomized controlled trials[41–49] and 3 nested case-control studies.[25–27] The reported randomized controlled trials initially were designed to assess the relation between statins and cardiovascular outcomes, follow-up ranged from 24 weeks[41,44] to 6.1 years,[49] and the number of cases ranged from 0 to 58. Results from some studies suggested trends toward a reduced risk,[22,24,50–52] with pooled analyses of fluvastatin indicating a nonsignificant reduction in risk of melanoma (3 cases vs 7 cases; relative risk, 0.40; 95% CI, 0.10–1.55).[22] Others results have suggested a trend toward an increase in melanoma risk.[53–56] Only Downs et al reported a significant reduction in melanoma incidence among individuals who were randomized to receive lovastatin, including 14 patients in the treatment group versus 27 patients in the placebo group (relative risk, 0.52; 95% CI, 0.27–0.99).[24] Similarly, nested case-control studies have not demonstrated a significant effect of statins and melanoma risk.[25–27]

It is possible that clinical and population-based studies of statins and melanoma do not demonstrate a preventive effect of statins because of inadequate dosing and drug concentrations at the cellular level. These results are in contrast to in vitro data, which suggest an anticarcinogenic effect in melanoma cell lines.[19,39] A recent analysis indicated

that the efficacy of statins in reducing colorectal cancer risk may be related to genetic variation in HMG-CoA reductase activity,[57] which suggests that genetic heterogeneity may play a role in the lack of a protective effect of statins on cancer risk. Future studies that focus on individuals who have a greater risk of melanoma may provide more conclusive results.

Strengths of this study include the large cohort size as well as the large number of reported melanoma cases. In addition, we collected detailed information on a comprehensive range of melanoma risk factors, including blinded adjudication of malignant melanoma by pathology report review and description of melanoma histologic characteristics, and we had the ability to examine associations by statin category. Limitations include the observational design and that there may be residual confounding by unmeasured factors. For example, we did not have a direct measure of solar UV exposure, but we used other proxy measures, such as latitude of residence, physical activity, education, and income, to approximate sun exposure. Other limitations include the relatively low prevalence of statin use at baseline; inaccurate estimation of the overall duration of statin use, including the possibility that other statins may have been used after the last medication history was documented; the lack of information on statin dose; the low incidence of melanoma in our cohort; and the limited power to examine long-term effects.

In conclusion, although biologically plausible, there was no significant reduction in the risk of melanoma among users of statins among postmenopausal women in the WHI cohort. On current evidence, sun protection is the only way to prevent melanoma.

Acknowledgments

FUNDING SOURCES

The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), US Department of Health and Human Services through contracts N01WH22110, 24152, 32100–2, 32105–6, 32108–9, 32111–13, 32115, 32118–32119, 32122, 42107–26, 42129–32, and 44221 and by Cancer Center Support grant NIH:NCI P30CA022453.

We acknowledge the dedicated efforts of investigators and staff at the Women's Health Initiative (WHI) clinical centers; the WHI Clinical Coordinating Center; and the National Heart, Lung, and Blood program office (listing available at http://www.whi.org). We also recognize the WHI participants for their extraordinary commitment to the WHI program.

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Table 1

Baseline Characteristics of White Participants in the Women's Health Initiative Clinical Trial and Observational Study According to Statin Medication Use

	Statin Medication Use				
	No (N=110,902)		Yes (N=8824)		
Characteristic	**No.**	**%**	**No.**	**%**	***P*[a]**
Age group at screening, y					<.0001
50–59	36,858	33.2	1469	16.6	
60–69	50,009	45.1	4651	52.7	
70–79	24,035	21.7	2704	30.6	
Education					<.0001
<High school diploma/GED	3636	3.3	430	4.9	
High school diploma/GED	19,231	17.5	1911	21.8	
>High school diploma/GED	87,333	79.2	6427	73.3	
Smoking					<.0001
Never smoked	55,310	50.4	4132	47.4	
Past smoker	47,175	43	4077	46.8	
Current smoker	7232	6.6	503	5.8	
Alcohol intake					<.0001
Nondrinker/past drinker	27,710	25.1	2627	29.9	
<1 Drink/wk	36,632	33.2	3026	34.5	
≥1 drink/wk	45,944	41.7	3124	35.6	
HT use, y					<.0001
Never/past use	54,490	49.2	4738	53.8	
Current E-alone	28,137	25.4	2293	26	
Current E+P	28,202	25.4	1781	20.2	
Total expenditure from physical activity quartiles, METs/wk					<.0001
≤2.3	25,179	23.9	2054	23.9	
>2.3–8.3	25,393	24.1	2246	26.2	
>8.3–17.8	27,268	25.9	2261	26.3	
>17.8	27,480	26.1	2020	23.5	
BMI, kg/m^2					<.0001

	Statin Medication Use				
	No (N=110,902)		Yes (N=8824)		
Characteristic	**No.**	**%**	**No.**	**%**	***p*[a]**
<25	41,617	37.8	2234	25.5	
25 to <30	38,022	34.6	3521	40.2	
≥30	30,317	27.6	3000	34.3	
Current health care provider	103,523	94.1	8640	98.6	<.0001
Geographic region by latitude					.08
Southern: <35 °N	30,482	27.5	2450	27.8	
Middle: 35–40 °N	30,671	27.7	2343	26.6	
Northern: >40 °N	49,749	44.9	4031	45.7	
Family history of cancer					
Breast (women)	19,901	18.9	1651	19.8	.04
Ovarian	2654	2.6	201	2.5	.56
History of nonmelanoma skin cancer	8701	7.8	763	8.6	.007
NSAID use	38,883	35.1	4384	49.7	<.0001
Aspirin use (>80 mg)	22,677	20.4	3286	37.2	<.0001
CEE trial participant					.04
Not randomized	103,935	93.7	8223	93.2	
Placebo	3464	3.1	319	3.6	
CEE	3503	3.2	282	3.2	
E+P trial participant					.001
Not randomized	98,231	88.6	7928	89.8	
Placebo	6183	5.6	429	4.9	
E+P	6488	5.9	467	5.3	
DM trial participant					<.0001
Not randomized	75,662	68.2	6480	73.4	
Control	21,166	19.1	1427	16.2	
Intervention	14,074	12.7	917	10.4	
OS participant	61,711	55.6	5321	60.3	<.0001

Abbreviations: BMI, body mass index; CEE, conjugated equine estrogens; DM, dietary modification; E alone, estrogen alone; E+P, estrogen and progestin; GED, general education degree; HT, hormone therapy; METs, metabolic equivalents; °N, degrees north; NSAID, nonsteroidal anti-inflammatory drugs; OS, observational study.

[a] *P* values were determined with chi-square tests of independence.

Table 2

Statin Use Details Among White Clinical Trials and Observational Study Participants (N=8824)

Variable	No. of Patients	%
Type of statin used		
Atorvastatin calcium	675	7.6
Fluvastatin sodium	1036	11.7
Lovastatin	2354	26.7
Pravastatin sodium	1895	21.5
Simvastatin	2643	30
≥2 Statins	221	2.5
Statin potency[a]		
Low (lovastatin, fluvastatin)	3390	38.4
Medium (pravastatin)	1895	21.5
High (simvastatin, atorvastatin)	3318	37.6
Statin category[a]		
Lipophilic (fluvastatin, lovastatin, simvastatin)	6033	68.4
Other (atorvastatin, pravastatin)	2570	29.1
Statin use duration, y		
<1	2918	33.1
1 to <3	2966	33.6
≥3	2940	33.3
<5	7345	83.2
≥5	1479	16.8

[a]This category excludes participants who were receiving ≥2 statins.

Table 3

Malignant Melanoma Incidence (Annualized %) and Hazard Ratios According to Statin Use Among White Clinical Trial and Observational Study Participants

			Age-Adjusted Analysis[a]			Multivariate-Adjusted Analysis[b]		
Variable	**No. of Patients**	**Ann %**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Statin use					.53			.25
No	1111	0.09	1.00			1.00		
Yes	89	0.09	1.07	0.86–1.33		1.14	0.91–1.43	
Type of statin					.88			.81
No statin use	1111	0.09	1.00			1.00		
Atorvastatin	6	0.09	1.05	0.47–2.35		0.97	0.40–2.34	
Fluvastatin	9	0.08	0.95	0.49–1.82		1.07	0.55–2.06	
Lovastatin	31	0.12	1.34	0.93–1.91		1.40	0.97–2.03	
Pravastatin	17	0.08	0.96	0.59–1.55		1.08	0.67–1.74	
Simvastatin	24	0.08	0.97	0.65–1.45		1.03	0.68–1.55	
≥2 Statins	2	0.08	0.97	0.24–3.90		1.07	0.27–4.29	
Statin potency[c]					.68			.49
No statin use	1111	0.08	1.00			1.00		
Low	40	0.11	1.22	0.89–1.68		1.30	0.94–1.81	
Medium	17	0.08	0.96	0.59–1.55		1.08	0.67–1.74	
High	30	0.08	0.98	0.68–1.42		1.02	0.70–1.48	
Statin category[c]					.71			.46
No statin use	1111	0.08	1.00			1.00		
Hydrophobic	64	0.10	1.11	0.86–1.43		1.18	0.91–1.54	
Other	23	0.08	0.98	0.65–1.48		1.05	0.69–1.61	
Duration of statin use					.82			.59
No statin use, y	1111	0.08	1.00			1.00		
<1	26	0.08	0.95	0.65–1.41		1.02	0.69–1.53	
1 to <3	32	0.10	1.14	0.80–1.63		1.26	0.88–1.81	
≥3	31	0.10	1.12	0.78–1.60		1.14	0.79–1.65	
<5	70	0.09	1.01	0.79–1.29	.42	1.09	0.85–1.39	.32

				Age-Adjusted Analysis[a]		Multivariate-Adjusted Analysis[b]		
Variable	**No. of Patients**	**Ann %**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
≥5	19	0.12	1.38	0.88–2.17		1.43	0.89–2.28	

Abbreviations: Ann %, annual percentage; CI, confidence interval; HR, hazard ratio.

[a]Cox proportional hazards regression models were adjusted for linear age and were stratified by age decade, Women's Health Initiative trial randomization, and extension study participation.

[b]Cox proportional hazards regression models were adjusted for linear age, education, smoking, alcohol use, physical activity, body mass index, current health care provider, current hormone therapy use, geographic region, history of nonmelanoma skin cancer, and nonsteroidal anti-inflammatory drug use and were stratified by age decade, Women's Health Initiative trial randomization, and extension study participation.

[c]This category excludes participants who were receiving ≥2 statins.

Table 4

Malignant Melanoma Incidence (Annualized %) and Hazard Ratios According to Tumor Stage and Statin Use Among White Clinical Trials and Observational Study Participants

	No Statin Use		Statin Use		Age-Adjusted Analysis[a]			Multivariate-Adjusted Analysis[b]		
Tumor Stage	**No.**	**Ann %**	**No.**	**Ann %**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
In situ	495	0.04	40	0.04	1.09	0.79–1.51	.61	1.20	0.86–1.67	.29
Local	547	0.04	46	0.05	1.13	0.84–1.53	.43	1.17	0.86–1.61	.33
Regional/distant	48	<0.01	2	<0.01	0.52	0.13–2.16	.32	0.57	0.14–2.36	.40
Unknown/missing	21	<0.01	1	<0.01						
Competing-risk P^c						.60			.60	

Abbreviations: Ann %, annual percentage; CI, confidence interval; HR, hazard ratio.

[a] Cox proportional hazards regression models were adjusted for linear age and were stratified by age decade, Women's Health Initiative trial randomization, and extension study participation.

[b] Cox proportional hazards regression models were adjusted for linear age, education, smoking, alcohol use, physical activity, body mass index, current health care provider, current hormone therapy use, geographic region, history of nonmelanoma skin cancer, and nonsteroidal anti-inflammatory drug use and were stratified by age decade, Women's Health Initiative trial randomization, and extension study participation.

[c] This value tests for the difference between the HRs for in situ, versus local, versus regional/distant cancer.