Cancer Epidemiology, Biomarkers & Prevention

Research Article
See commentary, p. 582

Ultraviolet Exposure and Mortality among Women in Sweden

Ling Yang[1,2,3], Marie Lof[1], Marit Bragelien Veierød[4], Sven Sandin[1], Hans-Olov Adami[2,5], and Elisabete Weiderpass[1,3,6,7]

Abstract

Background: Ecological studies have reported possible effects of sunlight on the risk of several diseases. Little evidence is available on the association between mortality and solar and artificial UV exposure by individual level from prospective studies.

Methods: The Swedish Women's Lifestyle and Health cohort study included women aged 30 to 49 years in 1991–1992. Participants completed a questionnaire and were followed-up through linkages to national registries until the end of 2006. Cox models were used to estimate adjusted HRs and 95% CIs for all-cause mortality and for cancer and cardiovascular disease (CVD) mortality.

Results: During 15 years of follow-up, among the 38,472 women included in the present study, 754 deaths occurred: 457 due to cancer and 100 due to CVD. When combining the information on sun exposure from age 10 to 39 years, women who got sunburned twice or more per year during adolescence had a reduced all-cause mortality, compared with women who had been sunburned once or less. A reduced risk for all-cause and CVD mortality was observed in women who went on sunbathing vacations more than once a year over three decades. Solarium use once or more per month for at least one decade increased the risk of all-cause mortality, when compared with women who never used a solarium.

Conclusions: Solar UV exposure was associated with reduced overall and CVD mortality, whereas artificial UV exposure was associated with increased overall and cancer mortality among Swedish women.

Impact: Moderate sun exposure may protect against cause-specific mortality. *Cancer Epidemiol Biomarkers Prev; 20(4); 683–90. ©2011 AACR.*

Introduction

The convincing evidence for a causal relationship between UV exposure, be it solar or artificial, and the risk of skin cancer (1–6) has stimulated extensive public campaigns against excessive sunbathing. Nevertheless, most people depend on sun exposure to synthesize the amounts of vitamin D required for optimal health. In the skin, UV-B photons are absorbed by the precursor 7-dehydrocholesterol and converted to vitamin D_3. Vitamin D_3 is thereafter metabolized to 25(OH)D (25-hydroxyvitamin D) in the liver and then converted to its biologically active form, $1,25(OH)_2D$ in the kidney (7). Solar UV-B is thought to contribute about 90% of serum vitamin D levels, as few foods naturally contain it (8). Artificial tanning by solarium use can also increase vitamin D synthesis (8).

During the last decades, there has been accumulating evidence that UV exposure, via its effect on the body's vitamin D metabolic synthesis pathway, might have a wide range of beneficial effects on several conditions, such as multiple sclerosis, osteoporosis, cardiovascular disease (CVD), diabetes type 1 and several cancers, including breast, ovary, prostate, colon, and non-Hodgkin lymphoma (8–24). However, existing evidence is derived mostly from ecological studies and includes only a few case–control or prospective studies with individual data on both UV exposure and dietary vitamin D intake. Hence, uncertainties persist about the relationship between UV exposure and mortality, such as whether the associations differ according to UV exposure in different periods of life, and factors related to UV transmission and absorption, such as host characteristics related to UV sensitivity, and dietary or supplementary vitamin D intake.

The Swedish Women's Lifestyle and Health (WLH) cohort allows us to address these questions using detailed

Authors' Affiliations: [1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [2]Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, United Kingdom; [3]Department of Genetic Epidemiology, Folkhälsan Research Center, Helsinki, Finland; [4]Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; [5]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; [6]Department of Etiological Research, Cancer Registry of Norway, Oslo; and [7]Department of Community Medicine, University of Tromsø, Tromsø, Norway

Corresponding Author: Elisabete Weiderpass, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, 171 77 Stockholm, Sweden. Phone: +358-40-845-3406. E-mail: Elisabete.Weiderpass.Vainio@ki.se

doi: 10.1158/1055-9965.EPI-10-0982

data on solar and artificial UV exposure during different periods of life, host pigmentary characteristics, and vitamin D intake from foods and supplements.

Materials and Methods

Study cohort

Enrollment into the Swedish WLH cohort took place in 1991–1992. As previously described in detail (25), 96,000 women aged 30 to 49 years residing in the Uppsala Health Care Region were randomly selected from the Swedish Central Population Registry at Statistics Sweden and sent an extensive questionnaire. A total of 49,259 women (52%) returned a completed questionnaire which included demographic data, anthropometric characteristics, and information on a variety of lifestyle factors.

UV exposure and other relevant data

By means of the questionnaire, the women reported their history of sunburn, sunbathing vacations, and frequency of solarium use at ages 10 to 19, 20 to 29, 30 to 39, and 40 to 49 years. For each age period, sunburn history was retrieved from questions on the average number of times per year (none, 1, 2–3, 4–5, or $\geq$6 times) that the participant had been sunburned so severely that it resulted in pain or blisters that subsequently peeled. Sunbathing vacations were recorded as the average number of weeks per year (none, 1, 2–3, 4–6, or $\geq$7 weeks) spent in southern latitudes (typically southern Europe, e.g., Spain or Greece) or within Sweden for each age period. The participants also reported their average solarium use during each age period (never, rarely, once, twice, 3–4 times per month, or more than once per week).

Study participants were asked to categorize their natural hair color (dark brown/black, light brown, blond or red) and eye color (brown, gray/green, or blue) in the questionnaire. Information on skin pigmentation, based on reactions to both acute sun exposure in the beginning of the summer (brown without red, red, or red with pain or blisters) and chronic or long-lasting sun exposure (light or never brown, brown, or deep brown) were also asked. The questionnaire at baseline included a validated self-administrated food frequency questionnaire assessing habitual diet during the 6 months preceding the woman's enrollment into the study. It covered the frequency and quantity of consumption of about 80 food items and beverages as well as multivitamins (26). Individual dietary intake of vitamin D was calculated by linking the amount of foods assessed by means of the questionnaire to the food composition database from the National Food Administration (1989). Vitamin D supplement intake information was obtained from the question on overall multivitamin supplement, without specification of the dose of vitamin D in the multivitamin (and thus only results for overall multivitamin use can be reported).

Follow-up

Follow-up for deaths among the study participants was conducted through linkages with existing nationwide population and health registries, using the individually unique national registration number assigned to all residents in Sweden. Follow-up was virtually complete with respect to death and emigration. Information on dates and causes of death for women who died during the follow-up period was abstracted from the nationwide Causes of Death Register. The cause of death was coded to 3 digits using the 9th version of the International Classifications of Disease (ICD-9) from 1991 to 1996 and the 10th version (ICD-10) thereafter. Dates of emigration for women who moved out of Sweden were provided by the Emigration Register.

The following causes of death were considered as endpoints in the present study: all-cause, CVD (ICD-9: 390–459, ICD-10: I00-I99), and cancer (ICD-9: 140–208, ICD-10: C00-C98). Due to small numbers, no other specific cause of death was analyzed.

The start of follow-up was defined as the date of receipt of the returned baseline questionnaire and person-years were calculated until the date of death, the date of emigration, or the end of follow-up (31 December 2006), whichever came first. For the current study, we excluded 5,763 women with a history of major chronic disease reported at baseline (1,212 cancer, 158 heart attack or stroke, 4,393 diabetes), 843 subjects with a total energy intake outside the 1st and 99th percentiles and 9 participants who did not report any UV exposure information. We further excluded 4,172 participants with missing information on any of the covariates involved in the analyses. The final study cohort comprised 38,472 women (78% of those who returned the questionnaire).

Statistical analysis

We assessed the association between all-cause, CVD, and cancer mortality and UV exposure, host characteristics, and vitamin D intake by calculating HRs as estimates of relative risks, with associated 95% CIs by the Cox proportional hazards model. We combined the UV exposure across each of the 3 decades of life recorded for all participating women (10–19, 20–29 and 30–39 years of age; ref. 27). The first 4 categories of annual number of sunburns and annual number of weeks spent on sunbathing vacations represent exposure accumulating over successive decades (10–39 years), whereas the fifth category corresponds to exposure in adult years only (i.e., 20–39 years). For solarium use, we used 4 categories representing cumulative exposure (10–39 years). The proportional hazard assumption was checked by plotting the Schoenfeld residuals (28). Attained age was used as the time scale in the models. The models were further successively adjusted for education, smoking, alcohol drinking, body mass index (BMI), and physical activity. The potential confounding effect of hair and eye color, and skin response to acute and chronic sun exposure, was further controlled in the models estimating risk of death from

Table 1. Characteristics of the study population at baseline and by cause of death during follow-up (from 1991–1992 through 2006), the Swedish WLH cohort study

	Study sample	All-cause deaths	Total CVD	Total cancer
Numbers of subjects	38,472	754	100	457
Age group, y				
30–34	7,120 (18.5)	65 (8.6)	8 (8.0)	30 (6.6)
35–39	10,209 (26.5)	128 (17.0)	14 (14.0)	82 (17.9)
40–44	9,938 (25.8)	204 (27.1)	29 (29.0)	125 (27.4)
45–49	11,205 (29.1)	357 (47.4)	49 (49.0)	220 (48.1)
Education, y				
<10	7,218 (18.8)	224 (29.7)	46 (46.0)	129 (28.2)
10–12	14,885 (38.7)	289 (38.3)	38 (38.0)	178 (39.0)
13–15	10,659 (27.7)	158 (21.0)	10 (10.0)	98 (21.4)
≥16	5,710 (14.8)	83 (11.0)	6 (6.0)	52 (11.4)
Ever smoked	22,794 (59.3)	539 (71.5)	88 (88.0)	309 (67.6)
Alcohol drinking, g/d				
Nondrinkers	4,928 (12.8)	117 (15.5)	22 (22.0)	67 (14.7)
<1.23	8,271 (21.5)	160 (21.2)	22 (22.0)	99 (21.7)
1.23–2.87	8,229 (21.5)	134 (17.8)	12 (12.0)	84 (18.4)
2.88–5.49	8,536 (22.2)	170 (22.5)	21 (21.0)	112 (24.5)
≥5.50	8,508 (22.1)	173 (22.9)	23 (21.0)	95 (20.8)
BMI, kg/m^2				
<20.0	3,903 (10.2)	69 (9.2)	12 (12.0)	39 (8.5)
20.0–24.9	24,600 (63.9)	444 (58.9)	45 (45.0)	277 (60.6)
≥25	9,969 (25.9)	241 (32.0)	43 (43.0)	141 (30.9)
Physical activity				
Very low or low	5,547 (14.4)	167 (22.2)	27 (27.0)	87 (19.0)
Normal	22,928 (59.6)	443 (58.8)	53 (53.0)	288 (63.0)
High or very high	9,997 (26.0)	144 (19.1)	20 (20.0)	82 (17.9)

NOTE: All values are presented as number (percentage).

all-causes, CVD, or cancer. Subgroup analyses were confined to subjects with a low consumption of vitamin D, defined as a dietary vitamin D intake of less than 5 μg/d and no consumption of multivitamin supplements. When fitting the cause-specific models, death due to other causes were treated as censoring. All tests of statistical hypothesis were 2-sided with a 5% level of significance. The SAS software version 9.1 was used for all statistical analyses.

Ethics

This study was approved by the Data Inspection Board in Sweden and by the regional Ethical Committee. Consent was assumed by the return of the postal questionnaire.

Results

Characteristics of the study population

The 38,472 women included in this analysis were followed for an average of 14.9 years. During follow-up, a total of 754 deaths occurred: 457 (60%) due to cancer and 100 (13%) due to CVD. The baseline characteristics for the women in the entire cohort, as well as per cause of death are presented in Table 1. The patterns of mortality are in agreement with those expected on the basis of existing knowledge, in that mortality increases with smoking and BMI, and decreases with education and physical activity. At baseline, the mean dietary intake of vitamin D was 4.1 μg/d (SD = 1.7) and 15% of the women reported use of multivitamins. During the time period from age 10 to 39 years, 56% of the women reported having been sunburned once or more per year, 50% reported to have spent 1 week or more on sunbathing vacations every year, and 30% of women reported that they had used a solarium once or more per month (data not shown).

UV exposure and mortality

Table 2 shows all-cause mortality and mortality from CVD and cancer per annual number of sunburns, annual number of weeks spent on sunbathing vacations, and solarium use between ages 10 and 39 years.

Women who got sunburned twice or more per year during adolescence had a 30% lower all-cause mortality (HR = 0.7, 95% CI: 0.5–0.9) than women who had been

Table 2. Multivariable[a] HRs and 95% CIs of different causes of death according to UV exposure between age 10 and 39 years[b], the Swedish WLH cohort study, follow-up from 1991 to 1992 through 2006

	Study sample	All-cause mortality		Total CVD		Total cancer	
		No.	HR (95%CI)	No.	HR (95%CI)	No.	HR (95%CI)
Annual number of sunburns							
≤1, 10–19, 20–29, and 30–39, y	22,003	470	Ref.	64	Ref.	295	Ref.
≥2, 10–19, y only	2,896	34	0.7 (0.5–0.9)	4	0.6 (0.2–1.7)	21	0.7 (0.4–1.0)
≥2, 10–19, and 20–29, y	3,238	50	0.9 (0.7–1.2)	8	1.2 (0.6–2.5)	27	0.8 (0.5–1.2)
≥2, 10–19, 20–29, and 30–39, y	3,208	55	0.9 (0.7–1.2)	2	0.3 (0.1–1.1)	35	0.9 (0.7–1.3)
≥2, 20–29, and/or 30–39, y	2,790	58	1.1 (0.8–1.4)	5	0.7 (0.3–1.7)	37	1.1 (0.8–1.6)
Annual number of weeks spent on sunbathing vacations							
Never, 10–19, 20–29, and 30–39, y	4,214	123	Ref.	21	Ref.	68	Ref.
≥1 week, 10–19, y only	799	15	0.8 (0.5–1.4)	4	1.4 (0.5–4.0)	4	0.4 (0.2–1.1)
≥1 week, 10–19, and 20–29, y	1,450	24	0.8 (0.5–1.3)	5	1.2 (0.4–3.2)	13	0.8 (0.5–1.5)
≥1 week, 10–19, 20–29, and 30–39, y	18,845	320	0.7 (0.6–0.9)	28	0.5 (0.3–0.8)	209	0.9 (0.7–1.2)
≥1 week, 20–29, and 30–39, y	8,713	178	0.7 (0.6–0.9)	27	0.7 (0.4–1.3)	110	0.8 (0.6–1.1)
Average solarium use							
Never in all decades, 10–39 y	16,360	372	Ref.	55	Ref.	227	Ref.
Rarely but not ≥1 time/mo in any decade, 10–39 y	9,135	138	1.0 (0.8–1.3)	15	0.8 (0.5–1.5)	85	1.1 (0.8–1.4)
≥1 time/mo in 1 decade, 10–39 y	6,845	127	1.2 (1.0–1.5)	15	0.9 (0.5–1.6)	84	1.4 (1.1–1.8)
≥1 time/mo in 2 or 3 decades, 10–39 y	1,962	37	1.9 (1.3–2.7)	5	1.6 (0.6–4.2)	16	1.6 (1.0–2.8)

[a]Adjusted for education, smoking, physical activity, alcohol drinking, and BMI.

[b]Combined variable for UV exposure at ages 10 to 39 years. Women with 2 or more sunburns per year or 1 or more sunbathing vacation per year at ages 10 to 19 and 30 to 39 years were not included in the relevant analyses.

sunburned once or less per year between age 10 and 39 years. No statistically significant associations between annual number of sunburns and CVD or cancer mortality were found.

Women who had spent more than 1 week on sunbathing vacations per year between 10 and 39 years of age had a decreased all-cause mortality (HR = 0.7, 95% CI: 0.6–0.9) compared with women who never went on sunbathing vacations. Similar results were found for CVD mortality, but no statistically significant effect on cancer mortality was observed.

Solarium use once or more per month during 2 or 3 decades of life between 10 and 39 years of age was associated with an increased all-cause mortality (HR = 1.9, 95% CI: 1.3–2.7 for solarium use during 2 or 3 decades compared with women with no solarium use; Table 2; $P_{trend} < 0.01$). Similar associations were found for cancer mortality, but no statistically significant effect was observed for CVD mortality.

Table 3 shows relevant host characteristics related to UV sensitivity and vitamin D intake in relation to mortality. Compared with women with dark brown or black hair, women with blond hair had a higher all-cause and cancer mortality. No effect was found for eye color. A statistically significantly increased risk for CVD mortality (HR = 2.3, 95% CI: 1.2–4.3) was found in women who were more likely to get a deep brown tan after chronic sun exposure compared with women who got light brown or never browned. We observed a statistically significantly reduced risk for CVD mortality in relation to skin color after acute sun exposure, with women turning red with pain or blisters having a lower HR than those turning brown without red (HR = 0.5, 95% CI: 0.3–0.9); for those whose skin turned red the results were of borderline statistical significance (HR = 0.6, 95% CI: 0.4–1.0).

When we mutually controlled for hair and eye color, or skin color after acute and chronic sun exposure in the analyses, the HRs presented in Tables 2 and 3 changed only marginally (data not shown). These variables were not strongly correlated with each other (all <0.30, except for skin color after acute and chronic sun exposure, 0.44). Vitamin D intake (either from diet or supplement) was not associated with all-cause mortality or any cause-specific mortality (Table 3). When we confined the analyses to women with low vitamin D intake, the observed associations between UV exposure and mortality were basically not altered (data not shown).

Discussion

In this large prospective study of middle-aged Swedish women, natural sun exposure during sunbathing vacations was associated with reduced all-cause mortality and CVD mortality, whereas artificial UV exposure (by solar-

Table 3. Multiadjusted HRs and 95% CIs of different causes of death according to hair color, eye color, and skin color after chronic or acute sun exposure, and dietary and supplementary vitamin D intake, the Swedish WLH cohort study follow-up from 1991 to 1992 through 2006[a]

	Study sample	All-cause mortality		Total CVD		Total Cancer	
		No.	HR (95%CI)	No.	HR (95%CI)	No.	HR (95%CI)
Hair color							
Dark brown/black	10,700	197	Ref.	36	Ref.	112	Ref.
Light brown	16,549	336	1.1 (0.9–1.3)	41	0.8 (0.5–1.2)	209	1.2 (1.0–1.5)
Blond	9,595	194	1.2 (1.0–1.4)	21	0.7 (0.4–1.2)	121	1.3 (1.0–1.7)
Red	1,201	21	1.0 (0.6–1.6)	2	0.5 (0.1–2.2)	13	1.1 (0.6–1.9)
Eye color							
Brown	5,202	96	Ref.	17	Ref.	55	Ref.
Gray/green	13,457	273	1.1 (0.8–1.3)	34	0.7 (0.4–1.3)	170	1.1 (0.8–1.5)
Blue	19,108	377	1.0 (0.8–1.3)	49	0.7 (0.4–1.3)	226	1.1 (0.8–1.5)
Skin color after long-lasting or chronic sun exposure							
Light or never brown	8,293	162	Ref.	15	Ref.	100	Ref.
Brown	23,802	441	0.9 (0.8–1.1)	53	1.2 (0.7–2.2)	275	1.0 (0.7–1.2)
Deep brown	6,212	146	1.2 (1.0–1.5)	28	2.3 (1.2–4.3)	81	1.1 (0.8–1.4)
Skin color after acute sun exposure at the beginning of summer							
Brown without red	8,898	203	Ref.	38	Ref.	108	Ref.
Red	18,465	349	0.9 (0.8–1.1)	41	0.6 (0.4–1.0)	226	1.1 (0.9–1.4)
Red with pain or blisters	10,974	199	0.9 (0.7–1.1)	20	0.5 (0.3–0.9)	121	1.0 (0.8–1.4)
Vitamin D dietary intake							
Q1 (<2.906 μ/d)	9,293	171	Ref.	24	Ref.	101	Ref.
Q2 (2.906–3.935 μ/d)	9,792	207	1.2 (1.0–1.5)	28	1.3 (0.7–2.2)	130	1.3 (1.0–1.6)
Q3 (3.936–5.109 μ/d)	9,828	189	1.1 (0.9–1.4)	29	1.4 (0.8–2.4)	115	1.2 (0.9–1.5)
Q4 (>5.110 μ/d)	9,559	187	1.2 (0.9–1.4)	19	0.9 (0.5–1.6)	111	1.1 (0.9–1.5)
Multivitamin user							
No	32,751	653	Ref.	92	Ref.	398	Ref.
Yes	5,721	101	1.0 (0.8–1.3)	8	0.7 (0.3–1.5)	59	1.0 (0.8–1.3)

[a]Adjusted for education, smoking, physical activity, alcohol drinking, and BMI.

ium use) was associated with increased all-cause and cancer mortality. The associations were not essentially altered by adjustment for host characteristics of UV sensitivity or vitamin D intake.

In ecological studies, an inverse correlation was found between regional UV-B radiation and mortality due to various cancers, such as breast, colon, ovary, prostate, non-Hodgkin lymphoma, bladder, esophageal, kidney, and lung (17, 29–34). Little evidence is available from analytic epidemiologic studies with individual information on UV exposure and its association with all-cause mortality or that from specific diseases while taking into account potential confounders (11, 35).

Because UV exposure is the major source of vitamin D, studies on the association between circulating vitamin D and disease risk may be informative. A recent published study of a cohort of 13,331 adults aged over 20 years from the Third National Health and Nutrition Examination Survey (NHANES III) examined the association between serum levels of 25(OH)D and mortality (36) after 8.7 years of follow-up. After adjustment for baseline demographics and other lifestyle risk factors, 25(OH)D deficiency increased all-cause mortality (relative risk = 1.3, 95% CI: 1.1–1.5, the lowest vs. highest quartile), but not the mortality from CVD and cancer. However, in yet another study based on the NHANES III, Ginde and colleagues (37) reported that serum levels of 25(OH)D had an independent inverse association with CVD and all-cause mortality. On the basis of a male cohort study, Giovannucci and colleagues reported an inverse association between vitamin D and the risk of cancer and myocardial infarction (38, 39). The overall inverse association between sun exposure and all-cause or CVD mortality found in the present study is consistent with those studies (36, 39), as well as with newly published studies from the Nordic countries, where diet and sun exposure are relatively similar to those in our cohort. In Finland, Virtanen and colleagues reported an increased all-cause and CVD mortality among men and women with low concentrations of 25(OH)D (40) and Kilkkinen and colleagues (41) reported low vitamin D levels to be associated with a

higher risk of a fatal CVD event, particularly cerebrovascular death. Worryingly, in Sweden, Michaelsson and colleagues reported that both high and low concentrations of plasma 25(OH)D were associated with an elevated risk for all-cause and cancer mortality among men (42). In the North of Norway, Hutchinson and colleagues reported increased all-cause mortality among nonsmokers (but not among smokers) with low 25(OH)D (43). Newly published studies from other parts of the world also reported a decreased risk of all-cause and CVD mortality: in Italy, Semba and colleagues reported a decreased all-cause mortality and CVD mortality in 1 study from the Chianti Region among men and women (44); in Baltimore, Semba and colleagues (45) found that low serum 25(OH)D concentrations were associated with greater all-cause mortality in women. In Germany, Pilz and colleagues (46) reported that low 25(OH)D levels were associated with all-cause and CVD mortality. In Japan, 25(OH)D levels were found to be independent risk factors for all-cause mortality among women (47). However, at least 2 other methodologically well-conducted studies did not find such associations in California (48) and several states in the United States (49).

We did not find any protective effect of sun exposure on cancer mortality, in agreement with data on 25(OH)D from the NHANES III study (50) and the Norwegian study (43), but in contrast with other studies (9, 31, 38, 42, 51, 52).

Solarium use has been reported to increase the risk of melanoma and nonmelanoma skin cancer in fair-skinned populations (1, 27, 53). The present study also observed that solarium use was associated with an increased risk of all-cause and cancer mortality, after controlling for other lifestyle risk factors or host characteristics related to UV sensitivity. Also noteworthy, solarium use once or more per month over a period of 2 or 3 decades was associated with a 1.6-fold increased risk of CVD mortality (95% CI: 0.6–4.2) compared with never users. This finding is difficult to explain biologically. It could be a chance finding or it could be due to residual confounding from some lifestyle factor that we did not control for.

We would have expected that women who are more susceptible to sunburn (i.e., those with light or red hair, those whose skin response to acute sun exposure was turning red with pain or blisters, and those with skin that is light or never brown after long-lasting or chronic sun exposure) would avoid sun exposure due to increased risk of melanoma and therefore have lower circulating 25(OH)D levels, as observed in the United Kingdom (54). However, that did not seem to affect the outcomes of our study, as women with light or red hair or with skin reacting strongly to sun exposure did not have an increased mortality compared with women with other hair and skin characteristics. Women whose skin turned deep brown after long-lasting or chronic sun exposure had an increased risk for CVD, a fact that remains to be explained.

Low estimated vitamin D intake did not modify the associations between UV exposure and mortality in our study. The lack of association between multivitamin intake and mortality in our study is not consistent with the results of a meta-analysis based on 18 randomized clinical trials of vitamin D supplementation, in which a 7% decreased risk of all-cause mortality appeared among people using vitamin D supplementation (6). However, in a recently published study on an 8-year follow-up of the Women's Health Initiative cohort, multivitamin use was shown to have little or no influence on the risk of death from common cancers, CVD, or all causes (55). Nevertheless, the presence of any association between oral vitamin D intake and disease risk is complex, given that the amount of vitamin D obtained through use of supplements may differ substantially between studies. Moreover, the relative contribution to serum vitamin D from diet or supplement and UV exposure varies by latitude and seasonal variations; UV exposure being the most important source in most countries. We only had information on multivitamin supplement use, without specification of the dose of vitamin D. The dose of vitamin D in multivitamins in Sweden in the early 1990s, when the study women answered the questionnaire, was probably too low (200 IU/d, 5 μg/d) to produce any significant effect on mortality, for which doses of 1,000 IU/d (25 μg/d) would be needed (18, 56, 57).

Several mechanisms might be responsible for the association between UV exposure, through the vitamin metabolic pathway, and the risk of disease and death. Vitamin D deficiency is associated with hypertension, diabetes mellitus, insulin resistance, and an elevated BMI (58), all of which are risk factors for CVD and all-cause mortality. A protective effect of vitamin D on CVD mortality may arise due to inhibition of vascular smooth muscle proliferation, suppression of vascular calcification, downregulation of proinflammatory cytokines, upregulation of anti-inflammatory cytokines, and action of vitamin D as a negative endocrine regulator of the renin-angiotensin system (59).

Strengths of our study include its large size, prospective design, and virtually complete follow-up through linkages to national registries. The information on UV exposure at different periods in life and relevant data on host characteristics and lifestyle factors is also an important strength. A strong association between our questionnaire-based UV exposure measures and risk of malignant melanoma shown in previous analyses from this study (27, 60) suggested that those questions assessing sun and solarium exposure are appropriate. The lack of information about the changes in the exposure and other risk factors after the baseline survey is a major limitation. Moreover, although adjusted for the major traditional risk factors for mortality, some relevant risk factors have not been taken into account in the disease-specific analyses such as blood pressure. Nevertheless, the NHANES III study (36) indicated that adjustment for hypertension and diabetes mellitus did not change the

results of the mortality risk estimates associated with vitamin D levels.

In conclusion, in this large prospective study of Swedish women, natural sun exposure during sunbathing vacations was associated with a reduced overall mortality and CVD mortality, whereas artificial UV exposure (by solarium use) was associated with an increased overall mortality and cancer mortality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

The survey was supported by the Swedish Cancer Society and the Swedish Research Council.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 24, 2010; revised January 12, 2011; accepted January 19, 2011; published OnlineFirst February 4, 2011.

References

1. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 55: Solar and Ultraviolet Radiation. Lyon, France: IARC Press; 1992.
2. International Agency for Research on Cancer. Exposure to Artificial UV Radiation and Skin Cancer. IARC Working Group Reports. Lyon, France: IARC Press; 2006.
3. El Ghissassi F, Baan R, Straif K, Grosse Y, Secretan B, Bouvard V, et al. A review of human carcinogens–part D: radiation. Lancet Oncol 2009;10:751–2.
4. Van Der Rhee HJ, de Vries E, Coebergh JW. Does sunlight prevent cancer? A systematic review. Eur J Cancer 2006;42:2222–32.
5. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005;41:45–60.
6. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 2007;167:1730–7.
7. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008;87:S1080–6.
8. International Agency for Research on Cancer. Vitamin D and Cancer. IARC Working Group Reports. Vol 5. Lyon, France: IARC Press; 2008.
9. Boscoe FP, Schymura MJ. Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993–2002. BMC Cancer 2006;6:264.
10. Ainsleigh HG. Beneficial effects of sun exposure on cancer mortality. Prev Med 1993;22:132–40.
11. Freedman DM, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. Occup Environ Med 2002;59:257–62.
12. Kricker A, Armstrong B. Does sunlight have a beneficial influence on certain cancers? Prog Biophys Mol Biol 2006;92:132–9.
13. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80:S1678–88.
14. Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, et al. Associations between prostate cancer susceptibility and parameters of exposure to ultraviolet radiation. Cancer Lett 2003;200:141–8.
15. de Vries E, Soerjomataram I, Houterman S, Louwman MW, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: a protective role of ultraviolet radiation? Am J Epidemiol 2007;165:966–72.
16. Gandini S, Boniol M, Haukka J, Byrnes G, Cox B, Sneyd MJ, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer 2011;128:1414–24.
17. Grant WB. How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer? an examination using Hill's criteria for causality. Dermatoendocrinol 2009;1:17–24.
18. Grant WB. Relation between prediagnostic serum 25-hydroxyvitamin D level and incidence of breast, colorectal, and other cancers. J Photochem Photobiol B 2010;101:130–6.
19. John EM, Koo J, Schwartz GG. Sun exposure and prostate cancer risk: evidence for a protective effect of early-life exposure. Cancer Epidemiol Biomarkers Prev 2007;16:1283–6.
20. Kricker A, Armstrong BK, Hughes AM, Goumas C, Smedby KE, Zheng T, et al. Personal sun exposure and risk of non Hodgkin lymphoma: a pooled analysis from the Interlymph Consortium. Int J Cancer 2008;122:144–54.
21. Rukin NJ, Zeegers MP, Ramachandran S, Luscombe CJ, Liu S, Saxby M, et al. A comparison of sunlight exposure in men with prostate cancer and basal cell carcinoma. Br J Cancer 2007;96:523–8.
22. Tuohimaa P, Pukkala E, Scelo G, Luscombe CJ, Liu S, Saxby M, et al. Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: vitamin D as a possible explanation. Eur J Cancer 2007;43:1701–12.
23. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. Aliment Pharmacol Ther 2009;30:113–25.
24. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer 2010;46:2196–205.
25. Kumle M, Weiderpass E, Braaten T, Persson I, Adami HO, Lund E. Use of oral contraceptives and breast cancer risk: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. Cancer Epidemiol Biomarkers Prev 2002;11:1375–81.
26. Wolk A, Bergstrom R, Hunter D, Willett W, Ljung H, Holmberg L, et al. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. Arch Intern Med 1998;158:41–5.
27. Veierød MB, Adami HO, Lund E, Armstrong BK, Weiderpass E. Sun and solarium exposure and melanoma risk: effects of age, pigmentary characteristics, and nevi. Cancer Epidemiol Biomarkers Prev 2010;19:111–20.
28. Therneau TM, Grambsch PM. Modelling Survival Data: Extending the Cox Model. New York: Springer; 2000.
29. Grant WB, Mohr SB. Ecological studies of ultraviolet B, vitamin D and cancer since 2000. Ann Epidemiol 2009;19:446–54.
30. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer 2002;94:1867–75.
31. Grant WB, Garland CF. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res 2006;26:2687–99.
32. Grant WB. An ecologic study of cancer mortality rates in Spain with respect to indices of solar UVB irradiance and smoking. Int J Cancer 2007;120:1123–8.
33. Lefkowitz ES, Garland CF. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. Int J Epidemiol 1994;23:1133–6.
34. Mohr SB. A brief history of vitamin d and cancer prevention. Ann Epidemiol 2009;19:79–83.
35. Zittermann A, Fischer J, Schleithoff SS, Tenderich G, Fuchs U, Koerfer R. Patients with congestive heart failure and healthy controls differ in vitamin D-associated lifestyle factors. Int J Vitam Nutr Res 2007;77:280–8.

36. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008;168:1629–37.
37. Ginde AA, Scragg R, Schwartz RS, Camargo CA Jr. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. J Am Geriatr Soc 2009; 57:1595–603.
38. Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006;98:451–9.
39. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008;168:1174–80.
40. Virtanen JK, Nurmi T, Voutilainen S, Mursu J, Tuomainen TP. Association of serum 25-hydroxyvitamin D with the risk of death in a general older population in Finland. Eur J Nutr 2010 Oct 26. [Epub ahead of print].
41. Kilkkinen A, Knekt P, Aro A, Rissanen H, Marniemi J, Heliövaara M, et al. Vitamin D status and the risk of cardiovascular disease death. Am J Epidemiol 2009;170:1032–9.
42. Michaëlsson K, Baron JA, Snellman G, Gedeborg R, Byberg L, Sundström J, et al. Plasma vitamin D and mortality in older men: a community-based prospective cohort study. Am J Clin Nutr 2010;92: 841–8.
43. Hutchinson MS, Grimnes G, Joakimsen RM, Figenschau Y, Jorde R. Low serum 25-hydroxyvitamin D levels are associated with increased all-cause mortality risk in a general population: the Tromso study. Eur J Endocrinol 2010;162:935–42.
44. Semba RD, Houston DK, Bandinelli S, Sun K, Cherubini A, Cappola AR, et al. Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. Eur J Clin Nutr 2010;64:203–9.
45. Semba RD, Houston DK, Ferrucci L, Cappola AR, Sun K, Guralnik JM, et al. Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women. Nutr Res 2009;29:525–30.
46. Pilz S, Dobnig H, Nijpels G, Heine RJ, Stehouwer CD, Snijder MB, et al. Vitamin D and mortality in older men and women. Clin Endocrinol 2009;71:666–72.
47. Kuroda T, Shiraki M, Tanaka S, Ohta H. Contributions of 25-hydroxyvitamin D, co-morbidities and bone mass to mortality in Japanese postmenopausal women. Bone 2009;44:168–72.
48. Jassal SK, Chonchol M, von Mühlen D, Smits G, Barrett-Connor E. Vitamin D, parathyroid hormone, and cardiovascular mortality in older adults: the Rancho Bernardo Study. Am J Med 2010;123:1114–20.
49. Cawthon PM, Parimi N, Barrett-Connor E, Laughlin GA, Ensrud KE, Hoffman AR, et al. Serum 25-hydroxyvitamin D, parathyroid hormone, and mortality in older men. J Clin Endocrinol Metab 2010;95: 4625–34.
50. Freedman DM, Looker AC, Abnet CC, Linet MS, Graubard BI. Serum 25-hydroxyvitamin D and cancer mortality in the NHANES III study (1988–2006). Cancer Res 2010;70:8587–97.
51. Giovannucci E, Liu Y, Willett WC. Cancer incidence and mortality and vitamin D in black and white male health professionals. Cancer Epidemiol Biomarkers Prev 2006;15:2467–72.
52. Pilz S, Dobnig H, Winklhofer-Roob B, Riedmüller G, Fischer JE, Seelhorst U, et al. Low serum levels of 25-hydroxyvitamin D predict fatal cancer in patients referred to coronary angiography. Cancer Epidemiol Biomarkers Prev 2008;17:1228–33.
53. IARC Working Group. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: a systematic review. Int J Cancer 2007;120:1116–22.
54. Glass D, Lens M, Swaminathan R, Spector TD, Bataille V. Pigmentation and vitamin D metabolism in Caucasians: low vitamin D serum levels in fair skin types in the UK. PLoS One 2009;4:e6477.
55. Neuhouser ML, Wassertheil-Smoller S, Thomson C, Aragaki A, Anderson GL, Manson JE, et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. Arch Intern Med 2009;169:294–304.
56. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003;77:204–10.
57. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 2007;85:1586–91.
58. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
59. Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr 2005;94:483–92.
60. Veierød MB, Weiderpass E, Thorn M, Hansson J, Lund E, Armstrong B, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2003;95:1530–8.