

Risk Factors Associated with the Occurrence of Basal Cell Carcinoma

Dubravka Šimić¹, Asja Prohić², Mirna Šitum³ and Jasna Zeljko Penavić¹

¹ Clinic for Dermatology and Venerology, University Hospital Mostar, Mostar, Bosnia and Herzegovina

² Clinic for Dermatovenerology, University Hospital Center Sarajevo, Sarajevo, Bosnia and Herzegovina

³ Clinic for Dermatology and Venerology, University Hospital »Sestre milosrdnice«, Zagreb, Croatia

ABSTRACT

Basal cell carcinoma (BCC) is the most frequent malignant skin tumor, which is associated with both genetic factors and environmental influences. The objective of this study was to investigate the risk factors associated with the occurrence of BCC in the inhabitants of the Western Herzegovina area. The study took place during 1997 – 2003. We examined the risk factors which are presumably associated with the occurrence of BCC: skin type, exposure to UV rays and family occurrence of BCC, supplemented by the examination of the skin type, UV rays and existence of malignant tumors amongst the family members. We recorded a high correlation between the type of skin and the risk of occurrence of BCC. Long term and frequent skin exposure to UV rays were also associated with BCC. We also recorded increased risk for BCC in persons whose family members suffered from malignant skin tumors. Avoiding exposure to the sun as well as protection from UV rays may decrease the risk of BCC.

Key words: basal cell carcinoma, risk factors, ultraviolet rays, type of skin, family history

Introduction

BCC is the most frequent malignant skin tumor, and presents 70% of all skin cancers¹. Incidence of BCC is higher in Caucasian people with lightly tanned skin (skin types 1 and 2) than in dark skinned people^{2,3}. Endogenous and exogenous factors play significant role in the occurrence of BCC. The most important exogenous factors are physical factors like UV and ionizing rays, as well as different chemical factors and immunosuppressant. Endogenous factors are genetically inherited skin type and genetic disorder⁴. The basis for the occurrence of BCC increases proportionally to the degree of sun light accumulation, and decreases proportionally to the degree of skin pigmentation. Long term exposure to UV rays can cause a mistake in the reparation processes that, as a consequence, results with irreversible growth of malignant cells. This is why BCC occurs on the areas of skin frequently exposed to sun, or on atrophic scars: lupus vulgaris (carcinoma in lupo), on burns scars, on hypostatic ulcerations of lower extremities, and on the skin with chronic radio dermatitis⁵.

There is no relevant epidemiological data on frequency of BCC in the inhabitants of Herzegovina. Beyond the general statement on frequent BCC in inhabitants of Herzegovina, the real incidence rate was not examined up to date, neither the risk factors which contributed to occurrence of skin tumors were ever examined.

The objective of the study was to establish the risk factors that could be associated with the occurrence of BCC in the inhabitants of Western Herzegovina.

Patients and Methods

Total population under study was 184 318 in the area of Western Herzegovina, in the period from 1997 to 2003. The study was conducted as retrospective and prospective study. The retrospective part of the study contains analysis of all available data relevant to the process of BCC occurrence in the period from 1997 to 2001, while the

prospective part covers the period from 2002 to 2003. Every case of BCC in the selected area was actively monitored.

The following documents were used: medical history, work experience and histological findings from University Hospital Mostar according to which the following indicators were analyzed: sex, occupation, localization.

In every patient diagnosed with BCC on the basis of clinical and histological testing, the following risk factors which, presumably, significantly impact the occurrence of BCC, were tested:

- skin type (data available for 1148 patients)
- exposure to UV rays (data available for 879 patients)
- family history in view of malignant skin tumors occurrence, as well as the occurrence of other malignant diseases amongst the family members, which could have had an impact on the occurrence of BCC (data available for 103 patients)

A χ^2 -test was used in statistical analysis, supplemented by the odds ratio and Fleis quadratic confidence intervals. Statistic program EPI was used in the analysis. Statistical hypotheses were tested with the degree of significance of $p < 0.05$.

Results

During the study, from 1997 to 2003, a total of 1,148 people were diagnosed with BCC. In the retrospective part of the study the total number of patients diagnosed with BCC in the period from 1997 to 2001 was 729, whereas for the prospective part the total number of patients diagnosed with BCC from 2002 to 2003 was 419.

The average cumulative incidence for BCC was 622.83 patients diagnosed with BCC *per* 100,000 inhabitants for the whole research period, i.e. 89 patients diagnosed with BCC *per* year. The occurrence of BCC was more frequent in men, 600 (57.4%), whereas 448 (34.5%) patients were women, so that there is significant statistical difference between the number of people with BCC in relation to sex ($\chi^2=4.17$, $p < 0.05$). The greatest number of patients with BCC was found in persons older than 60 years – 64 (57.8%), whereas the smallest number covered the age group of 40 years old – 5 (0.44%), which shows significant

TABLE 1
EXAMINING HOW THE SKIN TYPE IMPACTS RISK AND PROBABILITY OF THE BCC OCCURRENCE

Research period	Number of patients skin type 1 and 2	Number of patients skin type 3 and 4	Total
1997–2001	509	220	729
2002–2003	298	121	419
Total	807	341	1148
%	70.3%	29.7%	100%

cant polarization between younger and older age groups ($\chi^2=12.13$, $p < 0.01$). With regards to occupation relative frequency in agricultural workers is higher in comparison to relative frequency in other occupations. In retrospective period it was 0.5945 while it was 0.5704 in prospective period, which shows the increased risk in BCC occurrence in agricultural workers. According to localization BCC rarely occurred at the covered part of the body. Statistical data processing showed the existence of unequal occurrence of BCC in relation to the location both in retrospective and prospective part of the research ($\chi^2=11.12$, $p < 0.01$).

The results of the study showed that 807 (70.3%) patients diagnosed with BCC have the skin types 1 and 2, while a lesser rate of patients diagnosed with BCC, 341 (29.7%), have skin types 3 and 4 (Table 1). According to the result, the number of patients with BCC in relation to the skin type has significant statistical difference ($\chi^2=33.10$, $p < 0.001$). The occurrence rate of BCC in persons with skin types 1 and 2 is higher than in persons with skin types 3 and 4, OR=1, 50 with 96% of accuracy. CI at the level of accuracy 0, 05 equals 1.30–1.72, so a conclusion can be drawn that there is a relation between the skin types 1 and 2 and the risk of BCC occurrence.

Out of 879 patients diagnosed with BCC, 696 (79.2%) stated they did different agricultural jobs and were often over-exposed to UV rays (Table 2). The data obtained from the medical history of the patients diagnosed with BCC shows significant statistical difference between the numbers of patients diagnosed with BCC and frequent exposure to UV rays ($\chi^2=29.80$, $p < 0.001$).

Frequent exposure to UV rays and incidence of BCC can be shown by OR=3.81 with statistical level of accuracy

TABLE 2
EXAMINING HOW EXPOSURE TO UV RAYS IMPACTS RISK AND PROBABILITY OF THE BCC OCCURRENCE

Research period	Number of patients diagnosed with BCC with prolonged exposure to UV rays (as per medical history)	Number of patients diagnosed with BCC with occasional exposure to UV rays (as per medical history)	Total
1997–2001	395	101	496
2002–2003	301	82	383
Total	696	183	879
Total %	79.2%	20.8%	100%

BCC – basal cell carcinoma, UV – ultra violet

TABLE 3
EXAMINING HOW GENETIC PREDISPOSITION IMPACTS RISK AND PROBABILITY OF THE BCC OCCURRENCE

Research period	Number of patients diagnosed with BCC with malignant skin tumors in family members (as <i>per</i> medical history)	Number of patients diagnosed with BCC with other malignant diseases in family members (as <i>per</i> medical history)	Total
1997–2001	54	12	66
2002–2003	27	10	37
Total	81	22	103
Total %	78.6%	21.4%	100%

BCC – basal cell carcinoma

of 95%, CI on the level of accuracy of 0.05, so it can be concluded that there is relation of 3.24 to 4.49 to the occurrence of BCC in persons frequently exposed to UV rays.

Based on the data from their medical histories, it was established that 81 patients diagnosed with BCC had family members with the same diagnosis, and 22 patients diagnosed with BCC had family members diagnosed with some other malignant disease (Table 3). The research established that there is a statistical difference in the occurrence of BCC and incidence of malignant diseases in the family of the patients diagnosed with BCC ($\chi^2=8.16$; $p<0.001$), OR=13.00 shows statistical accuracy of 95 % that there is a risk for occurrence of BCC in persons who had family members diagnosed with BCC, and that the risk of BCC occurrence in persons who had family members diagnosed with other malignant diseases is statistically insignificant.

Discussion

BCC is the most frequent malignant skin tumor. Its frequency depends on endogenous and exogenous factors and therefore the percentage of patients diagnosed with BCC varies significantly⁶. According to published statistical data, 25 to 350 inhabitants out of 100,000 are diagnosed with BCC *per* year⁷. The incidence of this tumor is directly dependant on the number of sunny days, i.e. exposure to UV rays. Therefore, it is more frequent in countries with high insolation (number of sunny days). Childhood and adolescence are the critical periods of life for later development of BCC as 80% of UV rays is being absorbed at that age. The remaining 20% is being absorbed at later age. This indicates that timely protection from UV rays may reduce the risk of occurrence of malignant skin tumors. In the period from 1997 to 2003 a total of 1148 patients were diagnosed with BCC, with an average annual incidence of 89 new cases *per* 100,000 inhabitants. The data from our study are similar to the data from some of the neighboring regions. For example, in the Split region, the incidence of BCC is 92 *per* 100,000 inhabitants, and in the central Dalmatian islands 315 *per* 100,000 inhabitants⁸. In the European countries the incidence of BCC is around 20 patients diagnosed with BCC *per* 100,000 inhabitants⁹, in USA 110 *per* 100,000¹⁰, while in Australia it is 788 *per* 100,000 inhabitants,

which is the biggest incidence in the world¹¹. Molecular mechanisms of UV cancer genesis are still not completely understood, although it has been discovered that non-melanoma tumors, one of which basal cell carcinoma is, is provoked by the damaged DNA as a target molecule. Photons of UVB rays damage DNA in the skin cells in the sense that keratin cells become cancer cells. In this process, an important role is given to tumor suppressive gene, or anti-oncogen, a normal cell gene whose physiological role is to regulate the cell growth through control of cell cycle interaction with cell and viral proteins¹². The most common target molecule where genetic mutation takes place in human cancer is p53 tumor, a suppressive gene¹³. Although the precise mechanism in which p53 acts as a tumor suppressive gene is not well known, there is some evidence that p35 acts as a molecule »guardian«, because it prevents multiplication of genetically damaged cells¹⁴. According to Fitzpatrick¹⁵, there are 6 types of skin. The classification was done on the basis of the skin color, minimum erythema dose, resistance to UV rays, occurrence of burns, and degree of skin tanning. In skin types 1, 2, 3, the color of the skin is light, while in type 4 the skin is light brown, type 5 belongs to the skin of red-brown color (Native Americans) and type 6 to the skin of black color. The skin types 1 and 2 belong to very sensitive skin, in which burns easily occur, the skin does not tan, or tan to a very low degree. The skin type 3 is sensitive, with minimal burns after exposure to UV rays and with possibility of tanning, while type 4 is the least sensitive. It is well known that persons with light skin (skin types 1 and 2), with ginger and blond hair and bright colored eyes are more frequently exposed to BCC occurrence^{2,3}. In our research, the majority of patients diagnosed with BCC (70%) belonged to skin types 1 and 2. There is a proven high co-relation between the skin types 1 and 2 and the risk of BCC occurrence. The risk of BCC occurrence increases proportionally to the degree of accumulation of sun light, and decreases proportionally to the pigmentation of the skin¹⁶. Researches show that intermittent sun tanning has significant role in basal cell carcinoma occurrence in young age, especially if burns have occurred at the parts of body exposed to the sun, while the cumulative effect of sun tanning is important for the occurrence of BCC in older age^{17,18}. On the basis of the data in patient's medical history, our study shows that 79% of patients with BCC stated they had been fre-

quently over exposed to UV rays either because of sun tanning, or their occupation, i.e. agricultural jobs. We have also established a pattern of familial relationship with BCC. This targeted epidemiological-clinical research observed occurrence of BCC disease in Western Her-

zegovina and represents contribution to the research in gathering important information on risk factors which are associated with the increasing number of BCC patients in this part of Bosnia and Herzegovina.

REFERENCES

1. MILLER D, WEINSTOCK M, *J Am Acad Dermatol*, 30 (1994) 774.
- 2. OLANZ K, CHANG L, SONG V, SILERIO R, MUNEKOA L, *J Am Acad Dermatol*, 38 (1998) 413.
- 3. LIM HW, COOPER K, *J Am Acad Dermatol*, 41 (1999) 81.
- 4. KRIPKE ML, GLOSSMAN HN, *J Am Acad Dermatol*, 2 (1980) 439.
- 5. TOMA S, LOSAREDO PL, VINCENT M, PALUMBO R, *Eur J Cancer Prev*, 4 (1995) 213.
- 6. BLACK HS, *Cancer Res*, 45 (1985) 6254.
- 7. SUTHERLAND BM, CIMINO JS, DELIHOS N, *Cancer Res*, 40 (1980) 1934.
- 8. STIPIĆ V, VIDOVIĆ R, MAROEVIĆ D, *Acta Derm Jug*, 6 (1979) 231.
- 9. LEFFELL DJ, *J Am Acad Dermatol*, 42 (2000) 18.
- 10. URANO Y, ASANO T, YOSHIMOTO K, IWAHANA H, *I Invest Dermatol*, 104 (1995) 928.
- 11. OUHTIT A, NAKAZAWA WH, ARMSTRONG BK, KRICKER E, TAM E, YAMASAKI H, ENGLISH DR, *J Nat Cancer Inst*, 90 (1998) 523.
- 12. CRAEMER KH, LEE MM, ANDREWS AD, LAMBER WC, *Arch Dermatol*, 130 (1994) 1018.
- 13. KPLING MD, COOK M, *Am Chem Soc*, 25 (1984) 165.
- 14. MADHU A, FITZPATRICK P, FITZPATRICK T, Preventive Treatment of Sunburn, Dermatoheliosis, and Skin Cancer with Sun – Protective Agents. In: FITZPATRICK TB, EISEN KW, WOLF K, FREEDBERG IM, AUSTEEN KF (Eds) *Dermatology in general medicine* (New York, McGraw – Hill, 1993)
- 15. CRESS RD, HOLLY EA, AHN DK, *Epidemiology*, 6 (1995) 538.
- 16. DEDAVID M, ORLOW SJ, PROVOST N, MARGHOUB AA, RAO BK, HUANG CL, WASTI Q, KOPF AW, BART RS, *J Am Acad Dermatol*, 36 (1997) 407.
- 17. ELWOOD JM, *World J Surg*, 16 (1992) 66.

D. Šimić

Clinic for Dermatology and Venerology, University Hospital Mostar, Alojzija Stepinca bb, 88 000 Mostar, Bosnia and Herzegovina.

e-mail: simicdubravka@gmail.com

ČIMBENICI RIZIKA U NASTANKU BAZECELULARNOG KARCINOMA

SAŽETAK

Bazeocelularni karcinom je najučestaliji maligni tumor kože u čijem nastanku značajnu ulogu imaju egzogeni i endogeni čimbenici. Cilj istraživanja bio je utvrditi čimbenike rizika koji bi se etiološki mogli povezati sa nastankom BCC u stanovnika na području Zapadne Hercegovine. Retrospektivnom i prospektivnom studijom, u razdoblju od 1997.–2003. godine ispitivani su čimbenici rizika za koje se pretpostavlja da su etiološki povezani sa nastankom BCC: tip kože, izlaganje UV zračenju i obolijevanje od BCC u obitelji, odnosno, ispitati povezanost između tipa kože, UV zračenja i postojanja zloćudnih tumora kože i ostalih zloćudnih tumora među članovima obitelji i njihov utjecaj na pojavu obolijevanja od BCC. Rezultati su pokazali da postoji povezanost između tipa kože 1 i 2 i rizika pojave obolijevanja od BCC, da dugotrajnije i učestalije izlaganje kože UV zračenju dovodi do pojave obolijevanja od BCC, te da ne postoji rizik obolijevanja od BCC u osoba u kojih su u obitelji postojala maligna oboljenja kože. Kontrolirano izlaganje uz zaštitu od sunčevih zraka mogu smanjiti rizik obolijevanja od bazeocelularnog karcinoma.