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Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: Vitamin D as a possible explanation

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ABSTRACT

Background: Skin cancers are known to be associated with sun exposure, whereas sunlight through the production of vitamin D may protect against some cancers. The aim of this study was to assess whether patients with skin cancer have an altered risk of developing other cancers.

Methods: The study cohort consisted of 416,134 cases of skin cancer and 3,776,501 cases of non-skin cancer as a first cancer extracted from 13 cancer registries. 10,886 melanoma and 35,620 non-melanoma skin cancer cases had second cancers. The observed numbers (O) of 46 types of second primary cancer after skin melanoma, basal cell carcinoma or non-basal cell carcinoma, and of skin cancers following non-skin cancers were compared to the expected numbers (E) derived from the age, sex and calendar period specific cancer incidence rates in each of the cancer registries (O/E = SIR, standardised incidence ratios). Rates

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from cancer registries classified to sunny countries (Australia, Singapore and Spain) and less sunny countries (Canada, Denmark, Finland, Iceland, Norway, Scotland, Slovenia and Sweden) were compared to each other.

Results: SIR of all second solid primary cancers (except skin and lip) after skin melanoma were significantly lower for the sunny countries (SIR(S) = 1.03; 95% CI 0.99–1.08) than in the less sunny countries (SIR(L) = 1.14; 95%CI 1.11–1.17). The difference was more obvious after non-melanoma skin cancers: after basal cell carcinoma SIR(S)/SIR(L) = 0.65 (95%CI = 0.58–0.72); after non-basal cell carcinoma SIR(S)/SIR(L) = 0.58 (95%CI = 0.50–0.67). In sunny countries, the risk of second primary cancer after non-melanoma skin cancers was lower for most of the cancers except for lip, mouth and non-Hodgkin lymphoma.

Conclusions: Vitamin D production in the skin seems to decrease the risk of several solid cancers (especially stomach, colorectal, liver and gallbladder, pancreas, lung, female breast, prostate, bladder and kidney cancers). The apparently protective effect of sun exposure against second primary cancer is more pronounced after non-melanoma skin cancers than melanoma, which is consistent with earlier reports that non-melanoma skin cancers reflect cumulative sun exposure, whereas melanoma is more related to sunburn.

1. Introduction

Skin malignancies (melanoma, squamous cell carcinoma and basal cell carcinoma) are the most common cancers in white populations. The incidence of skin cancers is increasing. This trend has been observed in all geographical regions covered by cancer registration, and is not restricted to any particular age group or sex. Ultraviolet (UV) radiation is thought to be the most important risk factor for skin cancers. Sunburn, in particular, and skin type are risk factors for melanoma.[1] Solar UV radiation prior to the age of 20 years is suggested to initiate a process of basal cell carcinogenesis.[2] Especially UV-B radiation seems to cause oncogenic mutations in skin cells leading to basal (BCC) and squamous cell carcinomas (SCC).[3]

On the other hand, it has been suggested that sunlight through production of vitamin D in the skin might have a protective effect on several internal cancers including cancer of the breast, colon, ovary, prostate, non-Hodgkin lymphoma, bladder, oesophagus, kidney, lung, pancreas, rectum, stomach and corpus uteri.[5–10] These ecological studies have been challenged by several studies suggesting that there is no correlation between serum vitamin D levels and cancer risk.[11–13] Several epidemiological studies, however, suggest that low serum vitamin D (calcidiol, 25(OH) vitamin D_3) or low sun exposure might increase risk of prostate cancer[14–21] (for review see [22,23]), colorectal cancer[5,21,24–26] female breast cancer[5,21] and non-Hodgkin lymphoma.[27]

We hypothesise that skin cancer patients have a higher mean sun exposure and a higher vitamin D serum level than the average population, and therefore they should have decreased risk of the vitamin D insufficiency-related cancers listed above. This effect should be stronger in countries with high solar exposure. To elucidate this hypothesis, we studied the joint occurrence of skin cancers and other primary cancers in a cohort extracted from 13 cancer registries.

2. Methods

In order to conduct a systematic analysis of second primary cancers, an international multicentre study has been initiated incorporating large cancer registries, which have been in operation for at least 25 years. Nineteen cancer registries that have consistently reported their cancer incidence figures in *Cancer Incidence in Five Continents*[3] were invited to participate. A similar analysis is underway in the US SEER cancer registries and they are therefore not included in this analysis. Of an initial group of 19 contacted registries, 15 provided all necessary data. Two registries were subsequently excluded because of discrepancies in the observed rates of second primaries, leaving 13 registries in the current analysis. These registries are British Columbia, Manitoba and Saskatchewan (Canada), New South Wales (Australia), Singapore, Norway, Denmark, Sweden, Finland, Iceland, Scotland, Slovenia and Zaragoza (Spain).

Anonymised data were provided from each cancer registry on all initial primary cancers, including age and sex of the subject, diagnosis and date of the first primary, follow-up for mortality and date and diagnosis of the second primary, if any. Information was also obtained from each cancer registry on the set of rules used for defining a second primary cancer. As these differ between cancer registries, and also over time, the International Association of Cancer Registries (IACR)/International Agency for Research on Cancer (IARC) rules on second primary cancers were adopted as a common set of rules. This was possible as all participating cancer registries currently use the IACR/IARC rules, or a local set of more extensive or detailed rules.

The registries contained 140,100 patients (1,125,430 person-years) with melanoma and 276,034 patients with non-melanoma skin cancers: 148,885 basal cell carcinomas (1,042,249 person-years) and 127,149 non-basal cell carcinomas (1,014,578 person-years). Together, there were 4,192,635 first and second primary cancers for the analyses.

To assess any possible excess of second primary neoplasms after skin cancer, we compared the observed number of neoplasms to the expected number derived from the age, sex and calendar period-specific cancer incidence rates of first primary cancers in each of the cancer registries. Standardised incidence ratios (SIRs) were defined as ratios of observed to expected numbers. Exact confidence intervals (CI) around the SIR were calculated assuming a Poisson distribution for the observed number of neoplasms. The SIRs for skin cancers as a second primary after other cancer sites as a first primary were calculated similarly.

The total UV exposure in the countries of 13 cancer registers varied considerably. The annual average erythemal UV doses were calculated from home page of Atmospheric Chemistry Division (http://www.acd.ucar.edu/TUV). The calculated average annual exposures were 0.7–0.9 kJ/m^2/day for British Columbia, Manitoba and Saskatchewan (Canada), 5.6 for New South Wales (Australia), 5.3 for Singapore, 0.6–0.7 for Norway, Denmark, Sweden and Finland, 0.9 for Iceland and Scotland, 1.7 for Slovenia and 2.8 for Zaragoza (Spain). The material was divided into two groups according to the UV exposure of the population: The sunny countries (S) (>2 kJ/m^2/day) were Australia, Singapore and Spain; Less sunny countries (L) (<2 kJ/m^2/day) were Canada, Denmark, Finland, Island, Norway, Scotland, Slovenia and Sweden. SIR(S) and SIR(L) and their ratios were calculated. 95% confidence intervals for these ratios were generated by using the computer program, Confidence Interval Analysis.[28]

3. Results

There were 140,100 skin melanoma cases as first primary cases; 7.8% of them had a second primary cancer (Table 1). Out of the 276,034 cases of non-melanoma skin cancer as the first primary cancer, 12.9% developed a second primary cancer (Table 2). Melanoma cases were younger and 30.5% of them provided at least 10 years of follow-up compared to 27.3% among non-melanoma skin cancer cases. Among the primary melanoma and non-melanoma cases, 42,049 (344,569 person-years) and 10,966 (75,752 person-years) came from the sunny countries (Spain, Singapore and Australia) and 98,051 (780,862 person-years) and 265,068 (1,981,075 person-years) from the less sunny countries (Canada, Slovenia, Scotland, Finland, Denmark, Iceland, Norway and Sweden), respectively.

Among the 140,100 melanoma first primary cases, there was a 23% overall increase in the risk of a second primary cancer other than melanoma (SIR = 1.23, 95% CI 1.21–1.25) (Table 3). The SIR decreased slightly with increasing time of follow-up (from 1.34 to 1.16). Out of the 2039 excess cancer cases after melanoma, 986 were non-melanoma skin cases; exclusion of them would decrease the SIR to 1.12 (95%CI 1.10–1.15). After melanoma, a significant excess was observed for cancers of lip, salivary gland, small intestine, colorectum, bone, soft tissue sarcoma, non-melanoma of skin, female breast, prostate, kidney, brain, thyroid, other endocrine glands, non-Hodgkin lymphoma and lymphoid leukaemia. Melanoma as a second primary was increased after all these cancers and after cancers of ovary, corpus uteri, testis, bladder, eye, multiple myeloma as well as after myeloid leukaemia. The risk of cancers of salivary gland, soft tissue sarcoma, non-melanoma skin, female breast, non-Hodgkin lymphoma and lymphoid leukaemia were higher shortly after melanoma. After the first primary melanoma, there was a significantly reduced risk of cancers of liver and gallbladder, larynx and lung and cervix uteri. The risk of melanoma as a second primary cancer decreased after these cancers, too.

Table 1 – Characteristics of patients with skin melanoma as first primary cancer

	First cancers		Second cancers	
	n	% out of all patients with melanoma as first cancer	*n* (excluding skin melanoma)	% out of first cancer patients in this category
Sex				
Women	73,659	52.6	5240	7.1
Men	66,441	47.4	5646	8.5
Age at first cancer registration				
<56	72,248	51.6	3683	5.1
56–65	26,952	19.2	2885	10.7
66–74	22,532	16.1	2665	11.8
75+	18,368	13.1	1653	9.0
Calendar period at first cancer registration				
<1975	19,109	13.6	2220	11.6
1975–1983	31,726	22.7	3364	10.6
1984–1990	38,915	27.8	3313	8.5
1991+	50,350	35.9	1989	4.0
Duration of follow-up				
Less than 12 months	17,210	12.3	1274	7.4
1–4 years	47,411	33.8	3591	7.6
5–9 years	31,991	22.8	2700	8.4
10+ years	43,488	31.0	3321	7.6
Total	140,100	100.0	10,886	7.8

Table 2 – Characteristics of patients with non-melanoma skin cancer as first primary cancer

	First cancers		Second cancers	
	n	% out of all patients with non-melanoma as first cancer	*n* (excluding skin non-melanoma)	% out of first cancer patients in this category
Sex				
Women	128,513	46.6	13,229	10.3
Men	147,521	53.4	22,391	15.2
Age at first cancer registration				
<56	51,025	18.5	4,875	9.6
56–65	52,640	19.1	8,323	15.8
66–74	71,089	25.8	11,224	15.8
75+	101,280	36.7	11,198	11.1
Calendar period at first cancer registration				
<1975	51,102	18.5	9,823	19.2
1975–1983	62,180	22.5	11,359	18.3
1984–1990	69,443	25.2	9,223	13.3
1991+	93,309	33.8	5,215	5.6
Duration of follow-up				
Less than 12 months	32,838	11.9	4,357	13.3
1–4 years	96,962	35.1	13,063	13.5
5–9 years	70,843	25.7	9,203	13.0
10+ years	75,391	27.3	8,997	11.9
Morphology				
Basal cell carcinoma	148,885	53.9	17,080	11.5
Non-basal cell carcinoma	127,149	46.1	18,540	14.6
Total	276,034	100.0	35,620	12.9

The overall cancer risk was increased after non-melanoma skin cancer involving basal and squamous cell carcinoma (SIR = 1.39; 95%CI 1.38–1.41). An exclusion of melanoma cases decreases the SIR to 1.37 (95%CI = 1.36–1.38). The SIRs were highest for cancers of salivary gland, lip and melanoma (Table 4). The risk of the second primary non-melanoma skin malignancies was increased similarly after all other cancers as first primary cancer (results not shown).

3.1. *Effect of sun exposure*

3.1.1. *Melanoma*

When all solid tumours except for cancers of skin and lip are analysed in detail in sunny countries, significant reductions in SIRs can be found (Table 5). The risks of cancers of liver and gallbladder as well as lung are significantly lower after melanoma as the first primary cancer and vice versa. There is a statistically significant reduction of SIR for cancers of oesophagus, stomach, bone and cervix uteri, but only unidirectionally. In sunny countries, significant increases of SIRs were seen for cancers of small intestine, sarcoma, non-melanoma skin, thyroid and non-Hodgkin lymphoma after melanoma as the first primary (result not shown).

In less-sunny countries, the SIR for cancer of liver and gallbladder and lung is lower for patients having melanoma as the first primary cancer than for the rest of the population (Table 5). When the sunny and less-sunny countries are compared, the SIR-S/SIR-L for all solid tumours, pancreas, female breast, bladder and brain are significantly lower in the sunny than in the less-sunny countries (Table 5). Melanoma was diagnosed in sunny and less-sunny countries at the same age (66.6 ± 13.9 years versus 63.5 ± 18.9 years).

3.2. *Non-melanoma skin cancer*

3.2.1. *Basal cell carcinoma*

In the sunny countries (S) (>2 kJ/m^2/day), the SIR for all solid tumours (except for cancers of lip and skin) is 0.86 after the first primary basal cell carcinoma, whereas it is 1.35 in less-sunny countries (Table 6). Thus, the risk of all solid tumours in the sunny countries is significantly lower than in less-sunny countries (SIR(S)/SIR(L) = 0.64). Most of the solid cancers show a significantly lower SIR(S) than SIR(L), especially cancers of stomach, colorectum, liver and gallbladder, pancreas, lung, female breast, prostate and kidney. Basal cell carcinomas were clinically detected at the same age in sunny and less-sunny countries (66.6 ± 13.9 y versus 66.4 ± 13.9).

3.3. *Non-basal cell carcinomas*

SIR(S) was significantly lower for cancers of liver, gallbladder, bile duct, pancreas and prostate after non-basal cell carcinomas (squamous cell carcinoma) (Table 7). The ratio SIR(S)/SIR(L) was significantly reduced for cancers of all solid tumours (excluding cancers of lip and skin), but among solid cancers individually only the risk of stomach, colorectal, liver and gallbladder, pancreas, lung, prostate and bladder cancers were significantly lower in sunny countries (Table 7). The age

Table 3 – Incidence from selected second cancers following melanoma of skin (140,100 subjects and 1,125,431 person-years), by site

Cancer sites (ICD 9th revision)	Observed	Expected	SIR	95% CI
All malignant (140–208)	10,886	8847	1.23	1.21–1.25
Oral cavity, pharynx (140–149)	237	217	1.09	0.96–1.24
Lip (140)	87	62	1.41	1.13–1.73
Tongue (141)	27	34	0.79	0.52–1.15
Salivary gland (142)	34	20	1.73	1.20–2.42
Mouth (143–145)	48	47	1.01	0.75–1.34
Pharynx (146–149)	41	55	0.75	0.54–1.02
Oesophagus (150)	86	103	0.84	0.67–1.03
Stomach (151)	339	361	0.94	0.84–1.04
Small intestine (152)	45	26	1.73	1.26–2.32
Colorectal (153,154)	1369	1209	1.13	1.07–1.19
Colon (153)	886	763	1.16	1.09–1.24
Rectum (154)	483	446	1.08	0.99–1.18
Liver, gallbladder, bile ducts (155–156; excl. 155.2)	127	169	0.75	0.63–0.89
Liver (155; excl. 155.2)	69	75	0.92	0.71–1.16
Gallbladder, bile ducts (156)	58	94	0.62	0.47–0.80
Pancreas (157)	262	262	1.00	0.88–1.13
Peritoneum (158)	10	11	0.92	0.44–1.69
Nose and nasal cavity (160)	10	16	0.62	0.30–1.15
Larynx (161)	56	74	0.75	0.57–0.98
Lung (162)	887	1027	0.86	0.81–0.92
Bone (170)	22	11	2.06	1.29–3.12
Soft tissue sarcoma (171)	113	42	2.72	2.24–3.27
Other neoplasm of skin (173)	1404	418	3.36	3.18–3.54
Female breast (174)	1353	1134	1.19	1.13–1.26
Male breast (175)	9	7.7	1.17	0.54–2.22
Cervix uteri (180)	113	143	0.79	0.65–0.95
Placenta (181)	1	0.41	2.46	0.06–13.7
Corpus uteri (182)	255	226	1.13	0.99–1.27
Ovary (183)	217	204	1.06	0.93–1.22
Other female genital (179, 184)	42	49	0.85	0.61–1.15
Prostate (185)	1486	1174	1.27	1.20–1.33
Testis (186)	20	21	0.97	0.59–1.50
Other male genital (187)	15	12	1.25	0.70–2.06
Bladder (188, 189.3, 189.4)	392	396	0.99	0.89–1.09
Kidney (189; excl. 189.3-4)	312	244	1.28	1.14–1.43
Eye (190)	32	22	1.44	0.98–2.03
Brain, nervous system (191–192)	189	125	1.51	1.30–1.74
Thyroid gland (193)	118	64	1.84	1.53–2.21
Other endocrine gland (194,164.0)	22	8	2.68	1.68–4.06
Lymphohaematopoietic (200–208)	861	639	1.35	1.26–1.44
Lymphomas (200–202)	429	306	1.40	1.27–1.54
Hodgkin disease (201)	34	28	1.21	0.84–1.69
Non Hodgkin lymphoma (200, 202)	395	277	1.42	1.29–1.57
Multiple myeloma (203)	136	124	1.10	0.92–1.30
Leukaemias (204–208)	296	210	1.41	1.25–1.58
Lymphoid leukaemia (204)	153	90	1.69	1.44–1.98
Myeloid leukaemia (205)	87	73	1.19	0.95–1.47
Other leukaemia (206–208)	56	46	1.21	0.91–1.57
Other	482	432	1.12	1.02–1.22

of the diagnosis of non-basal cell carcinomas were significantly lower in sunny countries than in less-sunny countries (63.5 ± 18.9 years versus 70.3 ± 13.9), suggesting that the average sun exposure per person is higher in sunny countries. The SIR of all cancers following non-melanoma skin cancers decreased with time in sunny countries from 1.12 (0.92–1.35) during the first year of follow-up to 0.70 (0.57–0.85) after 10 years since the diagnosis of the skin cancer, whereas it did not change in less-sunny countries.

4. Discussion

The final result was somewhat unexpected: The risk of internal solid cancers after the primary skin cancers was decreased only in the sunny countries, but not in the less sunny countries. The difference was more pronounced after non-melanoma skin cancers than after melanoma. Registration of skin cancers may not be as complete as of other cancers. The basal cell cancers are not registered at all in many

Table 4 – Incidence from selected second cancers following non-melanoma skin cancer (276,034 subjects and 2,056,827 person-years), by site

Cancer site (ICD-9)	Observed	Expected	SIR	95% CI
All malignant (140–208)	35,620	25,616	1.39	1.38–1.41
Oral cavity, pharynx (140–149)	1447	598	2.42	2.30–2.55
Lip (140)	688	199	3.45	3.20–3.72
Tongue (141)	122	80	1.53	1.27–1.83
Salivary gland (142)	223	47	4.73	4.13–5.39
Mouth (143–145)	205	135	1.51	1.31–1.74
Pharynx (146–149)	209	137	1.53	1.33–1.75
Oesophagus (150)	526	449	1.17	1.07–1.28
Stomach (151)	2175	1761	1.23	1.18–1.29
Small intestine (152)	115	67	1.72	1.42–2.06
Colorectal (153, 154)	5218	4016	1.30	1.26–1.33
Colon (153)	3425	2519	1.36	1.31–1.41
Rectum (154)	1793	1498	1.20	1.14–1.25
Liver, gallbladder, bile ducts (155–156; excl. 155.2)	729	595	1.22	1.14–1.32
Liver (155; excl. 155.2)	355	279	1.27	1.14–1.41
Gallbladder, bile ducts (156)	374	316	1.18	1.07–1.31
Pancreas (157)	1092	898	1.22	1.14–1.29
Peritoneum (158)	65	41	1.58	1.22–2.02
Nose and nasal cavity (160)	111	51	2.17	1.79–2.62
Larynx (161)	383	257	1.49	1.35–1.65
Lung (162)	5984	3975	1.51	1.47–1.54
Bone (170)	29	27	1.07	0.72–1.54
Soft tissue sarcoma (171)	157	96	1.64	1.40–1.92
Melanoma of skin (172)	1051	375	2.80	2.63–2.97
Female breast (174)	2743	2059	1.33	1.28–1.38
Male breast (175)	35	27	1.30	0.90–1.81
Cervix uteri (180)	276	268	1.03	0.91–1.16
Placenta (181)	0	0.1	0.00	0.00–39.1
Corpus uteri (182)	593	464	1.28	1.18–1.39
Ovary (183)	517	426	1.21	1.11–1.32
Other female genital (179,184)	229	136	1.68	1.47–1.92
Prostate (185)	4222	3314	1.27	1.24–1.31
Testis (186)	46	32	1.45	1.06–1.93
Other male genital (187)	73	59	1.24	0.98–1.56
Bladder (188, 189.3, 189.4)	2153	1677	1.28	1.23–1.34
Kidney (189; excl 189.3–4)	848	659	1.29	1.20–1.37
Eye (190)	55	54	1.02	0.77–1.33
Brain, nervous system (191–192)	282	225	1.25	1.11–1.41
Thyroid gland (193)	144	100	1.44	1.21–1.69
Other endocrine gland (194, 164.0)	29	19	1.55	1.04–2.23
Lymphohaematopoietic (200–208)	2824	1728	1.63	1.57–1.70
Lymphomas (200–202)	1299	692	1.88	1.78–1.98
Hodgkin disease (201)	109	66	1.65	1.35–1.99
Non Hodgkin lymphoma (200, 202)	1190	626	1.90	1.79–2.01
Multiple myeloma (203)	447	369	1.21	1.10–1.33
Leukaemias (204–208)	1078	667	1.62	1.52–1.71
Lymphoid leukaemia (204)	606	344	1.76	1.62–1.90
Myeloid leukaemia (205)	347	229	1.52	1.36–1.69
Other leukaemia (206–208)	125	94	1.33	1.10–1.58
Other	1469	1160	1.27	1.20–1.33

cancer registries, or they may be partly mixed with other non-melanoma skin cancers. The incompleteness of skin cancer registration should not be related to later appearance of other malignancies, especially not in cases where the diagnoses are made years apart of each other and registration processes are independent. It may be that in some cases simultaneous diagnoses of skin cancer with some other cancer may add the likelihood of reporting also the skin cancer to the cancer registry. Similarly, reporting of a second malignancy may include information of an earlier skin malignancy that would not have been reported without existence of the second cancer. These potential biases would bias the SIR estimates upwards.

The second cancers were coded according the IACR/IARC rules in all participating cancer registries. Therefore, the definition of the second primary cancer should be valid and comparable throughout the registries. Because observed and

Table 5 – Standardised incidence ratios (SIR) for selected cancer sites following skin melanoma (42,049 subjects and 344,569 person-years) in sunny countries (S) and less sunny countries (L)

Cancer site (ICD 9)	Sunny countries (Spain, Singapore and Australia)				Less sunny countries (Canada, Slovenia, Scotland, Finland, Denmark, Iceland, Norway and Sweden)				Comparison between sunny and less sunny countries	
	Observed	Expected	SIR(S)	95% CI	Observed	Expected	SIR(L)	95% CI	SIR(S)/SIR(L)	95% CI
All solid tumours except skin and lip	2423	2343.76	1.03	0.99–1.08	5629	4952.45	1.14	1.11–1.17	0.91	0.87–0.95
Pharynx (146–149)	20	23.22	0.86	0.53–1.33	21	31.28	0.67	0.42–1.03	1.28	0.66–2.49
Oesophagus (150)	30	37.15	0.81	0.54–1.15	56	65.61	0.85	0.64–1.11	0.95	0.59–1.50
Stomach (151)	87	92.56	0.94	0.75–1.16	252	268.87	0.94	0.83–1.06	1.00	0.78–1.28
Colorectal (153,154)	494	437.80	1.13	1.03–1.23	875	771.00	1.13	1.06–1.21	0.99	0.89–1.11
Liver, gallbladder, bile ducts (155–156; excl. 155.2)	27	43.92	0.61	0.41–0.89	100	125.47	0.80	0.65–0.97	0.77	0.49–1.19
Pancreas (157)	58	73.07	0.79	0.60–1.03	204	188.80	1.08	0.94–1.24	0.74	0.54–0.99
Lung (162)	309	363.20	0.85	0.76–0.95	578	663.50	0.87	0.80–0.95	0.98	0.85–1.12
Female breast (174)	318	308.94	1.03	0.92–1.15	1035	824.61	1.26	1.18–1.33	0.82	0.73–0.93
Corpus uteri (182)	49	42.89	1.14	0.85–1.51	206	183.53	1.12	0.97–1.29	1.02	0.73–1.40
Ovary (183)	34	37.83	0.90	0.62–1.26	183	166.15	1.10	0.95–1.27	0.82	0.55–1.18
Other female genital (179,184)	10	11.19	0.89	0.43–1.64	32	38.08	0.84	0.57–1.19	1.06	0.47–2.22
Prostate (185)	559	466.48	1.20	1.10–1.30	927	707.63	1.31	1.23–1.40	0.92	0.82–1.02
Bladder (188,189.3,189.4)	90	108.37	0.83	0.67–1.02	302	287.54	1.05	0.94–1.18	0.79	0.62–1.00
Kidney (189; excl. 189.3–4)	101	74.89	1.35	1.10–1.64	211	169.15	1.25	1.08–1.43	1.08	0.84–1.38
Brain, nervous system (191–192)	45	41.09	1.10	0.80–1.47	144	83.85	1.72	1.45–2.02	0.64	0.45–0.90

Table 6 – Standardised incidence ratios (SIR) for selected cancer sites following basal cell carcinoma of the skin cancer in sunny countries (S) and less sunny countries (L)

Cancer site (ICD 9)	Sunny countries (Spain, Singapore and Australia)				Less sunny countries (Canada, Slovenia, Scotland, Finland, Denmark, Iceland, Norway and Sweden)				Comparison between sunny and less sunny countries	
	Observed	Expected	SIR(S)	95% CI	Observed	Expected	SIR(L)	95% CI	SIR(S)/SIR(L)	95% CI
All solid tumours except skin and lip	368	421.19	0.86	0.80–0.92	13917	10341.52	1.35	1.32–1.37	0.65	0.58–0.72
Pharynx (146–149)	3	5.45	0.55	0.11–1.61	107	71.33	1.50	1.23–1.81	0.37	0.07–1.10
Oesophagus (150)	6	7.89	0.76	0.28–1.66	247	237.50	1.04	0.91–1.18	0.73	0.27–1.61
Stomach (151)	36	45.00	0.80	0.56–1.11	747	607.32	1.23	1.14–1.32	0.65	0.45–0.91
Colorectal (153, 154)	66	70.97	0.93	0.72–1.18	2511	1860.00	1.35	1.30–1.41	0.69	0.53–0.88
Liver, Gallbladder, bile ducts (155–156; excl. 155.2)	9	23.08	0.39	0.18–0.73	295	239.84	1.23	1.10–1.38	0.32	0.14–0.61
Pancreas (157)	7	12.73	0.55	0.22–1.13	478	391.80	1.22	1.11–1.34	0.45	0.18–0.94
Lung (162)	80	76.92	1.04	0.82–1.29	3062	2171.63	1.41	1.36–1.46	0.74	0.58–0.92
Female breast (174)	24	26.67	0.90	0.58–1.34	1559	1105.67	1.41	1.34–1.48	0.64	0.41–0.96
Corpus uteri (182)	6	6.52	0.92	0.34–1.99	300	238.10	1.26	1.12–1.41	0.73	0.27–1.61
Ovary (183)	2	5.00	0.40	0.05–1.43	263	217.36	1.21	1.07–1.36	0.33	0.04–1.21
Other female genital (179,184)	1	3.13	0.32	0.01–1.80	97	65.10	1.49	1.21–1.82	0.21	0.01–1.22
Prostate (185)	33	52.38	0.63	0.44–0.89	1832	1317.99	1.39	1.33–1.46	0.45	0.31–0.64
Bladder (188, 189.3, 189.4)	37	38.54	0.96	0.67–1.32	1019	789.92	1.29	1.21–1.37	0.74	0.52–1.03
Kidney (189; excl. 189.3–4)	5	8.93	0.56	0.18–1.31	401	292.70	1.37	1.24–1.51	0.41	0.13–0.96
Brain, nervous system (191–192)	6	5.66	1.06	0.39–2.31	156	118.18	1.32	1.12–1.54	0.80	0.29–1.79

expected numbers were based on the same cancer registry data, possible changes in the reporting and coding, and variation in the diagnostic criteria among pathologists should have no effect on the O/E estimates. The current analyses based on 13 registries, with 46,506 subsequent cancers diagnosed after skin cancers, offer an unique possibility to identify risk patterns related to cancer sites, even when SIRs are only moderately increased.

4.1. *Treatment effects*

Since most skin cancers are treated by surgery, it seems unlikely that treatment effects can account for substantial numbers of second primary cancers. In metastatic melanoma some chemotherapy (possibly with radiotherapy) is used, but not commonly.[29]

4.2. *Common risk factors*

Human Papillomaviruses (HPV) types 5/8 have been identified in non-melanoma skin cancers among transplant recipients. Melanoma is also increased among transplant recipients, raising the possibility of an infectious aetiology, although the exact nature of viruses that might be involved is unclear. Presumably immune suppression can work in two ways: either by increasing the risk of acquiring infection with an oncogenic virus, and/or reducing the body's ability to mount defences against a developing tumour, irrespective of the presence or absence of infection.

The increase in cancer of the oropharynx after skin cancer was relatively constant over time, and was mirrored by a similar increase in skin cancers after an initial diagnosis of oropharynx cancer, arguing for a common exposure. Risk factors for cancers of the oropharynx include tobacco and alcohol. Alternatively, the excess risk may be linked to the viral aetiology of oropharyngeal cancer associated with moderate immune suppression.

4.3. *Detection and misclassification bias*

The increase in second primary skin cancer after the primary one was strongly concentrated on the first 12 months after diagnosis, indicating a possible detection bias. Similarly, salivary gland and testis carcinomas as well as lymphomas and leukaemias showed high SIR values within the first 12 months after squamous cell carcinoma as the first primary cancer suggesting a detection bias. Because liver and lung are known to be metastatic sites for skin cancers, the low SIR values for them could be due to an underestimation of these cancers. However, this does not explain, why the relative risk of skin cancers is decreased after lung cancer. Confounding by socio-economic status could explain this observation, but seems unlikely to account for all the associations emerging in this study.

4.4. *Limitations of second primary cancer analyses*

This analysis results from a pooling of data from 13 cancer registries, and some level of heterogeneity in risk of second cancer is inevitable, due to different underlying treatment

Table 7 – Standardised incidence ratios (SIR) for selected cancer sites following non-melanoma skin cancer (excluding basal cell carcinoma) in sunny countries (S) and less sunny countries (L)

Cancer site (ICD 9)	Sunny countries (Spain, Singapore and Australia)				Less sunny countries (Canada, Slovenia, Scotland, Finland, Denmark, Iceland, Norway and Sweden)				Comparison between sunny and less sunny countries	
	Observed	Expected	SIR(S)	95% CI	Observed	Expected	SIR(L)	95% CI	SIR(S)/SIR(L)	95% CI
All solid tumours except skin and lip	188	237.66	0.79	0.68–0.91	15115	11151.12	1.36	1.33–1.38	0.58	0.50–0.67
Pharynx (146–149)	3	3.49	0.86	0.18–2.51	96	56.14	1.71	1.38–2.09	0.50	0.10–1.51
Oesophagus (150)	4	5.26	0.76	0.21–1.93	269	197.79	1.36	1.20–1.53	0.56	0.15–1.45
Stomach (151)	22	28.57	0.77	0.48–1.17	1370	1078.74	1.27	1.20–1.34	0.61	0.38–0.92
Colorectal (153, 154)	29	39.73	0.73	0.49–1.05	2612	2056.69	1.27	1.23–1.32	0.58	0.39–0.83
Liver, gallbladder, bile ducts (155–156; excl. 155.2)	6	14.63	0.41	0.15–0.89	419	317.42	1.32	1.19–1.45	0.31	0.11–0.68
Pancreas (157)	1	7.14	0.14	0.00–0.77	606	488.71	1.24	1.15–1.35	0.11	0.004–0.63
Lung (162)	48	45.28	1.06	0.78–1.41	2794	1673.05	1.67	1.61–1.73	0.64	0.47–0.84
Female breast (174)	10	11.11	0.90	0.43–1.66	1150	912.70	1.26	1.18–1.33	0.71	0.34–1.32
Corpus uteri (182)	2	2.45	0.82	0.10–2.96	285	217.56	1.31	1.17–1.48	0.63	0.07–2.27
Ovary (183)	1	2.04	0.49	0.01–2.72	251	202.42	1.24	1.10–1.41	0.40	0.01–2.22
Other female genital (179,184)	1	1.75	0.57	0.01–3.16	130	65.99	1.97	1.65–2.34	0.29	0.01–1.65
Prostate (185)	13	30.23	0.43	0.23–0.73	2344	1921.31	1.22	1.18–1.28	0.35	0.19–0.61
Bladder (188,189.3,189.4)	14	20.90	0.67	0.36–1.12	1083	826.72	1.31	1.23–1.39	0.51	0.28–0.86
Kidney (189; excl. 189.3–4)	3	4.76	0.63	0.13–1.84	439	354.03	1.24	1.13–1.36	0.51	0.11–1.50
Brain, nervous system (191–192)	2	2.70	0.74	0.09–2.66	118	98.33	1.20	1.00–1.44	0.62	0.07–2.28

and exposure characteristics, as well as specific cancer registry characteristics. The latter was minimised by ensuring a common protocol between the registries for reporting second primaries, as well as detailed comparison of results for discrepancies, and the dropping of two registries due to apparent under-reporting in one instance and over-reporting in the other that could not be reconciled. This resulted in limited heterogeneity between the registries, for both all cancers combined and specific cancers.

Similarly, when comparing the results from individual registries for other common cancer sites, such as skin melanoma or kidney, the results were very consistent. Also, none of the observed excesses can be explained by a substantial increase in any one centre.

4.5. *Ultraviolet (UV) light and/or altered immunity*

In our entire material, we find a clearly increased risk of several second primary cancers after any skin cancer. Only after melanoma, but not after non-melanomas, some decreased SIR values were found such as liver and gallbladder, larynx, lung and cervix uteri. These cancers are not previously described as protected by vitamin D/sun exposure. The relationship between these cancers appeared to be bidirectional suggesting a common risk/protective factor, which so far remains obscure. Previous large studies of second primary cancers after skin cancers have shown a similar excess of all second primary cancers after skin cancer.[30–33] The relative risk was increased for other skin cancers*, lip*, salivary gland*, larynx, lung, kidney*, small intestine*, breast*, prostate*, non-Hodgkin lymphoma* and leukaemia*. Our study on second primary cancer after melanoma confirms the results marked with an asterisk. In addition, an increased relative risk was found for cancers of colon, bone, soft tissue sarcoma and thyroid gland. The risk was increased for all cancers after non-melanoma skin cancer. No decrease of the relative risk was found in the earlier studies. If sun exposure is a risk factor for melanoma, it could be a protective factor for internal cancers through production of vitamin D. However, sun exposure may also modify the immune system to enhance cancer development.[34] Some studies are focused mainly on the relationship between non-Hodgkin lymphoma and skin melanoma and squamous cell skin cancers from the Swedish and Danish cancer registries.[35] There seems to be an association between all skin cancers and non-Hodgkin lymphoma which, it has been suggested, is explained on the basis of UV light and altered immunity. Both melanoma and non-melanoma skin cancers were strongly increased after NHL diagnosis although there was a suggestion that this risk decreased with time since initial diagnosis. Similarly, an increased risk of NHL was observed after both melanoma and non-melanoma skin cancers which showed signs of decreasing with longer follow-up. That the relationship is bi-directional, and similar for both melanoma and non-melanoma argues strongly against detection bias as an explanation for the increase. Instead the joint association is likely to be due to a common risk factor or shared mechanism that is stronger during the initial period of diagnosis. The role of UV light has previously been put forward as explaining this joint association.[36] Similarly, it is possible that the increase in risk of lip and tongue cancers could also be explained by UV exposure. Although tongue cancer is not normally considered to be a UV related cancer, there is over a 1000-fold increase in tongue cancer among patients with xeroderma pigmentosum, a rare inherited cancer prone DNA disorder due to marked UV radiation hypersensitivity.[37]

While a possible association between UV light and NHL is appealing, recent evidence fails to support such an association. In the first study to report detailed individual level data on UV exposure, no increased risk of NHL was observed with increasing UV exposure among 704 cases and 694 controls from New South Wales.[27] Indeed, if anything, exposure to UV light was found to be protective against NHL. Another possibility is that the joint association is due to a common mechanism such as general immune suppression, possibly modulated by UV exposure in the case of skin cancers but by other exposures for NHL. In a recent case-control study based on 3740 malignant lymphoma patients, a history of high UV exposure was associated with reduced risk of non-Hodgkin lymphoma, therefore the positive association between skin cancer and malignant lymphomas is unlikely to be mediated by UV exposure.[38] It is of interest to note that skin cancers, and in particular squamous cell cancers, are strongly increased among subjects who experience extreme immune suppression (e.g. among transplant patients and others receiving immunosuppressive drugs), raising the possibility of an infectious aetiology for some of these cancers.[39]

Based on the above mentioned reasons, we excluded from the final analysis, all directly sun-linked cancers such as lip and other skin cancers as well as lymphoma and leukaemia, because they seem to be directly linked with the immunosuppression caused by sun exposure. The remaining solid cancers were analysed according to the UV-exposure of the country. The cutoff level for sun exposure is difficult to set. The cutoff level at 2 kJ/m^2/day seems to be valid, because countries below it have a clear seasonal variation meaning that during winter UV is insufficient to cause vitamin D production. Our UV data contain both UV-A and -B. Only UV-B can convert 7-dehydrocholesterol to pre-vitamin D, but the total UV exposure well reflects UV-B exposure. When the total UV exposure is low, there is no UV-B irradiation, because it can weakly penetrate the atmosphere. Therefore, Nordic populations are suffering from winter-time vitamin D insufficiency. A dark skin colour reduces cutaneous vitamin D production, however, there are only small differences in skin colour among the countries studied. On the other hand, small skin colour differences may not be significant, because the vitamin D is less degraded by UV irradiation in a darker skin than in a paler skin, thus the net vitamin D production is similarly dependent on the sun exposure. Different clothing styles in the countries studied determine the skin area exposed to sun, and therefore it may also affect vitamin D production in the skin, but it was not possible to analyse its effect on cancer incidence in the present study.

It seems that the effect of UV light is not as dominating for basal cell carcinoma (BCC) as for squamous cell carcinoma (SCC) or melanoma,[4] therefore it was reasonable to analyse the material on the basis of skin cancer type and sun exposure. The overall risk of all second solid primary cancers after any skin cancer was significantly decreased in sunny coun-

tries, whereas it was significantly increased in less-sunny countries. This is the first report on such a finding, which needs a large study population. The following second primary cancers after melanoma showed significantly decreased SIR values in S countries compared with LS countries: cancers of pancreas, female breast, bladder and brain after melanoma; and cancers of stomach, colorectum, liver and gallbladder, pancreas, lung, female breast, prostate, bladder, kidney and brain after non-melanoma skin cancer, respectively. Decreased SIR values for many of these cancers were found in another ecological study.[10] It is interesting to note that our study can confirm 11 out of these 13 cancers, but not three of them (cancers of ovary, corpus uteri and oesophagus) which yield SIRs below 1.00, although the results are not statistically significant. The SIR of non-Hodgkin lymphoma in sunny and less-sunny countries after any skin cancer is significantly increased. Many of these cancers have been studied in vitro and an inhibitory effect of vitamin D metabolites on cancer growth has been described (for review see [40]).

It seems that UV-B can cause certain oncogenic mutations in the skin cells,[3] whereas by vitamin D production it can suppress cell proliferation, cancer development and metastasis. It is interesting to note that basal cell carcinoma or non-basal cell carcinoma (squamous cell carcinoma) appears to signal less risk of the development of subsequent solid cancer than melanoma. If melanoma is more related to sun-burn during childhood, whereas basal cell carcinoma and SCC reflect cumulative UV-exposure, our result makes sense. It means that the development of basal cell carcinoma and SCC reflects more directly vitamin D availability. Most of the melanoma cases appear in the skin areas not commonly exposed to sunlight, therefore its development might be affected by other risk factors besides UV radiation. However, in very sunny countries such as Australia sun must play an important role also in melanoma carcinogenesis. Australia is an optimal country for comparisons in this study, because it is mainly populated by light-skinned people. Vitamin D production is much lower in dark skin.

Assuming that cumulative sun exposure plays a major role in the development of non-melanoma skin cancers, it is difficult to understand why there is such a significant difference between sunny and less-sunny countries. The fact that people living in less-sunny countries tend to travel to sunny areas during the winter may decrease the difference between sun exposures. In the present ecological study, such factors are not controlled. Because sun tourism has very much increased during the very latest decades, its possible effect was not yet seen in this data set. However, it should be seen as a change in SIR estimates in future calendar periods.

The protective role of sun as indicated by primary skin cancer on internal solid cancers is prominent only in the sunny countries. The reason for this discrepancy could be explained by seasonal variations in the effective UV-exposures leading to a high seasonal variation in serum vitamin D concentration in the northern countries as mentioned above. It has been shown that in countries near equatorial areas there is minimal seasonal variation in the serum vitamin D concentration.[41] It has been speculated that the seasonal variation in serum vitamin D might be important in the development of diseases related to vitamin D insufficiency. Our results support this idea. Furthermore, non-melanoma skin cancers were diagnosed at earlier age in the sunny countries than in less-sunny countries suggesting a higher sun exposure.

Conflict of interest statement

There is no conflict of interest.

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