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ORIGINAL REPORT

Sunscreen Use and Subsequent Melanoma Risk: A Population-Based Cohort Study

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ABSTRACT

Purpose

To assess melanoma risk in relation to sunscreen use and to compare high– with low–sun protection factor (SPF) sunscreens in relation to sunbathing habits in a large cohort study.

Materials and Methods

We used data from the Norwegian Women and Cancer Study, a prospective population-based study of 143,844 women age 40 to 75 years at inclusion with 1,532,247 person-years of follow-up and 722 cases of melanoma. Multivariable Cox proportional hazards regression was used to estimate the association between sunscreen use (never, SPF $<$ 15, SPF $\geq$ 15) and melanoma risk by calculating hazard ratios and 95% CIs. The population attributable fraction associated with sunscreen use was estimated.

Results

Sunscreen users reported significantly more sunburns and sunbathing vacations and were more likely to use indoor tanning devices. SPF $\geq$ 15 sunscreen use was associated with significantly decreased melanoma risk compared with SPF $<$ 15 use (hazard ratio, 0.67; 95% CI, 0.53 to 0.83). The estimated decrease in melanoma (population attributable fraction) with general use of SPF $\geq$ 15 sunscreens by women age 40 to 75 years was 18% (95% CI, 4% to 30%).

Conclusion

Use of SPF $\geq$ 15 rather than SPF $<$ 15 sunscreens reduces melanoma risk. Moreover, use of SPF $\geq$ 15 sunscreen by all women age 40 to 75 years could potentially reduce their melanoma incidence by 18%.

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INTRODUCTION

Cutaneous melanoma (hereafter termed melanoma) is one of the most rapidly increasing cancers and a major public health challenge in white populations.[1,2] In Norway, melanoma incidence rates have increased faster in the past decade than for any other malignancy to become among the highest in the world.[1,3]

Solar ultraviolet radiation is an established cause of melanoma,[4] and sunscreen use is recommended for sun protection in addition to clothing and shade.[5,6] Sunscreen can decrease the risk of sunburn, squamous cell carcinoma,[7] actinic keratosis,[8] and nevi in children.[9] Melanoma may also be preventable by sunscreen use,[10,11] but high-quality evidence is still scarce.

To date, all observational studies on the association of sunscreens and melanoma have been case-control studies mostly conducted before 2000. They are difficult to interpret due to lack of adjustment for potential confounding and because most were conducted before high–sun protection factor (SPF) sunscreens were available. Meta-analyses showed no effect of sunscreens on melanoma risk.[12,13] The single case-control study published after the meta-analyses showed that routine sunscreen use decreases melanoma risk.[11]

The only randomized controlled trial found decreased melanoma occurrence among adults who used SPF16 sunscreen daily compared with discretionary sunscreen use.[10] However, this trial was conducted among adults who lived in a climate with high ambient solar radiation and high skin cancer awareness. Patterns and intensity of

sun exposure are different in northern Europe where people receive high ultraviolet exposure mainly during summer sunbathing. To date, the effectiveness of sunscreens in preventing melanoma when sun exposure is intentional is unclear.[14]

The Norwegian Women and Cancer (NOWAC) study provided us with the unique opportunity to prospectively examine melanoma risk according to sunscreen usage. In addition, we investigated whether the use of high-SPF (ie, ≥ 15) compared with low-SPF sunscreens reduces melanoma risk, especially in relation to intentional sunbathing.

MATERIALS AND METHODS

The NOWAC Cohort Study

Established in 1991, NOWAC is a large national population-based prospective cohort study.[15] A nationwide random sample of > 300,000 women age 30 to 75 years was drawn from the Norwegian National Population Register. All women received an invitation letter and gave written informed consent between 1991 and 2007, and 171,725 were enrolled (response rate, 54%). The unique identity number of Norwegian citizens was used to link individuals from NOWAC to the population register at Statistics Norway for postal addresses and to the Cancer Registry of Norway for follow-up of vital status (alive, emigrated, or dead) and cancer incidence until December 31, 2012. Melanoma is registered according to International Classification of Diseases, Seventh Edition, codes 190.0 to 190.9, and 99.9% of melanomas currently are morphologically verified.[3] Participants completed a comprehensive baseline questionnaire and follow-up questionnaires every 4 to 6 years. Questions about sunscreen use were added in 1997, and most of those (81%) who enrolled in 1991 to 1997 answered sunscreen questions at the first follow-up in 1998 to 2010. The national data inspection board and medical ethical committee approved the study.

Data Collection

Questions about host characteristics, sun exposure, and sunscreen use have been described in detail.[16-18] Participants were asked to report whether they used sunscreen within Norway or other northern locations (hereafter termed high latitudes) and on sunbathing vacations in low latitudes (typically southern European countries with latitude < 45° [eg, Spain or Greece]) and the precise SPF of the sunscreen if used on these occasions (predefined SPF categories [1 to 4, 5 to 9, 10 to 14, 15 to 29, ≥ 30] used instead in a minority of questionnaires). Participants also reported the brands of sunscreens they used. Skin lotions, self-tanning lotions, and other cosmetics with low SPF were not considered as sunscreen in this study. Reliability coefficients were good for current sunscreen use in high and low latitudes (0.54 and 0.74, respectively) and for SPF used on these occasions (0.69 and 0.73, respectively) and were not affected by age, education, or skin color.[17]

Participants were classified as nonusers of sunscreen if they did not indicate sunscreen use or if they answered 0 to the SPF question for the corresponding occasion. Other participants were classified as SPF < 15 or SPF ≥ 15 users according to their answers because SPF15 is considered sufficient to prevent sunburn if applied properly.[19] The participants were further classified into four categories according to sunscreen use in both high and low latitudes as none/none, none/SPF < 15 or SPF < 15/none, SPF < 15/SPF < 15, and SPF ≥ 15 on at least one occasion (Appendix Table A1, online only). The Appendix provides additional details and rationale for sunscreen categorization.

On the basis of average ambient ultraviolet radiation hours,[20] the region of residence (latitudes 70° to 58°) was categorized as low (north Norway), medium-low (central Norway), medium (southwest Norway), and highest (southeast Norway). Years of education were categorized as ≤ 10, 11 to 13, 14 to 16, and ≥ 17 years. Untanned skin color was recorded by a 1 × 9-cm color scale graded from 1 (very fair) to 10 (very dark brown; very dark [8 to 10] skin color was excluded from the study) and was categorized as dark (grades 6 to 7), medium (4 to 5), and light (1 to 3). Participants reported their hair color (dark brown/black, brown, blond/yellow, red), freckling after sunbathing (yes, no), and number of asymmetric nevi > 5 mm on the legs (0, 1, 2 to 3, 4 to 6, 7 to 12, 13 to 24,

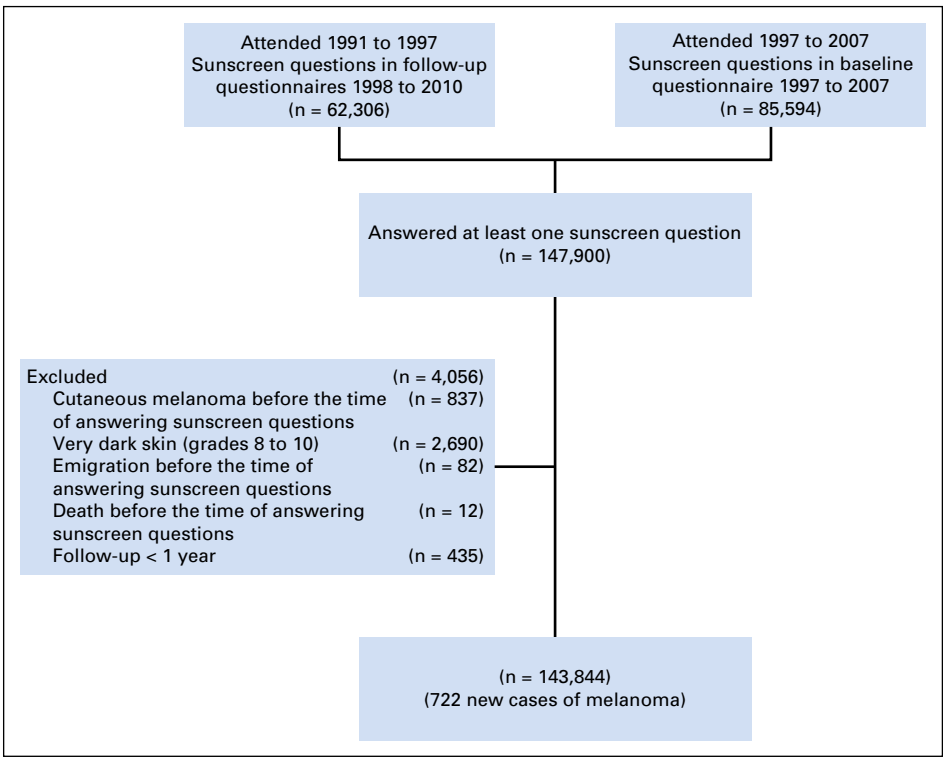

Fig 1. Study sample.

Table 1. Characteristics of NOWAC Study Sample According to Total Number of Sunburns and Weeks of Sunbathing

Characteristics	Cumulative No. of Sunburns* (n = 134,594)				Cumulative No. of Weeks Sunbathing† (n = 119,065)			
	None	Lowest Tertile	Middle Tertile	Highest Tertile	None	Lowest Tertile	Middle Tertile	Highest Tertile
No. of participants	16,384	42,332	38,309	37,569	4,766	39,318	37,094	37,887
Person-years of follow-up								
Sum	174,912	447,032	429,263	387,261	51,219	443,491	373,410	380,232
Mean	10.6	10.5	11.2	10.3	10.7	11.2	10.0	10.0
No. of incident cases	50	185	198	246	15	170	189	224
Mean age at start of follow-up (years)	54.9	52.5	51.8	53.4	56.1	51.8	52.5	53.5
Ambient ultraviolet radiation of residence (%)								
Low (north Norway)	35	25	21	17	33	24	23	16
Medium-low (central Norway)	10	11	11	11	9	13	11	8
Medium (southwest Norway)	15	18	19	21	15	18	19	19
Highest (southeast Norway)	40	46	49	52	42	45	47	56
Education (%)								
≤ 10 years	46	35	29	25	51	34	28	25
11-13 years	25	29	30	28	19	28	30	30
≥14 years	21	31	36	42	22	34	37	40
Missing	8	5	4	4	8	4	5	5
Skin color (%)								
Dark	26	22	18	14	12	17	19	22
Intermediate	32	36	38	35	25	35	37	37
Light	28	34	38	45	45	40	39	35
Missing	13	8	6	6	17	8	6	6
Hair color (%)								
Black/dark brown	25	18	15	12	22	16	15	16
Brown	40	41	41	38	34	40	41	40
Blond/yellow	32	37	40	43	37	39	39	40
Red	1	2	3	6	4	3	3	3
Missing	2	2	1	1	2	1	1	1
Skin reaction after acute sun exposure‡ (%)								
Brown	34	21	10	4	11	14	12	13
Red	17	27	32	24	27	33	21	21
Red with pain	1	5	11	14	13	13	7	6
Red with pain and blisters	0	1	2	4	5	3	2	2
Missing	47	46	43	53	43	35	59	58
Skin reaction after repeated sun exposure‡ (%)								
Deep brown	14	10	6	3	3	7	6	8
Brown	30	31	34	24	22	36	24	26
Light brown	8	11	15	17	23	20	10	8
Never brown	1	1	1	1	6	1	0	0
Missing	48	47	44	54	45	36	59	58
Freckling when sunbathing (%)								
No	76	68	61	51	60	62	61	63
Yes	15	27	34	45	29	35	35	33
Missing	9	5	5	4	11	3	4	4
No. of asymmetric nevi > 5 mm on legs (%)								
0	80	83	82	78	77	84	82	80
1	4	5	6	8	5	6	7	7
≥ 2	2	3	4	7	3	4	5	6
Missing	14	9	7	8	15	6	7	7
Total No. of sunburns* (%)								
None	n/a	n/a	n/a	n/a	27	10	10	10
Lowest tertile	n/a	n/a	n/a	n/a	24	27	24	22
Middle tertile	n/a	n/a	n/a	n/a	23	33	32	28
Highest tertile	n/a	n/a	n/a	n/a	21	28	33	38
Missing	n/a	n/a	n/a	n/a	5	2	2	2
Indoor tanning§ (%)								
Never	34	27	27	28	71	33	24	24
Ever	60	68	69	68	26	66	75	75
Missing	6	5	4	4	3	1	1	2
Sunscreen use in high latitudes‖ (%)								
None	39	25	20	17	64	24	17	17
SPF < 15	47	59	64	65	18	59	66	67
SPF ≥ 15	9	12	13	15	11	12	14	13
Missing	5	4	3	3	6	4	3	2

(continued on following page)

Table 1. Characteristics of NOWAC Study Sample According to Total Number of Sunburns and Weeks of Sunbathing (continued)

Characteristics	Cumulative No. of Sunburns* (n = 134,594)				Cumulative No. of Weeks Sunbathing† (n = 119,065)			
	None	Lowest Tertile	Middle Tertile	Highest Tertile	None	Lowest Tertile	Middle Tertile	Highest Tertile
Sunscreen use in low latitudes‖¶ (%)								
None	30	26	24	22	n/a	32	18	17
SPF < 15	46	47	47	46	n/a	42	50	52
SPF ≥ 15	18	23	25	28	n/a	22	28	27
Missing	6	4	4	4	n/a	4	4	4

Abbreviations: n/a, not applicable; NOWAC, Norwegian Women and Cancer; SPF, sun protection factor.
*Cumulative frequency of sunburns categorized into none and tertiles of total number of sunburns.
†Cumulative frequency of sunbathing in high and low latitudes categorized into none and tertiles of total number of weeks spent on sunbathing vacation.
‡Recorded only for those who received the early version of the questionnaire (1991 to 1997).
§Cumulative number of indoor tanning sessions categorized as never/ever.
‖From baseline questionnaire.
¶Restricted to those who reported at least 1 week of sunbathing in low latitudes.

and ≥ 25; categorized as 0, 1, and ≥ 2). About one half of the participants (those recruited in 1991 to 1997) were also asked about skin reaction to acute sun exposure at the beginning of the summer (turns brown without becoming red, turns red, red with pain, or red with pain and blisters) and skin reaction after repeated sun exposure (turns deep brown, brown, or light brown; never turns brown). Participants reported history of severe sunburns per year that resulted in pain or blisters and subsequent peeling (never, 1, 2 to 3, 4 to 5, or ≥ 6 weeks per year) in childhood (0 to 9 years), adolescence (10 to 19 years), and later-age decades in adulthood. The average number of weeks per year spent on sunbathing vacations (never, 1, 2 to 3, 4 to 6, or ≥ 7 weeks per year) and the history of indoor tanning (never, rarely, one, two, three to four times per month, or more than one time per week) were reported for the same age periods. The question about sunbathing vacations was later divided into two: one that concerned high latitudes and the other, low latitudes. To obtain the cumulative number of sunburns, the observed frequencies in all age periods were multiplied by the number of years for the given period, summed, and categorized as none, the lowest (one to 29 sunburns), middle (30 to 53 sunburns), or highest (≥ 54 sunburns) tertile. Cumulative number of weeks of sunbathing vacation was calculated in the same way and categorized as none, the lowest (1 to 100 weeks), middle (101 to 180 weeks), or highest (≥ 181 weeks) tertile. For participants who explicitly answered questions about sunbathing in low latitudes, total number of weeks sunbathing in low latitudes was calculated similarly and categorized as none, the lowest (1 to 29 weeks), middle (30 to 62 weeks), or highest (≥ 63 weeks) tertile. Indoor tanning was categorized as never/ever.

Study Sample

From 171,725 women enrolled in NOWAC, 21,646 were not asked sunscreen-related questions, and another 2,179 did not answer the questions. A total of 147,900 (86.1%) answered questions about sunscreen use at least once. We found no significant difference between women who answered the question at least once and those who never answered in terms of years of education (P = .35), place of residence (P = .10), or mean age at enrollment (P = .52). We excluded 837 women who had been given a diagnosis of melanoma before answering the sunscreen questions, 2,690 women with very dark brown/black skin (grades 8 to 10), 94 women who had emigrated or died before the sunscreen questions were asked, and 435 women with follow-up time < 1 year. The final sample included 143,844 women who answered sunscreen-related questions either in baseline questionnaires during 1997 to 2007 at age 45 to 70 years or in follow-up questionnaires during 1998 to 2010 at age 40 to 75 years (Fig 1). Analysis of sunscreen use in low latitudes was restricted to women who reported at least 1 week of sunbathing vacation in low latitudes in their lifetime (n = 42,479).

Statistical Analysis

Cox proportional hazards regression was used to estimate the association between sunscreen use and melanoma risk, which included the calculation of hazard ratios and 95% CIs. Entry time was age at answering the sunscreen questions for the first time (baseline), and exit time was age at melanoma diagnosis, emigration, death, or end of follow-up, whichever occurred first. Sunscreen use was modeled by using only the information recorded at baseline and as a time-dependent variable by using updated information from follow-up. The proportional hazards assumption of the Cox models was checked by using Schoenfeld residuals.[21] We used age as time scale,[22] and models were stratified by calendar year when answering the questionnaires to adjust for both age and calendar year (model 1). We further adjusted for hair color, freckling, and ambient ultraviolet radiation of residence (model 2) and cumulative number of sunburns and sunbathing vacations and indoor tanning (model 3). Additional adjustment for education and skin color did not change the results (data not shown). In all models, total number of sunburns and sunbathing vacations were modeled as time dependent by updating information from the follow-up questionnaires. Interaction effects between sunscreen and hair color (light/dark), sunburn (never/ever), sunbathing vacations (never/ever), and freckling (yes, no) were evaluated by using the likelihood ratio test. We used multiple imputations with chained equation,[23] which involved 10 data sets to evaluate the influence of missing information on the estimates (Appendix). The population attributable fraction (PAF) associated with sunscreen use was estimated by the punafcc function in Stata.[24] We calculated PAF for the total population of women and for three high-risk subpopulations (those with blond/red hair color, those who used SPF < 15 sunscreen, and those freckling when sunbathing [Appendix]). We used two-sided tests and a .05 significance level. Stata 13 software (StataCorp, College Station, TX) was used for the statistical analyses.

RESULTS

The mean follow-up of 10.7 years (range, 1.0 to 15.6 years) comprised 1,532,247 person-years, during which 722 women were given a diagnosis of incident melanoma. Mean ages at start of follow-up and diagnosis were 53 years (range, 40 to 75 years) and 60 years (range, 42 to 83 years), respectively. Lower limb was the most common site of melanoma (n = 266) followed by the trunk (n = 249), upper limb (n = 118), head and neck (n = 49), and multiple sites (n = 40). The majority of cases were superficial spreading melanoma (56%) followed by nodular melanoma (15%).

Participants who reported the highest cumulative number of sunburns compared with those who reported no history were more

likely to live in areas with higher ambient ultraviolet radiation (52% *v* 40%); to have ≥ 14 years of education (42% *v* 21%), light skin color (45% *v* 28%), and blond or red hair (49% *v* 32%); and to have used sunscreen (Table 1). Those who reported the highest cumulative number of sunbathing vacations compared with no sunbathing were similarly more likely to live in areas with higher ambient ultraviolet radiation and to have more education; they also were more likely to report a high number of sunburns (38% *v* 21%), ever indoor tanning (75% *v* 26%), and sunscreen use in high latitudes (80% *v* 29%) but less likely to have light skin color (35% *v* 45%; Table 1).

Users and nonusers of sunscreen were significantly different (Table 2). Sunscreen users were more likely to be in the youngest age-groups; to live in areas with high ambient ultraviolet radiation; have higher education, light skin color, blond or red hair, and freckling when sunbathing ($P < .001$); and to report significantly more sunburns and sunbathing vacations and indoor tanning ($P < .001$; Table 2). Moreover, compared with nonusers, sunscreen users with a history of sunburn tended to have a higher risk of melanoma, whereas sunscreen users with no history of sunburn tended to have a lower risk ($.01 \leq P_{\text{interaction}} \leq .04$; Appendix Table A2, online only).

Table 2. Characteristics of Participants by Sunscreen Use (N = 143,844)

Characteristics	Sunscreen Use*				
	Users†		Nonusers†		
	No.	%	No.	%	*P*‡
Age (years)§					< .001
40-49	37,815	87	5,684	13	
50-59	63,322	82	13,766	18	
≥ 60	15,480	67	7,777	33	
Ambient ultraviolet radiation of residence					< .001
Low (north Norway)	23,958	74	8,507	26	
Medium-low (central Norway)	12,658	81	2,906	19	
Medium (southwest Norway)	22,774	85	4,139	15	
Highest (southeast Norway)	57,227	83	11,675	17	
Education (years)					< .001
≤ 10	33,577	71	13,727	29	
11-13	34,553	86	5,678	14	
≥14	43,136	89	5,368	11	
Skin color					< .001
Dark	43,927	81	10,243	19	
Intermediate	42,614	85	7,781	15	
Light	22,203	84	4,272	16	
Hair color					< .001
Black/dark brown	17,916	76	5,543	24	
Brown	46,245	82	9,914	18	
Blond/yellow	45,661	83	9,624	17	
Red	3,748	84	705	16	
Freckling when sunbathing					< .001
No	70,983	80	17,353	20	
Yes	40,702	86	6,779	14	
No. of asymmetric nevi > 5 mm on legs					.37
0	93,489	83	19,339	17	
1	7,457	86	1,240	14	
≥2	5,553	86	927	14	
Cumulative No. of sunburns‖					< .001
None	11,030	67	5,354	33	
Lowest tertile	27,626	81	6,554	19	
Middle tertile	35,574	85	6,038	15	
Highest tertile	36,909	87	5,509	13	
Cumulative no. of weeks sunbathing¶					< .001
None	1,485	31	3,281	69	
Lowest tertile	31,321	80	7,997	20	
Middle tertile	33,171	89	3,923	11	
Highest tertile	34,108	90	3,779	10	
Indoor tanning#					< .001
Never	28,497	72	11,160	28	
Ever	80,875	87	12,272	13	

*Sunscreen use in both high and low latitudes.
†Numbers may not sum to the total due to missing values.
‡Logistic regression model adjusted for all variables in the table.
§Age when answering baseline questionnaire.
‖Cumulative number of sunburns categorized into none and tertiles of total number of sunburns.
¶Cumulative number of sunbathing in high and low latitudes categorized into none and tertiles of total number of weeks spent on sunbathing vacation.
#Cumulative number of indoor tanning sessions categorized as never/ever.

In the SPF analyses, SPF < 15 sunscreen was defined as the reference category because of the heterogeneity of sun exposure between sunscreen users and nonusers. Use of SPF ≥ 15 sunscreen on at least one occasion was associated with a significantly decreased melanoma risk compared with consistently using SPF < 15 (time-dependent model: hazard ratio, 0.67; 95% CI, 0.53 to 0.83; Table 3). Similarly, in a subanalysis of sunscreen use in low latitudes, SPF ≥ 15 was associated with significantly decreased melanoma risk compared with SPF < 15 (Appendix Table A3, online only). As expected, nonuse of sunscreen was associated with decreased melanoma risk compared with consistent use of SPF < 15 (Table 3; Appendix Table A3). Sensitivity analysis by additional adjustment for skin reaction after both acute and chronic sun exposure yielded similar results (data not shown). We found no significant interaction between sunscreen use and hair color, sunbathing vacations, or freckling ($.13 \leq P_{interaction} \leq .78$). Results of multiple imputation analyses did not suggest that bias due to missing data influenced the associations (Appendix Tables A4 and A5, online only).

The estimated PAF for melanoma associated with use of SPF ≥ 15 sunscreens for the total population of women age 40 to 75 years was 18% (95% CI, 4% to 30%), which rose to 21% (95% CI, 3% to 35%) in women with blond/red hair. Among women who used sunscreen with SPF < 15, the estimated PAF for changing to SPF ≥ 15 sunscreens was 33% (95% CI, 16% to 46%; Table 4).

DISCUSSION

In this first cohort study of sunscreen use and melanoma (to our knowledge), risk was reduced by approximately 30% among women who used SPF ≥ 15 compared with SPF < 15 sunscreen. According to our estimates, melanoma incidence among adult women age 40 to 75 years in Norway could potentially decrease by 18% if all were to use SPF ≥ 15 sunscreen.

The Nambour Trial[10] is the only randomized controlled trial of sunscreen use and melanoma risk. Trial participants were randomly assigned to daily sunscreen use with an unlimited supply of broad-spectrum SPF16 sunscreen for 5 years, whereas control participants followed their usual sunscreen practices. After intervention cessation, both groups were followed up for 10 years. Melanoma risk was reduced in those assigned to regular sunscreen use. This trial was conducted in subtropical Australia where sun exposure is mainly unintentional. Conversely, Norwegians (and many other Europeans and North Americans) intentionally expose themselves to high levels of ultraviolet radiation during the summer.[14] In an Australian national survey in 2010/2011 (n = 5,412; age 18 to 69 years), > 70% of adults no longer preferred a suntan,[25] whereas in a Norwegian survey in 2014 (n = 1,024; ≥ 18 years), 74% agreed with the statement, "I sunbathe to get a tan."[26] Sunscreen use in the current study was different from the trial setting with free supply. However, in agreement with the Nambour Trial, we found that the use of SPF ≥ 15 sunscreen reduced melanoma risk compared with SPF < 15 sunscreen. In the most recent case-control study, frequent routine use of sunscreen for two decades was inversely associated with melanoma, although the association for using SPF ≥ 15 sunscreen did not show a statistically significant effect.[11]

We used SPF < 15 as the referent because the nonusers of sunscreen were a small group and had different sun exposure compared with sunscreen users. Sunscreen is the most popular sun protection method in many populations,[27] including Norweigan.[26] In 2007, 81% of NOWAC women reported the use of sunscreen in Norway or other high latitudes, and 91% reported use in low latitudes.[18] Nonusers were more likely to live in areas of low ambient ultraviolet radiation and to report no sunbathing vacations, no sunburns, and never use of indoor tanning devices. Thus, a priori nonusers of sunscreen were at a lower melanoma risk than consistent users of SPF< 15 sunscreen; that is, there is no causal link between their decreased melanoma risk and lack of sunscreen use.

Table 3. Association Between Sunscreen Use With SPF < 15 and ≥ 15 and Risk of Melanoma (n = 109,886)

Sunscreen Use in High/Low Latitudes*	No. of Cases	Model 1†, HR (95% CI)	Model 2‡, HR (95% CI)	Model 3§, HR (95% CI)
Baseline	543			
None/none	54	0.51 (0.38 to 0.69)	0.56 (0.42 to 0.76)	0.63 (0.46 to 0.86)
None/SPF < 15, SPF < 15/none	145	0.85 (0.69 to 1.05)	0.88 (0.71 to 1.08)	0.92 (0.75 to 1.14)
SPF < 15/SPF < 15 (consistently SPF < 15)	231	1.00 (reference)	1.00 (reference)	1.00 (reference)
SPF ≥ 15 on at least one occasion‖	113	0.70 (0.56 to 0.88)	0.68 (0.54 to 0.86)	0.69 (0.55 to 0.88)
Time dependent¶	543			
None/none	63	0.58 (0.42 to 0.75)	0.62 (0.47 to 0.82)	0.69 (0.51 to 0.93)
None/SPF < 15, SPF < 15/none	125	0.73 (0.59 to 0.91)	0.76 (0.61 to 0.94)	0.79 (0.63 to 0.99)
SPF < 15/SPF < 15 (consistently SPF < 15)	232	1.00 (reference)	1.00 (reference)	1.00 (reference)
SPF ≥ 15 on at least one occasion‖	123	0.68 (0.54 to 0.85)	0.66 (0.53 to 0.82)	0.67 (0.53 to 0.83)

Abbreviations: HR, hazard ratio; SPF, sun protection factor.
*Sunscreen use in high and low latitudes are separated by a "/" (eg, none/none means no sunscreen use in high and low latitudes).
†Model 1: stratified Cox proportional hazards regression model (by calendar year of answering sunscreen questions) with attained age as time scale.
‡Model 2: model 1 + hair color, freckling, and ambient ultraviolet radiation of residence.
§Model 3: model 2 + cumulative number of weeks sunbathing, cumulative number of sunburns, and indoor tanning.
‖SPF ≥ 15/SPF ≥ 15, SPF < 15/SPF ≥ 15, SPF ≥ 15/SPF < 15, SPF ≥ 15/none, none/SPF ≥ 15.
¶Sunscreen use modeled as time dependent (ie, sunscreen use reported at baseline and updated with the follow-up information [for those who answered the follow-up questionnaire]).

Table 4. Estimated Reduction in Melanoma Incidence in Total and Three Subpopulations of Adult Women

Characteristics	Proportion in Total Population (%)	PAF (95% CI)
Total population	100	0.18 (0.04 to 0.30)
Subpopulation of women with blond/red hair color	43	0.21 (0.03 to 0.35)
Subpopulation of women freckling when sunbathing	35	0.20 (0.01 to 0.37)
Subpopulation of women who used SPF < 15 sunscreen	33	0.33 (0.16 to 0.46)

Abbreviations: PAF, population attributable fraction; SPF, sun protection factor.

According to our PAF estimates on the basis of follow-up time, general use of SPF ≥ 15 sunscreen for an average of 10 years (average follow-up) could potentially reduce melanoma incidence among women age 40 to 75 years by 18% or by up to 33% among SPF < 15 sunscreen users if they were using SPF ≥ 15 sunscreen. In 2010, approximately 28% of Australians reported daily sunscreen use, and an estimated 14% of incident melanomas were prevented by sunscreen use.[28] We previously showed in NOWAC that sunscreen use increased from 1997 to 2007 in Norwegian women at both high and low latitudes.[18] The upward trend of using broad-spectrum high-SPF sunscreens along with improvement in application has the potential to decrease the incidence of melanoma and lower its burden in coming years.

NOWAC is a large prospective study of women randomly selected from the general population. We have detailed exposure information across several decades of life, complete follow-up through high-quality national registries, and 99.9% of melanomas morphologically verified.[3] Follow-up is long, and NOWAC has good external validity.[29] In the multivariable analyses, the complete case and multiple imputation analyses yielded similar results. Misclassification of exposure, inevitable in epidemiologic studies, is likely nondifferential in a cohort study. Nevertheless, previous analysis of ultraviolet exposure and pigmentary characteristics in NOWAC has shown consistent effects on melanoma risk.[16,30]

In practice, the overall effectiveness of a sunscreen depends not only on its SPF but also on ultraviolet spectral absorption, amount used, reapplication, and coverage of sun-exposed parts. Unfortunately, we do not have this detailed information. In everyday settings, most people use one fifth to one half of the recommended amount and do not reapply as recommended, resulting in sunburn.[31] In the 2014 survey, 96% of Norwegians reported using sunscreen in sunbathing vacations in low latitudes, and 36% reported sunburn in the past 12 months in these regions.[26] Thus, our risk estimates and calculated risk reduction attributable to sunscreen use are in the context of imperfect sunscreen use and may be conservative. Moreover, we lack information about other methods of sun protection, although use of other methods of sun protection not related to the SPF of sunscreen was reasonably assumed and, therefore, did not affect estimates among sunscreen users. However, nonusers of sunscreen may have had a greater tendency to use other, more efficient methods of sun protection, such as protective clothing, which might explain part of their reduced melanoma risk compared with SPF < 15 sunscreen users. Our study included only women age ≥ 40 years; however, whereas others have found that the frequency of sunscreen use is lower in men,[26,32] other findings[10,33] have suggested that the association with melanoma is similar in women and men.

In summary, these prospective data support the hypothesis that during intentional sunbathing, use of SPF ≥ 15 sunscreen can reduce melanoma risk compared with use of SPF < 15 sunscreen. Moreover, use of SPF ≥ 15 sunscreen by all women age 40 to 75 years could lead to an 18% drop in melanoma incidence in approximately 10 years.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Sunscreen Use and Subsequent Melanoma Risk: A Population-Based Cohort Study

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Appendix

Rationale for Sunscreen Categorization

In categorizing sunscreen use in both high and low latitudes according to sun protection factor (SPF), we had nine combinations that we categorized into four groups: nonusers in both occasions, sunscreen use with SPF $<$ 15 in only one occasion, sunscreen use with SPF $<$ 15 in both occasions, and sunscreen use with SPF $\geq$ 15 on at least one occasion (Table A1). The majority of the participants in the latter group (78%) used sunscreen with SPF $<$ 15 in high latitudes and SPF $\geq$ 15 in low latitudes or SPF $\geq$ 15 in both locations.

Multiple Imputations

Approximately 20% of the observations had missing information on one or more covariates in the multivariable analyses. We used multiple imputations with chained equation, and the imputation models included all covariates in the multivariable models.

The number of imputations was based on the reproducibility argument, which considers the Monte Carlo error of the results, to be confident that a repeat analysis of the same data would produce essentially the same results (White et al: Stat Med 30:377-399, 2011; Graham et al: Prev Sci 8:206-213, 2007). The estimates, CIs, and *P* values were identical in the results from five and 10 imputations.

Population Attributable Fraction

In a cohort study, population attributable fraction (PAF) is defined as the proportion of disease incidence that could be avoided during the follow-up time interval if the current exposure distribution was replaced by the hypothetically preferable distribution (Samuelsen et al: Stat Med 27:1447-1467, 2008). We defined women who reported sunscreen use with SPF $\geq$ 15 as unexposed in the equation and calculated PAF for four scenarios: What if the total population of women would have used sunscreen with SPF $\geq$ 15 during the study period; what if all women with blond/red hair would have used sunscreen with SPF $\geq$ 15 during the study period; what if all women who reported freckling after sunbathing would have used sunscreen with SPF $\geq$ 15 during the study period; and what if all women who used sunscreen with SPF $<$ 15 would have used sunscreen with SPF $\geq$ 15 during the study period? Adjusted time-dependent hazard ratios were used to calculate PAFs. We used adjusted time-dependent hazard ratios (model 3; Table 4) to calculate PAF. Norwegian Women and Cancer is a population-based study and has been shown to be representative of the Norwegian female population.[9]

Table A1. Frequency of Sunscreen Use According to SPF

Sunscreen Use in High /Low Latitudes	Frequency (%)	Category	Frequency (%)
None/none	27,227 (18.9)	None/none	27,227 (18.9)
None/SPF $<$ 15	9,199 (6.4)	None/SPF $<$ 15 SPF$<$15/none	33,801 (23.5)
SPF $<$ 15/none	24,602 (17.1)		
SPF $<$ 15/SPF $<$ 15	46,807 (32.5)	SPF $<$ 15/SPF $<$ 15	46,807 (32.5)
None/SPF $\geq$ 15	2,313 (1.6)	SPF $\geq$ 15 on at least one occasion	36,009 (25.1)
SPF $\geq$ 15/none	5,283 (3.6)		
SPF $<$ 15/SPF $\geq$ 15	15,132 (10.5)		
SPF $\geq$ 15/SPF $<$ 15	338 (0.2)		
SPF $\geq$ 15/SPF $\geq$ 15	12,943 (9.0)		
Total	143,844 (100.0)		143,844 (100.0)

Abbreviation: SPF, sun protection factor.

Table A2. Association Between Sunscreen Use in High and Low Latitudes and Risk of Melanoma (n = 109,886)

Sunscreen	No. of Cases	Model 1*, HR (95% CI)	Model 2†, HR (95% CI)	Model 3‡, HR (95% CI)	Sunburns§	
					Never, HR (95% CI)	Ever, HR (95% CI)
Baseline	543					
Nonuser	54	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	489	1.70 (1.28 to 2.26)	1.44 (1.07 to 1.93)	1.34 (0.99 to 1.82)	0.62 (0.29 to 1.29)	1.53 (1.09 to 2.14)
					$P_{interaction}$ = .03	
Time dependent‖	543					
Nonuser	63	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	480	1.45 (1.11 to 1.90)	1.22 (0.93 to 1.61)	1.13 (0.85 to 1.50)	0.47 (0.23 to 0.97)	1.30 (0.95 to 1.77)
					$P_{interaction}$ = .01	
Combined¶	543					
Consistent nonuser	47	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Inconsistent	21	1.46 (0.86 to 2.48)	1.29 (0.76 to 2.21)	1.30 (0.76 to 2.21)	0.77 (0.17 to 3.50)	1.49 (0.84 to 2.65)
Consistent user	475	1.71 (1.26 to 2.32)	1.32 (0.96 to 1.83)	1.33 (0.96 to 1.85)	0.52 (0.24 to 1.11)	1.57 (1.09 to 2.26)
					$P_{interaction}$ = .04	

Abbreviation: HR, hazard ratio.
*Model 1: stratified Cox proportional hazards regression model (by calendar year of answering sunscreen questions) with attained age as time scale.
†Model 2: model 1 + hair color, freckling, and ambient ultraviolet radiation of residence.
‡Model 3: model 2 + cumulative number of weeks sunbathing, cumulative number of sunburns, and indoor tanning.
§Model 4: model 3 + interaction between sunscreen use and sunburns history.
‖Sunscreen use modeled as time dependent (ie, sunscreen use reported at baseline and updated with follow-up information [for those who answered the follow-up questionnaire]).
¶Sunscreen use categorized according to the baseline (for those who answered once) and follow-up (for those who answered the follow-up questionnaire).

Table A3. Association Between SPF < 15 and ≥ 15 Sunscreen Use in Low Latitudes and Risk of Melanoma Among Participants Who Reported at Least 1 Week of Sunbathing Vacation in Low Latitudes (n = 42,479)

Sunscreen Use	No. of Cases	Model 1*, HR (95% CI)	Model 2†, HR (95% CI)	Model 3‡, HR (95% CI)	Model 4§, HR (95% CI)
Baseline	188				
None	14	0.56 (0.32 to 0.97)	0.55 (0.31 to 0.96)	0.56 (0.32 to 0.98)	0.54 (0.30 to 0.97)
SPF < 15	115	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
SPF ≥ 15	59	0.79 (0.57 to 1.09)	0.75 (0.54 to 1.03)	0.74 (0.54 to 1.02)	0.62 (0.42 to 0.93)
Time dependent‖	188				
None	16	0.58 (0.34 to 0.98)	0.57 (0.33 to 0.96)	0.57 (0.34 to 0.98)	0.55 (0.32 to 0.96)
SPF < 15	114	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
SPF ≥ 15	58	0.76 (0.55 to 1.05)	0.71 (0.52 to 0.99)	0.71 (0.51 to 0.98)	0.59 (0.40 to 0.88)
Baseline or baseline/follow-up¶	188				
None or none/none	11	0.45 (0.24 to 0.85)	0.45 (0.24 to 0.83)	0.45 (0.24 to 0.85)	0.43 (0.22 to 0.83)
Inconsistent#	10	1.05 (0.49 to 2.24)	1.01 (0.47 to 2.16)	1.00 (0.47 to 2.15)	0.97 (0.45 to 2.07)
SPF < 15 or SPF < 15/SPF < 15	110	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
SPF ≥ 15 or SPF ≥ 15/SPF ≥ 15	57	0.78 (0.56 to 1.08)	0.73 (0.53 to 1.02)	0.73 (0.52 to 1.01)	0.61 (0.40 to 0.91)

Abbreviations: HR, hazard ratio; SPF, sun protection factor.
*Model 1: stratified Cox proportional hazards regression model (by calendar year of answering sunscreen questions) with attained age as time scale.
†Model 2: model 1 + hair color, freckling, and ambient ultraviolet radiation of residence.
‡Model 3: model 2 + cumulative number of weeks sunbathing, cumulative number of sunburns, and indoor tanning.
§Model 4: model 3 + sunscreen use in high latitudes.
‖Sunscreen use modeled as time dependent (ie, sunscreen use reported at baseline and updated with follow-up information [for those who answered the follow-up questionnaire]).
¶Sunscreen use categorized according to baseline (for those who answered once) and follow-up (for those who answered the follow-up questionnaire) as consistently did not use, changed over time (inconsistent), consistently used SPF < 15, and consistently used SPF ≥ 15.
#None/SPF < 15, none/SPF ≥ 15, SPF < 15/none, SPF ≥ 15/none, SPF ≥ 15/SPF < 15, SPF <1 5/SPF ≥ 15.

Table A4. Multiple Imputation Analysis of the Association Between Total Sunscreen Use (never/ever) and Risk of Melanoma (N = 143,844)

Sunscreen Use	Model 1*, HR (95% CI)	Model 2†, HR (95% CI)	Model 3‡, HR (95% CI)	Total No. of Sunburns§	
				Never, HR (95% CI)	Ever, HR (95% CI)
Baseline					
Nonuser	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	1.61 (1.30 to 2.00)	1.48 (1.20 to 1.83)	1.28 (0.98 to 1.63)	0.73 (0.47 to 1.49)	1.34 (1.04 to 1.72)
Time dependent‖					
Nonuser	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	1.53 (1.16 to 1.89)	1.37 (1.08 to 1.56)	1.20 (0.95 to 1.46)	0.64 (0.32 to 1.03)	1.29 (1.04 to 1.58)
Combined¶					
Consistent nonuser	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Inconsistent	1.32 (0.84 to 2.06)	1.21 (0.85 to 2.01)	1.20 (0.86 to 2.00)	0.80 (0.33 to 2.20)	1.35 (0.80 to 2.29)
Consistent user	1.62 (1.14 to 2.31)	1.38 (0.98 to 1.78)	1.28 (0.97 to 1.80)	0.71 (0.39 to 1.14)	1.62 (1.05 to 2.05)

NOTE. Multiple imputation of covariates in multivariable analyses conducted with chained equations. Ten imputed data sets were generated. Abbreviation: HR, hazard ratio.
*Model 1: stratified Cox proportional hazards regression model (by calendar year of answering sunscreen questions) with attained age as time scale.
†Model 2: model 1 + hair color, freckling, and ambient ultraviolet radiation of residence.
‡Model 3: model 2 + cumulative number of weeks sunbathing, cumulative number of sunburns, and indoor tanning.
§Model 4: model 3 + interaction between sunscreen use and sunburns.
‖Sunscreen use modeled as time dependent (ie, sunscreen use reported at baseline and updated with follow-up information [for those who answered follow-up questionnaire]).
¶Sunscreen use categorized according to baseline (for those who answered once) and follow-up (for those who answered follow-up questionnaire).

Table A5. Multiple Imputation Analysis of the Association Between Total Sunscreen Use With SPF < 15 and ≥ 15 and Risk of Melanoma (N = 143,844)

Sunscreen Use in High/Low Latitudes	Model 1*, HR (95% CI)	Model 2†, HR (95% CI)	Model 3‡, HR (95% CI)
Baseline			
None/none	0.52 (0.40 to 0.68)	0.58 (0.45 to 0.76)	0.69 (0.52 to 0.92)
SPF < 15/none, none/SPF < 15	0.81 (0.67 to 0.97)	0.84 (0.70 to 1.01)	0.90 (0.74 to 1.09)
SPF < 15/SPF < 15 (consistently SPF < 15)	1.00 (reference)	1.00 (reference)	1.00 (reference)
SPF ≥ 15 on at least one occasion§	0.71 (0.58 to 0.87)	0.70 (0.57 to 0.87)	0.73 (0.59 to 0.89)
Time-dependent‖			
None/none	0.51 (0.40 to 0.67)	0.57 (0.44 to 0.74)	0.67 (0.51 to 0.89)
SPF < 15/none, none/SPF < 15	0.76 (0.62 to 0.93)	0.79 (0.65 to 0.96)	0.84 (0.69 to 1.03)
SPF < 15/SPF < 15 (consistently SPF <15)	1.00 (reference)	1.00 (reference)	1.00 (reference)
SPF ≥ 15 on at least one occasion§	0.72 (0.59 to 0.88)	0.71 (0.58 to 0.87)	0.73 (0.59 to 0.89)

NOTE. Multiple imputation of covariates in multivariable analyses conducted with chained equations. Ten imputed data sets were generated.
Abbreviations: HR, hazard ratio; SPF, sun protection factor.
*Model 1: stratified Cox proportional hazards regression model (by calendar year of answering sunscreen questions) with attained age as time scale.
†Model 2: model 1 + hair color, freckling, and ambient ultraviolet radiation of residence.
‡Model 3: model 2 + cumulative number of weeks sunbathing, cumulative number of sunburns, and indoor tanning.
§SPF ≥ 15/SPF ≥ 15, SPF < 15/SPF ≥ 15, SPF ≥ 15/SPF < 15, SPF ≥ 15/none, none/SPF ≥ 15.
‖Sunscreen use modeled as time dependent (ie, sunscreen use reported at baseline and updated with the follow-up information [for those who answered the follow up questionnaire]).