Risk Factors for Basal Cell Carcinoma

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The aim of this study was to assess the risk factors for basal cell carcinoma (BCC). A case-control study, carried out in two towns in Yugoslavia, comprised 200 BCC cases and 399 controls. For statistical analysis, univariate and multivariate logistic regressions were used. The risk factors found for BCC were: freckling before the age 15, seven or more weeks per year spent at the seaside during holidays (lifetime average), outdoor work during summer-time, occupational exposure to organic and non-organic dissolvents and organophosphatic compounds, use of tar for cosmetic purposes, and previous BCC in personal history. Subjects who tended to burn and not to tan after sun exposure also showed a significantly higher risk for BCC. Brown eyes and history of acne had a protective effect. This study confirmed the role of both constitutional and environmental factors in the development of BCC.

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Basal cell carcinoma (BCC) of the skin is the most common type of cancer in white populations. It is believed that constitutional and environmental factors account for the risk of this tumor. Among the constitutional factors, pigmentary traits, such as light skin and light hair color, blue eyes and prominent freckling as well as a tendency to sunburn easily have been related to the occurrence of BCC in most investigations (1–5). Family history of skin cancer is also found to be a risk factor for BCC (4, 6), and, according to Lindelof et al. (7), other malignant tumors were more frequently present in BCC patients in comparison to the general population.

Among the environmental factors ultraviolet radiation is generally accepted as the most important factor in the development of BCC.

The collaboration between molecular biology and epidemiology has contributed to assessing the potential synergism between environmental and genetic factors, such as the capacity to repair UV-induced DNA damage, in the etiology of non-melanoma skin cancer (8). According to Gailani et al. (9), inactivation of a gene on chromosome 9q22 may be a necessary event for BCC. The mutations in this gene may interfere with factors other than sunlight in a large proportion of tumors. That is, although ultraviolet exposure is critical, many patients develop tumors at less-exposed sites such as the trunk, which may reflect an etiologic contribution of additional environmental agents. And, indeed, many other factors have also been associated with the appearance of BCC: infrared radiation, x–radiation, human papilloma virus, inorganic arsenic, PUVA therapy (psoralens and ultraviolet A radiation), trauma, and depressed immunity (10).

The aim of this study was to assess the role of some suspected risk factors in the occurrence of BCC.

MATERIAL AND METHODS

The study was carried out in two towns (Belgrade and Zrenjanin) in Yugoslavia in 1996–1997. The case group comprised 200 histologically confirmed cases of BCC, consecutively diagnosed at City Departments for Skin and Venereal Diseases. Controls (399 subjects) were selected from among consecutive patients, >30 years old, visiting the same institutions for dermatologic diseases other than cancer, the most frequent being mycotic diseases.

All participants were interviewed by two physicians. The following data were obtained using a questionnaire: basic demographic characteristics, eye color, skin color, hair color, mole and freckle frequencies, skin reaction to sun exposure, history of sunburns, occupational and recreational exposure to sunlight, exposure to ultraviolet radiation for therapeutic or cosmetic reasons, exposure to various chemicals including herbicides, insecticides and

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pesticides, radiotherapy in anamnesis, history of acne, seborrhea, psoriasis, eczema and malignant tumors, tobacco and alcohol use, and history of trauma or constant pressure at skin cancer site.

Mole and freckling frequencies were assessed according to charts introduced by Dubin et al. (11). For statistical analysis, univariate and multivariate logistic regressions were used.

RESULTS

The demographic characteristics of the cases and controls are presented in Table 1.

The study group comprised 61% males and 39% females, 13% of whom were < 50 years of age, 16% were in the age group 50–59 years, 31% in the age group 60–69 and 40% were 70 or more years old. The youngest case was 32 and the oldest 90 years old. Age and sex distribution, marital status, formal education and occupation of cases and controls were similar.

Distributions of postulated risk factors for BCC in cases and controls are presented in Table 2.

All variables which, according to univariate logistic regression analyses, were related to BCC at the level of $p \leq 0.10$, entered the model for multivariate logistic regression analysis, the results of which are presented in Table 3. Risk factors found for BCC were: freckling before the age 15, seven or more weeks per year spent at the seaside during holidays (lifetime average), outdoor work during summer-time, occupational exposure to various chemicals (organic and non-organic dissolvents and organophosphatic compounds), use of tar for cosmetic purposes and previous BCC in personal history. Subjects who tended to burn and not to tan after exposure to sun also showed a significantly higher risk for BCC. Brown eyes and history of acne had a protective effect.

DISCUSSION

Previous studies have shown that BCC cases were significantly more likely to have blue eye color, light hair color (especially red) and light skin (1–4). In our investigation cases and controls significantly differed in their eye and skin color, but only brown eyes remained as a protective factor when other factors were accounted for.

Association between freckling in childhood and BCC, found in the present study was already reported by some authors (2, 4, 5). In Hogan et al.'s study (4) prominent freckles in childhood were the most important phenotype risk factor for BCC. Freckling is a well-established risk factor for melanoma and may be a marker for UV radiation damage to the skin (2).

In the present study, the risk for BCC was increased (odds ratio being 4.3) in subjects who tended to burn and

Table 1

Demographic characteristics of BCC cases and their controls

Variable	BCC cases (n = 200)		Controls (n = 399)	
	No	%	No	%
Age				
≤49	25	12.5	53	13.3
50–59	35	17.5	61	15.3
60–69	68	34.0	118	29.6
≥70	72	36.0	167	41.8
Sex				
Men	124	62.0	239	59.9
Women	76	38.0	160	40.1
Formal education				
Elementary school	71	35.5	144	36.1
Secondary school	71	35.5	159	39.8
University	58	29.0	96	24.1
Marital status				
Single	7	3.5	16	4.0
Married	143	71.5	264	66.2
Divorced	7	3.5	19	4.8
Widowed	43	21.5	100	25.0
Occupation				
Agriculture worker	26	13.0	69	17.3
Industrial worker	35	17.5	77	19.3
Trade and service sector worker	32	16.0	64	16.0
Administrative worker	26	13.0	44	11.0
Professional	50	25.0	71	17.8
Other	31	15.5	74	18.5

Table 2

Distribution of postulated risk factors for BCC in cases and in their controls

Variable	BCC cases (n = 200)		Controls (n = 399)		p-value*
	No.	%	No.	%	
Hair color					
Dark	167	83.5	349	87.5	
Blond/Red	33	16.5	50	12.5	0.1861
Skin color					
Dark	13	6.5	57	14.3	
Medium light	101	50.5	223	55.9	
Light	86	43.0	119	29.8	0.0002
Eye color					
Brown	4	2.0	48	12.0	
Hazel	88	44.0	171	42.9	
Green, grey	67	33.5	123	30.8	
Blue	41	20.5	57	14.3	0.0013
Nevus density					
None or slight	168	84.0	360	90.2	
Moderate	25	12.5	31	7.8	
Heavy	7	3.5	8	2.0	0.0930
Freckle density					
None	163	81.5	354	88.7	
Slight	27	13.5	32	8.0	
Moderate	9	4.5	8	2.0	
Heavy	1	0.5	5	1.3	0.0430
Freckles before age 15	24	12.0	19	4.8	0.0017
Skin reaction to sun exposure					
Usually burns with no or little tan	78	39.0	91	22.8	
Never or rarely burns and always tans	122	61.0	308	77.2	0.0009
Sunburn pain (lifetime)	67	33.5	67	16.8	0.0000
Sunburn pain before age 15	24	12.0	21	5.3	0.0041
No. of vacations at seaside before age 10					
0	162	81.0	307	76.9	
1–4	21	10.5	41	10.3	
5–9	17	8.5	51	12.8	0.5599
No. of vacations at seaside from age 10 to 23					
0	131	65.5	245	61.4	
1–9	38	19.0	84	21.1	
10+	31	15.5	70	17.5	0.7578
No. of vacations at seaside from age 24 to 39					
0	79	39.5	154	38.6	
1–10	73	36.5	176	44.1	
11+	48	24.0	69	17.3	0.2910
No. of vacations at seaside after age 40					
0	112	56.0	228	57.1	
1–10	57	28.5	156	39.1	
11+	31	15.5	15	3.8	0.0198
Average number of weeks per year spent at seaside during vacation					
0	47	23.5	125	31.3	
1–6	34	17.0	267	66.9	
7+	19	9.5	7	1.8	0.0010
Outdoor work during summer	22	11.0	9	2.3	0.0000
Outdoor sports and recreation	46	23.0	59	14.8	0.0133
Use of sun-protective cream	35	17.5	58	14.5	0.3455
Ultraviolet radiation for therapy purposes	6	3.0	11	2.8	0.5047
Ultraviolet radiation in solarium	1	0.5	–	–	0.5524
Radiotherapy	21	10.5	12	3.0	0.0004
Occupational exposure to chemicals**	37	18.5	21	5.3	0.0000
Previous BCC in personal history	24	12.0	2	0.5	0.0000
History of					
Acne	14	7.0	65	16.3	0.0021
Seborrhea	9	4.5	23	5.8	0.5174

Table 2 *Continued*

Variable	BCC cases (n = 200)		Controls (n = 399)		p-value*
	No.	%	No.	%	
Eczema	16	8.0	30	7.5	0.8348
Psoriasis	9	4.5	9	2.3	0.1366
For cosmetic purposes use of					
Tar	6	3.0	3	0.8	0.0484
Arsenic	2	1.0	3	0.8	0.7537
Mineral oils	2	1.0	1	0.3	0.2571
Current smoker	40	20.0	73	18.3	0.6152
Former smoker	93	46.5	163	40.9	0.2075
Use of alcohol	78	39.0	162	40.6	0.7061

*According to univariate logistic regression analysis.
**Organic and non–organic dissolvents and organophosphatic compounds.

not tan after sun exposure. In the multicenter south European study 'Helios' (1), subjects who always burn and never tan showed an adjusted odds ratio of 2.7. A history of sunburns was associated with an increased risk for BCC in several studies (1, 2, 4). According to Zanetti et al. (1), although the effect of sunburns, as an indicator of both exposure and sun sensitivity of the skin, is not quite clear, its relationship with BCC suggests, by analogy with melanoma, a relationship with intense sun exposure. Zanetti et al. (1) and Gallagher et al. (2) found that sunburn in childhood, not in adult life, increased the risk for later BCC, suggesting that skin may be more sensitive in childhood to initiation of events that eventually lead to malignancy, but in a study by Wallberg et al. (6), sunburn after the age of 60 was a strong independent risk factor for multiple BCC. In the present study a history of sunburns and a young age at first sunburn were also more frequently reported by cases than by controls, but this association was not an independent one.

Exposure to sunlight is generally accepted to be the most important environmental risk factor for BCC. The incidence of BCC is in correlation with latitude, and occupational and recreational exposure to sunlight has frequently been related to BCC (2, 4). High solar exposure is the most probable explanation for outdoor work during summer time being a risk factor for BCC as found in the present study. Farming (outdoor work) was identified as the most significant risk factor for BCC by Hogan et al. (4). On the other hand, in a study conducted in Finland (12), farmers, forestry workers, and fishermen showed low incidence of BCC, whereas occupations requiring a high level of education or compulsory checkups and medical care occupations seemed to have an increased incidence of BCC. Outdoor occupation was not related to BCC in a study conducted in Australia (13), but this was at least partly explained by significant self-selection among outdoor workers, whereby people with fair or medium complexions and a tendency to sunburn were systematically underrepresented among those in long-term outdoor occupations. In the present study, cases and controls also did not differ in their occupations, but BCC cases in comparison with controls were significantly more frequently involved in farming during summer, as helpers to their relatives. This is in line with the observation that intermittent and intense sun exposure, e.g. during beach holidays, outdoor work or recreation activities during summer-time increase the risk of BCC, while prolonged exposure to sun, as in the case of outdoor occupations, was not associated with BCC (14). Gallagher et al. (2) found a significantly increased risk of BCC in subjects with recreational sunlight exposure in adolescence and childhood. In the 'Helios' study, (1) recreation activities such as sun exposure during holidays at the beach or during water sports were associated with an increased risk for BCC. In the present study outdoor sports and recreation were also more frequently reported by cases than by controls, but this association was not an independent one. Graham et al. (15) and Proper et al. (16) found cumulative lifetime solar exposure to be essential for the occurrence of BCC, but the relationship of BCC to cumulative ultraviolet-B exposure was not confirmed in some other studies (2, 17, 18). In the study conducted by Gallagher et al. (2) even an inverse relationship between lifetime recreational exposure and risk of BCC was found. The most probable explanation of this puzzling finding, given by the authors themselves, was that sun-sensitive case patients substantially decrease recreational sun exposure as adults because of unpleasant experiences with sunburn early in life. Studies from Australia (19) and Canada (2) emphasize the importance of solar exposure in childhood and adolescence, although according to the studies from Italy (14) and the USA (3) the importance of solar exposure continued into adulthood. We did not calculate cumulative lifetime solar exposure, either recreational or occupational, but on average, BCC cases in comparison with the control group spent more weeks per year (lifetime average) at the seaside during their holidays.

In the present study occupational exposure to chemicals, organic and non-organic solvents and organophosphate

Table 3

Factors related to basal cell carcinoma according to multivariate regression analysis

Variable	Odds ratio	95% confidence interval	p-value
Brown eyes	0.09	0.02–0.37	0.0006
Freckling before age of 15	2.65	1.29–5.46	0.0083
Skin reaction to sun exposure: usually burns with no or little tan	4.34	2.27–8.31	0.0000
Average of 7+ weeks per year of seaside vacation	1.81	1.24–2.64	0.0022
Outdoor work during summer	3.95	1.62–9.66	0.0026
Occupational exposure to chemicals	2.97	1.58–5.58	0.0007
Previous BCC in personal history	26.92	5.00–121.0	0.0000
History of acne	0.39	0.20–0.77	0.0067
Use of tar for cosmetic purposes	7.99	1.79–35.57	0.0064

compounds was a risk factor for BCC as well as the use of tar for cosmetic purposes. This is in line with data from some other studies. It is known that mineral oils, tar and arsenic are skin carcinogens (20). An increased risk of BCC was observed in psoriasis patients extensively treated with tar, methotrexate and photochemotherapy (21). Increased risks of BCC were seen in subjects exposed to fiberglass dust and dry cleaning agents (22). The risk of developing a basaloma was also significantly higher in the group of furriers than in the control population, and it is recommended that basaloma be accepted as an occupational cancer in the event of contact with carcinogens among furriers (23).

In the present study a history of previous BCC was a strong risk factor for development of a new occurrence. There is evidence that the number of patients who develop more than one BCC is increasing (6). In particular, patients whose first tumor is truncal are at increased risk of further BCC, which points to a genetic predisposition, as suggested by specific genetic studies (22, 24, 25).

In some earlier investigations it was found that a number of patients with BCC had a history of acne (26) and it was suggested that this connection could partly be attributed to the use of benzoyl peroxide for acne treatment (27). In the present study a history of acne was significantly more frequently reported by controls than by BCC cases, and the protective effect of acne remained after controlling other factors related to BCC. Friedman et al. (28) also found acne vulgaris and seborrheic skin to be protective factors against the development of BCC. There is still no clear explanation for this protective effect. Friedman et al. (28) postulated that ultraviolet radiation absorption by sebum, or anticancer activity of Propionibacterium acnes plays a protective role, but the possibility that some other factors are involved cannot be excluded.

Case-control studies generally rely upon retrospective data, which have their own inherent problems. Records of past exposure may be incomplete or incorrect, but there is no reason to believe that in the present study cases and controls differ in their recall of past events.

In conclusion, our study confirms the role of constitutional factors (pigmentary traits, sun sensitivity of the skin and previous BCC in personal history), and environmental factors (sunlight exposure, exposure to chemicals) in the development of BCC. The protective effect of acne vulgaris on BCC, found in the present study, is of particular interest since such an effect was observed in only one other investigation of BCC.

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