Non-Melanoma Skin Cancer: Statistical Associations between Clinical Parameters

ALEXANDRA-ROXANA CIUCIULETE¹, ALEX EMILIAN STEPAN², BIANCA CĂTĂLINA ANDREIANA², CRISTIANA EUGENIA SIMIONESCU²

¹PhD Student, Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania
²Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: Non-melanoma skin cancer (NMSC) represent an important health problem in medical practice. This is the most frequent type of cancer and its incidence is constantly increasing. Basal cell carcinoma and squamous cell carcinoma constitute the majority of NMSC, respectively 70% and 25% of total cases. The present retrospective study was conducted over a one-year period and included 439 cases of NMSC, of which 336 BCC and 103 SCC. We analyzed a series of clinical parameters: gender, age, tumor size and tumor topography. The statistical analysis of the investigated parameters indicated gender-age associations for BCC, and topography-gender, as well as topography-age for SCC.

KEYWORDS: Non-melanoma skin cancer, basal cell carcinoma, squamous cell carcinoma.

Introduction

Non-melanoma skin cancers (NMSCs) represent an important health problem in medical practice [1], being the most frequent types of cancer [2,3,4].

In this heterogeneous group, the majority of cancers are basal cell carcinoma (BCC)-70% and squamous cell carcinoma (SCC)-25% [3,4].

Their incidence is constantly increasing [5], accounting for 90% of all malignant skin tumors [2], and studies suggest that this trend will continue until at least the year 2040 [5].

Between 2007-2017, the incidence of NMSCs increased by 33%, reaching 7.7 million cases worldwide [3].

In the last decade, in Europe, the incidence of BCC has increased annually by 5% [6], and some studies on SCC show that the incidence is rising and tends to approach that of BCC [7].

Data from Scotland, Denmark and Germany indicated annual increases in BCC and SCC incidence as following: 1.4-3.5%, 3.1-4.6% and 3.3-11.6%, respectively, and Germany expects the incidence rate of NMSC to double in the next 10 years [8].

According to the latest data, 3.6 million cases of BCC and 1.8 million cases of SCC are diagnosed annually in the United States [9].

The incidence increases with age [10,11,12], and also multiplicity of SCC has been correlated with age [10].

The prevalence values revealed significant increase during the last 20 years, 35% for BCC and 133% for SCC [4].

Most NMSCs have a good prognosis and a low metastatic rate [4].

The incidence of metastatic BCC is 1 in 14 million, while for SCC it varies [4].

According to data from a 5-year evaluation, SCC has a metastasis rate of 5% and a recurrence rate of 8% [13].

European studies report a metastasis rate of 2.1%, higher among males [10], but according to other studies it can reach up to 9.9% [4].

Although for NMSC the impact on mortality is low [12], globally it causes 5,400 deaths per month [9], most of which are attributed to SCC [1].

The United States reports 15,000 deaths annually from SCC [9]. Survival is as low as 10-20% for metastatic SCC [13], this type being responsible for 75% of deaths caused by NMSC [4].

For BCC, the mortality rate is 0.02 per 10,000 cases [4].

The aim of this study was to assess the epidemiological development trends of BCC and SCC, and to analyze the associations between representative clinical parameters.

Material and Methods

We conducted a retrospective study over a period of one year, which included 439 cases diagnosed with NMSC.

Among these, we identified 336 cases of BCC and 103 cases of SCC.
The analyzed cases came from the Dermatology and Plastic Surgery Clinics of the Emergency County Hospital of Craiova.

The diagnosis was established following the histopathological examination in the Pathology Department within the same hospital.

The clinical parameters followed were represented by gender, age, tumor size and tumor topography.

The data was processed and statistically analyzed to highlight any relation between the parameters.

For the statistical analysis we used the Chi square comparison test ($\chi^2$), in the SPSS10 (statistical package for the social Sciences) software, considering the significant difference a level $p<0.05$.

This study was approved by the Local Ethics Committee (number 37/29.03.2021), and included informed consent from patients.

Results

The study included 439 cases of NMSC: 336 cases of BCC and 103 cases of SCC. For BCC, the age range at the time of diagnosis was between 25-103 years, with an average age of 70.1 years.

Patients were predominantly in the seventh decade of life (39.9%), followed by the sixth decade (27.7%), the eighth (15.2%), the fifth (10.4%), the fourth (3.3%), the third (2.4%) and finally, with an equal percent, the ninth decade and patients under 30 years (0.6%).

Gender distribution showed a predominance of females (53%).

The most common location for BCC was the head and neck region (80.4%), followed by the thorax (16.1%), lower limbs (1.8%), upper limbs (1.5%) and groin (0.3%).

Figure 1. Distribution of BCC cases depending on age and gender.

Regarding the tumor size, most tumors were under 2cm (81%), followed by tumors between 2-4cm (17%), and finally those over 4cm (2.1%).

As for the statistical analysis of the previously mentioned parameters, we highlighted significant associations between the gender and the age categories, in female patients BCC being frequently diagnosed over the age of 80 ($p=0.038$, $\chi^2$ test) (Figure 1).

No statistically significant results were obtained regarding the gender, age, or tumor size and the topography of the lesions, nor for the tumor size and gender ($p>0.05$, $\chi^2$ test) (Table 1).

Table 1. Statistical associations between the analyzed parameters for BCC.

| Parameters | Topography | Gender | Age |
|------------|------------|--------|-----|
| Gender     | $p>0.05$   | -      | $p=0.038$ |
| Age        | $p>0.05$   | $p=0.038$ | - |
| Tumor size | $p>0.05$   | $p>0.05$ | $p>0.05$ |

Although a predominance of larger tumors was observed in patients aged 70-90 years, no statistically significant associations were obtained ($p>0.05$, $\chi^2$ test).

For SCC, the age range at the time of diagnosis was between 44-102 years, with an average age of 74.2 years.

Most patients, representing 35% of the total, were in the eighth decade of life, followed by those in the seventh decade (31%), sixth (18.4%), fifth (10.7%), fourth (3.9%), and over 90 years of age (1%). Gender distribution showed male predominance (59.2%).

The tumor size was in most cases under 2cm (60.2%).

In 24.3% of the cases, the tumors were between 2-4cm, and in 15.5% of the cases, the size was over 4cm.

In terms of location, the head and neck region was the most common, accounting for 76.7%, followed by the upper limbs (9.7%) and lower limbs (6.8%), groin (4.9%) and thorax (1.9%).

The head and neck were the predominant topographic region in both women and men.

In female patients, tumor lesions of the groin and upper limb were next in order, while in men it was a predominance for tumors of the lower limb and thorax (Figure 2), with a statistically significant association ($p=0.01$, $\chi^2$ test) (Table 2).
Figure 2. Distribution of SCC cases depending on gender and topography.

Table 2. Statistical associations between the analyzed parameters for SCC.

| Parameters | Topography | Gender | Age |
|------------|------------|--------|-----|
| Gender     | p=0.01     |        | p>0.05 |
| Age        | p=0.018    | p>0.05 | p>0.05 |
| Tumor size | p>0.05     | p>0.05 | p>0.05 |

We also obtained a statistically significant association between the age category and tumor topography, the SCC diagnosed over the age of 60 years predominating in the head and neck region (p=0.018, χ2 test) (Figure 3).

Figure 3. Distribution of SCC cases depending on age and topography.

No statistically significant associations were obtained regarding tumor size and topography, tumor size and gender, tumor size and age, or between age and gender (p>0.05, χ2 test) (Table 2).

Discussions

Known as the most common type of cancer worldwide, NMSC continues to show an increasing incidence rate as a result of the accumulation of multiple risk factors [1,11].

Among those, exposure to UV radiation is the most important [2].

Studies have shown the link between the development of BCC and SCC and both natural and artificial UVA/UVB radiation exposure, which are responsible for DNA mutations, alteration of the repair pathways, induction of oxidative stress, activation of the inflammatory process, and suppression of the antitumor immunity [11].

The ageing population is another important factor that contributes to the increasing incidence, as the body loses its ability to repair and regenerate, to which the inflammatory status and physiological and/or drug-induced immunosuppression is added [11,14].

Recently, the easier access to information has increased the addressability to the medical personnel, followed by an early diagnosis, also contributing to the increased incidence of NMSC [15].

In this regard, some authors estimate a decrease or stabilization of the BCC’s incidence in people under 40 in the coming decades [16].

Analyzing the gender distribution, the data from the literature regarding BCC, indicate a predominance in males [11], with a ratio of 1.5-2:1 [5].

The increasing incidence among women has recently been observed [6].

This is consistent with the results of the present study, in which we found a slight predominance for BCC in females (53%).

As for SCC, according to several epidemiological data the diagnosis is more common among male patients [7,10], with a ratio of up to 3:1 [7].

A higher incidence among men (per 100,000) was found in the United Kingdom (77 vs. 34.1 females), Ireland (66.1 vs. 30.6) and Norway (20 vs. 15) [10].

Another study, conducted in Germany, found 58.1% males [17].

Likewise, in our study, the gender distribution shows the predominance of SCC among males, with a percentage of 59.2%.

However, other authors seem to believe that gender differences appear insignificant in people under 40 [5].

Dutch researchers have observed an approximately equal increase in incidence for both sexes, a result correlated with the tendency of equalization in terms of risk factors distribution [18].

The same results were observed following a study conducted in Poland from 1999 to 2019 [16].

Male gender and age are independent risk factors when it comes to BCC [5].

The incidence increases significantly over 40 years of age [6], and even doubles from 40 to 70 years [5].
With the main risk factor being chronic exposure to ultraviolet radiation, SCC is more common in elderly individuals [5,16].

However, the incidence is also increasing among people under the age of 40 [5].

The mean diagnostic age in the present study was 70.1 years for BCC and 74.2 years for SCC.

Similar results were obtained by Ciazynska et al., highlighting a NMSC peak incidence in the seventh decade of life, followed by the sixth and eighth decades.

According to them, for BCC, the mean age for males was 70.9±11.4 years, and for females 71.4±11.9 years. As for SCC, the mean age for males was 75.9±12.2 years, and for females 77.2±12.1 years [16].

In our study, for BCC, tumors diagnosed over the age of 80 were more frequent in females, with a statistically significant association (p=0.038, χ²).

Other studies on BCC show, the most important increase in incidence in people aged between 65-79 years and over 80 years [11], while for SCC, 80% of the diagnosed people are found into the age category over 60 years [10].

In the United Kingdom, 62.7% of patients with SCC have an average age of 80 years [10], while in Germany the average age for SCC is 75.4 years, and 68.9 years respectively for BCC [17].

In Norway, the incidence rate by age increased 9 times in females and 6 times in males, especially in people aged 70-79 years, between 1963 and 2011 [10].

In agreement with the literature data [19,20,21], the results of this study indicate the preferential development of BCC and SCC tumors in the photo-exposed areas.

The most common topography was the head and neck region (80.4% for BCC and 76.7% for SCC), followed by the thorax and limbs for BCC (16.1% and 3.3%, respectively), and limbs for SCC (16.5%).

These results are in accordance with the data covering the fields of activity that involve repeated and prolonged exposure to the action of UV radiation.

Outdoor-environment working professions are known as a risk factor, and some countries, including Romania, recognize NMSC as an occupational disease [22].

CAREX (CARcinogen EXposure) data show that over 9 million workers in the European Union are regularly exposed for most of their working time (75%) to the harmful effects of UV radiation [23].

Among male patients, the involuntary exposure to solar radiation is very frequent while practicing jobs like farmer, fisherman, driver, or site worker [24].

Studies recognize the occupational risk among men for the development of skin carcinomas [21,24], the most important after the agricultural sector being the construction field [23].

In addition to professional activities, some recreational practices, including the use of UV devices for artificial tanning, mainly among females [25], represent a major risk factor [19,6].

Tanning bed use increases the risk of developing BCC by up to 29%, and up to 83% for SCC [9], being categorized as a group 1 carcinogen [26].

For both genders, voluntary sun exposure is further added, with incorrect use of sunscreen [27,28].

A study conducted in Brazil in 2019 estimates that 63% of individuals do not use any protection measure when exposed to the sun [29].

Also, treatment with psoralen and UVA, UVB increases the risk of skin carcinomas [6,30], along with other photosensitizing drugs such as tetracycline [1,31] or some antihypertensives (beta-blockers and calcium channel blockers) [32].

However, NMSC can also develop on non-photo-exposed or intermittently exposed skin, suggesting genetic susceptibility to UV-induced carcinogenesis [33].

For SCC, we obtained statistically significant associations regarding patients’ gender and the tumor topography.

Thus, SCC tumors in the head and neck region predominated in both women and men.

The next area in female patients was the groin, followed by the upper limbs, while in men the tumors were located in the lower limbs followed by the thorax (p=0.01, χ² test).

Although tumor localization in the groin is usually less common, about 5% [33,34], the upper or lower limbs and the thorax are relatively common, being responsible for 18%, 13% [4], and 10% respectively, of SCC cases [16].

The existence of chronic inflammatory lesions, burns, ulcers or scars, predisposes to the appearance of SCC [36], although the most common precursor lesion is actinic keratosis [37].
Some types of HPV (human papilloma virus) infections increase the risk of developing SCC in the genital and anal areas [2].

We also obtained statistically significant associations between the SCC topography and the age category, tumors located in the head and neck region predominating in patients over 60 years old (p=0.018, χ² test).

Indeed, studies show that facial localization of SCC has been identified more frequently in older individuals [16].

Another parameter of great importance, both for classification and as a prognostic factor, is the tumor size [20]. Studies revealed that SCC tumors larger than 2 cm in diameter have twice the risk of recurrence and a triple risk of metastasis, while being the most common risk factor associated with disease-specific death [7].

According to the results of our study, both for BCC and for SCC, tumor lesions smaller than 2 cm in size predominated (BCC-81%, SCC-60.2%).

In BCC, tumor dimensions between 2 and 4 cm were registered in 17% of the cases, and those over 4 cm in 2.1%.

In 24.3% of the SCC cases the dimensions were between 2 and 4 cm, and in 15.5% of the cases the size was greater than 4 cm.

The location of a tumor ≥2 cm in size in the L area (trunk and extremities, excluding hands, feet, nails, ankles and pretibial area) is considered high risk, as is the location in the M area (cheeks, forehead, scalp, cervical area, pretibial area) of a SCC tumor ≥1 cm [20].

Dimensions equal to or larger than 4 cm include the tumor in the T3 category (according to the TNM classification) [1,37]. Zone H is considered a high-risk area, regardless of the tumor size [38]. It includes the central part of the face, temples, ears, hands, feet and genital area [10].

Conclusions
The results obtained indicated associations or trends of association of age, gender, location and size of NMSC, which were specific to BCC and SCC.

The aspects support the importance of clinical-epidemiological parameters in assessing the impact of NMSC on the exposed population.

These data underline the importance of action in order to establish prevention programs and to offer people medical education regarding skin cancers.

Conflict of interests
None to declare.

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