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ORIGINAL PAPER

Is Occupational Skin Cancer More Aggressive than Sporadic Skin Cancer?

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ABSTRACT

Background: *Non-melanoma skin cancer (NMSC) represents the most frequently diagnosed cancer in humans. Occupational solar UV radiation exposure is associated with a higher-risk of developing NMSC, but still Romania does not acknowledge this affliction as an occupational disease.*

The study aims to determine if occupationally-induced NMSC is associated with more aggressive clinical and histopathological features compared to sporadic NMSC.

Material and methods: *A retrospective, analytical, comparative study was conducted during 2017-2019 in a University Department of Dermato-venereology in Bucharest, Romania, with focus on patients presenting with NMSC who underwent surgical excision of lesions followed by histopathological examination, classified as outdoor or indoor workers. High-risk clinical and histopathological characteristics were analysed and correlated with outdoor UV exposure.*

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Outcomes: *The study included 51 consecutive patients diagnosed with NMSC, of which 25 outdoor workers (OW) and 26 controls as indoor workers with no occupational UV exposure background. OW presented with 21 BCC and four SCC, while controls with 22 BCC and four SCC. Males were predominant in both groups and most patients came from urban environment. The mean age value was lower for the OW group compared to controls. OW had a 4.66 times higher risk of developing NMSC with aggressive location and size* χ^2 *(1, N=51) = 6.246, p=0.013, OR=4.66 (95% CI: 1.34, 16.23) and a 24-fold risk of developing NMSC with clinically poorly defined margins* χ^2 *(1, N=51) = 21.697, p<0.001, OR=24.44 (95% CI: 5.38,110.92). The risk of developing a high-risk histopathological subtype was 15 times greater for OW* χ^2 *(1, N=51) = 13.814, p<0.001, OR=15.27 (95% CI: 2.94,79.08). Moderate to severe desmoplastic reaction was 8.57 more frequent in controls* χ^2 *(1, N=51) = 12.244, p=0.001, OR=8.57 (95% CI: 2.42, 30.30). Grades 2 and 3 of actinic elastosis were significantly associated with outdoor work (*χ^2 *(1, N=51) = 33.382, p<0.001, OR=131.25 (95% CI: 13.60, 1266.37). The presence of ulceration and pigment association of tumors on the histopathological report were not significantly associated with outdoor working.*

Conclusions: *1. Occupational NMSC in Romania is associated with high-risk clinical features; 2. Poorly defined borders is a significant clinical high-risk factor associated with occupational UV exposure in NMSC; 3. High-risk histopathological subtypes are more frequently encountered in outdoor workers diagnosed with NMSC compared to indoor workers with no occupational UV exposure background; 4. Occupational NMSC is associated with significantly higher grades of desmoplastic reaction and of actinic elastosis compared to indoor workers.*

Keywords: solar UV radiation, occupational skin cancer, skin cancer characteristics.

INTRODUCTION

Non-melanoma skin cancer (NMSC), also called keratinocyte cancer, represents the most frequently diagnosed cancer in humans (1) and includes actinic keratoses (AK) as intraepidermal cancerous lesions and basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) as malignant neoplasms (2).

In 2018, The World Health Organisation (WHO), through the International Agency for Research on Cancer (IARC), reported over one million new cases of NMSC, of which almost 40 000 new cases occurred in Central and Eastern Europe (3).

In Romania, epidemiological data of skin cancer are lacking. In 2018, the Romanian National Institute of Public Health reported 83 000 new cases of cancer, without identifying the exact number of NMSC (4). These aspects are related to the inexistence of a National Cancer Registry, which includes NMSC, as well as to the lack of an up-to-date coding system in the State Health Care electronic system. In 2020, the 10th International Statistical Classification of Diseases and Related Health Problems (ICD) is in use, which classifies all NMSC as C44 – Other and unspecified malignant neoplasm of skin (5).

Solar ultraviolet (UV) radiation represents the most relevant risk factor of developing NMSC, being included as a group I carcinogen (carcinogen to humans) by the IARC since 2012, along with ionizing radiation, asbestos, plutonium, etc (6). Recent studies suggest a relationship between cumulative, long-term exposure to UV radiation and development of AK and SCC, while intermittent high-intensity UV exposure, especially at young ages, correlates with BCC and melanomas (7), even though prolonged UV exposure seems to be related to BCC as well (8). Other risk factors of developing NMSC include genetic predisposition, immunosuppression, HPV infection, etc (9-11).

Occupational natural UV radiation exposure is associated with a higher-risk of developing NMSC (12), providing a two-fold increased risk for BCC and SCC in the highly UV exposed workers (13, 14). Even though a strict relationship between occupational exposure and development of skin cancer is established, only a few case studies in literature aim to identify if occupationally UV-induced NMSC is associated with more aggressive tumour characteristics than sporadic NMSC.

Current Guidelines of care for the management of BCC and SCC provided by the American Academy of Dermatology indicate the necessity of differentiating high-risk and low-risk NMSC, features which are essential nowadays for establishing the course of treatment, as well as for evaluating prognosis factors (15, 16).

Study aim

The study aims to determine if occupationally-induced NMSC are associated with more aggressive clinical and histopathological features when compared to sporadic NMSC.

MATERIALS AND METHODS

Study design

A retrospective, analytical, comparative study was conducted during 2017-2019 in a University Department of Dermato-venereology in Bucharest, Romania, consecutively including patients presenting with NMSC which underwent surgical excision of lesions followed by histopathological examination.

Outdoor workers are mentioned as OW and indoor workers (no occupational UV exposure back ground) as controls (C).

Inclusion and exclusion criteria

Inclusion criteria for subjects and controls were as follows: (1) clinical diagnosis of NMSC; (2) histopathological confirmation of BCC or SCC; and (3) identified profession by personal history taking at the time of admission or followed by telephone conversations.

Exclusion criteria were represented by patients under 25 years of age with known predisposition of genodermatoses associated with skin cancer or any other additional significant risk factor such as immunosuppression and radiation therapy at site of tumor development.

Analysed features

High-risk characteristics were classified according to National Comprehensive Cancer Centre (NCCN) including clinical features (such as location and size of lesions – area L>20 mm, M>10 mm, area H, aspect of borders, primary or recurrent lesions and histopathological criteria such as subtype (mixed infiltrative, basosquamous BCCs, adenoid SCC) and perineural involvement (17, 18). Other analysed histopathological criteria included ulceration, pigment association, desmoplastic reaction and grades of associated actinic elastosis.

According to NCCN, area L represents the trunk and extremities, area M includes the cheeks, forehead, scalp, neck, and pretibial region, and area H consists of the central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet (17, 18).

Desmoplastic reaction was classified as absent-reduced or moderate-extensive and actinic elastosis was classified as absent/grade 1 or grade 2/3.

Clinical criteria were based on personal examinations and histopathological criteria were analysed through each patient's personal report.

Data analysis

Data was analysed using the software SPSS for Windows version 20 (SPSS, Chicago, IL, USA). Mean values and standard deviations (SD) were calculated for numerical data, odds ratio (OR)

Socio-demographic features		S	C
Gender	Male	18 (72%)	16 (61.5%)
	Female	7 (28%)	10 (38.5%)
Environment	Rural	10 (40%)	14 (52.8%)
	Urban	15 (60%)	12 (46.2%)
Age	Mean±SD	68.92 (±12.09)	70.00 (±10.42)
NMSC type	BCC	21 (84%)	22 (84.6%)
	SCC	4 (16%)	4 (15.4%)

TABLE 1.
Socio-demographic and general characteristics of groups

and 95% confidence intervals (95% CI) were assessed and statistical significance was tested by Chi-square analysis (χ^2). P<0.05 was considered to indicate statistical significance.

Outcomes

The study included 51 consecutive patients diagnosed with NMSC, 25 OW and 26 controls. OW presented with 21 BCC and four SCC, controls with 22 BCC and four SC, respectively. General characteristics of the studied population are detailed in Table 1. Males were predominant in both groups, with 18 males as OW and 16 males as controls. Most patients came from urban environments. The mean age value was lower for the OW group [68.92 (SD ±12.09)] compared to controls [70.00 (SD ±10.42)].

The number of lesions per patient was associated with higher mean values of 1.60 (SD±1.25) in the OWs compared to controls [1.27 (SD ±0.45)]. OW presented with higher mean diameters of lesions [15.00 mm (SD ±6.70)] compared to controls [12.19 (SD ±8.55)]. Mean values of tumour thickness on the histopathological report were similar in both groups (2.35 mm and 2.30 mm, respectively).

Statistical analysis of clinical and histopathological high-risk criteria, which was detailed Table 2, identified significant differences in terms of high-risk location and size as well as for clinically poorly defined margins. Subjects associated a 4.66 times higher risk of developing NMSC with aggressive location and size χ^2 (1, N=51) = 6.246, p=0.013, OR=4.66 (95% CI: 1.34, 16.23) and a 24-fold risk of developing NMSC with clinically poorly defined margins χ^2 (1, N=51) = 21.697, p<0.001, OR=24.44 (95% CI: 5.38, 110.92). Most frequent high-risk subtype for subjects was an area M greater than 10 mm (Figure 1). No metastasis was found in any of the studied subjects.

Significant statistical differences were also observed in terms of high-risk histopathological subtypes, grades of desmoplastic reaction and of actinic elastosis. Risk of developing a high-risk

TABLE 2. Comparison of clinical and histopathological high-risk criteria between subjects and controls

High-risk criteria		N	%	OR	95% CI	χ^2 (1, N=51)
Clinical high-risk location and size*	**S**	20	80	4.66	1.34-16.23	**6.246 (p=0.013)**
	C	12	46.2			
Clinically poorly defined margins*	**S**	22	88	24.44	5.38-110.92	**21.697 (p<0.001)**
	C	6	23.1			
Histopathological high-risk subtype	**S**	14	56	15.27	2.94-79.08	**13.814 (p<0.001)**
	C	2	7.7			
Ulceration on histopathology report	**S**	17	68	1.32	0.41-4.20	0.233 (p=0.425)
	C	16	61.5			
Desmoplastic reaction¶	**S**	18	72	8.57	2.42-30.30	**12.244 (p=0.001)**
	C	6	23.1			
Actinic elastosis†	**S**	21	84	131.25	13.60-1266.37	**33.382 (p<0.001)**
	C	1	3.8			
Pigment association	**S**	5	20	1.37	0.32-5.84	0.187 (p=0.475)
	C	4	15.4			

*According to NCCN

¶ Desmoplastic reaction was classified as absent-reduced or moderate-extensive

† Actinic elastosis was classified as absent/grade 1 or grade 2/3.

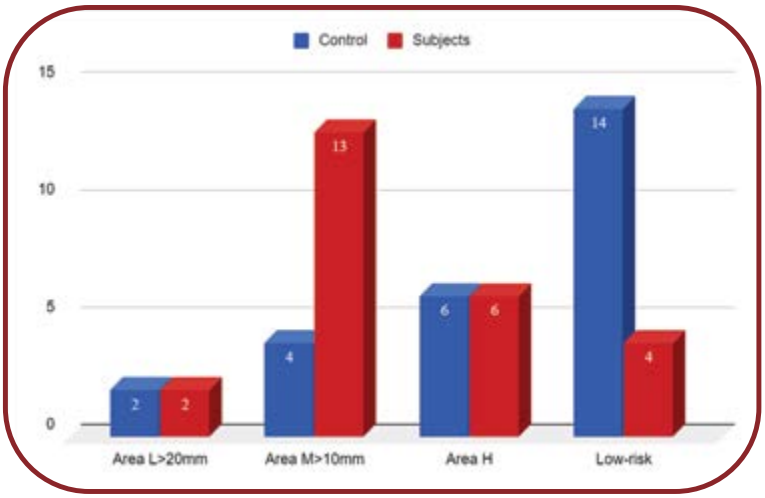

FIGURE 1. Distribution of high-risk clinical criteria

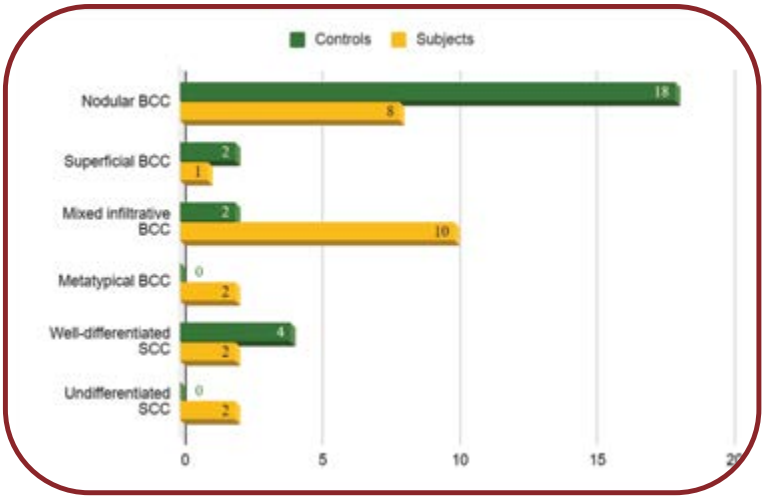

FIGURE 2. Distribution of histopathological subtypes

histopathological subtype was 15 times greater for OW χ^2 (1, N=51) = 13.814, p<0.001, OR=15.27 (95% CI: 2.94, 79.08).

Most frequent histopathological subtype was mixed infiltrative BCC and undifferentiated SCC (Figure 2). Moderate to severe desmoplastic reaction was 8.57 more frequent in controls χ^2 (1, N=51) = 12.244, p=0.001, OR=8.57 (95% CI: 2.42, 30.30).

Grades 2 and 3 of actinic elastosis were significantly associated with outdoor work (χ^2 (1, N=51) = 33.382, p<0.001, OR=131.25 (95% CI: 13.60, 1266.37).

The presence of ulceration and pigment association of tumours on the histopathological report were not significantly associated with working outdoors.

A binary logistic regression analysis was performed in order to predict high-risk histopathological subtypes using as covariates professional exposure to UV radiation, gender, age, tumor diameter and clinical high-risk subtypes according to NCCN. The probability of the chi-square model (25.37), P<0.01, supports a relationship between dependent and independent variables. The Wald criterion highlighted the most predictive factors as the presence of occupational UV exposure (Wald=7.992, p=0.005) and presence of a clinically aggressive location and size (Wald=3.993, p=0.046).

Discussion

In 2018, the National Institute of Statistics reported 19 million inhabitants in Romania, of which 10 millions were living in urban areas and nine millions in rural environments. In 2017, the average number of employees was approximately five millions, of which 120 000 were agriculture workers and 370 000 construction workers, making at least a half of million workers in Romania exposed to solar UV radiation constantly at their workplace (19). Recent dosimetry studies performed in a few European countries, including Romania, found that the level of exposure to solar UV radiation in outdoor workers significantly exceed the level of non-occupational exposure, including leisure (20, 21). In spite of epidemiological data on an increasing incidence of NMSC in the last decades and the well-established role of UV radiation in its pathogenesis, Romania does not recognize occupationally solar UV-induced NMSC as an occupational disease (22), thus no reporting or compensation system is reachable for this pathology.

From the author's knowledge, this is one of the few studies which compares high-risk clinical and histopathological criteria of NMSC in indoor and outdoor workers.

The study confirms the known hypothesis that BCC is the most common skin cancer, with almost five times more cases than SCC (23) and that NMSC is more frequently encountered in male subjects [24].

Mean age values are insignificantly lower for the outdoor workers' group, suggesting either that outdoor workers in Romania decide to visit a Dermatology Unit earlier, or constitutional darker skin photo type, that is of II/III for the ma-

jority of Romanians, provide a protective effect until higher age groups.

Outdoor workers diagnosed with BCC and SCC presented a higher mean value of multiple lesions compared to the control group; although multiple NMSC are not uncommon, and can be sometimes associated with genodermatoses such as Gorlin-Goltz syndrome (25), such cases would have been excluded from the study. Also, the mean lesion diameters were higher for the outdoor workers' group, suggesting a more rapid evolution of lesions in these cases, taking into consideration the fact that patients reported to the Dermatology Clinic after a similar period of time.

Statistical significance was observed for high-risk location and size and for poorly defined borders of lesions, being an important high-risk feature, correlated with possible risks associated with positive margins on the histopathological report (17, 18). Clinical topography identified high-risk criteria for outdoor workers in case of BCC and of SCC. Most frequently identified areas included an area M higher than 10 mm, being defined in past studies as "mask area" located on area H. These findings are similar to those reported in previously published studies, in which outdoor workers developed most lesions on the "mask area" of the face (26).

High-risk histopathological subtypes were identified as significantly more numerous in outdoor workers, with mixed infiltrative type as the most frequent form for BCC and undifferentiated adenoid type as the most frequent for SCC. Similar studies identified similar high-risk histopathological subtypes, mixed with an aggressive component as the most frequent histopathological subtype (26, 27).

Presence of ulceration, independent of any additional high-risk criteria, is considered a risk factor for an aggressive form of NMSC (28). Nonetheless, this statistical analysis did not identify a significant difference in terms of ulceration between groups.

Pigment association was not increased in outdoor workers compared to controls even though UV radiation is involved in stimulation of melanogenesis and acts as an additional risk factor (29, 30).

Desmoplastic reaction represents an atypical factor of analysed lesions (31) and was identified frequently in both cases of NMSC. Actinic elastosis is the most predictive factor of (cumulative) UV-induced skin damage (32) and was identified in higher proportion for both groups.

Strengths of our study include identifying cases of occupational NMSC which associate a strong occupational component, as well as histopathological interpretation of their characteristics. Limitations include the relatively small sample size, missing data and potentially lower generalizability, as cases were consulted by a single dermatologist in a state health care system (referral bias). For ethical, medical, administrative and preventive issues, all patients with a strong evidence for an occupational disease were referred to an occupational physician.

Our finding emphasises the importance of appropriate dermatological screening for all outdoor workers exposed to solar UV radiation, as well as the importance of notifying all the occupational skin diseases, including cancer, especially in Eastern European countries, where this issue is deeply neglected (33).

CONCLUSIONS

1. Occupational NMSC in Romania is associated with high-risk clinical features.

2. Poorly defined borders is a significant clinical high-risk factor associated with occupational UV exposure in NMSC.

3. High-risk histopathological subtypes are more frequently encountered in outdoor workers diagnosed with NMSC compared to indoor workers with no occupational UV exposure background.

4. Occupational NMSC is associated with significantly higher grades of desmoplastic reaction and of actinic elastosis compared to indoor workers. ❑

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