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Previous extensive sun exposure and subsequent vitamin D production in patients with basal cell carcinoma of the skin, has no protective effect on internal cancers

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ABSTRACT

Background: It has been suggested that sunlight through production of vitamin D might have a protective effect on a number of internal cancers. Consequently, in spite of the well known skin cancer risks, some researchers advocate more exposure to ultraviolet radiation, supported by the solarium industry. We estimated the risk of internal cancer before the patient contracted a basal cell carcinoma (BCC) of the skin, the most common cancer in white populations and strongly associated with extensive sun exposure.

Methods: A nested case control study was undertaken in the whole Swedish population. 115,016 patients with BCC and 987,893 controls were linked to population based registers.

Findings: The cases had an increased risk of getting another form of cancer before the BCC diagnosis: odds ratio (OR) = 1.84; 95% confidence interval (CI) 1.81–1.86. This risk was mainly due to skin cancer: OR = 4.95; 95% CI 4.81–5.09 but also non-skin cancer risk was elevated: OR = 1.37; 95% CI 1.35–1.39. We adjusted the estimates for age, level of income, occupational status in national censuses, place of living and sex, where appropriate. Of the cancers specifically suggested to be related to vitamin D status: colon, prostate, breast, and ovary cancer, all had slightly increased ORs whilst for pancreatic and gastric cancer no increased OR was found.

Interpretation: Patients with BCC, a proxy for extensive sun exposure, run an increased risk of other forms of cancer prior to the diagnosis of BCC. The findings in this study contradict that vitamin D production through extensive sun exposure has any protective effect on internal cancer but emphasise the increased risk for skin cancer.

1. Introduction

There is ample evidence and general agreement that excessive exposure to sunlight, by altering DNA, is the most important environmental cause of skin cancer. Basal cell carcinoma (BCC) of the skin is the most common cancer in white populations[1] and its association with sun exposure is well documented.[2–4]

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A number of studies have shown an increased risk for a subsequent cancer after diagnosis of a BCC[5–8] but have been somewhat conflicting. There is little known about the risk of other cancers before the patients develop BCC.[5]

It has recently been suggested that sunlight through production of vitamin D might have a protective effect on a number of internal cancers[9–11] and some groups advocate increasing vitamin D status through more exposure to ultraviolet radiation (UV).[12,13] However, other authors suggest a more critical and balanced view[14] and an international working group reviewing the literature has not recommended any change in vitamin D requirements.[15]

In contrast to other studies[5–7] a specific international study of a large cohort extracted from 13 cancer registries found a decreased risk of vitamin D insufficiency related cancers[8] in skin cancer patients and concluded that vitamin D production in the skin seemed to decrease the risk. However, the decreased risk appeared after the patients had contracted a skin cancer and the period before was not analysed. It is reasonable to believe that patients, after the diagnosis of a skin cancer, have reduced their mean sun exposure according to general advice of sun avoidance/protection and thus instead lowered their vitamin D serum levels. Therefore, the period of the patient's life before the appearance of the skin cancer might be a more adequate period to study with regard to the importance of the vitamin D status. Patients with BCC should then have lower risks for certain internal cancers before they develop skin cancer.

In an effort to test this hypothesis and also to address limitations of the prior works, the current case-control study, nested in the whole Swedish population, was undertaken to examine the association between BCC and other cancers. We used a large number of BCC patients and control patients and employed the public, population-based, and non-insurance-based Swedish health care system and the population-based mandatory and virtually complete national cancer register. The unique personal identification number allowed register linkage. We also adjusted for the patients' and controls' demographics, socioeconomic status, occupation status and place of living in order to get reliable data.

2. Methods

2.1. Ethics

This study was approved by the Regional Ethics Review Board, Stockholm (2009/55).

2.2. Study population

During the years 2004 to 2008 a total number of 115,016 cases of BCC were reported to the Swedish Cancer Registry. We considered a case of cancer to be a BCC for all topography codes between T01000 and T02830 with a histopathology code between M80903 and M80953 (variants of BCC). 17% of the patients had two or more BCC reported to the registry but only the first verified BCC was included in the study. A random selection of age and gender matched controls per case were identified from the Register of Total Population (2004–2008) with the aim to have 10 controls per case. They were further required to be alive and free of BCC at the time of BCC diagnosis of the case. For most cases it was possible to select 10 control subjects but not for all due to limitations of the Swedish population of approximately 9 million citizens. 16,192 of the selected control subjects were also cases and were omitted from the control cohort. After these adjustments the control cohort consisted of 987,893 subjects. For each case (n = 115,016) and control (n = 987,893) information was received from the Swedish Cancer Registry and from the database at Statistics Sweden.

2.3. National registries

All Swedish inhabitants have a unique 12-digit identification number, enabling identification of patients in national registries.

The **National Swedish Cancer Registry** managed by the Swedish Board of Health and Welfare has registered BCC since 2004.[16] According to regulations all pathology and cytology departments in Sweden must report all cases of BCC to the registry. Thus, all diagnoses of BCC in the registry file are based on histopathological examination. In contrast to BCC, the reporting of all other forms of cancer has been mandatory since 1958, not only for the pathologist but also for the treating physician. Thus most cases diagnosed are reported by two sources making the completeness of the register to be close to 100% for all cancers.[17] No figures on the completeness of registration of BCC have been presented up to now.

Statistics Sweden runs a large number of registers covering the whole Swedish population: i.e. historical population register, occupational register, educational and income register. All BCC cases and controls were linked to these registers in order to get information about all other prevalent cancers and socioeconomic data. The register linkages were made at Statistics Sweden and Swedish Board of Health and Welfare and before the database was sent for analysis the personal identification numbers were deleted.

2.3.1. Level of income

Disposable income for each case and control for the year of BCC diagnosis was stratified in three different levels: low; <200,000, middle; 200,000–360,000, high; >360,000 Swedish crowns (SEK). The current exchange rate: 1 Euro = 8.9 SEK.

2.3.2. Occupations

Occupations were classified by a dermatologist (B.L.) into three categories (= type of occupation): primary indoor work, work that combined indoor and outdoor work (mixed) and primarily outdoor work. We employed mainly the codes of ISCO 88 (International Standard Classification of Occupation) on a two digit level giving 60 specific occupations based on six national censuses 1960–1990. Main occupation status at 31–50 years of age could be determined for 93% of the study population.

2.3.3. Geographical regions

The country of Sweden was divided into three geographical regions based on latitude 69–55° and cases and controls were referred to northern (63–69°), middle (59–62°) or southern

(55–58°) part of Sweden according to their home addresses for the year of BCC diagnosis.

2.4. Statistical analysis

All statistical analyses were performed with the SAS® software, version 9.2 for Windows using PROC LOGISTIC. In addition to a crude logistic regression analysis, a model containing age, level of income, place of living, occupational status and gender was analysed. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) based on the model are presented.

3. Results

Characteristics of the cases and the matched control subjects are displayed in Table 1.

The BCC cases had slightly higher income than controls and also lived more often in the south of Sweden. The proportion of indoor and outdoor occupations showed a tendency to more indoor work for cases as compared to controls.

In 24,236 BCC patients a total of 31,221 other cancers and in 118,533 control subjects a total of 133,628 other cancers were found. Table 2 presents the crude and adjusted ORs of other cancers before the diagnosis of the patients BCC for each gender separately. The BCC patients had an overall almost doubled risk of getting an internal cancer before the diagnosis of BCC. This risk was mainly due to increased risk of skin cancer other than BCC (malignant melanoma (MM) and squamous cell carcinoma (SCC)) OR = 4.95 (95% CI: 4.81–5.09). Also the risk of other cancers than skin was elevated: OR 1.37 (95% CI: 1.35–1.39). A number of selected cancers suggested to be associated with the vitamin D status were also separately analysed: colon, prostate, breast and ovary cancer had all a slightly increased OR whilst pancreatic and gastric cancer showed no significant difference between cases and control subjects.

4. Discussion

Our study has the advantage of using individual data on cancer and socioeconomic factors from population-based registries covering the whole Swedish population and it provides estimates on cancer for more than 1.1 million subjects. The results show that various types of cancer are found significantly in excess before the diagnosis of BCC. Specific cancer sites suggested to be related to vitamin D status; colon, breast, prostate and ovary, were also in excess, contradicting the hypothesis that extensive sun exposure through production of vitamin D has a protective effect on these forms of cancer. Patients with BCC at least seem to have no such beneficial effect. In fact the risk of the other more malignant skin cancers MM and SCC was greatly increased, obviously due to prior sun exposure. It is difficult to believe that any positive effect of extensive sun exposure could overwhelm the almost four-folded risk of MM.

Whilst we consider the internal validity of our study to be high, several limitations should be emphasised. The Swedish Cancer Registry started to register BCC in 2004 in contrast to the registration of all other forms of cancer which started 1958. Thus we have no control over the patients' and control subjects' previous history of BCC before 2004. A limited number of control subjects were in fact cases and some of the cases had already had a BCC before the entry in the study and might already have decreased

Table 1 – Distribution of characteristics amongst basal cell carcinoma (BCC) cases and controls.

		BCC cases n = 115,016	Controls n = 987,893
Gender	Females	52.0% (59 860)	53.2% (525 596)
	Males	48.0% (55 156)	46.8% (462 297)
	Total	115 016	987 893
Age	Mean (STD)	70.0 (13.6)	68.9 (13.8)
	Median	71.0	70.0
Age-group	<40 years	2.4% (2 754)	2.7% (27 295)
	40–70 years	45.3% (52 105)	48.5% (478 738)
	>70 years	52.3% (60 157)	48.8% (481 860)
Level of income	Low	50.0% (57 470)	56.1% (554 325)
	Middle	34.1% (39 166)	32.1% (316 734)
	High	15.9% (18 244)	11.8% (116 798)
	Missing	136	36
Occupation	Indoors	50.1% (53 231)	44.8% (400 269)
	Outdoors	4.8% (5128)	7.0% (62 512)
	Mixed	35.5% (37 750)	37.1% (331 756)
	Unemployed	9.6% (10 235)	11.1% (99 190)
	Missing	7.5% (8672)	9.5% (94 195)
Place of living	North	6.7% (7542)	10.4% (103043)
	Middle	39.1% (44183)	40.8% (403146)
	South	54.3% (61389)	48.8% (481704)
	Missing	1902	

Table 2 – Odds ratio (OR) and 95% confidence interval (CI) of other cancers before the diagnosis of basal cell carcinoma (BCC).

		BCC cases n = 115,016	Controls n = 987,893	OR (95%CI) crude	OR (95%CI) adjusted*
Total number of cancers	Females	14 172	67 629	NA	
	Males	17 049	65 999	NA	
	Total	31 221	133 628	NA	
All cancer	Females	11 431 (19.1%)	59 965 (11.4%)	1.83 (1.79–1.87)	1.73 (1.70–1.78)
	Males	12 805 (23.2%)	58 568 (12.7%)	2.08 (2.04–2.13)	1.94 (1.89–1.98)
	Total	24 236 (21.1%)	118 533 (12.2%)	1.96 (1.93–1.99)	1.84 (1.81–1.86)
Skin cancer (MM and SCC)[a]	Females	3578 (6.0%)	6743 (1.3%)	4.89 (4.70–5.10)	4.52 (4.33–4.72)
	Males	5196 (9.2%)	8 087 (1.8%)	5.84 (5.64–6.06)	5.29 (5.10–5.49)
	Total	8774 (7.6%)	14 830 (1.5%)	5.42 (5.27–5.57)	4.95 (4.81–5.09)
All non-skin cancers[b]	Females	8568 (14.3%)	54 312 (10.3%)	1.45 (1.41–1.49)	1.37 (1.33–1.40)
	Males	8828 (16.0%)	52 100 (11.3%)	1.50 (1.46–1.54)	1.37 (1.33–1.40)
	Total	17 396 (15.1%)	106 412 (10.8%)	1.48 (1.45–1.50)	1.37 (1.35–1.39)
Malignant melanoma (MM)	Females	1472 (2.5%)	3543 (0.7%)	3.72 (3.50–3.95)	3.44 (3.23–3.67)
	Males	1724 (3.1%)	3327 (0.7%)	4.45 (4.20–4.72)	3.92 (3.69–4.17)
	Total	3196 (2.8%)	6870 (0.7%)	4.08 (3.91–4.26)	3.69 (3.54–3.86)
Squamous cell carcinoma (SCC)	Females	2191 (3.7%)	3275 (0.6%)	6.06 (5.74–6.40)	5.56 (5.25–5.89)
	Males	3653 (6.6%)	4898 (1.1%)	6.62 (6.34–6.92)	6.04 (5.77–6.32)
	Total	5844 (5.1%)	8173 (0.8%)	6.42 (6.20–6.64)	5.86 (5.65–6.07)
Lip cancer	Females	95 (0.16%)	187 (0.04%)	4.47 (3.49–5.72)	4.05 (3.14–5.23)
	Males	182 (0.33%)	584 (0.13%)	2.62 (2.22–3.09)	2.60 (2.18–3.09)
	Total	277 (0.24%)	771 (0.08%)	3.09 (2.69–3.55)	2.96 (2.56–3.41)
Prostate cancer	Males	4276 (7.8%)	26,900 (5.8%)	1.36 (1.32–1.41)	1.23 (1.19–1.28)
Breast cancer	Females	3757 (6.3%)	23,045 (4.4%)	1.46 (1.41–1.51)	1.40 (1.35–1.45)
Ovary cancer	Females	332 (0.6%)	2397 (0.5%)	1.22 (1.08–1.37)	1.14 (1.01–1.28)
Colon cancer	Females	758 (1.3%)	5039 (1.0%)	1.33 (1.23–1.43)	1.24 (1.15–1.35)
	Males	759 (1.4%)	4923 (1.1%)	1.30 (1.20–1.40)	1.17 (1.08–1.27)
	Total	1517 (1.3%)	9962 (1.0%)	1.31 (1.24–1.39)	1.21 (1.14–1.28)
Pancreas cancer	Females	20 (0.03%)	117 (0.02%)	1.50 (0.93–2.41)	0.95 (0.52–1.73)
	Males	22 (0.04%)	124 (0.03%)	1.49 (0.94–2.34)	1.05 (0.61–1.79)
	Total	42 (0.04%)	241 (0.02%)	1.50 (1.08–2.08)	1.00 (0.67–1.50)
Gastric cancer[c]	Females	72 (0.12%)	590 (0.11%)	1.07 (0.84–1.37)	0.97 (0.75–1.26)
	Males	121 (0.22%)	945 (0.20%)	1.07 (0.89–1.30)	1.01 (0.83–1.24)
	Total	193 (0.17%)	1535 (0.16%)	1.08 (0.93–1.26)	1.00 (0.85–1.17)
Malignant lymphomas[d]	Females	423 (0.7%)	1653 (0.3%)	2.26 (2.03–2.51)	2.04 (1.82–2.28)
	Males	633 (1.2%)	2043 (0.4%)	2.62 (2.39–2.86)	2.42 (2.20–2.66)
	Total	1056 (0.9%)	3696 (0.4%)	2.47 (2.30–2.64)	2.25 (2.10–2.42)

* Estimates adjusted for age, level of income, occupation and place of living (and sex for total).
[a] ICD7; diagnosis 190 or 191.
[b] ICD7; other diagnosis than 190 or 191.
[c] ICD7; diagnosis 150 or 151.
[d] ICD7; diagnosis 200, 201 (Hodgkin's disease) or 202.

their sun exposure due to that fact. This caused some overlapping of cases and controls but in our opinion this effect only tends to underestimate the differences between cases and controls found in this study and does not interfere with the conclusions of the study.

Also, we have no figures on completeness of the BCC register. However, we find no reason to believe that the pathology and cytology departments report BCC to the authorities in a different way than other forms of cancer. The reporting is performed automatically via the histopathology code.

Furthermore, there is a risk of surveillance bias. Patient with cancer see a doctor often and the possibility to discover another cancer i.e. BCC increases. However, we consider that risk to be low and do not believe that this bias has any major impact on the results. Independently if they are cancer patients or not they are able to spot a BCC themselves without any help from a physician.

Our results might also have been affected by a generalised carcinogenic role of some of the BCC risk factors and by rare inherited cancer susceptibility syndromes such as nevoid basal cell syndrome.[7] Theoretically, this might at

least partly explain the increased risk of cancer prior to the BCC diagnosis. However, the magnitude of the risk of skin cancer found in this study, a five folded increase, before contracting a BCC and the absence of any protective effect on any internal cancer lead to the conclusion that this weakness has not had any major impact on the result. Furthermore, there might be a systemic immunosuppressive effect of the previous sun exposure to explain the increased risk of internal cancer.[18]

Lastly we have no information on serum levels or oral intake of vitamin D and further no information on risk factors for BCC as skin type. However, we consider BCC to be a good proxy for the patients' prior sun exposure. Therefore, we hypothesised that BCC patients have a higher mean sun exposure and a higher vitamin D serum level than the average population and tested the hypothesis that these patients have a decreased risk of internal cancer specifically vitamin D insufficiency-related cancers. In contrast to all other previous studies, except for our own,[5] we looked at the period prior to the diagnosis of BCC. The patients' most extensive sun exposures should appear before the diagnosis of a skin cancer and not after and BCC is the disease of the elderly. The largest study that concludes that vitamin D production in the skin seems to decrease the risk of several solid cancers was a register study of cancer cases extracted from 13 cancer registries.[8] However, this effect was only seen in sunny countries (Australia, Singapore and Spain) and not in less sunny countries (Canada, Denmark, Finland, Iceland, Norway, Scotland, Slovenia and Sweden) and only after contracting a skin cancer. There are a number of limitations of that study: the heterogeneity in risks in different populations, confounding by socioeconomic status and specific cancer registry characteristics such as under- or over-reporting might have an impact on the results.[19] A decreased risk of internal cancer might also be the result of the patients decreased sun exposure e.g. after contracting a skin cancer if there is a systemic immunosuppressive effect of sun exposure. This could perhaps be an explanation of the decreased risk of internal cancer after contracting a skin cancer in sunny countries reported in that study[8] but the results are not in line with other epidemiological studies that have reported increased risks of a variety of cancers following an initial diagnosis of BCC.[5–7]

Patients with nevoid basal cell syndrome who often practise stringent photo protection because of their genetic predisposing to BCC may be at increased risk for vitamin D deficiency.[20] Thus, this group of patients may require supplementary intake of oral vitamin D. It has also been observed an increased BCC risk with higher prediagnostic serum vitamin D levels.[21] This indicates that the carcinogenic effects of the amount of UV exposure that leads to high serum vitamin D levels overwhelm any possible protective effect of vitamin D noted *in vitro*.

In conclusion, this study does not support the hypothesis that vitamin D production through sun exposure has a protective effect on cancer development.

Conflict of interest statement

None declared.

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