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Avoidance of sun exposure is a risk factor for all-cause mortality: results from the Melanoma in Southern Sweden cohort

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Abstract. Lindqvist PG, Epstein E, Landin-Olsson M, Ingvar C, Nielsen K, Stenbeck M, Olsson H (Clintec, Karolinska University Hospital, Stockholm; Karolinska University Hospital, Stockholm; Lund University Hospital, Lund; Lund University Hospital, Lund; Lund University, Lund; Karolinska Institutet, Stockholm; Lund University Hospital, Lund). Avoidance of sun exposure is a risk factor for all-cause mortality: results from the MISS cohort. *J Intern Med* 2014; **276**: 77–86.

Background. Sunlight exposure and fair skin are major determinants of human vitamin D production, but they are also risk factors for cutaneous malignant melanoma (MM). There is epidemiological evidence that all-cause mortality is related to low vitamin D levels.

Methods. We assessed the avoidance of sun exposure as a risk factor for all-cause mortality for 29 518 Swedish women in a prospective 20-year follow-up of the Melanoma in Southern Sweden (MISS) cohort. Women were recruited from 1990 to 1992 and were aged 25 to 64 years at the start of the study. We obtained detailed information at baseline on their sun exposure habits and potential confounders. Multivariable flexible parametric survival analysis was applied to the data.

Results. There were 2545 deaths amongst the 29 518 women who responded to the initial questionnaire. We found that all-cause mortality was inversely related to sun exposure habits. The mortality rate amongst avoiders of sun exposure was approximately twofold higher compared with the highest sun exposure group, resulting in excess mortality with a population attributable risk of 3%.

Conclusion. The results of this study provide observational evidence that avoiding sun exposure is a risk factor for all-cause mortality. Following sun exposure advice that is very restrictive in countries with low solar intensity might in fact be harmful to women's health.

Keywords: evolution, longevity, melanoma, population attributable risk, UV radiation, vitamin D.

Introduction

Ultraviolet (UV) radiation from the sun is known to heighten the risk of developing malignant melanoma (MM) of the skin. This condition is primarily responsible for increased mortality due to UV radiation exposure. The risk of MM varies widely amongst people of different skin colour, depending on the type of melanin in their skin. MM is most common amongst Northern Europeans with pale skin and is rare amongst Africans with very dark skin [1]. Individuals with red hair or a tendency to develop freckles are at increased risk of developing MM. The highest risk has been found amongst those of European ancestry living in Northern Australia [1]. This has been the basis for considering UV radiation as the major cause of MM. Programmes for avoiding UV radiation are widely implemented in societies in which a large proportion of the population is descended from Europeans [2].

Nevertheless, exposure to sunlight remains the main source of vitamin D. Sunlight UVB radiation with a wavelength between 290 and 315 nm penetrates the skin and converts 7-dehydrocholesterol to 25-hydroxycholecalciferol vitamin D_3 via previtamin D [3]. Low vitamin D levels have been

associated with an increase in both all-cause and cardiovascular disease mortality, but results are inconsistent [4–8]. Low vitamin D concentrations have also been linked to thicker, more aggressive melanomas with shorter survival times [9]. Thus, opposing mechanisms may act with regard to MM and sunlight exposure.

Our longitudinal cohort study was carried out to assess how all-cause mortality risk may be influenced by avoidance of sun exposure in women.

Methods

Study design

The study was approved by the Ethics Committee of Lund University (LU 632-03). In 1990, the Melanoma in Southern Sweden (MISS) study was initiated. Our subjects consisted of approximately 1000 Sweden-born women of each age from 25 to 64 years (n = 39 973) with no history of malignancy. The subjects were selected from the general population registry of the South Swedish Health Care Region by random computerized selection and represented 20% of the female population of South Sweden in the selected age groups.

The women were invited to complete a standardized written questionnaire concerning risk factors for MM. The initial inquiry was carried out from 1990 to 1992, and 29 518 women subsequently entered the study (response rate 74%). A written follow-up was then conducted between 2000 and 2002. A total of 184 women emigrated during the study period and were censored after emigration. The questionnaire was a detailed inquiry into several factors of potential interest for longevity, such as sun exposure habits, marital status, educational level, smoking habits, alcohol consumption, number of pregnancies, body mass index (BMI) and physical exercise. As sun exposure may depend on economic resources, we collected information on mean personalized family income between 1990 and 1993, that is, approximately the time of study initiation, from official income and taxation records at Statistics Sweden (for further details see http://www.scb.se/en_/). Four questions were asked regarding sun exposure: (i) How often do you sunbathe during the summertime? (never, 1–14 times, 15–30 times, >30 times); (ii) Do you sunbathe during the winter, such as on holiday to the mountains? (no; 1–3 days, 4–10 days; >10 days); (iii) Do you use tanning beds? (never; 1–3 times per year; 4–10 times per year; >10 times per year); and (iv) Do you go abroad on holiday to swim and sunbathe? (never; once per 1–2 years; once per year; two or more times per year). The four questions were dichotomized into yes/no in the analysis (i.e. 'no/never' or 'sometimes'). As a measure of total sun exposure, we created a four-score variable depending on the number of 'yes' responses to the above questions from 0 (avoiding sun exposure: reference) to 4 (highest sun exposure). For the purpose of presentation in the figures and to estimate population attributable risk (PAR), sun exposure habits were categorized into three groups: zero 'yes' responses (avoidance of sun exposure); 'yes' response to one or two questions (moderate exposure); and 'yes' response to three or four questions (highest exposure). Hereditary disposition towards MM was defined as having a first-degree relative with MM. Red hair was considered a risk factor for developing MM. Known prognostic factors for MM include gender, *in situ*/invasive MM, Breslow thickness, location of MM, ulceration and age at diagnosis. In this study, we included only women, and Breslow thickness was dichotomized into ≥0.8 mm or <0.8 mm. In the analysis of case fatality for MM, characteristics of MM were dichotomized into invasive MM and Breslow thickness ≥0.8 mm versus other, due to an empty group. As the hazard ratio (HR) for the extremities and head/neck area was similar, location was dichotomized into trunk or other. We did not have access to information on whether or not ulceration was present.

Cases of MM were identified up to 1 January 2011 by cross-linking with the National Cancer Register and Cause of Death Register. Vital statistics were determined from the National Population Register and the Cause of Death Register also up to 1 January 2011.

Smoking habits at baseline were recorded and categorized into lifetime number of cigarettes smoked: none (reference), <100 000 and ≥100 000. This was based on self-reported estimations of mean cigarette consumption over 5-year intervals.

As a measure of comorbid illness at the start of the study, we created a dummy variable 'comorbidity' identifying women who have been treated with antidiabetic [Anatomical Therapeutic Chemical Classification System (ATC) A:10] or anticoagulant (ATC B:01) drugs or medications for cardiovascular disease (ATC C:01–C:10) for more than 1 month.

Weight and height were recorded at the second questionnaire in the year 2000, and BMI was calculated (in kg m^{-2}). BMI was classified into three groups: <25 (reference), 25 to <30 (overweight) and ≥30 kg m^{-2} (obese). The level of regular exercise was categorized at the second interview into three groups: none, walking at least once per week or strenuous exercise [10].

Statistical analysis

Descriptive statistical analysis was performed using cross-tabulation with the 95% confidence interval (CI) (Table 1). Because we were interested in evaluating both differences in mortality rate with attained age as timescale and relative risk, we chose flexible parametric models for survival analysis [11]. All-cause mortality was used as a dependent variable and time variable as time from inception and at attained age in Figs 1 and 2, respectively. Time from inception was calculated from inclusion (see above definition) to death, emigration or 1 January 2011, whichever occurred first. As shown in Table 2, model 2 included BMI and physical exercise from the second interview; data before the year 2000 were censored. Missing values were represented by a dummy variable and included in the analysis. The model was fitted with a combination of backward and forward selection. Red hair, heredity for MM, parity and alcohol consumption were not found to be significant in multivariable analysis of all-cause mortality and were not included in the final model (Table 2). Red hair and hereditary disposition towards MM are known risk factors for MM and were included as adjustments in model 1, as shown in Table 3. In model 2 (see Table 3), comorbidity and earlier known variables such as location, Breslow thickness, *in situ*/invasive MM and age at diagnosis were included. As Breslow thickness and invasiveness are correlated, a new dummy variable 'MM characteristics' was created and categorized into two groups: *in situ* MM/invasive MM and Breslow <0.8 mm or invasive MM and Breslow ≥0.8 mm. A logistic regression analysis was performed (with the same adjustments as in the models shown in Table 2) to estimate PAR. To computed PAR, the following formula was used: PAR = Pe × [adjusted odds ratio (OR) − 1]/adjusted OR (Table 2, model 2), where Pe is the proportion of cases assigned to a given variable [12].

IBM SPSS 21 (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) software was used for descriptive analysis and logistic regression analysis, and STATA 12 (Statacorp, College Station, TX, USA) was used for the multivariable flexible parametric regression model. *P*-values <0.05 were considered statistically significant.

Results

There were 2545 deaths amongst the 29 518 women – representing 540 577 person-years – who responded to the initial questionnaire. As can be seen in Table 1, all the potential confounders were significantly related to sun exposure habits and were initially included in the model. In model 1 (Table 2), we show how sun exposure relates to all-cause mortality. Most comparisons showed significantly lower HR values amongst those with the highest sun exposure habits, as compared to those who avoided sunshine. In model 2 (Table 2), BMI and physical exercise were included, and the data were censored before the year 2000. HR values were similar, and the CIs were wider. In both models, the summary sun exposure variables showed a 'dose-dependent' inverse relation between sun exposure and all-cause death.

In Fig. 1, all-cause mortality was presented as an adjusted flexible parametric regression survival model with three sun exposure groups. Adjustments were made for comorbidity, age, smoking habits, education level, marital status and disposable income. Figure 2 shows all-cause mortality rate by attained age, in the three sun exposure groups. As compared to the highest sun exposure group, the mortality rate was doubled (2.0, 95% CI 1.6–2.5) amongst avoiders of sun exposure and increased by 40% (1.4, 95% CI 1.1–1.7) in those with moderate exposure. We found that the assumption of proportional hazards seemed reasonable. We estimated that PAR for mortality for those avoiding sun exposure was 3%.

Table 3 shows the risk of developing MM by sun exposure habits (as both number of women and HR values). In addition, the overall prognosis and MM case fatality-related deaths amongst the 267 women who developed MM during the study are presented (Table 3, models 2 and 3). Adjustments were made for known risk factors including age at diagnosis, MM characteristics, location (trunk or other) and comorbidities.

Table 1 *Demographic characteristics of women with active and not active sun exposure habits at inception of study*

	Not active sun exposure habits		Active sun exposure habits[b]		Significance of difference (*P*)
	(*n* = 1721)	%	(*n* = 27 797)	%	
Women's characteristics and habits[a]					
Education					
≤9 years	741	43.1	4842	17.4	<0.001
9 years	143	8.3	2630	9.5	
10–12 years	219	12.7	7440	26.8	
≥12 years	344	20.0	9353	33.6	
Other	274	15.9	3532	12.7	
Marital status					
Unmarried	149	8.7	2414	8.7	<0.001
Married	1239	72.0	21 771	78.3	
Divorced	140	8.1	2527	9.1	
Widow	149	8.7	1004	3.6	
Unknown[a]	44	2.6	81	0.3	
Parity					
0	325	18.9	4647	16.7	<0.001
1–2	820	47.6	15 637	56.3	
≥3	576	33.5	7513	27.0	
Smoking					
Nonsmokers	947	55.0	11 370	40.9	<0.001
<100 000 cigarettes	355	20.6	9298	33.4	
≥100 000 cigarettes	334	19.4	6490	23.3	
Unknown[a]	85	4.9	639	2.3	
Alcohol consumption					
None or <5 g day^{-1}	1280	74.4	17 171	61.8	<0.001
5 to <10 g day^{-1}	73	4.2	4822	17.3	
10 to <15 g day^{-1}	32	1.9	1788	6.4	
≥15 g day^{-1}	27	1.6	1261	4.5	
Unknown[a]	309	18.0	2755	9.9	
Red hair					
Yes	92	5.3	1028	3.8	0.001
Heredity risk of melanoma					
Yes	86	5.0	1046	3.8	0.01
Disposable income					
Low	787	45.7	5661	20.4	<0.001
Moderate	459	26.7	8454	30.4	
High	475	27.6	13 682	49.2	
Comorbidity[c]					
Yes	1351	20.4	2571	9.2	<0.001

Table 1 (*Continued*)

	Not active sun exposure habits		Active sun exposure habits[b]		Significance of difference (*P*)
	(*n* = 1721)	%	(*n* = 27 797)	%	
Data from second interview	*n* = 1210		*n* = 22 888		
Body mass index					
<25 kg m^{-2}	421	34.8	12 662	55.3	<0.001
25 to <30 kg m^{-2}	346	28.6	6434	28.1	
≥30 kg m^{-2}	237	19.6	2242	9.8	
Unknown	206	17.0	1550	6.8	
Physical exercise					
None	167	13.8	1892	8.3	<0.001
Light	484	40.0	10 322	45.1	
Strenuous	224	18.5	7476	32.7	
Unknown	335	27.7	3198	14.0	

[a]Some women did not answer all questions.
[b]Answering 'yes' to at least one of the sun exposure questions.
[c]Women who have been treated for >1 month with drugs with the ATC codes A10, B01 or C01–10.

Discussion

We found that all-cause mortality was inversely related to sun exposure habits in a 'dose-dependent' manner. The mortality rate was increased twofold amongst avoiders of sun exposure as compared to those with the highest sun exposure habits. In this study focusing on avoidance of sun exposure, women with 'normal' sun exposure habits were not at significantly increased risk of MM or of MM-related death.

In this study, we did not focus on the cause of death. However, the effect was presumably attributed to cancer, heart disease and cerebrovascular disease. There is a known seasonal variation in both heart disease and cerebrovascular disease, with increased risk during winter/spring as compared to summer [13, 14]. There is some epidemiological evidence of an increased risk of cardiovascular disease and early death amongst individuals with low levels of vitamin D; however, these results are inconsistent [5, 6, 15–18]. Only women without a history of diagnosed cancer were included in this study. Thus, the comparison between those with and without cancer is biased in our study. Previously, it has been suggested that season-related differences in diseases are mainly due to cold or humidity, but we recently proposed that lack of sun exposure might be the environmental factor causing the increased risk of incident thromboembolism, type 2 diabetes and eclampsia in winter [10, 19, 20]. We speculated that insufficient vitamin D levels amongst those who avoid sun exposure might be the mechanism that increases the mortality rate. However, our findings are of association and not necessarily causal. Regarding diabetes, for example, the melatonin system might be involved in the lower risk of type 2 diabetes amongst those with the highest sun exposure habits [10, 21]. Another possible explanation is that UVB exposure induces cutaneous endorphins. It has been reported that the use of tanning beds induces mood enhancement, feelings of relaxation and socialization, due to UVB exposure [22, 23]. The presence of an awarding system at UVB exposure may also be interpreted as a mechanism for avoiding vitamin D deficiency. Another possibility is that solar UVA radiation causes an increase in skin-derived NO bioactivity lowering blood pressure and cardiovascular morbidity [24].

Skin tumours, the major concern of excessive sun exposure, consist of three types (with increasing severity): basal cell carcinoma, squamous cell carcinoma and MM. Sun exposure increases the risk of MM mainly through episodic sunburn or frequent use of tanning beds in individuals with unprotected fair skin. The incidence of MM repre-

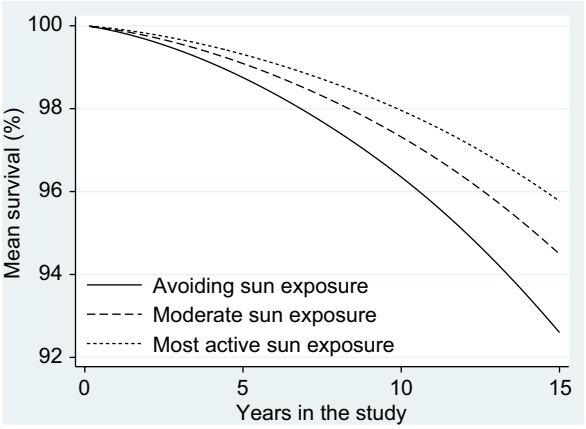

Fig. 1 *Adjusted all-cause survival plot of 29 518 women recruited in the Melanoma in Southern Sweden (MISS) cohort (1990–1992) and followed for sun exposure habits for 20 years. Sun exposure habits were classified by the number of 'yes' answers to the following questions: (i) Do you sunbathe during the summer? (ii) Do you sunbathe during the winter, such as during holidays to the mountains? (iii) Do you use tanning beds? (iv) Do you go abroad on holiday to swim and sunbathe? Significance of difference: P < 0.001 amongst all three sun exposure groups. Adjustments were made for comorbidity, age, smoking habits, education level, marital status and disposable income.*

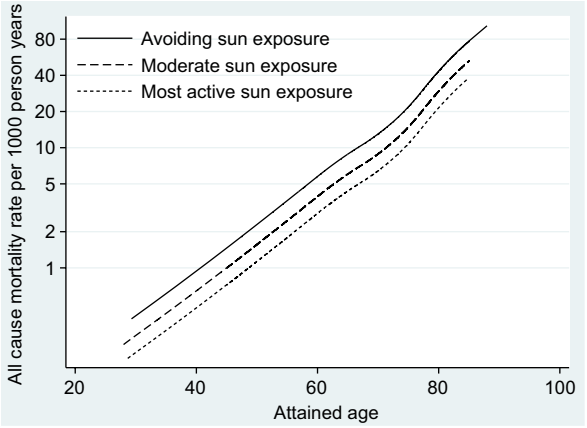

Fig. 2 *Mortality rate by sun exposure habits with attained age as the time variable for all 29 518 women included in the study. As compared to the highest sun exposure group, the mortality rate was twofold higher [2.0, 95% confidence interval (CI) 1.6–2.5] amongst avoiders of sun exposure and increased by 40% (1.4, 95% CI 1.1–1.7) in those with moderate exposure.*

sents the greatest increase of all cancers affecting women at lower age than men. The disease is fatal in approximately 20% of patients with MM. Basal cell carcinoma and squamous cell carcinoma often affect older individuals and are mostly associated with cumulative exposure to UV light. The incidences of both these types of tumour are increasing. Basal cell carcinoma is generally not fatal but could be locally aggressive, whilst surgery or radiotherapy provides a cure for most patients with squamous cell carcinoma [25].

US Navy personnel have been reported to be at high risk of skin cancer, but at a reduced risk of all-cause mortality (−26%) and other forms of cancer [26, 27]. However, using the contraction of basal cell carcinoma as a proxy for heavy sun exposure, without taking into consideration differences in *p53* polymorphisms, the finding of a lower risk of internal cancer has been questioned in a large well-executed case–control study [28]. Support for our results comes from Yang *et al.* [29], who reported a 30% lower all-cause mortality in individuals who took sunbathing holidays at least once a year over the course of three decades. These authors reported no difference in all-cause mortality amongst those who did not use tanning beds, as compared to those who did so <12 times per year. We focused on the low-sun-exposure group as a risk factor for mortality, whereas most other studies focused on the disadvantages of high sun exposure (so-called overuse).

In agreement with our results, Newton-Bishop and co-workers reported thinner, less aggressive melanoma with greater survival rates in the presence of higher vitamin D levels [9]. Our findings are also consistent with the results of a study by Måsbäck *et al.* [30]; these authors concluded that sun-associated MM was related to superficial spreading MM, in contrast to nodular MM, which had a worse prognosis. Because non-MM skin cancer risk increases with cumulative sun exposure, the finding of an increased incidence of this type of skin cancer with increasing vitamin D levels does not contradict our results [31–33].

Public health implications

Over the last 30–40 years, Sweden and other western countries have produced national guidelines and provided restrictive advice on sun exposure habits to lower the risk of skin cancer. These recommendations are based on Australian/English guidelines known as SunSmart [2], which may be appropriate in a country with a high UV index

Table 2 *Sun exposure habits and risk of all-cause mortality: multivariate analysis*

			Model 1		Model 2	
	Women alive	Women dead	Hazard ratio (HR)	95% CI	HR	95% CI
Use of sunbeds?[a]						
No	11 117	1825	1.0	Ref	1.0	Ref
Yes	12 856	720	0.77	0.7–0.8	0.87	0.8–0.98
Sunbathing during winter holiday?[a]						
No	21 777	2288	1.0	Ref	1.0	Ref
Yes	5196	257	0.81	0.7–0.9	0.85	0.7–1.02
Sunbathing during summer?[a]						
No	1719	425	1.0	Ref	1.0	Ref
Yes	25 254	2120	0.74	0.7–0.8	0.80	0.7–0.9
Sunbathing during holiday abroad?[a]						
No	11 331	1323	1.0	Ref	1.0	Ref
Yes	15 642	1222	0.83	0.8–0.9	0.88	0.8–0.97
Summary sun exposure (number of 'yes' answers to above four questions)						
0	1352	364	1.0	Ref	1.0	Ref
1	6229	771	0.80	0.7–0.9	0.83	0.7–1.0
2	8384	782	0.71	0.6–0.8	0.74	0.6–0.9
3	8081	508	0.61	0.5–0.7	0.66	0.5–0.8
4	2927	115	0.53	0.4–0.7	0.62	0.5–0.8
0	1352	369	1.0	Ref	1.0	Ref
1–2	14 613	1553	0.76	0.7–0.8	0.79	0.7–0.9
3–4	11 008	623	0.60	0.5–0.7	0.66	0.5–0.8

Model 1 adjusted for age, smoking, marital status, educational level, disposable income and comorbidity.
Model 2 adjusted for all the above and body mass index and physical exercise amongst those answering the second questionnaire, that is, censoring outcomes before second interview (in year 2000).
Cox regression analysis: [a]not all women answered all questions.

such as Northern Australia, where dense pigmentation would be an advantage. However, following generally restrictive guidelines in Sweden, a country located at the northern latitude of between 55° and 67° with limited sunshine and a low UV index, might not be optimal. In fact, our findings indicate that these guidelines may indeed be harmful in terms of overall health of the population. The Southern Australia (Tasmania) Cancer Council recommendations including daily short sun exposure might be more suitable in regions with low sun intensity levels [34].

Moreover, in areas with less intense sunlight, genetic variations appear to play a role as a risk factor for MM, and recent evidence shows that nonpigmentation-associated polymorphisms may be of major importance in risk of developing MM [35–37].

Our study population of women born in Sweden before 1966, that is, before widespread immigration took place, consisted almost entirely of light-skinned Caucasian women. If avoidance of sun exposure is a major risk factor for all-cause mortality in the case of Caucasian women, the problem may even be more serious amongst women who traditionally cover their skin or women more densely pigmented. In the USA, black women were reported to have a 26% excess all-cause mortality, as compared to Caucasian women [38]. Such data should direct our attention to a risk group whose health we may be in a position to improve.

Table 3 *Relation between sun exposure habits and risk of malignant melanoma (MM), all-cause and MM fatality*

	1. Women with MM			2. Overall case fatality amongst women with MM			3. MM case fatality amongst women with MM		
	n	Hazard ratio (HR)	95% CI	*n*	HR	95% CI	*n*	HR	95% CI
Use of sunbeds?									
No	143	1.0	Ref	24	1.0	Ref	15	1.0	Ref
Yes	124	1.2	1.0–1.6	15	1.0	0.5–2.0	9	1.2	0.5–2.9
Sunbathing during winter holiday?									
No	206	1.0	Ref	32	1.0	Ref	18	1.0	Ref
Yes	61	0.9	0.7–1.3	7	1.2	0.5–2.6	6	1.6	0.6–4.1
Sunbathing during summer?[a]									
No	20	1.0	Ref	7	1.0	Ref	3	1.0	Ref
Yes	247	1.1	0.7–1.8	32	0.6	0.2–1.3	21	0.9	0.3–3.2
Sunbathing during holiday abroad?									
No	89	1.0	Ref	15	1.0	Ref	8	1.0	Ref
Yes	178	1.0	0.8–1.3	24	1.3	0.6–2.5	16	2.0	0.8–4.8
Summary sun exposure adjusted[a]									
0	14	1.0	Ref	5	1.0	Ref	2	1.0	Ref
1	51	1.3	0.7–2.5	8	0.5	0.2–1.7	4	0.7	0.1–3.7
2	76	1.1	0.6–2.1	12	0.8	0.3–2.4	4	1.2	0.2–6.0
3	97	1.2	0.6–2.2	10	0.7	0.2–2.0	3	1.2	0.2–5.8
4	29	1.5	0.7–3.0	4	0.8	0.2–2.9	3	1.9	0.3–3.5
Summary sun exposure adjusted[a]									
0	14	1.0	Ref	5	1.0	Ref	2	1.0	Ref
1–2	127	1.18	0.6–2.2	20	0.6	0.2–1.8	12	0.9	0.2–4.3
3–4	126	1.24	0.7–2.3	14	0.44	0.08–2.5	10	1.3	0.3–6.2
Active sun exposure[a]									
No	14	1.0	Ref	5	1.0	Ref	2	1.0	Ref
Yes 1–4	250	1.2	0.7–2.2	34	0.7	0.2–1.7	22	1.1	0.3–4.8

Model 1: incidence of MM adjusted for age at diagnosis, red hair, hereditary disposition towards MM and smoking habits for the entire study population.
Model 2: all-cause mortality amongst women with MM; model 3: MM case fatality adjusted for age at diagnosis, MM characteristics (*in situ*/invasive and Breslow thickness <0.8 mm/invasive and Breslow thickness ≥0.8 mm), location (trunk or other) and comorbidity (being on antidiabetic, anticoagulant or cardiovascular disease medication).
Model 3: same as model 2 but MM characteristics dichotomized into invasive and Breslow thickness ≥0.8 mm or not, due to an empty cell.
[a]Summary sun exposure = number of 'yes' answers to above four questions.

Strengths and weaknesses

A strength of this study is its use of an unselected large population-based cohort drawn from the Swedish National Population Register and followed for 20 years. The information on sun exposure habits was gathered at the start of the study, as a result of which there is no recall bias. The assumption was made that sun exposure habits did not change over time, and consequently, information from one assessment alone was used in the models. This is a common assumption in cohort studies and tends to underestimate risk. Although a causal relationship has not been established, it cannot be ruled out. The inverse dose–response association between sun exposure and all-cause mortality increases the likelihood of a causal relationship (Table 2 and Fig. 1). However, additional evidence

and possibly other study designs are needed to draw causal conclusions.

A limitation of this study is the lack of information on physical exercise habits and BMI from baseline, although such information was included from the second interview. Further, we included a variable of comorbidity to adjust for differences in health at baseline. In addition, similar results were found after censoring the first 10 years (Table 2, model 2), further minimizing any differences that might have occurred due to illness at the start of the study. We have no data on vitamin D supplementation or vitamin D levels, but it is well known that sun exposure is the most important determinant of vitamin D status. Despite having adjusted for several potential confounders, the major shortcoming of this study is the inability to distinguish between the consequences of an unhealthy lifestyle and of avoidance of sun exposure.

Evolutionary perspective

From an evolutionary perspective, there must be a selection advantage in being less pigmented when living far from the equator; otherwise, differences in skin pigmentation would not have emerged. Fair skin might confer an evolutionary advantage in regions with low solar intensity by preventing vitamin D deficiency and thereby increasing longevity and reducing infections [39, 40]. However, a fair-skinned individual, for example emigrating from the UK, would not derive any benefit from light skin in Australia, where pigmented skin is an advantage due to high solar intensity.

Conclusion

We conclude that women who avoid sun exposure are at an increased risk of all-cause death with a twofold increased mortality rate as compared to those with the highest sun exposures. The implementation of restrictive sun exposure advice in countries with low solar intensity might not be beneficial to women's health.

Author contributions

HO was the initiator of the MISS cohort. PGL and HO were responsible for the study design. PGL performed data analysis, with input from all authors, and wrote the initial draft. All authors contributed to the literature search, data interpretation and writing the paper. Additionally, all authors have approved the final version of this paper.

Conflict of interest statement

No conflict of interest to declare.

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