

Risk Factors for Basal Cell Carcinoma: Results from the Case-control Study

Research Article

Slavenka Janković^{1*}, Nataša Maksimović¹, Janko Janković²,
Milena Ražnatović³, Jelena Marinković⁴, Vesna Tomić-Spirić⁵

¹ Institute of Epidemiology, School of Medicine, University of Belgrade,
Višegradska 26, 11000 Belgrade, Serbia

² Institute of Social Medicine, School of Medicine,
University of Belgrade, 11000 Belgrade, Serbia

³ Department of Dermatology and Venereology,
Clinical Center of Montenegro, 81000 Podgorica, Montenegro

⁴ Institute of Medical Statistics and Informatics,
School of Medicine, University of Belgrade, 11000 Belgrade, Serbia

⁵ Institute of Allergology and Immunology,
Clinical Center of Serbia, 11000 Belgrade, Serbia

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Abstract: The aim of the present case-control study was to assess the risk factors for Basal cell carcinoma (BCC) in the Montenegrin population. The study group was comprised of 100 consecutive patients with a diagnosis of BCC, while the control group consisted of patients who did not present skin cancer and who were individually matched to the cases by sex and age. The increased risk for BCC was associated with: the presence of nevi (odds ratio [OR] = 3.77; 95% confidence interval [CI] = 1.12–12.73), type of skin concerning to burn rather than to tan after repeated sun exposure in childhood or adolescence (OR = 3.14; 95% CI = 1.59–6.18), the skin reaction to burn after two or more hours of sunlight during childhood or adolescence (OR = 4.53; 95% CI = 2.37–8.63), the number of severe and painful sunburns during their lifetime (OR = 3.52; 95% CI = 1.68–7.38), outdoor work during the summer-time (OR = 2.73; 95% CI = 1.00–7.45), occupational exposure to chemicals (OR = 17.89; 95% CI = 2.82–113.52), history of eczema (OR = 4.17; 95% CI = 1.53–11.39), and history of previous BCC (OR = 3.86; 95% CI = 1.40–10.65). Our study confirms the role of environmental and constitutional factors in development of BCC.

Keywords: Basal cell carcinoma • Epidemiology • Risk factors • Skin

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1. Introduction

Basal cell carcinoma (BCC) is the most common cancer observed in the white population worldwide. It is estimated that BCC incidence increases by 5% annually and varies depending on the region in the world [1]. Although the rates remain highest among elderly men, the rates of young women with BCC are increasing [2,3]. An increasing incidence of BCC is in line with the changes in the living style and exposure to various environmental factors.

Exposure to ultraviolet radiation is generally accepted as the major cause of BCC [4-7]. The constitutional characteristics (fair hair, eye and skin color, presence of nevi) also play an important role in the development of BCC [8-9], although the relationship between exposure and host phenotype is still unclear [10]. One recent study suggests that the risk of certain cancers, particularly that of the digestive tract, is increased in first-degree relatives of BCC-patients, and that these findings may indicate a genetic predisposition to both skin and visceral malignancies in this patient group [11].

* E-mail: slavenka@eunet.rs

Table 1. Demographic characteristics of basal cell carcinoma patients and their controls.

Characteristic	Cases (100) N	Controls (100) N	P value†
Mean age (years)			0.99
	<49	13	13
	50-59	14	14
	60-69	27	25
	>70	46	48
Sex			1.00
	Male	52	52
	Female	48	48
Marital status			0.18
	Ever married	92	86
	Never married	8	14
Education			0.25
	None	5	10
	Elementary school	27	34
	Secondary school	51	45
	University	17	11
Occupation			0.31
	Manual	20	24
	Clerical	32	32
	Professional	17	10
	Other	31	34

† χ^2 -test.

The aim of the present study was to assess the risk factors for BCC in the Montenegrin population.

2. Material and Methods

This case-control study involved 100 newly diagnosed cases of BCC and 100 controls. The study was conducted in Podgorica (the capital of Montenegro) in 2006 and 2007. The study group was comprised of histologically confirmed cases of BCC, consecutively diagnosed at the Department of Dermatology and Venereology, Clinical Center of Montenegro. The control group (100 cases) consisted of a sequence of new patients whom spontaneously sought the Dermatology Department at the same time as the BCC cases were seen and did not present skin cancer, but different dermatologic diseases (e.g. fungal, bacterial and viral infections etc.). All the controls were individually matched to the patients for age (± 5 years), and sex.

Only the patients who gave their written informed consent were included in the study. The study was approved by the Clinical Centre's Research Ethics Committee in Podgorica. All participants were interviewed

by using a targeted and detailed questionnaire based on the latest research results in the field. The following data were obtained: basic demographic and behavioral characteristics, such tobacco and alcohol use, hair color, skin color, eye color, nevi and freckle frequencies, skin reaction to sun exposure, history of sunburns, occupational and recreational exposure to sunlight, exposure to chemicals, including insecticides, herbicides and pesticides, radiotherapy in anamnesis, history of acne, seborrhea, psoriasis, eczema and malignant tumors, and history of trauma or constant pressure at skin cancer site.

Three skin types were defined according to the Fitzpatrick classification: light – type I and II, medium light – type III, IV and V, and dark – type VI [12]. Nevus and freckling frequencies were assessed according to charts introduced by Dubin *et al.* [13].

Univariate and multivariate logistic regressions were used for statistical analysis. All variables that independently contributed to the risk of BCC were included in multiple logistic regression analysis. A two-tailed probability value of 0.05 or less was considered significant. The analysis was performed with the Statistical Package for the Social Sciences, SPSS, version 8.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Demographic characteristics of BCC cases and their controls are presented in Table 1.

There were no significant differences between the cases and the controls in terms of age, sex and marital status. The greatest percentage of cases and controls were in the oldest group (>70 years). Cases and controls did not differ in their educational profiles or occupations either. The majority of subjects had secondary school education.

Table 2 presents only statistically significant constitutional and environmental risk factors for BCC in cases and controls according to univariate logistic regression analysis.

In order to estimate the independent unconfounded effect of the potential risk factors, multivariate conditional logistic regression analysis was used. Only statistically significant variables, according to univariate logistic regression analysis (shown in Table 2), were retained in the model, while the others were excluded.

The results of multivariate logistic regression analysis are presented in Table 3.

The increased risk for BCC was associated with: presence of nevi, vacations at the seaside before age 10, from age 10 to 24, and after age 40, the type of skin that burns rather than tans due to repeated sun exposure as a

Table 2. Distribution of basal cell carcinoma cases and controls according to constitutional and environmental risk factors.

Variable	No. of cases	No. of controls	P value	OR† (95% CI)
Natural hair color				
Black	14	23		
Dark brown	20	43		
Light brown	44	26	0.000	1.84 (1.35–2.51)
Blonde	20	7		
Red	2	1		
Skin color				
Dark	6	12		
Medium light	48	55	0.033	1.64 (1.04–2.58)
Light	46	33		
Eye color				
Black	5	15		
Brown	30	42		
Green	35	25	0.006	1.41 (1.10–1.79)
Gray	12	4		
Blue	18	14		
Nevi				
No	7	36	0.000	7.47 (3.13–17.83)
Yes	93	64		
Skin reaction to first sun exposure without protection				
Always burns with no tan	6	5		
Always burns with little tan	52	33		
Sometimes burns and always tans	35	43	0.003	1.75 (1.20–2.55)
Never burns and always tans	7	19		
Skin reaction to 2 or more hours of sunlight as a child or adolescent				
Practically none	8	36		
Some redness only	43	55		
Burn	22	7	0.000	3.72 (2.39–5.79)
Painful burn	19	2		
Painful burn with blisters	8	0		
Lifetime number of severe and painful sunburns on the face or arms				
Never	27	72		
1-2 times	45	24		
3-5 times	24	4	0.000	4.48 (2.74–7.33)
6 or more times	4	0		
Vacations at seaside before age 10				
No	70	82	0.049	1.95 (1.00–1.33)
Yes	30	18		
Vacations at seaside from age 10 to 24				
No	46	64	0.011	2.09 (1.18–3.68)
Yes	54	36		
Vacations at seaside from age 25 to 40				
No	16	38	0.001	3.22 (1.65–6.29)
Yes	84	62		

Table 2. Distribution of basal cell carcinoma cases and controls according to constitutional and environmental risk factors.

Vacations at seaside after age 40				
No	18	35	0.006	2.56 (1.31–5.00)
Yes	82	65		
Type of tan after repeated sun exposure as a child or adolescent				
Practically none	8	3		
Light tan	27	6		
Average tan	51	30	0.000	2.92 (1.89–4.52)
Deep tan	14	61		
Exposure to sunlight out of vacation				
Outdoor work during the summer-time				
No	49	43		
Yes	51	57	0.001	1.26 (1.10–1.44)
Radiotherapy				
No	97	88	0.025	4.41 (1.20–16.14)
Yes	3	12		
Occupational exposure to chemicals†				
No	81	98	0.001	11.49 (2.60–3.93)
Yes	19	2		
History of acne				
No	74	89	0.008	2.84 (1.32–6.13)
Yes	26	11		
History of seborrhea				
No	78	90	0.024	2.54 (1.13–5.69)
Yes	22	10		
History of eczema				
No	63	85	0.001	3.33 (1.68–5.69)
Yes	37	15		
History of previous BCC				
No	94	100	0.001	3.33 (1.68–5.69)
Yes	6	0		

†Odds ratio according to univariate logistic regression estimates.

‡Organic and non-organic solvents and organophosphatic compounds.

child or adolescent, the skin reaction to burn after two or more hours of sunlight exposure as a child or adolescent, the number of severe and painful sunburns during the patient's lifetime, exposure to sunlight due to vacation, outdoor work during the summer-time, occupational exposure to chemicals, history of eczema, and history of previous BCC.

4. Discussion

This study included 100 histologically confirmed BCC cases and 100 controls that were individually matched to the cases by sex and age (± 5 years).

The greatest number of cases and controls in our study were elderly persons, which is in accordance to the

literature data [14,15]. Incidence rates are reported to be higher in men [14], although some authors showed an increase in rates among young women [2–3]. There was no significant difference between cases and controls in terms of sex distribution in the present study, as shown in some other studies [16–17].

Exposure to ultraviolet radiation is the main causative factor in the pathogenesis of BCC [4–5,18–19]. This relationship is complex [5]. Intense intermittent exposure to the sun is associated with a higher risk of BCC when compared to a similar degree of continuous exposure [20].

The risk of BCC is significantly increased by recreational exposure to the sun (e.g. during beach holidays, outdoor work or recreation activities during summer-time) during childhood and adolescence [18].

Table 3. Risk factors for basal cell carcinoma according to multivariate logistic regression analysis.

Variable	Coefficient	SE	P value	OR†	95%CI‡
Presents of nevi	1.33	0.620	0.032	3.77	1.12–12.73
Vacations at seaside before age 10	1.71	0.578	0.003	5.51	1.77–17.11
Vacations at seaside from age 10 to 24	1.81	0.815	0.027	6.09	1.23–30.05
Type of tan after repeated sun exposure as a child or adolescent	1.14	0.346	0.001	3.14	1.59–6.18
Skin reaction to 2 or more hours of sunlight as a child or adolescent	1.51	0.329	0.000	4.53	2.37–8.63
Lifetime number of severe and painful sunburns	1.26	0.378	0.001	3.52	1.68–7.38
Vacations at seaside after age 40	1.34	0.583	0.022	3.82	1.22–11.97
Exposure to sunlight out of vacation	1.91	0.717	0.008	6.75	1.66–27.49
Outdoor work during the summer	1.01	0.512	0.050	2.73	1.00–7.45
Occupational exposure to chemical	2.89	0.943	0.002	17.89	2.82–113.52
History of eczema	1.43	0.513	0.005	4.17	1.53–11.39
History of previous BCC	1.35	0.518	0.009	3.86	1.40–10.65

†Odds ratio; ‡Confidence interval.

According to our results, the BCC cases, in comparison with the control group, spent more time at the seaside during their holidays, and not just during their childhood, but also later in their life (odds ratio [OR] from 3.52 to 6.09). European case-control studies found an association between the risk of BCC and number of hours spent at the beach during vacation [21], lifetime average frequency of beach vacations [16], and number of beach vacations before the age 20 [22]. Leman and McHenry [3] emphasize the importance of solar exposure in childhood and adolescence, but according to the study of van Dam et al [23], the importance of solar exposure continued into adulthood. In the study by Ruiz Lascano et al [24], high recreational sun exposure after 20 years of age was an independent risk factor for BCC.

In the present study, the BCC cases, in comparison with the controls, were significantly more involved in working outdoors during the summer (OR = 2.73), and in exposure to sunlight outside of vacation (OR = 6.75). Outdoor work was identified as the significant risk factor for BCC in several studies [18,21,25–26]. A large US longitudinal cohort study found associations between BCC and the frequency of summertime outdoor activities in swimsuits during adolescence, and the lifetime number of blistering sunburns [23]. In the study conducted by Vlainac et al [16], the BCC cases, in comparison with the controls, were significantly more frequently involved in outdoor working during summer. High solar exposure is the most probable explanation for outdoor work during summer as a risk factor for BCC.

Several studies have shown an importance of the history of severe and painful sunburns as a risk factor of BCC [7,16,18,23,26]. Naldi et al [9] found an association between BCC and childhood sunburns. In

the study conducted by Walther et al [26], history of sunburns 20 years before sporadic BCC was diagnosed and associated with an increased risk for BCC (OR = 3.6). Rosso et al [21] found no association between BCC and sunburns during childhood. A hospital-based case-control study in Italy found no association between BCC and history of sunburn before age 20 [22] either. According to our results, the tendency to sunburn was associated with an increase in risk for BCC, but this association was not an independent one. There was increased risk of BCC for persons who usually burn with no or little tan. Consistent with this, the number of reported severe and painful sunburns on the face and arms was positively associated with the disease, with an adjusted odds ratio of 3.52, implying that even among subjects with tendency to burn, avoidance of sunburn was protective. The joint factors of a burning tendency and a higher number of reported severe and painful sunburns substantially increased the risk of BCC, consistent with their independent effects [27]. In the present study, BCC cases were significantly more likely to have light hair (blonde and red), light eyes (green, blue, gray), and fair skin, but these relations were diminished in the multivariate model. Several studies reported that fair hair, eyes and skin were risk factors for BCC [18,23,28–29].

The association between red or blonde hair and BCC has long been recognized [27], although some studies failed to find this association [30]. The recent study of Zanetti et al [31] confirmed the association between blond hair and BCC. In the study of Walther et al [26], the only phenotypic factor indicating risk of sporadic BCC was that those with red or fair hair color had a higher risk than those with brown or black hair (OR = 4.3). According to the results of Rosso et al [19] and Rocha et al [15], blond and

red hair showed a statistically significant and independent risk increase in BCC. Van Dam *et al* [23] found green, hazel or blue eyes to be a risk factor for BCC. In the study conducted by Vlajinac *et al* [16], BCC cases and controls differ significantly in their eye color, and brown eyes remained as a protective factor. In a Danish study, there were no differences between the BCC cases and controls concerning eye color [8].

Sun exposure and fair skin are well-known risk factors for BCC. White people with skin type I, II, or III have a twenty times higher risk for the development of BCC than Afroamericans [32], and skin type I, II and III was a significant risk factor according to multivariate analysis in the study of Ruiz Lascano *et al* [24]. According to Lear *et al* [29], skin type I (always burns, never tans) has been shown to be a risk factor for the development of BCC. Maia *et al* [30] found light skin colors (types I and II) to be a risk factor for BCC (OR = 2.8), but type III only represents a risk factor when the patient reports a history of intense sunburns.

In the present study, subjects with a light tan after repeated sun exposure as a child or adolescent were more frequently diagnosed with BCC (OR = 3.14). There was an increased risk of BCC (OR = 4.53) for persons who usually have painful burns with blisters after 2 or more hours of sunlight as a child or adolescent.

The number of melanocytic nevi in Caucasians is related to previous exposure to the sun. It is a well-documented major risk factor for cutaneous malignant melanoma [33–34]. Since BCC is also related to exposure to the sun, that is possible that an increased number of melanocytic nevi might be found in BCC patients. Kricke *et al* [28] found that the risk of BCC increased with the number of large nevi ($\geq 5\text{mm}$) on the back. Danish study showed the number of nevi to be a significant risk factor for BCC in females, i.e. the risk increased as the number of nevi increased. Nevi were not a risk factor for BCC in males [8]. According to our results, the presence of nevi was an independent risk factor for the development of BCC (OR = 3.77).

Various chemicals have been associated with the increased risk of BCC. According to Gallagher *et al.* elevated risks of BCC were seen in subjects exposed to fiberglass dust (OR = 2.0) and dry cleaning agents (OR = 4.6) [35]. Exposure to arsenic predisposes to multiple basal cell carcinomas [35]. An increased risk of BCC was observed in psoriasis patients extensively treated with tar, methotrexate, and photochemotherapy [36]. Exposure to chemicals, organic and non-organic solvents, and organophosphate compounds was a risk factor for BCC, as well as the use of tar for cosmetic purposes [16]. In the present study, occupational exposure to chemicals was a risk factor for BCC (OR = 17.89).

There is evidence that the number of patients who develop more than one BCC is increasing [27]. In a meta-analysis by Marcil and Stern, the three year cumulative risk varied between 33% and 77% [37]. This risk seems to depend on the number of lesions present. Patients with truncal tumors seem to be at increased risk of developing further lesions [35]. In the present study, a history of previous BCC was an independent risk factor for the development of a new occurrence (OR = 3.86).

In this study, subjects with atopic eczema were more frequently diagnosed as BCC. We failed to found such correlation in the literature. However, repeated application of the immunosuppressant drugs that have been introduced for the treatment of eczema (specifically of atopic dermatitis) prior to and during UVB exposure resulted in the infiltration of neutrophils and increased myeloperoxidase levels that have been linked with increased BCC development when chronically present in the skin [38].

BCC is undoubtedly a complex disease with a multifactor etiology. There is interplay between genotype, phenotype, and lifestyle factors. Although we are aware that a case-control design is susceptible to recall bias, our findings support the role of environmental factors (sunlight exposure, exposure to chemicals) and constitutional factors (sensitivity of the skin to the sun, presence of nevi, and previous BCC in personal history) in the development of BCC. Since the incidence of BCC and the number of immunocompromised patients who exhibit a higher risk is steadily increasing, further studies are needed. Education, especially about sun avoidance, early tumor detection, and on-time treatment, may help to prevent disease.

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