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Multiple Basal Cell Carcinoma

A Clinical Evaluation of Risk Factors

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Basal cell carcinoma (BCC) is the most common malignant skin tumour. There is evidence that the number of patients who develop more than one basal cell carcinoma (mBCC) is increasing. The aim of this study was to elucidate possible risk factors for developing mBCC. Among twelve risk factors considered, skin tumour among relatives was the strongest, with an odds ratio of 10.9 ($p<0.001$). The second strongest risk factor was sunburn after the age of 60, odds ratio 4.4 ($p<0.001$). The results suggest that the presence of skin tumour in the family and sunburn after age 60 are independent factors associated with mBCC. To our knowledge this has not previously been reported. ***Key words: heredity; sunburn; skin cancer; skin.***

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Basal cell carcinoma (BCC) is a malignant skin tumour, which grows slowly in a locally destructive manner. Metastases are extremely rare, a proportion of 0.1% being reported by von Domarus & Stevens (1). The tumour occurs most commonly in elderly people of Caucasian origin and is rare in coloured people (2). The incidence of BCC increased by 3–6% per year in the U.S. population between 1970 and 1978 (3), and in Sweden the incidence has recently been assessed at about 12% annually per 100,000 people 1971–1980 (4); in Malmö 100% in 15 years (5). It is not uncommon that another BCC develops after the first one. Three studies (6–8) have shown that there is a 36–50% excess risk, compared to the general population, of developing additional BCCs after the first one within 5 years. This also accords with our clinical experience, in that many of our patients often return with a new BCC at a different anatomical location. There are few reports on patients with multiple BCC (mBCC) lacking other phenotypic manifestations such as nevoid basal cell carcinoma syndrome (NBCCS), Rombos syndrome or Basex syndrome. However, it has been suggested that patients with mBCC have a certain over-representation of HLA-DR1 (9–11). This has been refuted in a recent study using cDNA-PCR (12). The purpose of the present study was to evaluate clinical risk factors in patients with mBCC.

MATERIAL AND METHODS

Patients

In all, 230 patients living in the southern part of the Stockholm area were interviewed and had a full skin examination. Of these, 110 patients had mBCC and 120 patients served as controls; the mean age was 70 years. Patients with the diagnosis mBCC, defined as two or more BCC in life, were consecutively collected, interviewed and examined in a case control study at the Department of Dermatology, Södersjukhuset, Stockholm. No patients with known syndromes such as NBCCS were included. The interviews were all conducted by P. W. according to a specially designed form concerning suspected risk factors for mBCC, during a one and a half year period in 1992 and 1993. The questions elicited: year of first BCC, skin tumours among relatives (parents and siblings), occupations with more than half the workday outdoors or indoors, respectively, number of years in these occupations (1, 2–5, 6–10, >10), age periods in these occupations set at 10-year intervals (<than 20 years–>60 years), history of severe sunburn (red and painful skin), number of times sunburned (1, 2–5, 6–10, >10), and attitude to sun exposure. Age periods with severe sunburn were set at 20-year intervals (<20 years–>60 years). Skin type was according to Pathak & Fitzpatrick (13): I.) never tan always burn, II.) sometimes tan often burn, III.) often tan sometimes burn, IV.) always tan never burn. Numbers II and III were combined. Eye colour, hair colour as a young adult, freckles as a child and arsenic therapy were also recorded. A complete skin examination, including a punch biopsy, was performed to assess the present number of BCC, or to exclude BCC among the control patients. The anatomic location of all BCC for every patient was depicted on an anatomic chart. The inclusion criterion was two or more histologically verified BCC in life. NBCC or any other well-defined syndrome with mBCC was excluded. A distinction between recurrence (a BCC in contact with the scar after the first tumour) and a new BCC was made on the basis of clinical and histopathological reports. A recurrent BCC was not counted. Control patients were randomly selected from a nearby geriatric hospital and at the departments of dermatology at Södersjukhuset, Stockholm, and Akademiska Sjukhuset, Uppsala. Patients with a past or present history of BCC were not included among the controls. The material was stratified according to 5-year age strata and to sex. Patients' and controls' informed consent was obtained.

Statistics

Unconditional logistic regression was used to compare the parameters between cases and controls univariately and to identify the individual risk factors. Variables significantly associated with risk of mBCC were then subjected to an exact logistic regression (14, 15).

RESULTS

In all, 653 histologically verified BCC were detected among the patients, and the men : women ratio was 1.9 : 1. The material was divided into three categories according to the number of BCC of each patient: 2–4, 5–7, and >7 tumours. The ratios between men and women in these groups were 2 : 1, 1.7 : 1, and 2.3 : 1, respectively. Two hundred and four clinically and 195 histopathologically verified BCC were located in the head and neck region. Correspondingly, 677 clinically and 460 histopathologically BCC affected the rest of the body. No BCC were found on the hands.

Univariate logistic regression analyses with respect to the group with >7 BCC, 30 patients, and the group with 2–4 BCC, 57 patients, were performed. No significant differences

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Table I. *Univariate logistic regression of risk factors among patients and controls*

	Cases % $n=110$	Controls % $n=120$	OR	95% CI	p-value
Male sex	66.40	64.20	1.10	0.64–1.90	0.727
Heredity	19.10	2.50	9.20	2.66–31.80	<0.001
Outdoor work >50%	27.30	37.50	0.63	0.36–1.09	0.099
Sun lover	40.00	35.00	1.24	0.73–2.11	0.434
Indiff. to sun	26.40	29.60	0.85	0.47–1.55	0.855
Skin type I v.s. II/III	26.4 ($n=106$)	29.6 ($n=108$)	0.85	0.47–1.55	0.853
Skin type I v.s. IV	48 ($n=83$)	13.6 ($n=88$)	0.32	0.10–1.04	0.057
Burned age period	Number	Number			
Never v.s. <20	17 v.s. 55	28 v.s. 56	1.62	0.80–3.29	0.183
Never v.s. 21–40	17 v.s. 52	28 v.s. 56	1.53	0.75–3.11	0.242
Never v.s. 41–60	17 v.s. 24	28 v.s. 21	1.88	0.81–4.36	0.140
Never v.s. >60	17 v.s. 8	28 v.s. 0	Infinite	3.12–infinite	0.001
N:o times burned	Number	Number			
0 v.s. 1	17 v.s. 23	28 v.s. 18	2.10	0.89–5.00	0.137
0 v.s. 2–5	17 v.s. 28	28 v.s. 50	1.25	0.60–2.61	0.549
0 v.s. 6–10	17 v.s. 10	28 v.s. 07	2.35	0.75–7.35	0.229
0 v.s. >10	17 v.s. 25	28 v.s. 14	2.94	1.21–7.16	0.018
Arsenic	2.70	2.50	1.09	0.22–5.54	0.915
Freckles	35.5 ($n=107$)	25.8 ($n=120$)	1.58	0.89–2.79	0.114
Hair colour:					
Red, blond, fair v.s. dark, black, grey	24.3 ($n=107$)	31.9 ($n=119$)	0.68	0.38–1.23	0.205
Eye colour:					
blue, green v.s. brown	9.6 ($n=104$)	11.7 ($n=120$)	0.91	0.39–2.15	0.910

Table II. *Exact logistic regression with respect to patients/controls*

Odds ratio (OR) and 95% confidence interval (CI). Competing factors, see Table I. β = regression coefficient, SE = standard error.

Factor	β	SE	p	OR	CI
Heredity	2.3898	0.6364	<0.001	10.9	3.1–38.0
Burned >60	Undefined	Undefined	<0.001	Infinite	1.8-Infinite

in the distribution of risk factors between these groups were detected. The same analysis was run with respect to cases and controls. Two individual risk factors emerged: skin tumour among relatives (heredity) and sunburn after age 60 (Table I). No statistical difference was detected when testing for total number of years of outdoor work, nor could we discover any significant risk of mBCC when testing for attitude to sun exposure, skin type, sunburned or not sunburned, ingestion of arsenic, presence of freckles in childhood, eye colour or hair colour (Table I). A statistical difference with borderline significance was found when testing for number of times sunburned.

The odds ratio (OR) for "heredity" was 10.9 ($p<0.001$) and for "sunburned after age 60" infinite (Table II). It was not possible to assess the OR simultaneously (multiple OR) for "heredity" and "sunburned after 60" since the cases were too few. Among cases of sunburned after the age of 60, only 2/8 (25%) had heredity for BCC. The corresponding ratio among cases not sunburned during this period was 11/91 (12.1%). No statistical difference between these two groups concerning heredity could be detected. Among the cases, 8 persons were sunburned after the age of 60 and among controls, none.

DISCUSSION

We investigated clinical risk factors associated with patients with mBCC. Our results suggest that recorded skin tumour among relatives (parents or siblings) is a strong risk factor associated with mBCC. Hogan et al. (16) found that family history of skin cancer carried a relative risk of developing BCC of 1.22. We have found that patients sunburned after the age of 60 had significantly increased risks associated with mBCC. To our knowledge this has not been reported previously. A popular belief is that BCC is the result of cumulative life exposure to UV radiation. Some recent studies have suggested a different aetiology (18, 19), indicating that sun exposure before the age of 20, and also intermittent sun exposure (19), could be important in the development of BCC. These findings are similar to those for malignant melanoma. Intermittent sun exposure within 10 years before the BCC develops is an increased risk according to Kricker et al. (19). Outdoor work is considered to be another important risk factor for developing BCC (20). Our results do not support this notion, as the number of years of outdoor work had no significant influence on the risk of mBCC. Burned by the sun more than 10 times in life was found to be a significant risk factor, without taking other factors into account. It is well known that the overwhelming majority of BCC are located in the face. In this study we could show that BCC, among patients who developed mBCC, were twice to three times as common on the trunk and extremities, compared to the face. This corresponds very well with our clinical experience.

Sun-sensitive skin as a skin type was not a significant risk factor for mBCC in our study. Neither did we find freckling in childhood, eye colour or hair colour to be significant. Others have reached different conclusions concerning risk factors for

BCC. In one study (21) it was found that only hair colour and freckling in childhood remained appreciably associated with risk of BCC when checking statistically for all the above qualities.

Our investigation does not permit conclusions on prevalence or incidence, but it is possible to identify risk factors for mBCC. The significant ORs found in this study represent excess risk levels. Risk factors for mBCC were detected by regression analysis, so that those with independent power to discriminate between cases and controls were identified. One weakness of an epidemiological study like this is the difficulty that subjects experience in trying to recall details. To overcome this difficulty we designed simple questions. For example we posed the question of total sun exposure as indoor or outdoor work. Another difficulty is recall bias. We consider recall bias (error due to differences in accuracy of recall to memory of prior events) to have had a minor influence in this study, as the controls were also patients. One can assume that the association between sun exposure and risk of skin cancer is common knowledge. The question of assessing sun sensitivity is often subjective and it is difficult to differentiate between patients with skin types II and III. We therefore merged Fitzpatrick's original four skin types into three.

Note that ours is a hospital-based case-control study and not a population-based one. There are four major dermatological clinics and a number of private dermatologists in Stockholm. We have no reason to believe that some patients with mBCC escaped our clinic; rather there was an even distribution of cases between the various clinics. Unfortunately we had to use dermatological patients and geriatric patients as controls, since access to the national demographic register was denied. Approximately 1/4 of the controls were collected in Uppsala, a university town 70 km from Stockholm with a similar type of population. We did not exclude patients with malignant skin diseases other than BCC because had we done so the two groups would not have been comparable.

The results of this investigation somewhat contradict the commonly held view of clinical risk factors for BCC. However, we focused on patients who had developed more than one BCC. Our finding that patients sunburned after 60 years of age might be valid only for this group. One possible explanation could be that the DNA repair system is impaired by approximately 25% in everyone between 20 and 60 years of age (22). This may partly explain why patients who had been burned by the sun after 60 years of age had an increased risk of developing mBCC.

In conclusion, we tried to elucidate risk factors among patients with mBCC. Univariate and exact logistic regression analysis produced two independent risk factors: skin tumour among relatives and sunburn after the age of 60. The clinical relevance of these factors remains to be proved.

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