Assessment of sun-related behavior and serum vitamin D in basal cell carcinoma: Preliminary results

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Abstract. Ultraviolet radiation (UV), mainly from sunlight, is the main risk factor of the most common human skin cancer, basal cell carcinoma (BCC). A positive effect of UV on the skin is its contribution to the synthesis of vitamin D, which is important in sustaining general health, but having high levels of vitamin D is considered a risk factor for BCC. However, vitamin D receptor has antagonistic effects to UV radiation in regulating Sonic Hedgehog pathway. This is a pilot study aimed at characterizing the sun-related behavior and vitamin D status of 52 BCC patients and 59 controls from our geographical area. Patients were included in 4 subgroups: Single, multiple, recurrent, and both multiple and recurrent BCCs. Patients, more than controls, had at least one sunburn in childhood and lentigines (P<0.001). Also, they spent daily, on average, more time in the sun than controls (P<0.001) (3.00-8.00 and 1.50-4.00 h respectively). Outdoor work was similar in both groups. Participants had lower vitamin D serum levels than expected. Due to the small number of cases, no statistically significant differences were found between the subgroups but some tendencies were noted. Patients with only one recurrent BCC had less sunburns than the ones who also developed tumors at multiple sites (P=0.2). Patients with multiple and recurrent tumors had slightly lower vitamin D levels compared with single BCC patients (P=0.1) although they used more vitamin D supplements after the BCC diagnosis (P=0.2). Having a diagnosis of BCC, made patients more compliant to the use of sunscreen cream, but even so, half of them still did not use it. In conclusion, more effort should be invested in sun-related education and public health actions should focus on vitamin D deficiencies.

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Abbreviations: BCC, basal cell carcinoma; UV, ultraviolet; VDR, vitamin D receptor; Shh, Sonic Hedgehog; BMI, body mass index; SPF, solar protection factor; CMIA, chemiluminescent microparticle immunoassay

Key words: basal cell carcinoma, multiple basal cell carcinoma, local neoplasm recurrences, ultraviolet radiation, vitamin D

Introduction

Basal cell carcinoma (BCC) is the most frequent malignancy in Caucasian population. Its incidence is increasing by 1/100,000 person per year in mainland Europe, although many cases are probably not reported (1). The diagnosis is mainly clinical, with aid from dermoscopy and confocal microscopy, but the histopathological examination remains the gold standard (2-4).

The most important risk factor for BCC is ultraviolet (UV) radiation, either natural or artificial. Moreover, light skin types (Fitzpatrick I,II) which are predisposed to sunburns are more prone to develop keratinocyte derived cancer according to the World Health Organization in 2006 (5). Thus high altitude, low latitude and outdoor work are consequent risks (1). Personal habits such as clothing or choice of outdoor activities also determine increased UV exposure (6). Other independent factors involved in UV exposure are increased life expectancy, ozone depletion, genetic alterations (6) also accidental exposure, and UV radiation used for treating different skin conditions (e.g. Psoriasis, dermatitis, etc.).

Alcohol intake, smoking and body mass index are indicators of low health interest more than a risk factor for BCC. As associated comorbidities with BCC, immunosuppression and other sun related diseases are mentioned (7). Arsenic is a recognized risk factor for non-melanoma skin cancers, both BCC and squamous cell carcinoma. In Romania, groundwater levels of arsenic are high near the border with Hungary, as well as in small towns of Arad, Bihor and Timis counties (8).

Also, in the etiopathogenesis of BCC the alpha and beta-HPV (human papilloma virus) could have an implication (9,10).

A beneficial effect of UV radiation on the skin is its contribution to the synthesis of vitamin D. In the skin, 7-dehydrocholesterol is transformed to pre-vitamin D while exposing the skin to sunlight. Afterwards it is converted to vitamin D by a heat-dependent process (11). The role of vitamin D seems to be important in aspects of general health such as immunity, chronic diseases and cancer including BCC (12-14) but also a support for athletic performance (15). It was shown that aged skin produces less vitamin D (16). The implication of vitamin D and its receptor in the pathogenesis of BCC is controversial. High levels of vitamin D seem to be a risk factor for BCC (17). However, in patients diagnosed with BCC some studies report high values (18) while other report low levels (19), one explanation could be the differences in vitamin D receptor.

The vitamin D receptor (VDR) is governed by genetic factors (20). VDR of epidermal basal keratinocytes has implications in the pathogenesis of BCC. Two of the major pathways of BCC formation are Sonic Hedgehog (Shh) and Wnt-β-catenin. In null-VDR mice there is possibly an accumulation of intracellular β-catenin leading to proliferation and no differentiation and thus, to BCC formation. UV radiation upregulates Shh pathway, also loss of VDR increases Shh components indicating that VDR might have an antagonistic effect to UV radiation. VDR is most probably protective in the formation of BCC as it may support the regeneration of the skin (21). Vitamin D that is synthetized in the skin can inhibit Shh, whereas dietary vitamin D cannot (22).

Levels of serum 25-OH vitamin D are influenced by UVB radiation, vitamin D intake and vitamin D-related genes. It is rarely found in food (mostly it is present in fatty fish, milk, meat, egg yolks and fortified cereals) (23), so the main source is endogenous by activation of pre-vitamin D3 in the skin in the presence of UVB (20). The indicator of vitamin D status is the level of serum total 25-OH cholecalciferol (sum of D2: Ergocalciferol and D3: Cholecalciferol) (24,25). Vitamin D deficiency is a pandemic (11). In Europe, it is reported from the Nordic countries (26) to Greece in the South (27).

Currently, there is no evidence to our knowledge concerning the implications of vitamin D in patients with special BCC evolution such as multiple recurrent tumors. Therefore, the aim of our study was to characterize the risk factors for the development of BCC in the population of our geographical area, with a special interest in vitamin D levels in patients with single, multiple and recurrent BCCs.

Patients and methods

An observational analytical, transversal, case-control study was performed between November 2017 and March 2018 in the Dermatology Department of Cluj County Emergency Clinical County Hospital (Cluj-Napoca, Romania). The study group was selected from consecutively admitted patients with single BCC, who were then treated by surgery and had a histopathological confirmation, and from patients who were previously treated by surgery and had a histopathologic diagnosis of BCC and had either multiple or recurrent tumors. Patients were included in 4 subgroups: Single, multiple, recurrent, and both multiple and recurrent BCCs. In March 2018, after the characterization of the patient group in terms of sex, age and urban/rural setting, a similar control group was selected from patients presenting themselves for routine consultations to the Dermatology clinic without skin cancer (present or history).

Exclusion criteria. This was based on medical history for both groups: Osteoporosis, organ transplant and HIV infection, acute or chronic liver disease, atopic dermatitis, vitiligo, psoriasis, inflammatory bowel diseases, other cancers, connective tissue autoimmune diseases and chronic wounds.

Signed written informed consent was obtained from all participants. Participants were asked about their sun exposure habits and other risk factors and blood samples for serum level of vitamin D were collected. All the data were collected by the same physician. The study was approved by the Ethics Committee of the Emergency Clinical County Hospital.

Setting. Data regarding age (present age and the age when the first BCC appeared), sex and body mass index (BMI) (calculated as weight in kilograms divided by height in squared meters) was collected. Patients were asked whether they lived most their lives in urban or rural setting (also town, county and altitude), if they have a tendency to develop sunburn and/or tan (Fitzpatrick skin type), their natural hair color when young-light (red/blonde) or dark (brown, black), smoking and alcohol consumption. We also recorded the eye color-light (green/blue), dark (brown) and the presence of freckles.

Sun-related behavior. Patients were asked if they had severe sunburn in childhood (yes/no), if they had outdoor work for more than 5 years, an estimation of number of hours spent outdoors per day and if they used tanning beds. As protective habits they were questioned on the use of SPF cream (always, sometimes or never), and use of SPF cream before the diagnosis of BCC (yes/no). The presence of solar lentigines on anterior or posterior thorax were recorded.

The use of vitamin D supplements before and after the diagnosis of BCC. Serum 25-OH vitamin D levels were determined by chemiluminescent microparticle immunoassay (CMIA) reagent kit 5P02 ARCHITECT 25-OH Vitamin D (Abbott) following standard protocol.

Statistical analysis was carried out using the MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020). Quantitative data were tested for normality of distribution using the Shapiro-Wilk test and were expressed by mean ± standard deviation or median and 25-75 percentiles. Quantitative variables were characterized by frequency and standard deviation. Comparison between groups were carried out using the Mann-Whitney, ANOVA or chi-square test, whenever appropriate. A P-value <0.05 was considered statistically significant.

Results

In total, 101 patients were included in this study, 52 were patients with one or more BCCs and 59 the controls, with no history of skin cancer. The patient group was compared with the control group. The four subgroups (single, multiple,

Table I. Setting: Patients vs. controls.

Features	Patients	Controls	P-value
Sex, n (%)			
Female	23 (44.2)	27 (45.8)	>0.999
Male	29 (55.8)	32 (54.2)	
Age, years[a]	71 (±11.3)	73.1 (±10.4)	0.317
Age of onset, years[b]	66 (55-72)	-	
BMI[a]	27 (±4.12)	29.07 (±6.79)	0.293
Alcohol, n (%)	15 (28.8)	17 (28.8)	>0.999
Smoking, n (%)	6 (11.5)	8 (13.5)	0.973
Altitude, n (%)			
<200 m	8 (15.4)	13 (22.0)	0.550
200-800 m	35 (67.3)	34 (57.6)	
>800 m	9 (17.3)	12 (20.3)	
Fitzpatrick skin type, n (%)			
I/II	17 (32.7)	7 (11.9)	<0.001
II	22 (42.3)	12 (20.3)	
II/III	13 (25.0)	40 (67.8)	
Light hair color, n (%)	14 (26.9)	20 (33.9)	0.556
Light eye color, n (%)	24 (46.2)	14 (23.7)	0.022
Freckles, n (%)	10 (19.2)	6 (10.2)	0.278

[a]Mean ± standard deviation; [b]median (percentiles 25-75). BMI, body mass index.

recurrent, both multiple and recurrent BCCs) were also compared.

Setting. Personal characteristics are presented in Table I. The median age was similar: 71 (±11.3) years for patient group and 73.1 (±10.4) years for the control group. The median age for the incidence of BCC was 66 years (55.0-72.0). Approximately half of the participants in both groups were male (55.8% of the patients vs. 54.2% of the controls). However, only 43% of patients aged <70 years were male vs. 63% of patients >70. Most of the participants in both groups have lived all their life at medium altitude (200-800 m). None of the participants came from the parts of Romania with high arsenic level in the groundwater.

There was a predominance of phototypes I and II in the patient group 39 (75%); the same characteristic was also observed in the single BCC (14/18 patients), multiple BCC (14/21 patients) and multiple and recurrent BCCs (9/9 patients). There were no patients with Fitzpatrick types IV, V or VI.

Sun-related behavior. Sun-related behavior is presented in Table II. Outdoor workers were evenly distributed between the groups, however, the average time per day spent in open air was significantly higher among patients (5.25 h) than controls (3.00 h) (P<0.001) (3.00-8.00 and 1.50-4.00 h, respectively). It was found that having at least one severe sunburn as a child was 3 times more frequent in patients and lentigines were four times more frequent in the study group compared with the control group (P<0.001).

Before having a diagnosis of BCC, only 8% of patients used sunscreen compared with 33.9% of the controls (P=0.005). After the diagnosis, patients were more likely to use sun protection cream occasionally (P=0.04), especially one with a high SPF of 50 compared with controls who used SPF 30 (P=0.019). However, most participants in both groups did not know what type of SPF cream they used.

Before the diagnosis of BCC, vitamin D supplementation was the same as in the control group. In patients with a previous histopathologic diagnosis of BCC, vitamin D supplementation was slightly more common than in controls. Also, patients who had multiple and recurrent tumors used more vitamin D supplements after the diagnosis of BCC (P=0.1) and unfortunately had a lower value of serum vitamin D compared with the single BCC subgroup (P=0.2). Vitamin D values were lower in patients (12.8 ng/ml) compared with controls (14.2 ng/ml) (P=0.1). Insufficient levels (20-30 ng/ml) were found in 16.9% of controls and 9.6% of patients. We found no statistically significant difference in vitamin D levels regarding the skin type, use of SPF or BMI.

Although statistical significance was not reached, we observed some differences between the subgroups (Table III).

Multiple tumors seem to appear more frequently in men. They spend less time outside, 5 h (3-7.5) compared with 7 (3.75-8.5) in patients with single BCC (P=0.9) but have similarly suffered of a severe sunburn as a child. They were more likely to have lentigines on the thorax (P=0.8). Half of the patients in the subgroup of multiple BCC never use SPF cream, similar to single BCC patients.

Patients with only one recurrent BCC were more likely women, with an age of onset lower than the other subgroups. They had less sunburns than those who also developed tumors at multiple sites (P=0.2).

Patients in the subgroup having multiple and recurrent BCCs had lighter phototype and sunburn as children more frequently than patients with single tumors (P=0.1), but the former were more compliant to the use of sunscreen at the time of the study compared with the other BCC subgroups.

Discussion

Basal cell carcinoma is the most common skin cancer in the Caucasian population. According to Wu *et al* (28) in 2015, most BCCs are caused by extrinsic factors, internal mutations not being enough to justify the high incidence. The exposure to the most well-known risk factor, UVB radiation, depends on other factors such as latitude, season, and skin type. The National Institute for Health and Clinical Excellence recommends research in the field of epidemiology of BCC, especially for multiple and recurrent tumors since there is scarce data from current reports (29).

The present study aimed at identifying the factors that might contribute to the development of BCC for the patients who attended our clinic for diagnosis, treatment and follow-up.

Our data revealed that male patients were more frequent than female, similar to a large cohort study in the US (30). A review showed that also in Europe in elderly population there

Table II. Sun-related behavior: Patients vs. controls.

Features	Patients	Controls	P-value
Severe sunburn, n (%)	22 (42.3)	9 (15.3)	0.003
Outdoor work, n (%)	26 (50)	29 (49.2)	>0.999
Average time outside, h[b]	5.25 (3.00-8.00)	3.00 (1.50-4.00)	<0.001
Lentigines, n (%)	38 (73.1)	10 (16.9)	<0.001
SPF before BCC, n (%)			
Yes	4 (8)	20 (33.9)	0.005
No	46 (92)	39 (66.1)	
SPF present, n (%)			
Always	2 (3.8)	5 (8.5)	0.040
Sometimes	25 (48.1)	15 (25.4)	
Never	25 (48.1)	39 (66.1)	
Known SPF, n (%)			
20	1 (5.3)	0 (0)	0.019
30	3 (15.8)	4 (80)	
50	15 (78.9)	1 (20)	
Unkown SPF, n (%)	33 (63.5)	54 (91.5)	
Vitamin D supplements, n (%)	14 (26.9)	6 (10.2)	0.041
Before BCC	6 (11.5)		
Serum 25OH vitamin D, ng/ml[a]	12.8 (±5)	14.2 (±4.2)	0.111

[a]Mean ± standard deviation; [b]median (percentiles 25-75). BCC, basal cell carcinoma; SPF, solar protection factor.

Table III. BCC patients: Subgroups.

Patients BCC	Single	Recurrent	Multiple	Multiple and recurrent	P-value
Sex, n (%)					
Female	8 (44.4)	3 (75.0)	6 (28.6)	6 (66.7)	0.243
Male	10 (55.6)	1 (25.0)	15 (71.4)	3 (33.3)	
Average time outside, h[a]	7 (3.750-8.5)	5 (2.0-9.5)	5 (3-7.5)	4.5 (3-6.75)	<0.001
Fitzpatrick skin type, n (%)					
I/II	4 (22.2)	1 (25.0)	7 (33.3)	5 (55.6)	0.001
II	10 (55.6)	1 (25.0)	7 (33.3)	4 (44.4)	
II/III	4 (22.2)	2 (50.0)	7 (33.3)	0 (0)	
Severe sunburn, n (%)	7 (38.9)	1 (25.0)	7 (33.3)	7 (77.8)	0.002
Lentigines, n (%)	12 (66.7)	3 (75)	17 (81.0)	6 (66.7)	<0.001
SPF present, n (%)					
Always	1 (5.6)	0 (0)	1 (4.8)	0 (0)	0.206
Sometimes	7 (38.9)	2 (50.0)	9 (42.9)	7 (77.8)	
Never	10 (55.6)	2 (50.0)	11 (52.4)	2 (22.2)	
Vitamin D supplements	3 (16.7)	1 (25.0)	6 (28.6)	4 (44.4)	0.076
Serum 25OH vitamin D (ng/ml)[a]	13.8 (±6.5)	11.2 (±4.6)	13.0 (±4.0)	11.0 (±4.0)	0.5

[a]Mean ± standard deviation. BCC, basal cell carcinoma; SPF, solar protection factor.

is a predominance in males with BCC whereas in the young there is a female predominance, similar to our results (31).

The median age in the US cohort study and a Polish study was around 66 years (30,32) corresponding to our patients'

reported age of onset of the disease, but lower than the age of the patients with single BCC at the time of diagnosis. This can be explained by a previous report on Romanian patients mainly because the patients' low educational level regarding skin health and because of a great deficiency in the health system as number of health care providers and their collaborations (33).

Our results showed that patients experienced three times more frequently sunburns as children and presented four times more frequently lentigines compared with controls. An association between BCC and solar lentigines, actinic keratosis, and sunburn before 15 years of age was reported previously (34). Blistering sunburns are associated with an increased risk of basal cell carcinoma (30,35) and there is also a correlation with young age at sunburn (35). In another study, solar keratosis on certain parts of the body were associated with BCC in the same area. The authors regarded solar keratosis as a sign of sun-damaged skin (36).

A higher proportion of patients with multiple tumors who also had recurrent BCC have experienced sunburns as children compared with patients only with recurrent BCC, which underlines the importance of intermittent sun exposure in the development of BCC. This is also supported by Verkouteren *et al* who suggested that a seldom, but intense exposure, to UVR is more likely to cause multiple superficial BCCs (37).

No significant differences between patients were found with multiple and single BCCs in accordance to previous studies from UK (which also recorded: The Fitzpatrick skin type, hours spent in the sun previously in the BCC diagnosis and childhood sunburns) and The Netherlands (37,38). We can assume that bias comes from mal-self-report or the fact that patients with multiple BCC tend to underestimate their exposure before the first diagnosis based on their current sun-avoidance behavior. Interestingly, a study conducted in Australia showed that multiple BCC were associated with male sex and age >60 years rather than the skin type (36). The most rapid development of multiple tumors in a UK study was observed in patients with an initial BCC located on the trunk and superficial as subtype compared with other sites or histologies (38). A Dutch study reported recently that patients who get a first superficial BCC are younger (~5 years), female and have the lesion on the trunk or extremities (37).

Outdoor work, described as continuous sun exposure, was not associated with BCC according to Naldi *et al* (34) but was associated with both BCC and squamous cell carcinoma according to Iannacone *et al* (35). In Spain, nodular BCC appears more frequently in outdoor workers, with no increased risk for superficial BCC (39). However, a study by Surdu *et al* (40) on a similar population to ours showed that natural UV exposure during work was, surprisingly, a protective factor for BCC, especially for light skin types. The authors explained the results through the increased use of protective factors. This result is similar to ours, as outdoor work was as common among patients as it was among controls. However, in our study patients reported that they spent in average more time per day outside (5.25 h) compared with non-BCC patients who spent 3.00 h outside. Unfortunately, the patients generally had a reluctance towards sunscreen use; the difference between our study and the results of Surdu *et al* (40) being probably due to the fact that only a third of the cases in their study came from Romania.

In the current literature, there is a debate whether sunscreen has a protective effect against skin cancer or not. Early studies did not assess the manner the cream was used in daily life. New FDA recommendations try to overcome these deficits by regulations of usage and selling of the creams (41). Recently, it was observed that it does not protect against BCC, but it protects against actinic keratosis and squamous cell carcinoma (42). A large cohort study reports that use of high SPF cream before the age of 25, but not after, protects against BCC (43). In our study, before having a diagnosis of BCC, only one tenth of patients used sun protection cream compared with one third of the non-BCC patients. Thus, SPF cream seems to have a protective effect. However, after the diagnosis, half of the patients still did not use SPF. The results are similar to that of a study in South Africa where 83% of the participants who presented themselves for a first non-melanoma skin cancer and 50% of the cases with previous non-melanoma skin cancer did not use sunscreen (44).

Vitamin D. Like BCC, vitamin D also depends on UV radiation. However, it is deficient even in countries with abundant sunlight such as in Southern Europe or Lebanon, so nutrition policies and fortified food should be taken into consideration also in these areas, not only in those with lower UV exposure (27,45,46). Unfortunately, dietary sources of vitamin D such as fatty fish and enhanced cereal or dairy products (13) are not yet commonly found or affordable by the elderly population in Romania. Moreover, exogenous vitamin D seems not to inhibit the Shh; (22) however, a recent study observed that supplementing patients with low vitamin D levels in order to keep it above 25 ng/ml can reduce the recurrence rate of tumors with negative margins (47).

Another factor that greatly influences the circulating level of 25OH vitamin D is latitude. In the United States, above 42.2˚N there is no production of vitamin D from November to February, whereas at 35˚N there is production of it all year long (48). A recent study on US medical students also shows a significant difference between values at 27˚N (Florida), 34.5 ng/ml, and 42˚N (Pennsylvania), 28.1 ng/ml, in February-March, with higher levels been recorded closer to the Equator (49).

Romania is located between 43.4˚N and 48.1˚N, and study focused on the seasonal influence of the vitamin D found that in Romania the lowest values are recorded in March-April (50). In a previous study, patients aged 60-89 years had mean vitamin D levels of ~22-29 ng/ml, and 65-70% of them had values above 20 ng/ml (51). Participants in our study were from 46-47˚N and were tested in November-March, so within the lowest levels. The median value of vitamin D in controls was 14.2 ng/ml, and just 17% had >20 ng/ml, similar to previous studies.

The relation between BCC and the level of vitamin D is controversial. We found in literature, in a meta-analysis, that higher levels of vitamin D increase the risk of having a BCC in the subsequent years (17). The observation was based on studies that addressed the baseline value of vitamin D and used a prospective model all reporting sun exposure as a cofounding factor (52-54). However, retrospectively, in US,

in patients from 32˚N to 45˚N latitude, a higher value of vitamin D was associated with a lower chance of having a history of BCC (55).

Once the patient presents with BCC, a Polish study that assessed vitamin D receptor polymorphisms showed that the level of vitamin D is significantly lower than the value of the controls (24.2 ng/ml, 35.4% having <20 ng/ml vs. 29.5 ng/ml, 10.9% having <20 ng/ml) (19). This result is similar to ours, although both the control and BCC groups had lower values that the ones observed in Poland, probably because they collected blood in April-May when vitamin D levels are higher while we tested in winter months. Another possible explanation is the difference in the affinity of the vitamin D receptor.

Season also has an influence even closer to the Equator, at 33˚S, in South Africa, ~50% of the patients with BCC and/or squamous cell carcinoma had levels below 20 ng/ml, and over 90% were below 30 ng/ml, also having a considerable seasonal variation (44).

As vitamin D comes mainly from the skin production under UV radiation, the question of sufficient vitamin D production when using SPF creams appears. Literature presents conflicting results. However, recent studies show that a correct use of SPF 15 with high UVA protection over a week of sun exposure can lead to increase in the vitamin D levels and also protect from sunburn (56). Physicians and researchers from Sunscreen Summit Policy Group from Australia and New Zealand recommend using sunscreen on a daily basis, when the forecast predicts UV index of 3 or greater, also they will consider the changes in the vitamin D status after this policy (57).

A study regarding the adherence of Australians to sun-protective behavior was conducted between 2007 and 2012. They observed that sunglasses and sunscreen were the preferred methods and the general population used them for >4.1 and 3.6, respectively on a scale of 1 (never) to 5 (always) (58).

In this study, the use of SPF cream was increased in the patients having a previous BCC clinical diagnosis compared with the patients in the control group. However, half of the participants still did not use sunscreen even after a BCC diagnosis and having received instructions from a dermatology specialist. As shown before, solar protection cream seems not impair the vitamin D status (vitamin D deficiency having a high media impact in recent years). Therefore, more effort should be invested in the education of the patients, especially in the young population where healthy behaviors are easier to be implemented, regarding the awareness of sun effects and reducing sun exposure. The easiest start could be by stimulating the use of sunglasses and sun creams on a daily bases during summer days, also hiding in the shade and use of protective clothes when the UV index is high. This can be done by the general practitioner, any health professional and in public health campaigns.

Also, public health should take notice of the high prevalence of vitamin D deficiency in the adult Romanian population as frequently presented by previous studies (50,51).

This study's limitations are the small number of cases and the fact that we did not take into account the localization of the BCCs. However, these are the first observations regarding the level of vitamin D and the risk factors for BCC in Romanian patients, especially for the multiple and recurrent tumors.

In conclusion, this is the first study to address the vitamin D serum levels and the sun-related behavior in Romanian patients with basal cell carcinoma. There is a lack of awareness regarding sun protection among more than half of the citizens included in this study. Vitamin D is more deficient than expected in the population attending due to skin diseases. Further studies should address the status of vitamin D in BCC patients after some years of health policies in improving the vitamin D status.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CV, LU, SCS and MCM contributed to the design of the study and were responsible for the literature research and the manuscript preparation. CV, LU, CIB, SCS, RC, MCM and SCV contributed to the design of the study, data collection, literature research, manuscript preparation, and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Emergency Clinical County Hospital (Cluj-Napoca, Romania). Signed written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Lomas A, Leonardi-Bee J and Bath-Hextall F: A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 166: 1069-1080, 2012.
2. Lupu M, Caruntu C, Popa MI, Voiculescu VM, Zurac S and Boda D: Vascular patterns in basal cell carcinoma: Dermoscopic, confocal and histopathological perspectives. Oncol Lett 17: 4112-4125, 2019.
3. Ilie MA, Caruntu C, Lupu M, Lixandru D, Tampa M, Georgescu SR, Bastian A, Constantin C, Neagu M, Zurac SA and Boda D: Current and future applications of confocal laser scanning microscopy imaging in skin oncology. Oncol Lett 17: 4102-4111, 2019.

4. Lupu M, Popa IM, Voiculescu VM, Boda D, Caruntu C, Zurac S and Giurcaneanu C: A retrospective study of the diagnostic accuracy of in vivo reflectance confocal microscopy for basal cell carcinoma diagnosis and subtyping. J Clin Med 8: 449, 2019.
5. Small J, Barton V, Peterson B and Alberg AJ: Keratinocyte carcinoma as a marker of a high cancer-risk phenotype. Adv Cancer Res 130: 257-291, 2016.
6. Leiter U and Garbe C: Epidemiology of melanoma and nonmelanoma skin cancer - the role of sunlight. Adv Exp Med Biol 624: 89-103, 2008.
7. Reinau D, Surber C, Jick SS and Meier CR: Epidemiology of basal cell carcinoma in the United Kingdom: Incidence, lifestyle factors, and comorbidities. Br J Cancer 111: 203-206, 2014.
8. Neamtiu I, Bloom MS, Gati G, Goessler W, Surdu S, Pop C, Braeuer S, Fitzgerald EF, Baciu C, Lupsa IR, *et al*: Pregnant women in Timis county, Romania are exposed primarily to low-level (<10 μg/l) arsenic through residential drinking water consumption. Int J Hyg Environ Health 218: 371-379, 2015.
9. Iannacone MR, Gheit T, Waterboer T, Giuliano AR, Messina JL, Fenske NA, Cherpelis BS, Sondak VK, Roetzheim RG, Ferrer-Gil S, *et al*: Case-control study of cutaneous human papillomavirus infection in basal cell carcinoma of the skin. J Invest Dermatol 133: 1512-1520, 2013.
10. Rotaru M, Iancu G, Mihalache M, Anton G and Morariu S: α-HPV positivity analysis in a group of patients with melanoma and non-melanoma skin cancers. Rev Rom Med Lab: Dec 30, 2014 (Epub ahead of print). doi: https://doi.org/10.2478/rrlm-2014-0044.
11. Holick MF and Chen TC: Vitamin D deficiency: A worldwide problem with health consequences. Am J Clin Nutr 87: 1080S-1086S, 2008.
12. Bersani FS, Ghezzi F, Maraone A, Vicinanza R, Cavaggioni G, Biondi M and Pasquini M: The relationship between vitamin D and depressive disorders. Riv Psichiatr 54: 229-234, 2019.
13. Holick MF: Vitamin D deficiency. N Engl J Med 357: 266-281, 2007.
14. Heaney RP: Vitamin D in health and disease. Clin J Am Soc Nephrol 3: 1535-1541, 2008.
15. de la Puente Yagüe M, Collado Yurrita L, Ciudad Cabañas MJ and Cuadrado Cenzual MA: Role of vitamin D in athletes and their performance: Current concepts and new trends. Nutrients 12: 579, 2020.
16. MacLaughlin J and Holick MF: Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 76: 1536-1538, 1985.
17. Caini S, Boniol M, Tosti G, Magi S, Medri M, Stanganelli I, Palli D, Assedi M, Del Marmol V and Gandini S: Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: A comprehensive review and meta-analysis. Eur J Cancer 50: 2649-2658, 2014.
18. Soares AM, Szejnfeld VL, Enokihara MY, Michalany N and Castro CH: High serum 25-hydroxyvitamin D concentration in patients with a recent diagnosis of non-melanoma skin cancer: A case-control study. Eur J Dermatol 28: 649-653, 2018.
19. Lesiak A, Norval M, Wodz-Naskiewicz K, Pawliczak R, Rogowski-Tylman M, Sysa-Jedrzejowska A, Sobjanek M, Wlodarkiewicz A and Narbutt J: An enhanced risk of basal cell carcinoma is associated with particular polymorphisms in the VDR and MTHFR genes. Exp Dermatol 20: 800-804, 2011.
20. Brouwer-Brolsma EM, Vaes AMM, van der Zwaluw NL, van Wijngaarden JP, Swart KMA, Ham AC, van Dijk SC, Enneman AW, Sohl E, van Schoor NM, *et al*: Relative importance of summer sun exposure, vitamin D intake, and genes to vitamin D status in Dutch older adults: The B-PROOF study. J Steroid Biochem Mol Biol 164: 168-176, 2016.
21. Vishlaghi N and Lisse TS: Exploring vitamin D signalling within skin cancer. Clin Endocrinol (Oxf) 92: 273-281, 2020.
22. Bijlsma MF and Roelink H: Skin-derived vitamin D3 protects against basal cell carcinoma. J Invest Dermatol 137: 2469-2471, 2017.
23. Spiro A and Buttriss JL: Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull 39: 322-350, 2014.
24. Belbasis L, Stefanaki I, Stratigos AJ and Evangelou E: Non-genetic risk factors for cutaneous melanoma and keratinocyte skin cancers: An umbrella review of meta-analyses. J Dermatol Sci 84: 330-339, 2016.
25. Makris K, Sempos C and Cavalier E: The measurement of vitamin D metabolites: Part I-metabolism of vitamin D and the measurement of 25-hydroxyvitamin D. Hormones (Athens) 19: 81-96, 2020.
26. Itkonen ST, Andersen R, Björk AK, Brugård Konde Å, Eneroth H, Erkkola M, Holvik K, Madar AA, Meyer HE, Tetens I, *et al*: Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries. Scand J Public Health: Jan 9, 2020 (Epub ahead of print). doi: 10.1177/1403494819896878.
27. Dimakopoulos I, Magriplis E, Mitsopoulou AV, Karageorgou D, Bakogianni I, Micha R, Michas G, Chourdakis M, Chrousos GP, Roma E, *et al*: Intake and contribution of food groups to vitamin D intake in a representative sample of adult Greek population. Nutrition 72: 110641, 2020.
28. Wu S, Powers S, Zhu W and Hannun YA: Substantial contribution of extrinsic risk factors to cancer development. Nature 529: 43-47, 2016.
29. Guidance on Cancer Services: Improving outcomes for people with skin tumours including melanoma (update). The management of low-risk basal cell carcinomas in the community: NICE guidance on cancer services update (May 2010). National Collaborating Centre for Cancer, pp57, 2010.
30. Wu S, Han J, Li WQ, Li T and Qureshi AA: Basal-cell carcinoma incidence and associated risk factors in U.S. women and men. Am J Epidemiol 178: 890-897, 2013.
31. Verkouteren JA, Ramdas KHR, Wakkee M and Nijsten T: Epidemiology of basal cell carcinoma: Scholarly review. Br J Dermatol 177: 359-372, 2017.
32. Ciążyńska M, Narbutt J, Woźniacka A and Lesiak A: Trends in basal cell carcinoma incidence rates: A 16-year retrospective study of a population in central Poland. Postepy Dermatol Alergol 35: 47-52, 2018.
33. Vlădescu C, Galan A, Olsavszky V and Scîntee SG: Romanian health system strategic directions for the next decade. Ital J Public Health 6: 21-29, 2009.
34. Naldi L, DiLandro A, D'Avanzo B and Parazzini F: Host-related and environmental risk factors for cutaneous basal cell carcinoma: Evidence from an Italian case-control study. J Am Acad Dermatol 42: 446-452, 2000.
35. Iannacone MR, Wang W, Stockwell HG, O'Rourke K, Giuliano AR, Sondak VK, Messina JL, Roetzheim RG, Cherpelis BS, Fenske NA and Rollison DE: Patterns and timing of sunlight exposure and risk of basal cell and squamous cell carcinomas of the skin - a case-control study. BMC Cancer 12: 417, 2012.
36. Richmond-Sinclair NM, Pandeya N, Williams GM, Neale RE, van der Pols JC and Green AC: Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: A 16-year longitudinal study. Int J cancer 127: 2622-2629, 2010.
37. Verkouteren JAC, Pardo LM, Uitterlinden AG and Nijsten T: Non-genetic and genetic predictors of a superficial first basal cell carcinoma. J Eur Acad Dermatol Venereol 33: 533-540, 2019.
38. Lovatt TJ, Lear JT, Bastrilles J, Wong C, Griffiths CE, Samarasinghe V, Roebuck J, Ramachandran S, Smith AG, Jones PW, *et al*: Associations between ultraviolet radiation, basal cell carcinoma site and histology, host characteristics, and rate of development of further tumors. J Am Acad Dermatol 52: 468-473, 2005.
39. Husein-Elahmed H, Gutierrez-Salmeron MT, Aneiros-Cachaza J and Naranjo-Sintes R: Basal cell carcinoma arising in outdoor workers versus indoor workers: A retrospective study. Cutis 99: 55-60, 2017.
40. Surdu S, Fitzgerald EF, Bloom MS, Boscoe FP, Carpenter DO, Haase RF, Gurzau E, Rudnai P, Koppova K, Févotte J, *et al*: Occupational exposure to ultraviolet radiation and risk of non-melanoma skin cancer in a multinational European study. PLoS One 8: e62359, 2013.
41. Chesnut C and Kim J: Is there truly no benefit with sunscreen use and Basal cell carcinoma? A critical review of the literature and the application of new sunscreen labeling rules to real-world sunscreen practices. J Skin Cancer 2012: 480985, 2012.
42. Perugini P, Bonetti M, Cozzi AC and Colombo GL: Topical sunscreen application preventing skin cancer: Systematic review. Cosmetics 6: 42, 2019.
43. Savoye I, Olsen CM, Whiteman DC, Bijon A, Wald L, Dartois L, Clavel-Chapelon F, Boutron-Ruault MC and Kvaskoff M: Patterns of ultraviolet radiation exposure and skin cancer risk: The E3N-sunexp study. J Epidemiol 28: 27-33, 2018.
44. van Deventer L, Kannenberg SMH and du Toit J: Vitamin D status in adult patients with nonmelanoma skin cancer in Cape Town, South Africa: A cross-sectional study. Int J Dermatol 57: 922-927, 2018.
45. Manios Y, Moschonis G, Lambrinou CP, Tsoutsoulopoulou K, Binou P, Karachaliou A, Breidenassel C, Gonzalez-Gross M, Kiely M and Cashman KD: A systematic review of vitamin D status in southern European countries. Eur J Nutr 57: 2001-2036, 2018.

46. Saad RK, Akiki VC, Rahme M, Ajjour S, Assaad M and El-Hajj Fuleihan GA: Time trends and predictors of hypovitaminosis D across the life course: 2009-2016. Metabolism 105: 154138, 2020.
47. Ince B, Yildirim MEC and Dadaci M: Assessing the effect of vitamin D replacement on basal cell carcinoma occurrence and recurrence rates in patients with vitamin D deficiency. Horm Cancer 10: 145-149, 2019.
48. Webb AR, Kline L and Holick MF: Influence of season and latitude on the cutaneous synthesis of vitamin D_3: Exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. J Clin Endocrinol Metab 67: 373-378, 1988.
49. Leary PF, Zamfirova I, Au J and McCracken WH: Effect of latitude on vitamin D levels. J Am Osteopath Assoc 117: 433-439, 2017.
50. Niculescu DA, Capatina CAM, Dusceac R, Caragheorgheopol A, Ghemigian A and Poiana C: Seasonal variation of serum vitamin D levels in Romania. Arch Osteoporos 12: 113, 2017.
51. Chirita-Emandi A, Socolov D, Haivas C, Calapiș A, Gheorghiu C and Puiu M: Vitamin D status: A different story in the very young versus the very old Romanian patients. PLoS One 10: e0128010, 2015.
52. Eide MJ, Johnson DA, Jacobsen GR, Krajenta RJ, Rao DS, Lim HW and Johnson CC: Vitamin D and nonmelanoma skin cancer in a health maintenance organization cohort. Arch Dermatol 147: 1379-1384, 2011.
53. Liang G, Nan H, Qureshi AA and Han J: Pre-diagnostic plasma 25-hydroxyvitamin D levels and risk of non-melanoma skin cancer in women. PLoS One 7: e35211, 2012.
54. Asgari MM, Tang J, Warton ME, Chren MM, Quesenberry CP Jr, Bikle D, Horst RL, Orentreich N, Vogelman JH and Friedman GD: Association of prediagnostic serum vitamin D levels with the development of basal cell carcinoma. J Invest Dermatol 130: 1438-1443, 2010.
55. Tang JY, Parimi N, Wu A, Boscardin WJ, Shikany JM, Chren MM, Cummings SR, Epstein EH, Bauer DC and Osteoporotic Fractures in Men (MrOS) Study Group: Inverse association between serum 25(OH) vitamin D levels and non-melanoma skin cancer in elderly men. Cancer Causes Control 21: 387-391, 2010.
56. Young AR, Narbutt J, Harrison GI, Lawrence KP, Bell M, O'Connor C, Olsen P, Grys K, Baczynska KA, Rogowski-Tylman M, *et al*: Optimal sunscreen use, during a sun holiday with a very high ultraviolet index, allows vitamin D synthesis without sunburn. Br J Dermatol 181: 1052-1062, 2019.
57. Whiteman DC, Neale RE, Aitken J, Gordon L, Green AC, Janda M, Olsen CM, Soyer HP and Sunscreen Summit Policy Group: When to apply sunscreen: A consensus statement for Australia and New Zealand. Aust N Z J Public Health 43: 171-175, 2019.
58. Koch S, Pettigrew S, Minto C, Slevin T, Strickland M, Lin C and Jalleh G: Trends in sun-protection behaviour in Australian adults 2007-2012. Australas J Dermatol 58: 111-116, 2017.