Basal cell carcinoma: review of risk factors

Darjania T.1 Galdava G.1,2 Kituashvili T.1,2

Abstract

Background: Basal cell carcinoma is the most common skin cancer and its incidence is rising worldwide. Its pathogenesis is still not well understood, although it is considered to be impacted by genetic and environmental factors.

Aim: The aim of the study is to review and summarize recent literature about basal cell carcinoma associated risk factors.

Methods: We searched all the available literature via Google Scholar and PubMed database by using keywords: basal cell carcinoma, risk factors, non-melanoma skin cancer, indoor and outdoor tanning, artificial sun exposure and UV radiation.

Results: Several papers reported that there are plenty of risk factors involved in the development of basal cell carcinoma including genetic alterations, intense sun exposure, Northern European ethnic origin, light skin color, tendency to burn rather than tan, history of blistering sunburns, tanning devices, immunosuppression, ionizing radiation and others.

Conclusions: Based on the literature review we identified that there are several main risk factors that can be associated with the development of basal cell carcinoma, from that the most principal is UV radiation and the population with fair skin has higher risk of getting basal cell carcinoma, although further prospective studies should be performed, that will establish the association between the existing and new risk factors and basal cell carcinoma, allowing to prevent the development of skin cancers.


Keywords: Basal cell carcinoma; BCC; Non-melanoma skin cancer; Risk factors.

Introduction

Basal cell carcinoma (BCC) is the most common skin cancer arising from the epidermal basal cells. It has low metastatic potential (0.0028% to 0.5%), however it tends to be locally invasive, aggressive and destructive of skin and sometimes the surrounding tissues including muscles and bones and is associated with high morbidity and mortality (1). Usually BCC has a good prognosis, especially when detected at its early stages, although a mortality rate of 0.02 per 10,000 is to be expected (2).

The part of BCC among all non-melanoma skin cancer (NMSC) is approximately 70%, following by squamous cell carcinoma (SCC) with 25% (2,3).

BCC is more common in middle-aged Caucasians and in the geographical zones close to the equator with higher Ultraviolet radiation (UVR) (4,5). Several studies have shown that there is significant difference between the numbers of BCC in relation to gender. Men are more often affected than women (1,5-2:1) (6,7) and the highest number of BCC cases is between 60 to 70 years old persons, however some of the recent studies have shown there are increased numbers of young female patients under 40 years old (6–9). It might be related to the increased fashion of tanning beds in young women and they more often seek dermatologic care that allows the early detection of the disease (8). By Foote et al. each year of life is associated with 2% increased risk of the development of BCC in the actinically damaged adults (9).

Incidence of BCC is increasing each year worldwide as a result of the increased longevity of the general population (10), sun exposure behaviors and the depleting ozone layer (11), moreover incidence rates of early-onset BCC also appear to be rising and its treatment is related to high healthcare costs (5,12). The total number of BCC is still unclear as there is no cancer registry that collects all data on BCC in the world and on the other hand, not every treated BCC is verified with histology (13).

The process of skin carcinogenesis in case of BCC remains still unclear, although it is considered to have multifactorial origin and both genetic and environmental factors play role in the development of the disease (14).
The most common localization for BCC are sun exposed areas like face, neck, decollate, less common is trunk and forearms and very rare mucous membranes, palmo-plantar areas and genitalia (2,15). It appears in four main clinical subtypes: nodular, superficial, morpheaform and fibroepithelial (also known as fibroepithelioma of Pinkus). All types of BCC may ulcerate, but it is more observed in nodular type. Even though generally BCC is amelanotic, variable amounts of melanin may be present in the lesions and misdiagnosed as melanoma (16).

**Risk factors of BCC**

BCC is often the consequence of the action of several etiological risk factors:

**Genetic risk factors**

According to the studies genetic predisposing of phenotypic characteristics, such as skin and hair color, ability to tan and freckling have been identified as high-risk factor for the development of BCC (6,17). People with skin type 1 and 2 have 1, 5 fold higher risk of getting BCC than people with skin types 3 and 4 (6). Although BCC is more common in Caucasians, there are also case reports about BCC in dark skin patients (18). Retrospective and prospective study performed by Simić et al. demonstrated 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, Odd Ratio (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 tumors is statistically insignificant (6). Compared to general population, individuals who have already had BCC are at increased risk for development another BCC lesions and melanoma (19–21). In addition, patients with a history of NMSC are at high risk for developing and dying from other noncutaneous cancers (22–24).

It is well established, that some genetic syndromes like Xeroderma pigmentosum, Gorlin-Goltz syndrome, Oculocutaneous albinism, Muir-Torre syndrome, Neviod basal cell carcinoma syndrome, Bazex and Rombo syndromes have markedly increased risk of developing multiple BCCs at early years of life (25–27).

**Environmental risk factors**

As established by several studies, generally the primary risk factor for cutaneous carcinogenesis is UV exposure from sunlight, which leads to UV-induced alteration in skin proteins expression (28). By the International Agency for Research on Cancer and by the World Health Organization UV radiation was classified as a Class 1 human carcinogen (29), since it affects each stage of carcinogenesis (14). By reduction of cell-mediated immune response, production of reactive oxygen species and DNA damage, it leads to cellular damage (30). The primary event after high UV exposure is keratinocyte apoptosis led by the p53/p21/bax/bcl-2 pathway followed by a phase of hyperproliferation that leads to epidermal hyperplasia (29,31).

Studies have shown that outdoor workers, especially farm laborers, sailors, fishermen, construction workers are at very high risk for basal cell carcinoma and generally for NMSC (6,32–34). Frequent exposure to UV rays and incidence of BCC can be shown by OR=3.81(6). The risk of BCC development appears to be dependent on the nature of UV exposure also. A population-based, case-control study of 226 male patients with BCC conducted in Canada revealed that the subjects with increased recreational sunlight exposure in childhood and adolescence (age under 19) had significantly increased risk of BCC, although an inverse relationship was seen with lifetime cumulative recreation exposure (35). No association was found between mean annual cumulative summer sunlight exposure and risk of BCC. The same study also showed, that the subjects with tendency to sun burn than tan ( Fitzpatrick type 1 and 2) and a history of severe sunburn and freckling in childhood significantly increased the risk of the disease (35). Like this study findings, Foote et al. also found not significant association between prolonged sun exposure during the first 2 decades of life and BCC incidence among their study population (9).

Use of artificial UV exposure devices, such as tanning lamps and tanning beds for nonmedical purposes has become increasingly popular in the world last years, especially in young adults and women (29). There are several studies that demonstrate the association between use of tanning devices and increased incidence of BCC, moreover using artificial UV exposure might be associated with early onset of the disease before age 40 years and is characterized by more aggressive histologic subtypes (infiltrative, sclerosing, morpheaform and micronodular) (8,36–39). The meta-analysis of more than 9300 cases of non-melanoma skin cancer from 12 studies by Wehner et al. demonstrated the relatively significant association between the development of BCC and artificial indoor tanning. According to the same study, ever exposure to
indoor tanning was associated with a 29% higher risk for BCC and indoor tanning before age 25 years had 40% increased risk compared to controls (95% confidence interval (CI)= 1.29-1.52) (40). Although same study demonstrated that high dose exposure to indoor tanning has a non-significant increased risk for BCC. This suggests a critical period for exposure during early life and a potential dose-response effect. Another population-based, case-control study on the association of BCC and tanning devices, conducted by Karagas et al. that included 603 BCC patients, showed that use of tanning devices was associated with an OR of 1.5 (95% CI 1.1 to 2.1) similar in men and women. Although the ORs were highest among those who began using tanning devices before age 20 years(41). In the US population-based study the strongest association was found for first exposure as an adolescent or young adult, with a 10% increase in the OR with each age younger at first exposure (OR per year of age #23 = 1.1; 95% Confidence Interval, 1.0–1.2) (8).

There is a relation between PUVA therapy and developing BCC, however unlike SCC, PUVA has far less effect on the risk of BCC (42). According to the study of Stern et al. risk of BCC was substantially increased only in those patients exposed to very high levels of PUVA (> or =337 treatments) (43).

Ionizing radiation used for the treatment of several skin conditions is also related to increased risk of BCC especially in white skin patients. In the US population-based study the elevated risk was found in the patients who were irradiated for acne (OR= 3.30) (44). In addition, the study of Lichter et al. showed a relative risk of 3.6 for BCC in the patients irradiated for scalp ringworm (45).

Multiple chemical exposures have been described to be related to the increased risk of NMSC including asphalt, tar, pesticides, polycyclic aromatic hydrocarbons and arsenic (46). There is high evidence of arsenic being promoter of the modulation of signaling pathways that are responsible for the cell growth that leads to skin cancer (47,48). There is long 20-40 years latency period from chemical exposure to clinical appearance.

**Immunosuppression**

Organ transplant recipients, patients who take immunosuppressive drugs and HIV patients have markedly high risk for NMSC (49). The incidence of BCC in such individuals is from five to ten times greater than in general population (50). Moreover, in immunocompromised patients usually BCC lesions are multiple, more aggressive and metastatic (51).

**Other risk factors**

The role of dietary factors in the development of BCC has been investigated for many years(52). Studies show that there might be a positive relationship between fat intake and BCC. The association between vitamin E, vitamin C and selenium is very low. An inconsistent association is for retinol and little relation between B-carotene and BCC (53). There are different study results on Vitamin D association to BCC. Park et al. found modestly positive association between vitamin D consumption and the risk of BCC (54), while according to the case-control study performed by Darjani et al. there was no significant difference in vitamin D deficiency between the two groups including controls (55). Most of the existing studies contain limitations and further well-designed studies are required to clarify the role of diet in BCC.

Smoking is considered to be skin cancerogenic. In the German study about risk factors of early onset BCC researchers found that smoking was associated to early onset of BCC (OR=13.34; CI 95%: 1.56-113.8), although the study has limited patients number(38). Another study found no relation between smoking and BCC and a slight excess risk of BCC was found among former smokers, whereas no increased risks were observed among current smokers, although there are several study limitations including lack of information about confounder major risk factors (56).

**Conclusion**

Basal cell carcinoma is one of the most common malignancy in the world. BCC is often a consequence of the several etiological factors and the genetic predisposition, skin type and environmental factors all influence on the development of it. Although BCC has low mortality and morbidity, it still remains a big global healthcare problem due to its rising incidence. Out of many risk factors of BCC the most principal are UV radiation and the population with fair skin, although further prospective studies should be performed that will establish the association between the existing risk factors and BCC, allowing us to prevent the development of skin cancers.

**References**


17