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Research Article

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Prospective Study of UV Exposure and Cancer Incidence Among Swedish Women

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Abstract

Background: Except for skin melanoma and nonmelanoma skin cancer, little evidence from prospective studies is available on the association between UV exposure and cancer risk.

Methods: We followed prospectively 49,261 women aged 30 to 49 years at enrollment in 1991 to 1992 for 15 years. Cancer incidence was analyzed by fitting Cox models, and estimating hazard ratios (HR) and 95% confidence intervals (CI).

Results: 2,303 incident cases of cancer were diagnosed (breast: 1,053, ovary: 126, lung: 116, colon-rectum: 133, and brain: 116). No associations were found between any cumulative measure of UV exposure at ages 10 to 39 years and overall cancer risk. However, spending ≥1 week/year between ages 10 and 29 years on sunbathing vacations led to an inverse association with overall cancer risk (HR: 0.70, 95% CI: 0.53–0.93) and breast cancer risk (HR: 0.56, 95% CI: 0.36–0.89) when compared with women who never went on such vacations. Solarium use was inversely associated with breast cancer risk, whereas ≥2 sunburns/year was inversely associated with lung cancer risk. No other associations were found between sun exposure or solarium use at ages 10 to 39 years and cancer risk.

Conclusion: We found no evidence of an association between any cumulative measure of UV exposure at ages 10 to 39 years and overall cancer risk. UV exposure earlier in life was related to reduced overall and breast cancer risk.

Impact: Further research is needed to define the amount of solar or artificial UV exposure that may, or may not, be beneficial for cancer prevention. *Cancer Epidemiol Biomarkers Prev; 20(7); 1358–67. ©2011 AACR.*

Introduction

In 1992, after reviewing epidemiologic, experimental and other relevant evidence, the International Agency for Research on Cancer (IARC) concluded that solar UV exposure is the main environmental cause of skin melanoma (1). Most people, however, depend on sun exposure to satisfy their vitamin D requirement. Solar UVB exposure is indeed the main source of vitamin D_3 for most populations, other sources of vitamin D (vitamin D represents either vitamin D_2 or vitamin D_3) being certain foods, food supplements such as multivitamins, and the use of artificial tanning devices (2, 3).

Accumulating evidence shows that vitamin D inhibits cell proliferation and promotes apoptosis *in vitro*, whereas its physiologically active form, $1,25(OH)_2D_3$, has anticarcinogenic properties. Host pigmentary characteristics such as eye, hair and skin color, as well as skin reaction to chronic and acute sun exposure, may also be associated with skin melanoma risk (1, 4). Moreover, skin pigmentation influences vitamin D_3 synthesis, and therefore may influence other cancer types besides melanoma (2).

In 2008, the IARC suggested an inverse association between vitamin D and the incidence of colorectal cancer based on a systematic review of the epidemiologic literature and a meta-analysis of observational studies of serum 25-hydroxyvitamin D (25(OH)D) levels, the major circulating form of vitamin D. Evidence for a causal link was, however, considered limited due to possible confounding by other dietary or lifestyle factors, and heterogeneity of studies (2). Little or no evidence was found for an effect on cancers of the breast or prostate. However, the IARC report has been criticized as being biased against the hypothesis of a beneficial effect of vitamin

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D on cancer incidence (5). Although ecological studies have suggested that there is a beneficial effect of sun exposure on the risk of some cancers, such as ovarian, bladder, brain, and lung (6–8), and seasonal variations in breast and colorectal cancer incidence rates suggest that serum 25(OH)D levels may be inversely associated with risk (9, 10), almost no prospective studies have yet evaluated these associations. Furthermore, whether host pigmentary characteristics are relevant to the risk of developing other cancers, or whether they modify the effects of UV exposure, remains unclear.

The Swedish Women's Lifestyle and Health cohort provides an opportunity to address these questions due to its detailed individual data on solar and artificial UV exposure in different periods of life, as well as information on host pigmentary characteristics, vitamin D intake from food and multivitamins and other relevant lifestyle factors.

Material and Methods

Study cohort

As previously described (11), in 1991–1992 a sample of women aged 30 to 49 years residing in the Uppsala Health Care Region in Sweden was randomly selected from the Swedish Central Population Registry at Statistics Sweden and sent an extensive questionnaire. A total of 49,259 women (51.3% of those invited) returned a completed questionnaire, which included demographic data, anthropometric characteristics, information on a variety of lifestyle factors (including UV exposure and diet), and host pigmentary characteristics.

Exposure assessment

History of UV exposure was evaluated in three ways: history of sunburn, sunbathing vacations, and frequency of solarium use (i.e., a sun bed or a sunlamp that emits artificial UV light), at ages 10–19, 20–29, 30–39, and 40–49 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. Similarly, for each age-period, a history of vacations involving sunbathing was derived from information that participants gave on the average number of weeks per year (none, 1, 2–3, 4–6, or $\geq$7 weeks) spent on sunbathing vacations in southern latitudes (typically southern Europe, e.g., Spain or Greece) or within Sweden. Participants also reported their average solarium use during each age-period (never, rarely, 1–2, 3–4 times per month, or one time or more per week). Study participants were asked to categorize their natural hair (dark brown/black, light brown, blond, red) and eye color (brown, gray/green, blue). Information on skin pigmentation, based on reported skin reactions to both acute sun exposure at the beginning of summer (brown without red, red, red with pain or blisters), and chronic or long-lasting sun exposure (light or never brown, brown, deep brown), was also sought.

The questionnaire included a validated self-administrated semiquantitative food-frequency questionnaire assessing habitual diet during the 6 months preceding a 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 (12). Individual dietary vitamin D intake 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 multivitamin use. However, there may be different doses of vitamin D in different brands of multivitamins, and there is also potential for inconsistent use of different brands over time, which can lead to a large probability of error in vitamin D dose estimates in multivitamins. Therefore it was decided not to combine dietary vitamin D intake and vitamin D intake from multivitamins.

Follow-up

The cohort was followed-up through linkages with national registries for causes of death, population emigration, and the national cancer registry, using the individually unique national registration number assigned to all Swedish residents. The start of follow-up was defined as the date of receipt of the returned questionnaire, and person-years were calculated until the date of cancer diagnosis, date of emigration or death, or the end of follow-up (December 31, 2006), whichever occurred first.

For the present study, we excluded 1,212 women diagnosed with cancer before baseline, 843 subjects with a total energy intake outside the 1st and 99th percentiles, and nine participants who did not report any host pigmentary characteristics or UV exposure information. We further excluded 4,636 women with missing information on covariates involved in the analyses (education, smoking, alcohol drinking, body mass index, and physical activity). Thus, the final study cohort comprised 42,559 women.

The risk of five types of cancer, for which at least 100 cases had been diagnosed during follow-up, are presented here: cancer of the breast (ICD-7: 170), ovary (ICD-7: 175), lung (ICD-7: 162), colon-rectum (ICD-7: 153 + 154), and brain and nervous system (ICD-7: 193). Melanoma and non-Hodgkin lymphoma results are not presented, because combined detailed results based on both our cohort and a Norwegian cohort have recently been reported (4, 13).

Statistical analysis

We assessed the association between UV exposure, host pigmentary characteristics, dietary vitamin D intake, multivitamin use, and the overall and site-specific cancer incidence. For each category of UV exposure history, we combined the exposure across each of the three decades of life recorded for all participating

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women (10–19, 20–29, and 30–39 years) (4). For sunburns (categories of annual number of sunburns: ≤ 1/, 10–19, 20–29, and 30–39 years; ≥2, 10–19 years only; ≥2, 10–19 and 20–29 years; ≥2, 10–19, 20–29, and 30–39 years; ≥2, 20–29 and/or 30–39 years) and sunbathing vacations (categories of annual number of weeks spent on sunbathing vacations: never, 10–19, 20–29, and 30–39 years; ≥1, 10–19 years only; ≥1, 10–19 and 20–29 years; ≥1, 10–19 only/and-or ≥1, 10–19 and 20–29 years; ≥1, 10–19, 20–29, and 30–39 years; ≥1, 20–29, and/or 30–39 years) the first categories represent exposure accumulating over successive decades from age 10 to 39 years, whereas the last category reflects exposure in adult age only (i.e., 20–39 years). Solarium use is separated into four categories representing cumulative exposure from age 10 to 39 years. As information on history of sunburn, sunbathing vacations, and frequency of solarium use at ages 40–49 years was only available for women who were at least 40 years of age at cohort enrollment, we did not include exposure in this age-period in the present analysis.

We calculated hazard ratios (HR) as estimates of relative risk, with associated 95% confidence intervals (CI) by the Cox proportional hazards model. The proportional hazard assumption was checked by plotting the Schoenfeld residuals (14). 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, and physical activity. Additional controlling for reproductive factors, such as parity, age at first birth, age at menarche, oral contraceptive use, breastfeeding, and family history of breast cancer was carried out in the analyses for cancers of the breast and ovary. Additional controlling for host pigmentary characteristics was done in the models. Subgroup analyses were restricted to subjects having a dietary vitamin D intake of less than 5 μg per day and reporting no multivitamin use.

The 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

During an average of 14.9 years (SD, 1.6) of follow-up, among 42,559 women, 2,303 incident cases of cancer were diagnosed, the most common site being the breast (1,053 cases). Mean age of women at study entry was 40.8 years (range, 30–49). More than 10% of brain cancer cases were diagnosed before age 35 years, whereas for the other cancer sites half or more were diagnosed after age 45 years. Table 1 presents the different characteristics of the study population at baseline. Generally, cancer incidence was higher among women who were less educated, had ever smoked, drank more alcohol, were overweight, or had a low level of physical activity (Table 1). The mean calculated dietary vitamin D intake was 4.1 μg per day (SD, 1.7). The majority of the women (85%) reported not taking multivitamins at baseline.

Overall cancer incidence

Table 2 shows cancer incidence according to UV exposure, whereas Table 3 presents cancer incidence according to host pigmentary characteristics and dietary vitamin D intake. We found no statistically significant association with overall cancer incidence for either solar UV exposure (as indicated by the number of sunburns, or the number of weeks spent on sunbathing vacations), or artificial UV exposure (by solarium use) at ages 10 to 39 years, except for the category of sunbathing vacations between ages 10 and 29 years (Table 2). Skin color after chronic or acute sun exposure, eye color, dietary vitamin D intake, or multivitamin use were not related to overall cancer risk. Increased overall cancer risk was, however, observed in women with blond and red hair (Table 3). Further controlling the analyses for skin color after acute and chronic sun exposure, or hair color, or confining the analysis to subjects with a dietary vitamin D intake of less than 5 μg per day and reporting no multivitamin use, did not change the results (data not shown).

Site-specific cancer incidence

Breast cancer. Reduced breast cancer risk consistently appeared among women who spent one week or more per year on sunbathing vacations between ages 10 and 29 years, or who used solarium between ages 10 and 39 years, after controlling for the other risk factors, or following further adjustment for skin color after acute and chronic sun exposure, hair color, or confining the analysis to women with a dietary vitamin D intake of less than 5 μg per day and reporting no multivitamin use. A 15% statistically significant decreased risk of breast cancer was found for women whose skin color was brown after chronic sun exposure, compared with those whose skin was light or never brown. No statistically significant association was found for women whose skin color after acute or chronic sun exposure was deep brown. We found no association between dietary vitamin D intake and breast cancer risk (Table 3).

Ovarian cancer. No association was observed for ovarian cancer risk, with either UV exposure or host pigmentary characteristics in the cohort as a whole, or in an analysis restricted to women with a dietary vitamin D intake of less than 5 μg per day and reporting no multivitamin use. The risk of ovarian cancer was approximately halved in women with moderate dietary vitamin D intake (3.9–5.1 μg per day compared with those whose dietary vitamin D intake was <2.9 μg per day, i.e., the third quartile vs. the lowest quartile of intake), although no statistically significant trend was observed (Table 3).

Lung cancer. Lung cancer incidence was reduced in women who reported two or more sunburns per year in all three age-periods between ages 10 and 39 years, or whose skin color changed to red or red with pain or blisters after acute sun exposure. We found no association between other measures of UV exposure, host pigmentary

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Table 1. Characteristics of study cohort at baseline, by cancer site during follow-up from 1991–1992 through 2006, the Swedish Women's Lifestyle and Health cohort study

	Study cohort	Overall cancer (all sites)	Cancer sites				
			Breast	Ovary	Lung	Colon-rectum	Brain
Number	42559	2303	1053	126	116	133	116
Mean age at cancer diagnosis (years)		51.8	51.6	52.4	54.7	53.7	50.4
Mean BMI (kg/m^2)	23.2	23.7	23.4	24.3	23.5	23.5	23.8
Mean education (years)	12.2	11.9	12.2	11.9	10.6	11.8	11.9
Ever smoker (%)	59.1	62.2	59.1	63.5	87.9	64.7	63.8
Nonalcohol drinkers (%)	13.1	13.4	12.1	16.7	18.1	8.3	14.7
Mean alcohol consumed (g/day) among alcohol drinkers	4.1	4.4	4.6	3.9	4.4	4.9	4.2
Percentage of women reporting different physical activity levels (%)							
Very low or low	14.8	16.4	15.5	15.1	21.6	9.8	19.0
Normal	59.6	60.7	60.8	59.5	62.1	66.2	53.5
High or very high	25.5	22.9	23.7	25.4	16.4	24.1	27.6
Mean age at menarche (years)	13.1	13.0	13.0	13.0	13.0	12.9	13.0
Ever oral contraceptive user (%)	83.2	80.6	82.9	73.9	79.3	80.4	85.3
Family history of breast or ovarian cancer (%)	9.1	12.0	14.1	14.3	6.0	11.3	7.8
Nulliparous (%)	13.5	14.2	14.6	12.7	13.8	15.0	12.9
Among parous women							
Mean number of children	2.1	2.2	2.2	2.3	2.3	2.2	2.4
Mean age at first birth	24.2	24.0	24.7	23.5	21.5	24.3	23.0
Breastfeeding duration (months)	11.6	10.7	11.2	10.3	8.4	10.5	11.3

Abbreviation: BMI, body mass index.

characteristics, dietary vitamin D intake, or use of multivitamins and lung cancer risk (Tables 2 and 3).

Colorectal cancer. UV exposure was not associated with the risk of colorectal cancer. An increased risk for colorectal cancer was observed among women with gray or green eyes, compared with those with brown eyes. Moreover, a 50% decreased risk was seen among those whose dietary vitamin D intake was between 3.9–5.1 μg per day compared with those whose dietary vitamin D intake was less than 2.9 μg per day (the third quartile vs. the lowest quartile of intake), but no statistically significant trend was observed (Table 3). When we confined the analysis to subjects with a dietary vitamin D intake of less than 5 μg per day and reporting no multivitamin use, the association between UV exposure and colorectal cancer risk was not altered.

Brain cancer. We found no association between UV exposure, host pigmentary characteristics, or dietary vitamin D intake on brain cancer incidence (Tables 2 and 3).

Discussion

Based on our 15-year follow-up of this large prospective study of middle-aged Swedish women, we found no consistent association between any cumulative measure of UV exposure at ages 10 to 39 years and overall cancer incidence, or cancers of the breast, ovary, lung, colon-rectum, or brain. However, a reduced breast cancer risk was observed among women who spent one week or more per year on sunbathing vacations earlier in life (between age 10 and 29 years). There was also a reduced breast cancer risk among women who used solarium between ages 10 and 39 years. For ovarian and colorectal cancer, a 50% decreased risk was seen among those whose dietary vitamin D intake was between 3.9–5.1 μg per day compared with those whose dietary vitamin D intake was less than 2.9 μg per day (the third quartile vs. the lowest quartile of intake), but no statistically significant trends were observed. Although we observed that a moderate level of dietary vitamin D intake was inversely associated with ovarian and colorectal cancer incidence, we found no association between UV exposure and the risk of these cancers among women reporting a dietary vitamin D intake of less than 5 μg per day and reporting no multivitamin use. Lung cancer incidence was reduced in women who reported two or more sunburns per year in all three age-periods between 10 and 39 years, or whose skin

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Table 2. Multiadjusted hazard ratios (HR) and 95% confidence intervals (CI) of cancer incidence according to UV exposure in different age-periods during follow-up from 1991–1992 through 2006[a], the Swedish Women's Lifestyle and Health cohort study

	Study sample	Overall cancer		Breast cancer		Ovarian cancer		Lung cancer		Colorectal cancer		Brain cancer	
		No.	HR (95% CI)[b]	No.	HR (95% CI)[c]	No.	HR (95% CI)[c]	No.	HR (95% CI)[b]	No.	HR (95% CI)[b]	No.	HR (95% CI)[b]
Annual number of sunburns[d]													
≤1/, 10–19, 20–29, and 30–39 years	24252	1375	Ref.	619	Ref.	82	Ref.	86	Ref.	83	Ref.	65	Ref.
≥2, 10–19 years only	3221	160	0.99 (0.84–1.17)	69	0.90 (0.70–1.16)	11	1.20 (0.64–2.26)	3	0.36 (0.11–1.14)	10	1.11 (0.57–2.13)	13	1.63 (0.90–2.96)
≥2, 10–19, and 20–29 years	3565	178	1.03 (0.88–1.20)	90	1.11 (0.89–1.38)	9	0.93 (0.46–1.85)	3	0.34 (0.11–1.08)	9	0.93 (0.46–1.85)	7	0.81 (0.37–1.78)
≥2, 10–19, 20–29, and 30–39 years	3582	192	1.01 (0.87–1.18)	90	1.02 (0.81–1.27)	13	1.20 (0.67–2.16)	3	0.30 (0.09–0.94)	14	1.26 (0.71–2.22)	9	0.98 (0.49–1.96)
≥2, 20–29, and/or 30–39 years	3094	162	0.97 (0.83–1.15)	70	0.91 (0.71–1.16)	3	0.32 (0.10–1.03)	7	0.75 (0.35–1.63)	7	0.71 (0.33–1.54)	9	1.12 (0.56–2.25)
Annual number of weeks spent on sunbathing vacations[d]													
Never, 10–19, 20–29, and 30–39 years	4744	319	Ref.	137	Ref.	22	Ref.	19	Ref.	18	Ref.	12	Ref.
≥1, 10–19 years only	888	42	0.85 (0.62–1.17)	19	0.81 (0.49–1.33)	2	0.59 (0.14–2.53)	2	0.82 (0.19–3.54)	3	1.14 (0.33–3.87)	3	1.52 (0.43–5.40)
≥1, 10–19, and 20–29 years	1585	57	0.70 (0.53–0.93)	22	0.56 (0.36–0.89)	3	0.60 (0.18–2.01)	4	1.13 (0.38–3.33)	6	1.40 (0.55–3.55)	0	-
≥1, 10–19 only/and-or ≥1, 10–19, and 20–29 years[e]	2473	99	0.76 (0.60–0.95)	41	0.65 (0.46–0.93)	5	0.60 (0.22–1.58)	6	1.00 (0.40–2.52)	9	1.30 (0.58–2.91)	3	0.59 (0.16–2.09)
≥1, 10–19, 20–29, and 30–39 years	20742	1097	0.90 (0.79–1.03)	517	0.88 (0.72–1.08)	52	0.70 (0.41–1.18)	43	0.81 (0.46–1.42)	60	0.81 (0.47–1.39)	59	1.30 (0.68–2.48)
≥1, 20–29 and/or 30–39 years	9647	578	0.88 (0.77–1.01)	266	0.87 (0.70–1.07)	39	0.94 (0.55–1.60)	36	1.05 (0.60–1.85)	37	0.89 (0.50–1.57)	26	1.10 (0.55–2.20)
Average use of a solarium[d]													
Never in all decades, 10–39 years	18251	1193	Ref.	561	Ref.	71	Ref.	61	Ref.	69	Ref.	56	Ref.
Rarely but not ≥1 time/month in any decade, 10–39 years	9946	428	0.89 (0.79–1.00)	202	0.81 (0.68–0.96)	22	0.85 (0.52–1.40)	19	1.13 (0.66–1.94)	25	1.03 (0.64–1.66)	22	0.84 (0.50–1.40)
≥1 time/month in one decade, 10–39 years	7574	380	1.02 (0.91–1.15)	165	0.87 (0.73–1.05)	25	1.24 (0.77–2.01)	23	1.57 (0.95–2.60)	19	0.98 (0.58–1.66)	22	1.08 (0.64–1.80)
≥1 time/month in two or three decades, 10–39 years	2169	80	1.11 (0.87–1.40)	25	0.63 (0.41–0.96)	2	0.54 (0.13–2.28)	1	0.49 (0.07–3.63)	5	1.77 (0.68–4.59)	1	0.21 (0.03–1.56)

[a]P for trends were not statistically significant in any of the categories analyzed.

[b]Adjusted for education, smoking, alcohol drinking, body mass index, and physical activity. Attained age was used as the time scale in the models.

[c]Adjusted for education, smoking, alcohol drinking, body mass index, physical activity, parity, age at first birth, age at menarche, oral contraceptive use, breastfeeding, and family history of breast cancer. Attained age was used as the time scale in the models.

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

[e]Sum of the two categories above, i.e., ≥1, 10–19 years only/and-or ≥1, 10–19 and 20–29 years.

Table 3. Multiadjusted hazard ratios (HR) and 95% confidence intervals (CI) of cancer incidence according to host pigmentary characteristics and vitamin D intake during follow-up from 1991–1992 through 2006[a], the Swedish Women's Lifestyle and Health cohort study

	Study sample	Overall cancer		Breast cancer		Ovarian cancer		Lung cancer		Colorectal cancer		Brain cancer	
		No.	HR (95% CI)[b]	No.	HR (95% CI)[c]	No.	HR (95% CI)[c]	No.	HR (95% CI)[b]	No.	HR (95% CI)[b]	No.	HR (95% CI)[b]
Skin color after acute sun exposure at the beginning of summer													
Brown without red	9815	540	Ref.	235	Ref.	33	Ref.	43	Ref.	28	Ref.	32	Ref.
Red	20355	1119	1.04 (0.94–1.15)	502	1.05 (0.90–1.23)	64	0.99 (0.65–1.51)	49	0.66 (0.44–1.00)	72	1.32 (0.85–2.04)	53	0.82 (0.53–1.28)
Red with pain or blisters	12238	634	1.03 (0.92–1.16)	310	1.12 (0.94–1.33)	29	0.78 (0.47–1.29)	23	0.57 (0.34–0.96)	33	1.14 (0.68–1.89)	31	0.81 (0.49–1.34)
Skin color after long-lasting or chronic sun exposure													
Light or never brown	9305	528	Ref.	248	Ref.	28	Ref.	25	Ref.	30	Ref.	23	Ref.
Brown	26216	1374	0.91 (0.82–1.00)	604	0.85 (0.73–0.99)	79	1.00 (0.64–1.54)	72	0.98 (0.62–1.54)	83	0.90 (0.59–1.37)	75	1.16 (0.73–1.86)
Deep brown	6847	387	0.97 (0.86–1.11)	194	1.05 (0.87–1.27)	18	0.86 (0.47–1.56)	19	0.90 (0.50–1.65)	20	0.82 (0.46–1.45)	18	1.06 (0.57–1.96)
Hair color													
Dark brown/black	11854	595	Ref.	297	Ref.	37	Ref.	30	Ref.	29	Ref.	30	Ref.
Light brown	18339	1011	1.10 (1.00–1.22)	450	0.96 (0.83–1.12)	50	0.89 (0.58–1.36)	46	0.99 (0.63–1.57)	59	1.30 (0.84–2.03)	52	1.13 (0.72–1.77)
Blond	10555	589	1.18 (1.06–1.33)	251	0.95 (0.80–1.13)	35	1.20 (0.75–1.90)	35	1.44 (0.88–2.34)	38	1.56 (0.96–2.54)	32	1.26 (0.76–2.07)
Red	1333	83	1.30 (1.03–1.63)	42	1.30 (0.94–1.79)	4	1.03 (0.37–2.88)	3	0.96 (0.29–3.14)	6	1.90 (0.79–4.59)	2	0.60 (0.14–2.51)
Eye color													
Brown	5699	301	Ref.	139	Ref.	15	Ref.	16	Ref.	9	Ref.	21	Ref.
Gray/green	14899	819	1.00 (0.87–1.14)	370	0.97 (0.80–1.18)	46	1.10 (0.62–1.98)	45	0.99 (0.56–1.75)	60	2.36 (1.17–4.75)	41	0.73 (0.43–1.23)
Blue	21185	1150	1.01 (0.89–1.15)	528	1.00 (0.83–1.21)	63	1.10 (0.63–1.93)	54	0.87 (0.50–1.53)	62	1.79 (0.89–3.61)	52	0.65 (0.39–1.09)
Dietary vitamin D intake (μg/day)													
Q1 (<2.906)	10639	587	Ref.	265	Ref.	38	Ref.	40	Ref.	40	Ref.	28	Ref.
Q2 (2.906–3.935)	10640	605	1.05 (0.94–1.18)	298	1.13 (0.96–1.34)	38	1.04 (0.66–1.63)	24	0.67 (0.40–1.11)	28	0.70 (0.43–1.13)	30	1.10 (0.65–1.84)
Q3 (3.936–5.109)	10640	542	0.95 (0.84–1.07)	245	0.95 (0.79–1.13)	21	0.57 (0.33–0.97)	24	0.71 (0.43–1.18)	21	0.53 (0.32–0.91)	21	0.77 (0.44–1.37)
Q4 (≥5.110)	10640	569	0.99 (0.88–1.12)	245	0.95 (0.80–1.13)	29	0.77 (0.47–1.26)	28	0.83 (0.51–1.34)	44	1.13 (0.73–1.73)	37	1.35 (0.83–2.22)
			$P = 0.51$		$P = 0.24$		$P = 0.09$		$P = 0.42$		$P = 0.75$		$P = 0.40$
Multivitamin user													
No	36281	1988	Ref.	903	Ref.	102	Ref.	103	Ref.	114	Ref.	103	Ref.
Yes	6278	315	0.98 (0.87–1.11)	150	0.96 (0.81–1.15)	24	1.53 (0.98–2.41)	13	1.00 (0.56–1.80)	19	1.05 (0.64–1.71)	13	0.78 (0.43–1.39)

[a]P for trends were not statistically significant in any of the categories analyzed; only the P for trend of dietary vitamin D intake is reported in the table.
[b]Adjusted for education, smoking, alcohol drinking, body mass index and physical activity. Attained age was used as the time scale in the models.
[c]Adjusted for education, smoking, alcohol drinking, body mass index, physical activity, parity, age at first birth, age at menarche, oral contraceptive use, breastfeeding, and family history of breast cancer. Attained age was used as the time scale in the models.

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color changed to red or red with pain or blisters after acute sun exposure.

Strengths of our study include its large size, prospective design, detailed assessment of UV exposure (as annual number of sunburns, annual number of weeks spent on sunbathing vacations, and solarium use) during different periods of life, assessment of host pigmentary characteristics, dietary vitamin D intake, use of multivitamins, adjustment for confounding factors, and virtually complete follow-up through linkages to national registries.

The study also has several limitations, the most important being the small number of cases for individual cancer sites, with the exception of breast cancer. Nondifferential misclassification of UV exposure and dietary vitamin D intake may have biased the results toward zero. Although circulating serum or plasma 25(OH)D levels were not directly assessed, a previous study based on this cohort has shown consistent associations between UV exposure measures, host pigmentary characteristics and risk of malignant melanoma, suggesting that the questions on sun exposure included in the study questionnaire are probably appropriate proxy variables for UV exposure (4, 15). Our study lacks information on seasonal variations, variations in stratospheric ozone, atmospheric aerosols and pollution, cloud cover and surface reflection, which may influence terrestrial UV radiation exposure. Nevertheless, we have included most host pigmentary characteristics relevant to cutaneous UV transmission, scatter or absorption, including immediate and delayed skin reaction to UVB exposure (i.e., skin color after acute sun exposure at the beginning of summer and skin color after long-lasting or chronic sun exposure), hair and eye color. Synthesis of vitamin D in the skin is dictated by host characteristics, and in light-skinned people synthesis decreases after 5 to 10 minutes of sun exposure (16). Longer durations of sun exposure may not further increase serum 25(OH)D levels, and increase skin cancer risk (2). However, information about the duration of acute UV exposure is not available for this study.

We also lacked information on ethnic background (race), as this information was not collected in our questionnaire, and is purposefully not available in any registry in Sweden. However, virtually all the women in our cohort were born in Sweden or in other Nordic countries. Thus it is a fair assumption that the vast majority were Caucasian. Dietary vitamin D intake and use of multivitamins were measured in adulthood, whereas annual number of sunburns, annual number of weeks spent on sunbathing vacations, and average solarium use were recorded for different decades of life, including teenage years. Thus, the results for dietary vitamin D intake and multivitamin use and UV exposure are not directly comparable. Sunburns are an erythemal reaction to UVB exposure (8) and were used in our study as a crude proxy of solar UV exposure. Sunburns are a risk factor for melanoma but not nonmelanoma skin cancer, and melanoma rates are often inversely correlated with nonmelanoma skin cancer (8). A large ecological study suggested that solid tumors are less frequently observed after a diagnosis of nonmelanoma skin cancer (related to chronic sun exposure) than with melanoma skin cancer (related to sunburns) (17).

The UVB doses in Sweden are lower than in latitudes below 45 degrees, where other studies have found a protective effect of solar UV exposure on cancer risk (18). This may explain why studies in Spain (8), France (19), Italy (20), Mexico (21), and the United States (22) have found an inverse association between solar UV exposure and cancer risk. Solar UV exposure in Uppsala, where our cohort was recruited, is too low during several months of the year to have a significant effect on skin production of vitamin D_3, and more solar UVB exposure occurs during sunbathing vacations. Indeed, we found indications of decreased risk of cancer with increasing number of sunbathing vacations, but not with overall number of sunburns. Several studies (8, 17, 23–28) used incidence or mortality rates of nonmelanoma skin cancer as a proxy of long-term UVB irradiance, or directly measured 25(OH)D levels. Both these approaches may be considered more objective and reliable than our questionnaire-based assessment of UV exposure, host pigmentary characteristics and dietary vitamin D and multivitamin intake.

Sweden implemented national regulations for indoor tanning devices in 1982, and the UVB-rich sunlamps were gradually replaced with UVA-rich fluorescent lamps. The UVA and UVB irradiances of approved tanning devices in Sweden were similar to those in Norway, and varied little between 1982/1983 and 1992 (4, 29). In this cohort, where women were aged 30 to 49 years in 1991 (i.e., birth cohorts 1942–1961), solarium use before 20 years of age occurred before 1981, use from 20 to 29 years occurred between 1962 and 1991, and use from 30 to 39 years between 1972 and 1991. Thus, solarium users were exposed to UVB-rich sunlamps until about 1982/1983 and then UVA-rich fluorescent lamps (4). Mean UVB and UVA irradiances of inspected tanning devices in Norway in 2003 were 1.5 and 3.5 times higher, respectively, than the irradiance of the natural summer sun at noon in Oslo (29). We can assume that these irradiances are similar in Sweden.

We found evidence for a reduced overall cancer and breast cancer risk among women who spent one week or more per year on sunbathing vacations early in life, between ages 10 and 29 years, or, for breast cancer, evidence of a reduced risk among those who used solarium between ages 10 and 39 years. Thus there was evidence that solar or artificial UV exposure (but not sunburns), in particular early in life, may reduce breast cancer risk. Similar findings on breast cancer risk were reported in a case-control study in Canada in relation to age at exposure to sun and solarium (30). This finding suggests that exposures relatively early in life, in particular during breast development, may be more relevant than exposures in peri- or postmenopausal periods (30).

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As in our cohort, the French E3N cohort study (19) found no association between dietary and supplemental vitamin D intake and breast cancer risk. However, in regions with the highest UV levels, postmenopausal women with a high dietary or supplemental vitamin D intake had a significantly lower breast cancer risk as compared with women in the lowest category of vitamin D intake. The results from the French E3N study suggest that a threshold of vitamin D, originating from both sun exposure and diet may be required to reduce breast cancer risk (19). In our own previous detailed analysis of sun exposure in different decades of life, based partially on the same cohort but with a shorter follow-up time, we found no association with breast cancer risk (31). The difference in our current results may be due to the larger number of breast cancer cases in the cohort, and the longer follow-up. Therefore we cannot rule out the possibility that a clearer association will be observed in our cohort in forthcoming years.

Ecological studies have consistently shown an inverse association between UV exposure and breast cancer risk (32). Some (30, 32–37) but not all (31, 38–40) observational studies have supported a protective association of vitamin D on breast cancer risk. Giovannucci (41) reviewed the evidence for an association between vitamin D and breast cancer in the Harvard cohorts, describing a 30% reduction in risk comparing the highest with the lowest quintiles of serum 25(OH)D levels. Moreover, a recent meta-analysis on breast cancer risk found that in case-control studies that recorded serum 25(OH)D levels after diagnosis, there is a possible inverse association, whereas a statistically significant inverse association remained unconfirmed in prospective studies that recorded serum 25(OH)D levels years before diagnosis. Further prospective studies are needed to clarify the potential role, and the relevant exposure time, of vitamin D in breast cancer risk (42).

Although we did not find an association between ovarian cancer risk and UV exposure or host pigmentary characteristics in the cohort as a whole, nor when we restricted the UV exposure analyses to women with dietary vitamin D intake of less than 5 μg per day and reporting no multivitamin use, we did find an approximately halved risk among women with moderate dietary vitamin D intake, although no statistically significant trend was observed. Previous studies are controversial: a nested case-control study (43) and the Cohort Consortium of Vitamin D Pooling Project of Rarer Cancers (44), indicated that vitamin D may not have a protective role in ovarian cancer risk, whereas inverse associations were found in a large ecological study on solar UV exposure and ovarian cancer risk (45), a Finnish case-control study on pre-diagnostic serum calcium and 25(OH)D on the risk of later development of ovarian cancer (46), and a Mexican case-control study on dietary vitamin D intake and ovarian cancer (21). A recent systematic literature review concluded that there is no consistent or strong evidence to support the claim made in numerous review articles that vitamin D exposures reduce the risk of ovarian cancer occurrence or mortality (47).

Ecological studies (6,8,48) have suggested that higher UVB exposure is associated with reduced lung cancer risk. In our study, lung cancer incidence was reduced in women who reported two or more sunburns per year in all three age-periods between ages 10 and 39 years, or whose skin color changed to red or red with pain or blisters after acute sun exposure. We found no other associations between other measures of UV exposure, namely sunbathing vacations and solarium use, host pigmentary characteristics, dietary vitamin D intake, or use of multivitamins and lung cancer risk. However, the number of cases in our study was relatively small, precluding firm conclusions. Giovanucci and colleagues (49) observed a nonsignificant inverse association for an increment of 25 nmol/L in predicted plasma 25(OH)D level for individual cancers in the Health Professionals Follow-up Study (1986–2000). A prospective study in Finland found no overall associations between serum 25(OH)D levels and lung cancer in men, but a decreased risk with increasing 25(OH)D in women (50). Freedman and colleagues (51) found no correlation between 25(OH)D levels and lung cancer mortality. Ecological studies have also suggested an association between latitude and melanoma incidence and lung cancer risk (8, 48).

In this study UV exposure was not associated with the risk of colorectal cancer in the cohort as a whole, or after restricting analyses to women with a vitamin D intake of less than 5 μg per day and reporting no multivitamin use. A 50% decreased risk of colorectal cancer was observed among those whose dietary vitamin D intake was between 3.9 μg and 5.1 μg per day compared with those women who consumed less than 2.9 μg per day, but no statistically significant trend was observed. This finding is somewhat consistent with a previous IARC systematic review and results from Harvard studies (2, 41). A study from Japan reported that higher levels of dietary vitamin D were significantly associated with a decreased risk of colorectal cancer among those who had fewer opportunities to be exposed to sunlight (52). A recent meta-analysis of longitudinal studies suggested that serum 25(OH)D level is inversely related to colorectal cancer risk. (53).

Our study does not support an association between sun exposure, solarium use, or vitamin D intake, and brain cancer risk. However, as a previous ecological study has suggested an association (54), reports from other observational studies and pooled analyses of existing cohort studies are warranted.

In conclusion, in this cohort of Swedish women we found no evidence of an association between any cumulative measure of UV exposure at ages 10 to 39 years and subsequent incidence of overall cancer, or cancers of the breast, ovary, lung, colon-rectum, and brain. However, a reduced overall cancer risk and breast cancer risk was observed among women who spent one week or more per year on sunbathing vacations between ages 10 and 29 years, and a reduced breast cancer risk among women

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who used solarium between ages 10 and 39 years. For ovarian and colorectal cancer, a 50% decreased risk was seen among those whose dietary vitamin D intake was between 3.9–5.1 μg per day compared with those whose dietary vitamin D intake was less than 2.9 μg per day (the third quartile vs. the lowest quartile of intake), but no statistically significant trends were observed. Lung cancer incidence was reduced in women who reported two or more sunburns per year between 10 and 39 years of age, or whose skin color changed to red, or red with pain or blisters after acute sun exposure.

Many questions about the possible association between UV exposure, either from solar or artificial sources, through the vitamin D metabolic pathway, and the risk of cancer incidence remain unanswered. These include the usefulness of assessing vitamin D intake through sun exposure and diet, the importance of biomarkers of vitamin D, such as circulating plasma metabolite levels, and how other cancer risk factors may affect associations between UV exposure, dietary vitamin D intake or use of vitamin D supplements, and cancer. Excessive sun exposure at all ages is discouraged largely because of the increased risk of melanoma and other skin cancers. However, further research is needed to define the amount of solar or artificial UV exposure that might be beneficial. Longer follow-up and additional prospective studies with comprehensive assessment of UV exposure and vitamin D measurement are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Prospective Study of UV Exposure and Cancer Incidence Among Swedish Women

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