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Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort

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Abstract. Lindqvist PG, Epstein E, Nielsen K, Landin-Olsson M, Ingvar C, Olsson H (Karolinska University Hospital, Lund University, Lund, Sweden). Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort. *J Intern Med* 2016; **280**: 375–387.

Objective. Women with active sunlight exposure habits experience a lower mortality rate than women who avoid sun exposure; however, they are at an increased risk of skin cancer. We aimed to explore the differences in main causes of death according to sun exposure.

Methods. We assessed the differences in sun exposure as a risk factor for all-cause mortality in a competing risk scenario 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 (aged 25–64 years at the start of the study). We obtained detailed information at baseline on sun exposure habits and potential confounders. The data were analysed using modern survival statistics.

Results. Women with active sun exposure habits were mainly at a lower risk of cardiovascular disease (CVD) and noncancer/non-CVD death as compared to those who avoided sun exposure. As a result of their increased survival, the relative contribution of cancer death increased in these women. Nonsmokers who avoided sun exposure had a life expectancy similar to smokers in the highest sun exposure group, indicating that avoidance of sun exposure is a risk factor for death of a similar magnitude as smoking. Compared to the highest sun exposure group, life expectancy of avoiders of sun exposure was reduced by 0.6–2.1 years.

Conclusion. The longer life expectancy amongst women with active sun exposure habits was related to a decrease in CVD and noncancer/non-CVD mortality, causing the relative contribution of death due to cancer to increase.

Keywords: cigarette smoke, cohort study, CVD, melanoma, mortality, public health.

Introduction

There is ongoing debate about whether avoidance of sunlight or vitamin D deficiency is a major risk factor for health. The findings of two recent reviews on the impact of vitamin D were completely different, with one showing that no firm conclusions could be drawn [1] and the other demonstrating a population attributable risk of death in the same range as smoking, inactivity or obesity [2]. Studies regarding sun exposure are rare, but recently, we reported that the mortality rate was doubled in women in the Melanoma in Southern Sweden (MISS) cohort who avoided active sun exposure, compared to those with the highest sun exposure [3]. In addition, we found no differences in all-cause or cutaneous malignant melanoma (MM) mortality between those who expose themselves to and those who avoid the sun.

Most studies have analysed the relationship between the upper extreme of sun exposure and skin cancer and have showed an increased incidence. Therefore, it is difficult to investigate sun

exposure without taking skin cancer into consideration. Skin cancer is usually divided into three types according to increasing severity: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and cutaneous MM. The two former are often grouped as nonmelanoma skin cancer (NMSC) due to their similarity and generally nonfatal prognosis. SCC is mostly related to cumulative exposure to UV light, whilst UV light mainly increases the risk of MM through episodic sunburn and excessive exposure including frequent use of tanning beds [4]. The incidence of MM in Sweden has doubled during the last 15 years, whilst the mortality rate has been constant since 1980s [5].

What causes the excess mortality amongst women in the small subgroup (5.8%) who avoid sun exposure is currently unknown. In this study, we have classified mortality into three main categories, death due to cardiovascular disease (CVD), cancer and noncancer/non-CVD, and analysed all-cause death in a competing risk scenario. The aim of this study was to determine how sun exposure is related to these main causes of death.

Materials and methods

The study was approved by the Ethics Committee of Lund University (LU 632-03). The MISS study, initiated in 1990, included approximately 1000 Sweden-born women of each age from 25 to 64 years (n = 39 973) who had no history of malignancy. 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 at each age.

Women were invited to complete a standardized written questionnaire concerning risk factors for MM. The initial questionnaire was administered from 1990 to 1992 and resulted in 29 518 women participating in the study (response rate 74%). The questionnaire was a detailed inquiry into several factors of potential interest for mortality, such as sun exposure habits, marital status, educational level, smoking, alcohol consumption and the number of births. A total of 184 women emigrated during the study period and were censored after emigration. We collected information on mean personalized family income between 1990 and 1993 from official income and taxation records at Statistics Sweden (further details available at http://www.scb.se/en_/). Four predetermined questions were posed 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 vacation 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 vacation to swim and sunbathe? (never, once every 1–2 years, once a year, two or more times per year). The four questions were dichotomized into yes/no in the analysis (i.e. sometimes versus no or never). We created a four-score variable as a measure of sun exposure depending on the number of 'yes' responses to the above questions on a scale from 0 (avoid sun exposure: reference) to 4 (greatest sun exposure). Sun exposure habits were categorized into three groups: zero 'yes' responses (avoidance of sun exposure; the main study group); 'yes' responses to one or two questions (moderate exposure); and 'yes' responses to three or four questions (greatest exposure). Vital statistics and cancer data were determined from the National Population Register up to 1 January 2011. The presence of skin cancer was recorded in the following hierarchical order: MM, NMSC or no skin cancer. Thus, a woman with NMSC was reclassified to MM upon MM diagnosis.

With regard to smoking habits, women were recorded as either smokers or nonsmokers at baseline. As a measure of comorbid illness at the start of the study, we created a dummy variable termed 'comorbidity' to identify women who had been treated with antidiabetic [Anatomical Therapeutic Chemical (ATC) classification system A : 10] or anticoagulant (ATC B : 01) drugs or medication for CVD (ATC C : 01–C : 10) for more than 1 month.

Age was categorized into 10-year intervals. For comparison of ages, approximately 50 and 60 years of age referred to women in the age groups 45–54 and 55–64 years at the start of the study. Data regarding BMI and physical exercise were recorded at the second questionnaire in the year 2000.

Statistical analysis

Descriptive statistical analysis was performed using cross-tabulation with 95% confidence interval (CI). Cox regression was performed to assess all-cause mortality, as the dependent variable, with

sun exposure, age, smoking, education, marital status, disposable income and comorbidity as independent variables. Subdistribution Cox regression analysis was performed to determine whether avoidance of sun exposure is a risk factor for CVD, cancer and noncancer/non-CVD. When a specific death was used as the dependent variable, the other two causes of death were censored, and sun exposure and other confounders were introduced as independent variables. In the final cause-specific regression, we included comorbidity, smoking, sun exposure, age, education, marital status and disposable income. The subdistribution hazard ratio (sHR) and 95% CI were used to formally assess whether the resulting cumulative incidence functions differed significantly by level of sun exposure. Fine and Gray regression models were used to estimate cause-specific cumulative incidence functions for death due to cancer, CVD and noncancer/non-CVD in the presence of competing risks [6]. The model-based cause-specific cumulative incidence functions were used to quantify the absolute as well as the relative contribution of each cause of death to all deaths (Fig. 1). The competing risks regression models were adjusted for the same potential confounding factors as the cause-specific Cox regression models.

As a complement to the competing risk models, we also quantified the loss in average life expectancy over a 20-year observation period by estimating the differences in restricted mean survival (RMS), that is the area under the survival curve between two time-points. This provides a measure of average survival between exposure groups. We predicted the RMS based on a flexible parametric survival

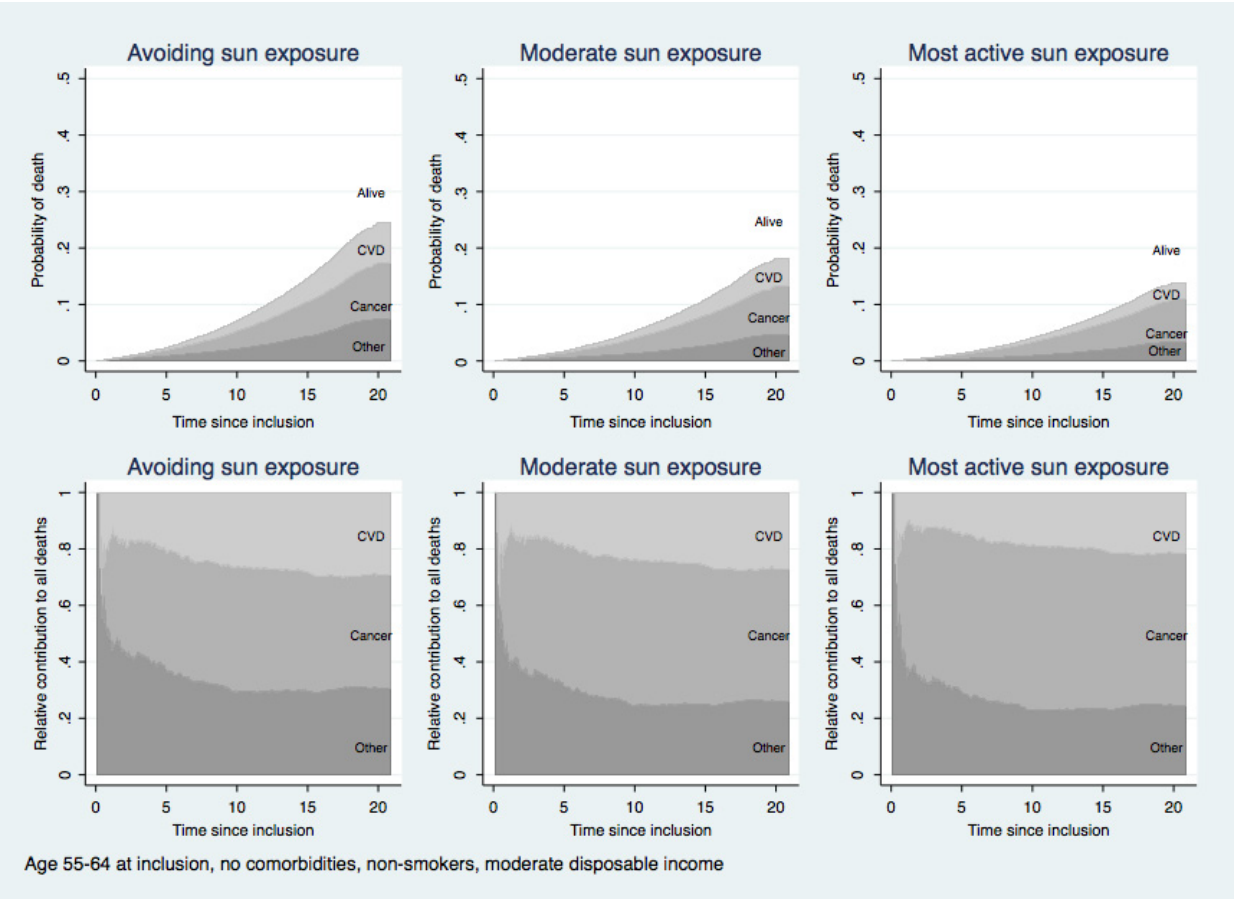

Fig. 1 *Probability of death by sun exposure habits in a competing risk scenario. Upper three graphs show death categorized into CVD, cancer and other (according to time in years since study inclusion). Bottom three graphs show relative contribution to death by sun exposure habits (according to time in years since study inclusion).*

model that uses restricted cubic splines to model the baseline hazard function [7]. Specifically, we calculated the difference in RMS between the three different sun exposure groups over a 20-year follow-up period, adjusted for age at study inclusion, comorbidities, disposable income and smoking status. The results are presented for smokers and nonsmokers of different ages who had a previous record of comorbid conditions and a low disposable income.

Both the Cox regression and Fine and Gray competing risks analyses used time from inception as the timescale. Time from inception was calculated from inclusion to cause-specific death (cancer, CVD and other causes), emigration or 1 January 2011, whichever occurred first.

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

Results

Table 1 shows selected variables in relation to sun exposure habits. It is clear that almost all these variables vary significantly with sun exposure.

Subdistribution Cox regression analysis showed that with CVD death as a dependent variable, avoidance of sun exposure (yes/no) was related to a 60% increased risk of death (sHR 1.6, 95% CI 1.3–2.0), and the relationship was 'dose dependent' compared to the moderate and high sun exposure groups: sHR 1.5 (95% CI 1.2–1.8) and 2.3 (95% CI 1.8–3.1), respectively. The corresponding sHR values for death due to noncancer/non-CVD were 1.7 (95% CI 1.4–2.1), 1.6 (95% CI 1.3–1.9) and 2.1 (95% CI 1.7–2.8) and due to cancer were 1.2 (95% CI 0.98–1.4), 1.1 (95% CI 0.9–1.4) and 1.4 (95% CI 1.04–1.6), respectively.

The top three graphs in Fig. 1 show the cumulative probability of death due to CVD, cancer and noncancer/non-CVD by sun exposure group. The three bottom graphs show the relative contribution of CVD, cancer and noncancer/non-CVD to all-cause mortality. The graphs clearly show that when the risk of dying from CVD and noncancer/non-CVD decreases, the relative proportion of cancer deaths increases with more active sun exposure habits, probably as a result of longer life expectancy.

Figure 2 shows the age-dependent increase in the probability of death 20 years after inclusion in the study, categorized into the three main causes for the three sun exposure groups, stratified by smoking. The largest differences were seen amongst smokers in all three mortality groups.

Differences in life expectancy depending on sun exposure habits, stratified by smoking, are compared in Fig. 3. Life expectancy was reduced in nonsmokers of approximately 50 and 60 years of age who avoided sun exposure by 0.6 and 1.3 years, respectively, compared to those with the highest sun exposure during the 20-year follow-up. The same comparison amongst smokers demonstrated a shorter life expectancy of 1.1 and 2.1 years, respectively. It can also be seen from the graphs that nonsmokers who avoided sun exposure had a similar life expectancy compared to smokers with the highest sun exposure (Fig. 3). Thus, avoidance of sun exposure seems to be a risk factor of magnitude similar to smoking in terms of life expectancy.

Table 2 shows the analysis of risk of death: model 1 was adjusted only for age group, model 2 was additionally adjusted for all confounders measured at inception, and model 3 was additionally adjusted for exercise for those women who answered the second questionnaire in the year 2000. The sHRs for avoidance of sun exposure as compared to moderate and high sun exposure amongst those participants who answered the second questionnaire including exercise and the same independent variables as mentioned previously were 1.4 (95% CI 1.01–1.8) and 2.2 (95% CI 1.5–3.2) for CVD, 1.0 (95% CI 0.8–1.3) and 1.1 (95% CI 0.8–1.5) for cancer and 1.6 (95% CI 1.2–2.1) and 2.1 (95% CI 1.5–2.9) for noncancer/non-CVD mortality, respectively. Because age is such a strong determinant of death, we also introduced age as a continuous variable in model 2. The sHR estimates for moderate and high sun exposure were 0.75 (95% CI 0.6–0.9) and 0.5 (95% CI 0.4–0.6) for CVD and 0.7 (95% CI 0.6–0.9) and 0.6 (95% CI 0.4–0.7) for noncancer/non-CVD mortality, respectively. To assess confounding due to the differences in BMI between groups, we conducted a stratified analysis according to BMI for all women with reported BMI values (n = 22 342). The HRs for moderate and high sun

Table 1 *Demographic characteristics of women with active and inactive sun exposure habits at study inception*

	Avoiding sun exposure		Moderate sun exposure[b]			Highest sun exposure[c]		
	(*n* = 1721)	%	(*n* = 16 166)	%		(*n* = 11 631)	%	
Women's characteristics and habits								
Education					*			*
≤9 years	741	43.1	3575	22.1		1267	10.9	
9 years	143	8.3	1549	9.6		1081	9.3	
10–12 years	219	12.7	4029	24.9		3411	29.3	
≥12 years	344	20.0	4850	30.0		4503	38.7	
Other	274	15.9	2163	13.4		1369	11.8	
Marital status					*			*
Unmarried	149	8.7	1174	7.3		1240	10.7	
Married	1239	72.0	12 868	79.6		8903	76.5	
Divorced	140	8.1	1359	8.4		1168	10.0	
Widowed	149	8.7	714	4.4		290	2.5	
Unknown[a]	44	2.6	51	0.3		30	0.3	
Parity					*			*
0	325	18.9	2250	13.9		2397	20.6	
1–2	820	47.6	8951	55.4		6686	57.5	
≥3	576	33.5	4965	30.7		2548	21.9	
Smoking								
Yes	463	26.9	5691	35.2	*	4945	42.5	*
Alcohol consumption					*			*
None or <5 g/day	1280	74.4	10 890	67.4		6281	54.0	
5–<10 g/day	73	4.2	2175	13.5		2647	22.8	
10–<15 g/day	32	1.9	727	4.5		1061	9.1	
≥15 g/day	27	1.6	543	3.4		718	6.2	
[a]Unknown	309	18.0	1831	11.3		924	7.9	
Age groups at inception					*			*
25–34	150	8.7	3659	22.6		3738	32.1	
35–44	195	11.3	3970	24.6		3208	27.6	
45–54	366	21.3	4000	24.7		3072	26.4	
55–64	1010	58.7	4537	28.1		1613	13.9	
Disposable income					*			*
Low	787	45.7	3942	24.4		1719	14.8	
Moderate	459	26.7	4492	30.9		3462	29.8	
High	475	27.6	7232	44.7		6450	55.5	
Comorbidity[d]								
Yes	1351	20.4	1794	11.1	*	777	6.7	*
NMSC								
Yes	20	1.2	216	1.3	ns	145	1.2	ns
MM								
Yes	14	0.8	127	0.8	ns	126	1.1	ns

[a]Some women did not answer all questions (see text for further details).
[b]Answering yes on one or two of the sun exposure questions.
[c]Answering yes to three or four of the sun exposure questions.
[d]Women who have consumed drugs with the ATC codes A10, B01 or C01 to C10 for more than 1 month.
NMSC, nonmelanoma skin cancer; MM, cutaneous malignant melanoma.
*$P < 0.001$ as compared to avoiders of sun exposure.

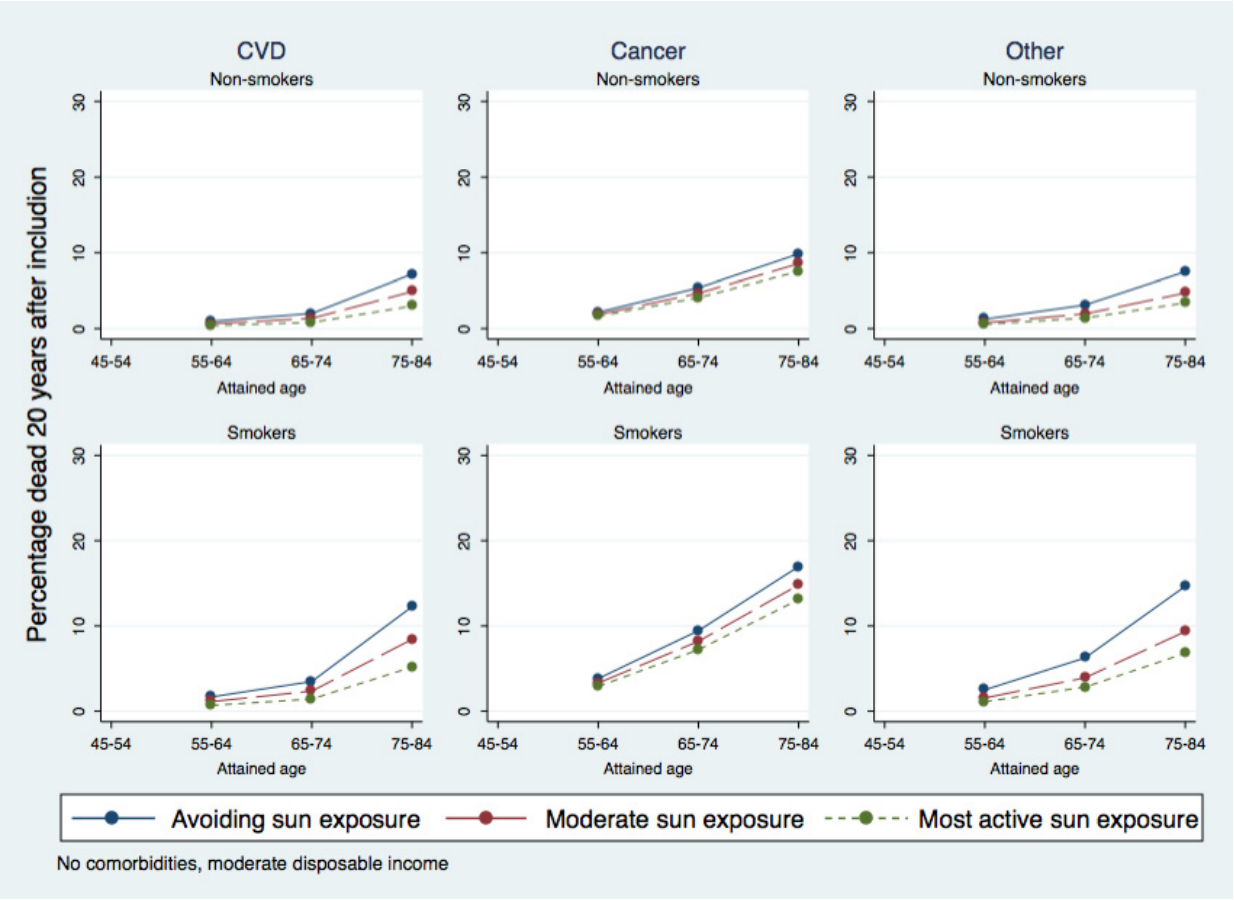

Fig. 2 *Percentage of cohort dead after 20 years according to major disease groups and sun exposure habits, stratified by smoking status. CVD, cardiovascular disease.*

exposure for BMI <25, 25 to <30 and ≥30 kg m^{-2} were 0.8 (95% CI 0.6–1.1) and 0.7 (95% CI 0.5–0.9), 0.7 (95% CI 0.5–1.0) and 0.6 (95% CI 0.4–0.9), and 0.8 (95% CI 0.6–1.2) and 0.7 (95% CI 0.4–1.2), respectively.

In a 3 × 3 table, we present adjusted HRs for combinations of skin cancer (no skin cancer/NMSC/MM) and sun exposure groups (Table 3). As compared to women who avoided sun exposure without skin cancer (reference), those with MM were at an increased risk of death. Women with the most active sun exposure habits with NMSC were at the lowest probability of death, that is the group with the highest life expectancy. The HRs decreased dose dependently in both non-MM and MM groups with increasing sun exposure, with fourfold lower HRs amongst those with the most active sun exposure habits.

We also estimated the prevalence of other internal cancers amongst women with NMSC (69/394; 17.5%) and those without skin cancer (3910/29, 124; 13.4%). Thus, women with NMSC had a 37% higher prevalence of other internal cancers than those without NMSC (OR 1.37, 95% CI 1.05–1.8) and a fourfold increased prevalence of MM (OR 4.0, 95% CI 2.3–7.1). The incidence of other internal cancer was not increased subsequently an NMSC diagnosis.

Discussion

In this competing risk scenario, we determined that the shorter life expectancy of women who avoided sun exposure was mainly due to a dose-dependent significantly increased risk of CVD and noncancer/non-CVD deaths, as compared to the moderate and high sun exposure groups. We conclusively showed

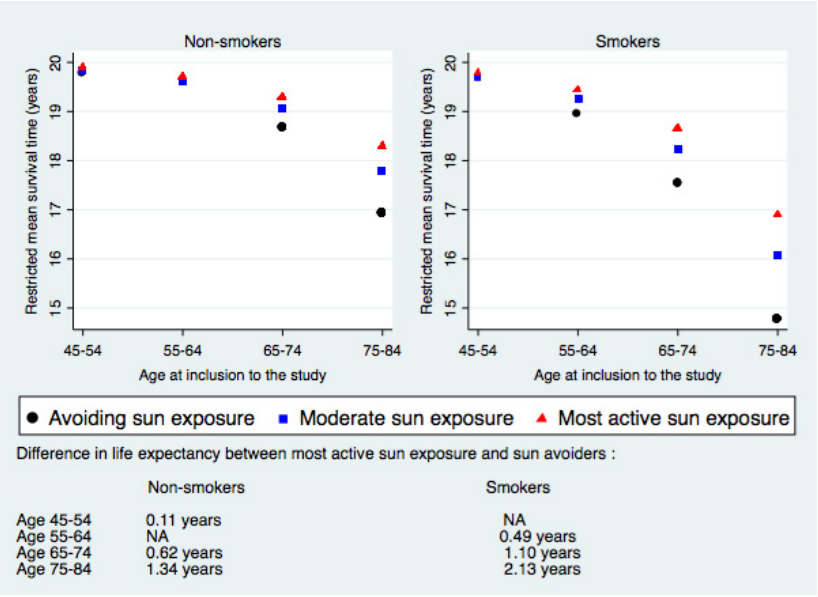

Fig. 3 *Mean survival by age groups and sun exposure habits, stratified by smoking status, and calculations of mean difference in life expectancy by age groups amongst smokers and nonsmokers. NA = not applicable.*

that as the risk of dying in the CVD and noncancer/non-CVD groups decreased with increasing sun exposure, the relative contribution of death due to cancer increased, probably as a result of extended life expectancy. Our finding that avoidance of sun exposure was a risk factor for all-cause death of the same magnitude as smoking is novel, but in agreement with systematic reviews of vitamin D and the risk of CVD [2]. The absolute difference in life expectancy, however, differed by age and smoking habits. For example, we estimated that smokers at approximately 60 years of age with the most active sun exposure habits had a 2-year longer life expectancy during the study period as compared to smokers who avoid sun exposure.

Strengths of our study include the unselected large cohort of women and the long follow-up period. The ability to demonstrate a dose-dependent relationship between sun exposure and life expectancy was also strength. Most previous studies have compared the upper extreme of sun exposure to lower levels, whereas we assessed the lower extreme of sun exposure to higher levels. Answers to the questionnaire do not necessarily provide a good measure of low sun exposure at an individual level. However, at the group level, we consider the data valid.

We acknowledge several major limitations of this study. First, it is not possible to differentiate between active sun exposure habits and a healthy lifestyle, and secondly, the results are of an observational nature; therefore, a causal link cannot be proven. A further limitation is that we did not have access to exercise data from study initiation; however, similar sHR values were obtained when including exercise for those women who answered the second questionnaire in 2000. With the introduction of whole-genome scanning, a new method of getting closer to causality using observational data is Mendelian random analysis. A potential causal link between BMI and vitamin D levels has been demonstrated with this method [8]. In addition, individuals with high BMI do not obtain the same increase in vitamin D levels by UV radiation as lean subjects [9]. As a consequence, as BMI seems to be involved in the causal pathway of vitamin D, it should not be included as a confounder in analyses as has been performed in many studies.

Possible mechanisms underlying the inverse dose-dependent relation between noncancer/non-CVD mortality and sun exposure

Melatonin is involved in the circadian system with higher levels during the night than in the daytime. Light information from the retina influences the production of melatonin via the suprachiasmatic nuclei of the hypothalamus. A mutation of the melatonin receptor affecting the melatonin system (MTNR1B) is known to be related to increased risk of type 2 diabetes, through the inhibition of insulin

Table 2 *Survival analysis comparing risk of death by sun exposure habits and confounders during the study period 1990–2011*

	Women alive		Women dead		Model 1[a]		Model 2[b]		Model 3[c]	
	26 937	%	2545	%	HR	95% CI	HR	95% CI	HR	95% CI
Sun exposure										
Avoiding sun exposure	1352	5.0	369	14.5	1.0	Reference	1.0	Reference	1.0	Reference
Moderate sun exposure	14 613	54.2	1553	61.0	0.7	0.6–0.7	0.7	0.6–0.8	0.8	0.7–0.9
Highest sun exposure	11 008	40.8	623	24.5	0.5	0.4–0.6	0.6	0.5-0.6	0.7	0.5-0.8
Age groups at inception										
25–34	7429	27.5	118	4.6	1.0	Reference	1.0	Reference	1.0	Reference
35–44	7112	26.4	261	10.3	2.4	1.9–2.9	2.5	2.0–3.1	2.9	2.1–4.0
45–54	6796	25.2	642	25.2	6.0	4.9–7.3	5.9	4.8–7.3	7.2	5.3-9.7
55–64	5636	20.9	1524	59.9	14.8	12.1–17.9	13.9	11.3–17.0	18.0	13.3–24.3
Smoking										
Yes	10 006	37.1	1093	42.9			1.9	1.7–2.0	1.8	1.6–2.0
Education										
≤9 years	4692	17.4	891	35.0			1.3	1.2–1.5	1.3	1.1–1.5
9 years	2441	9.0	332	13.0			1.1	1.0–1.3	1.1	0.9–1.3
10–12 years	7279	27.0	380	14.9			1.0	0.9–1.2	1.1	0.9–1.3
≥12 years	9135	33.9	562	22.1			1.0	Reference	1.0	Reference
other	3426	12.7	380	14.9			1.1	0.9–1.2	1.0	0.8-1.2
Marital status										
Unmarried	2387	8.8	176	6.9			1.5	1.3–1.8	1.5	1.2–1.8
Married	21 243	78.8	1767	69.4			1.0	Reference	1.0	Reference
Divorced	2315	8.6	352	13.8			1.5	1.4–1.8	1.6	1.4–1.9
Widowed	923	3.4	230	9.0			1.3	1.1–1.5	1.2	1.0–1.5
Unknown	105	0.4	20	0.8			1.6	1.0–2.6	2.2	1.2–4.2
Disposable income										
Low	5560	20.6	888	34.9			1.0	Reference	1.0	Reference
Moderate	8157	30.2	756	29.7			0.9	0.8–1.0	0.9	0.8–1.0
High	13 256	49.1	901	35.4			0.7	0.7–0.8	0.8	0.7–0.9
Comorbidity[d]										
Yes	2343	8.7	579	22.8			1.6	1.4–1.7	1.5	1.3–1.7
Exercise[c]										
No	1899	8.4	160	11.4					1.0	Reference
Moderate	10 230	45.1	576	40.7					0.6	0.5–0.8
Most active	7463	32.9	237	16.7					0.5	0.4–0.6
Unknown	3090	13.6	443	31.3					0.7	0.6–0.9

[a]Model 1: adjusted for age group.
[b]Model 2: additionally adjusted for smoking, education, marital status, disposable income and comorbidity.
[c]Model 3: additionally adjusted for exercise for those answering the second questionnaire in the year 2000.
[d]Women who have consumed drugs with the ATC codes A10, B01 or C01 to C10 for more than 1 month.

Table 3 *Hazard ratios (HR) of all-cause mortality by skin cancer and sun exposure groups*

Summary sun exposure[b]	Avoidance of sun exposure 0	Moderate sun exposure 1–2	Most active sun exposure 3–4
Skin cancer			
No skin cancer (HR, 95% CI)	1.0, Reference	0.75 (0.66–0.84)[a]	0.58 (0.50–0.66)[a]
Stratified analysis within group	HR 1.72 (1.5–2.0)	HR 1.29 (1.2–1.4)	1.0, Reference
(*n* = death/total)	(360/1687)	(1511/15 823)	(604/11 360)
NMSC (HR, 95% CI)	0.78 (0.3–2.1)[a]	0.45 (0.29–0.69)[a]	0.2 (0.08–0.49)[a]
Stratified analysis within group	HR 4.1 (1.0–16.6)	HR 2.3 (0.9–6.4)	1.0, Reference
(*n* = death/total)	(4/20)	(22/216)	(5/145)
(*n* = death/total[c])	(4/19)	(21/212)	(5/138)
MM (HR, 95% CI)[c]	4.1 (1.68–9.9)[a]	1.07 (0.7–1.7)[a]	0.97 (0.56–1.65)[a]
Stratified analysis within group	HR 8.0 (2.4–26.2)	HR 1.4 (0.7–2.9)	1.0, Reference
(*n* = death/total)	(5/14)	(20/127)	(14/126)

MM, malignant melanoma; NMSC, nonmelanoma skin cancer; CI, confidence interval.
[a]Adjusted for age, smoking, income, education, comorbidity and marital status.
[b]The number of yes answers to four questions regarding sun exposure habits (see text for further details). sunbeds?, Sunbathing during summer? and Sunbathing during vacation abroad?
[c]Thirteen cases with both MM and NMSC were classified as MM.

release [10]. Thus, sun exposure may affect susceptibility to type 2 diabetes mellitus by interfering with the melatonin system. This might also explain some of the differences in HbA1c levels by season and the inverse relation between vitamin D and incident type 2 diabetes mellitus [11, 12]. The incidence of childhood type 1 diabetes mellitus has been shown to depend on latitude, with the nadir close to the equator [13]. A Finnish long-term follow-up study showed approximately 80% lower incidence of childhood type 1 diabetes mellitus amongst those who received vitamin D supplementation during the first year of life, as compared to no supplementation, adding to evidence of an inverse relation between sun exposure/vitamin D and incidental type 1 diabetes [14]. However, we await the results of robust randomized controlled trials (RCTs) to determine whether vitamin D supplementation can lower the risk of type 1 diabetes mellitus [14]. Multiple sclerosis (MS) is another immunopathological autoimmune condition with a positive association with latitude and seasonal differences in incidence [15]. MS is characterized by Th1 and Th17 expression. It has been suggested that sun exposure lowers the risk of MS and that vitamin D deficiency is related to an increased frequency of relapse [15, 16].

The knowledge that 1, 25 vitamin D induces the production of antimicrobial peptides, such as cathelicidin and β-defensin, when combating infections has generated much research interest [17]. One area of such research is the role of vitamin D in respiratory tract infections. The findings of RCTs of vitamin D supplementation are not conclusive; some studies have shown a protective effect against tuberculosis [17, 18] or influenza [19, 20], whereas others did not find any beneficial effects on respiratory tract infections [21]. However, the latter study was conducted in a population with a high level of vitamin D. Notably, in a recent RCT, vitamin D supplementation (4000 U/day) was found to reduce antibiotic consumption by approximately 60% in patients with primary immune deficiency [22]. In another study, it was shown that patients >70 years of age given vitamin D supplementation consumed less antibiotics (50% reduction) compared to the placebo group [23]. Hypovitaminosis D (<50 nmol L^{-1}) has been reported to be an independent predictor of nonresolution of clostridium difficile-associated diarrhoea [24]. Individuals with chronic pulmonary disease are reported to have significantly more exacerbations in the presence of hypovitaminosis D [25]. Vitamin D has immunoregulatory properties, and vitamin D deficiency is associated with poor immune function and increased disease susceptibility [26–28]. Thus, there seem to be several plausible mechanisms for the inverse relation between sun exposure and noncancer/non-CVD death. However, most findings are from studies that were observational in nature, and

therefore, studies that can add causal evidence are needed.

Possible mechanisms underlying the inverse dose-dependent relation between CVD mortality and sun exposure

Already by 1981, Scragg had reported seasonal differences in CVD incidence [29]. There is an increased risk of coronary heart disease, stroke and both arterial and venous thromboembolism in winter as compared to summer in countries far from the equator [30–33]. In addition, venous thromboembolism has been reported to be less common amongst those with active sun exposure habits [32]. In comparing vitamin D levels, a Danish study showed an inverse dose–response relation between vitamin D levels and venous thromboembolism [34], whereas two other studies found no effect of concentration [35, 36]. In two well-executed systematic reviews, low vitamin D levels were related to both CVD incidence and CVD mortality [37, 38].

Hypertension is a major determinant of CVD. Observational data support the notion that lack of UVB radiation is involved in the pathogenesis of hypertension and CVD by (i) suppression of the renin–angiotensin–aldosterone system, (ii) a direct effect on endothelial cells and (iii) effects on calcium metabolism [39]. A lack of either UVB or UVA light produced a short-term reduction in blood pressure [40, 41]. Solar UVA radiation may also produce systemic NO with a sustained reduction in blood pressure and has been suggested to act in a cardioprotective manner [42].

Both high acute and chronic stress levels have a role in the activation of coagulation and may increase the risk of CVD [43, 44]. The finding that UV radiation induces β-endorphin synthesis, which may attenuate stress levels and have a cardioprotective effect, is interesting [45]. An inborn internal reward system for sun exposure indicates that UV exposure is important for health. Further, the differences in skin pigmentation depending on regional UV radiation indicate the presence of strong evolutionary mechanisms. Atherosclerosis is a chronic inflammatory disease with cardiovascular dysfunction including myocardial infarction, stroke and thromboembolism. There are a related increase in angiotensin II and a decrease in NO. Thus, sun exposure might lower the risk of arteriosclerosis, possibly by stabilizing arteriosclerotic plaque, which in turn would decrease CVD risk.

NMSC as a measure of sun exposure

In a large study in which the presence of BCC was used as a proxy for sun exposure, Lindelöf *et al.* [46] demonstrated a 37% higher *risk* of internal cancers amongst *survivors* of BCC and a 4.9-fold increased *risk* of MM (i.e. prevalence data). However, our prospective cohort provides access to both incidence and prevalence data. We found almost identical prevalence data amongst women with NMSC (a 37% and 4-fold increased *prevalence* of internal cancers and MM, respectively). However, the incidence of other subsequent internal cancer was not increased. If women survive by not dying from CVD or noncancer/non-CVD causes, they will have a higher probability of being diagnosed with cancer. Thus, even if paradoxical, our findings and those of Lindelöf *et al.* [46] are almost identical, only the interpretations differ. Most studies have investigated the effects of the upper extremes of sun exposure (over exposure) and have shown increased incidences of MM and NMSC. We have investigated the lower extremes of sun exposure (under exposure) and found that the HRs for all-cause mortality increased 4-fold in both NMSC and MM groups amongst avoiders of sun exposure as compared to the highest sun exposure group. In addition, women with NMSC and the highest sun exposure had the longest life expectancy. This finding is in agreement with several previous reports. Newton-Bishop and coworkers reported improved prognosis of MM by increasing vitamin D levels [47], Jensen and coworkers showed a 9% increase in 10-year survival of individuals with BCC [48], and Yang and coworkers reported 20% to 30% lower mortality amongst those reporting at least 1 week of sunbathing per year [49]. Thus, it seems that sun exposure causes an increased incidence of NMSC and MM, but not a decrease in life expectancy. Thus, when analysing factors that affect life expectancy, such as sun exposure, (i) results from case–control and cross-sectional (prevalence) studies must be interpreted with caution and (ii) not only should the incidence of NMSC or MM be reported, but also data on all-cause risk of death should also be provided.

Guidelines

Our findings indicate that UV exposure might have opposing effects on different health issues. Therefore, national guidelines should be based on careful weighing of both hazards and benefits. Indeed, it might not be beneficial to promote restrictive

year-round sun exposure advice in a country like Sweden, where the maximum UV index is low (<3) for 8–9 months of the year. During the summer, the midday UV index peak might reach 3–5, but rarely high (≥6). The UV level will reach at least high (≥6) UV index all year around in Northern Australia. Further, because there is no robust evidence to show that it is safe in terms of MM to be exposed to the sun for longer after applying sunblocker, we question the general interpretation of the guideline that 'as long as you use sunblock you may stay out in the sun for a long time'. An intriguing explanation for the rising MM incidence in Sweden is that the restrictive sun exposure advice that urges reliance on sunscreen use has resulted in overexposure, which is a major risk factor for MM. More importantly, strong recommendation to avoid sun exposure may have increased the risk of CVD and noncancer/non-CVD morbidity and death in the Swedish population. Greater focus on this risk might help in generating causal data.

Whether the positive effect of sun exposure demonstrated in this observational study is mediated by vitamin D, another mechanism related to UV radiation, or by unmeasured bias cannot be determined from our results. Vitamin D levels might be just a marker of sun exposure. Moreover, supposedly, it is not vitamin D levels *per se*, but the avoidance of vitamin D deficiency that is important [50]. Thus, adding vitamin D in a population at low risk of vitamin D deficiency is unlikely to be beneficial [50]. RCTs employing an adequate dose and duration of supplementation are needed. For example, when the supplemented dose of vitamin D in Finland decreased, the protective association with type 1 diabetes mellitus in childhood and adolescence decreased [14].

We conclude that the excess mortality rate amongst those who avoid sun exposure was mainly due to an increased risk of death due to CVD and noncancer/non-CVD. The increased life expectancy of women with active sun exposure habits will increase the proportion of cancer deaths. Our findings add to the ongoing debate regarding the nonskeletal effects of sunshine/vitamin D.

Author contributions

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

Conflict of interest statement

None of the authors has any conflict of interests to declare.

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