Melanoma and Basal Cell Carcinoma

Subjects: Dermatology

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Skin cancer is a common, preventable condition of global importance. Different types of skin cancer, like melanoma, basal cell carcinoma, and squamous cell carcinoma, have various risk factors, including UV exposure and genetics. Identifying these risk factors is crucial for targeting early detection and nuanced treatment.

Keywords: skin cancer risk factors ; melanoma ; basal cell carcinoma

1. Introduction

Skin cancer is the world's most common malignancy in populations with skin types I–III according to the Fitzpatrick classification. The incidence of melanoma and non-melanoma skin cancer (NMSC) has been increasing in recent decades and will persist in its upward trend. The World Health Organization (WHO) estimates the incidence of melanoma and NMSC at over 1.7 million new cases worldwide for 2025 [1]. Prolonged exposure to ultraviolet (UV) radiation is the primary risk factor, making skin cancer largely preventable through lifestyle modifications [2][3]. However, there is a need for further research to better understand and define the individual risk factors associated with skin cancer, to identify individuals at risk and provide early detection and therapy. Public health strategies recommend full body skin examinations for early diagnosis and to reduce skin cancer burden, but evidence supporting visual skin examination's efficacy in the general population is lacking [4]. So, how can skin cancer screening be made more effective and tailored to individual needs? For this purpose, there are various approaches integrating environmental, genetic, and behavioral factors, to develop risk scores for precise identification of high-risk individuals who require more detailed examination or tailored follow-ups [5][6][7].

2. Risk Factors for Melanoma

2.1. Extrinsic Risk Factors for Melanoma

Sun exposure is broadly accepted as the key environmental driver of cutaneous melanoma [8]. In 1992, the International Agency for Research on Cancer (IARC) concluded that the whole spectrum of UV radiation was carcinogenic to humans [8]. The main source of UV radiation exposure is the sun (solar radiation). Estimating the cases of melanoma that are attributable to UV radiation exposure is challenging, as solar UV radiation is ubiquitous and the carcinogenic effects are dependent on latitude and the individual's behavior [9][10]. In Canada, an estimated 62.3% of all melanomas can be linked to an increase in UV radiation exposure, comparing the incidence in 2015 with a 1920 cohort. Similar results are available for Australia, where approximately 63.3% of melanomas can be attributed to exposure to solar UV radiation [11][12]. However, the individual sun exposure pattern seems to be crucial. Specifically, intermittent exposure during activities like sunbathing, water sports, and vacations in sunny places plays a causative role in the development of melanoma, with a documented 60% elevated risk (relative risk (RR): 1.61, 95% confidence interval (CI): 1.31–1.99). Chronic cumulative sun exposure (e.g. occupational exposure) is not associated with melanoma risk in a metanalysis (RR: 0.95, 95% CI: 0.87–1.04) [9]. This observation could be explained by epithelial thickening through enhanced keratinocyte proliferation in response to (chronic) sun exposure, which has been shown to be UV-protective, independent of pigmentation [13]. Intermittent intense sun exposure, on the other hand, stimulates melanocytes: a single erythemal UVB exposure causes a delayed, dose-dependent increase of melanocyte proliferation, whereas the same amount of fractionated suberythemal UVB radiation has no discernible effects. Consequently, nevi and melanoma might be most effectively induced by intermittent UVB overexposure [14].

Sunburns are often used as markers for intermittent sun exposure, as they indicate a lack of adaptation in untanned skin. A history of sunburn is proven to be a significant risk factor for cutaneous melanoma, with a RR of 2.03 (95% CI: 1.73–2.37) [9]. Retrospective epidemiological data suggest that the susceptibility to the carcinogenic effects of solar radiation for melanoma is particularly pronounced during childhood, especially intermittent sun exposure during this period [15]. Experiments in mouse models demonstrate that a single dose of burning UV radiation to neonates, but not adults, is

necessary and sufficient to induce tumors resembling human melanoma with high penetrance [16]. Sunburns in childhood, therefore, represent a particular risk for the development of cutaneous melanoma [17].

Intentional UV exposure, whether from the sun or artificial sources, represents another notable risk factor for melanoma. ‘Ever’ intentional sun exposure is linked to an elevated melanoma risk of 1.44 (95% CI: 1.18–1.76) [11]. Notable distinctions in intentional tanning were observed across diverse latitude regions: European countries exhibited markedly higher levels of intentional sun exposure compared with their non-European counterparts. Additionally, pairwise comparisons indicate that intentional tanning is performed at a significantly higher frequency in Sweden and Italy than by individuals in other countries. Conversely, individuals in the UK and Poland show a significantly lower frequency of intentional tanning than the broader European sample. Overall, women express a stronger desire for a deeper tan and report more frequent intentional tanning [18]. For Canada, it was estimated that 18% of melanomas in 2015 could be attributed to sunbathing [11]. Similar results were calculated for Italy, where approximately 13% of melanomas in the year 2008 were attributable to high intentional sun exposure [19].

Not only is exposure to natural UV radiation relevant, artificial UV sources carry a risk too: the ‘ever’ use of tanning beds is associated with an approximately 20% increased risk of melanoma (RR: 1.2, 95% CI: 1.08–1.34). This risk rises by 1.8% (95% CI: 0–3.8%) with each additional session of sunbed use per year, indicating a dose-response effect. Commencing tanning at a very early age increases the risk even further: individuals with initial use of sunbeds before the age of 35 face a 59% higher risk of developing cutaneous melanoma (RR: 1.59, 95% CI: 1.36–1.85). The burden resulting from sunbed use can be quantified with specific figures: in Western European countries, approximately 5.4% of melanomas in the population are estimated to be attributable to the use of tanning beds. For women, the percentage is even as high as 6.9% of all melanoma cases [17]. The following data have been calculated for the individual countries and show a consistent trend: In Italy it is estimated, that 3.8% of melanoma cases are linked to sunbed use, more in women than in men (4.2% vs. 3.1%). The effect is particularly pronounced in young individuals, with sunbeds causing 17% of melanomas in those aged 35 years or younger [19]. For France, a total of 382 melanomas occurring in adults over 30 years in 2015 were likely attributed to the use of sunbeds, equivalent to 1.5% and 4.6% of all melanoma cases in men and women, respectively [20]. In Germany, approximately 4.7% of malignant melanomas in 2018 were attributable to ‘ever’ use of sunbeds. Additional analyses indicated that the vast majority of these cases (3.8%) could be due to highly frequent sunbed use (>10 times/year) [21]. These observations align with the knowledge that indoor tanning is significantly linked to well-established risk factors for melanoma, including a high number of nevi, the presence of atypical nevi, and sun damage. While still a matter of controversy, it seems that sunbeds have a causative role in melanoma [22][23].

Diet emerges as an additional lifestyle risk factor of melanoma. The average lifetime consumption of liquors and spirits showed to be significantly correlated with melanoma, with the highest intake (>3.08 g/day) associated with a 47% increased melanoma risk compared with the lowest intake (0–0.13 g/day). Additional analyses of skin cancer sites suggested that the positive association between alcohol intake and melanoma risk were stronger for tumors occurring on the trunk compared with those of the head, neck or extremities [24][25].

Immunosuppression is a long-known risk factor for melanoma, seen for example in HIV infection, iatrogenic post-organ transplantation immunosuppression, or in the context of lymphoproliferative disorders. The melanoma risk depends on the nature, duration, and intensity of immunosuppression. Notably, HIV-positive Caucasians exhibit a tenfold increase in melanoma incidence rates [26]. Among kidney and heart transplant recipients, the estimated incidence of melanoma is up to fivefold higher. It is known that in both sexes, renal transplant recipients have a 3.6-fold (95% CI: 3.1–4.1) increased rate of melanoma compared with the general population. Male recipients were 3.8 times more likely (95% CI: 3.2–4.4) to develop melanoma compared with men in the general population (p = 0.0001), while female recipients were 1.9 times more likely (95% CI: 1.4–2.7) compared with women in the general population. Among African Americans, who have a low melanoma prevalence, the incidence of melanoma in renal transplant recipients was 17.2 times greater than the reported rate for African Americans in the general population (13.32 per 100,000 population vs. 0.776 per 100,000 population, p = 0.0001) [27].

Moreover, older age, male gender, Caucasian ethnicity, and the use of ciclosporin and tacrolimus therapies are associated with a substantially increased risk of melanoma in OTR [28][29][30]. The risk for melanoma more than doubles for individuals with non-Hodgkin’s lymphoma (RR: 2.4, 95% CI: 1.8–3.2) or with chronic lymphocytic leukemia (RR: 3.1, 95% CI: 2.1–4.4) [31].

2.2. Intrinsic Risk Factors for Melanoma

Apart from extrinsic and behavioral risk factors associated with melanoma, there are also intrinsic ones. It is estimated that 55% of the variation in liability to melanoma is due to genetic influences [32]. Some intrinsic risk factors can be

discerned from the individual's phenotype. Considering skin color and type, the risk significantly increases with fair skin compared with dark skin. Remarkably, a recognizable dose-response trend emerges, with the Fitzpatrick phototype classification showing a progressive risk pattern: individuals with phototype III have an 70% increased risk for cutaneous melanoma compared with individuals with phototype IV (RR: 1.77, 95% CI: 1.23–2.56). Phototype II compared with IV is linked to an approximately 80% increased risk (RR: 1.84, 95% CI: 1.43–2.36), and the risk for cutaneous melanoma more than doubles when comparing phototype I to IV (RR: 2.09, 95% CI: 1.67–2.58). In addition to tanning ability and the tendency to sunburn, eye color is linked to the risk of developing cutaneous melanoma: having light eye color (blue or green vs. dark) is associated with an approximately 50% increased risk (RR: 1.47, 95% CI: 1.28–1.69 and RR: 1.61, 95% CI: 1.06–2.45, respectively). Hair color further contributes to the risk profile, with red hair carrying more than triple the risk compared with dark hair color (RR: 3.64, 95% CI: 2.56–5.37). Blonde hair poses an almost double risk (RR: 1.96, 95% CI: 1.41–2.74), while light-brown hair is associated with an approximately 60% increased risk compared with dark hair color (RR: 1.62, 95% CI: 1.11–2.34) [33]. Finally, freckles also play a role, as their high-density presence is associated with more than a twofold increased risk (RR: 2.10, 95% CI: 1.80–2.45) [34].

Another well-known risk factor, probably arising from an interplay of external influences, such as sun exposure and genetic predisposition, is the presence of nevi. A systematic meta-analysis confirmed that the number of common nevi and atypical nevi substantially influences the likelihood of cutaneous melanoma. The risk for people with a very high number of nevi (101–120) was found to almost seven times greater (RR: 6.89, 95% CI: 4.63–10.25) than for people with very few nevi (<15) [35]. A high nevus count is thereby strongly associated with melanoma on sites not usually exposed to the sun ($p < 0.001$) [36]. Moreover, the existence of abnormal or irregular nevi is recognized as a risk factor. The presence of 5 atypical nevi increases the risk of melanoma by 6 (RR: 6.36, 95% CI: 3.80–10.33), compared with individuals without any atypical nevus. The etiology of nevi is complex and is probably due to the interaction of multiple genes and environmental factors. Understanding the etiology of nevi and their changes during tumor progression, is important to better understand the pathomechanism of melanoma [35].

Nevus-associated melanomas represent 26–28% [37][38]. Traditionally, progression from nevi to melanoma was seen as linear, but in individual cases, stages may be skipped. Nevi constitute growth arrested, clonal neoplasms of melanocytes, caused by mutations in the mitogen-activated protein kinase (MAPK) pathway, most commonly by BRAFV600E-activating mutation. Most nevi will never progress to melanoma; some remain stable, while others regress. The low overall rate of nevus progression to melanoma suggests that robust tumor-suppressive mechanisms are initiated following BRAF and other mutations [39].

When considering gender-specific perspectives for melanoma, distinct patterns emerge in the incidence and localization of melanoma. Incidence rates among females aged 15–29 years are significantly higher than in males in the same age group (RR: 2.32; $p < 0.05$). Females being more affected in younger years, rates among both sexes increase with age, and differences between them attenuate with older age. From the age of 50 years onwards the incidence of melanoma among men is greater than in women [40][41]. At all ages, mortality rates are higher in males, whereas females show a highly consistent and independent advantage in overall survival, disease-specific survival, time to lymph node metastasis, and time to distant metastasis. These observations suggest differences in tumor–host interaction across gender [42]. In addition, gender-specific differences were found regarding tumor localization. In males, the trunk region predominates, comprising approximately 46.8% of melanoma cases, whereas women develop melanoma most frequently on the hip and lower extremities (39.5%) [43][44]. The observed differences may be linked to gender-specific clothing and sun exposure habits. Different risk patterns are particularly noticeable for intermittently sun-exposed areas. Sex-specific UV radiation exposure, such as men more commonly exposing their bare torso and women exposing their lower extremities, might contribute to melanoma risk in these regions [44][45].

Other intrinsic risk factors may be less apparent, but yet, are crucial: a personal medical history of skin cancer significantly increases the risk for melanoma. Melanoma survivors face an approximately 9-fold increased risk of developing subsequent melanoma compared with the general population. Furthermore, an individual's personal history of BCC is associated with an increased incidence of melanoma when compared with those without a BCC diagnosis (2.46% vs. 0.37%; $p < 0.0001$), leading to a 6.6-fold higher risk of melanoma in patients with BCC [46][47].

But not only is personal medical history significant: currently, family history is regarded as one of the most important risk factors for cutaneous melanoma [48]. Relatives of cases diagnosed with melanoma are at considerable lifetime risk of the disease, especially if the case was diagnosed at a young age. The relative risk of melanoma nearly doubles (RR: 1.74, 95% CI: 1.41–2.14) in subjects with first-degree relatives with melanoma and increases with the number of affected family members [34]. The cumulative risk of melanoma rises to 6.9% (6.1%) at age 80 in male (female) first-degree relatives of cases, and to 10.8% (9.5%) in relatives of cases diagnosed before age 50 [49]. Approximately 7–15% of all melanoma

cases occur in patients with a family history of melanoma. However, this does not necessarily indicate the transmission of a single genetic mutation in those families. In most cases of familial melanoma, shared experiences of sun exposure among family members with susceptible skin types must be considered [50][51].

Familial melanoma is a term used to describe families in which two or more first-degree relatives have been diagnosed with melanoma. It is a genetic condition and research is ongoing on potential melanoma susceptibility genes. To date, several genes have been linked to familial melanoma. CDKN2A, located on chromosome 9p21, is the major known high-risk melanoma susceptibility gene [52]. The largest familial melanoma sample yet available, included 466 families (2137 individuals) with at least three melanoma patients. The study revealed that CDKN2A mutation frequency varies from <25% to >50% in high-risk families, showing striking differences across geographic locations. These findings indicate that the development of tumors in CDKN2A mutation carriers is dependent on interactions between environmental and host factors other than the germline mutation. Familial melanoma cases with germline mutations in CDKN2A have younger ages at onset (40 vs. 50 years), have increased numbers of melanoma cases per family, and are more prone to developing multiple melanomas and other cancers, such as pancreatic cancer, compared with familial cases lacking CDKN2A mutations [53][54]. Mutations in CDKN2A are also detected in sporadic melanoma patients. The CDKN2A mutation frequency for patients without a family history, but with at least two primary melanoma, is around 8.2% [55]. Many other susceptibility genes have been discovered, including CDK4, BAP1, MITF, TERT, ACD, TERF2IP, POT1 and MC1R [56]. The melanocortin-1-receptor (MC1R) gene is the most common low risk susceptibility gene for melanoma, mutated in 70–90% of familial melanoma [57]. The gene is a key regulator of skin pigmentation by stimulating the preferential production of brown-black eumelanin compared with the red-yellow pigment of phaeomelanin [58]. MC1R is highly polymorphic and variants resulting in a partial loss of the receptor's signaling ability are associated with a quantitative shift of melanin synthesis from eumelanin to phaeomelanin, which is associated with the red hair color (RHC) phenotype [59]. It was demonstrated that individuals carrying a single MC1R variant exhibit 1.41 higher odds (95% CI: 1.07–1.87) of developing sporadic cutaneous melanoma compared with wildtype homozygous subjects. Moreover, carriers with two or more MC1R variants demonstrated 2.51 increased odds (95% CI: 1.83–3.44) of developing cutaneous melanoma. Interestingly, when considering phenotypic characteristics, it was shown that MC1R–associated melanoma risk increased only for darker-pigmented Caucasians, subjects with no freckles, no red hair and skin type III or IV. For individuals with the RHC phenotype, the risk of cutaneous melanoma was not independently predicted by having MC1R variants [60].

3. Risk Factors for Basal Cell Carcinoma

3.1. Extrinsic Risk Factors for BCC

In Australia, for example, it is assumed that nearly all BCCs are attributable to high UV exposure [12]. Both, intermittent and chronic sun exposure increase the risk for BCC. Intermittent sun exposure (>7000 h spent at the beach during holidays in a lifetime) is associated with a 2.1 increased odds (95% CI: 1.09–3.95) for BCC [61]. Sunburn often serves as a measure of intermittent sunlight exposure, and it is another, independent, extrinsic risk factor for BCC. Experiencing any sunburn during childhood or later in life is associated with a 1.43 (95% CI: 1.19–1.72) and 1.40 (95% CI: 1.02, 1.45) higher odds, respectively. A dose-dependent effect is observed: the risk of developing BCC doubles every 5 sunburns, regardless of whether they are experienced in childhood or later in life [62]. In addition to acute sun exposure, chronic UV exposure also contributes to the development of BCC. Individuals working outside have an odds ratio (OR) of 2.08 (95% CI: 1.24–3.50) to develop BCC in commonly UV-exposed body sites compared with controls without occupational sun exposure. The risk for outdoor workers increases independently of histological subtype, tumor localization and Fitzpatrick phototype [63]. While both intermittent and chronic sun exposure increase the risk of BCC, the exposure pattern and anatomical location appear to influence the histological subtype: nodular and infiltrative BCC primarily occur on the face, whereas superficial BCCs tend to develop on the trunk. This observation suggests that the nodular subtype is associated with chronic sun exposure, while intermittent sun exposure could be an etiological factor for superficial BCC [64]. This theory is further supported by divergent oncogenic mutations in the BCC subtypes, caused by different types of sun exposure: a significant association was observed between the superficial type of BCC and mutation of the Patched 1 (PTCH1) gene, which in turn was significantly associated with intermittent sun exposure [65]. The correlation between histologic subtype and the body region in which it occurs is further explained by variations in the extracellular matrix, which leads to a different susceptibility of different body regions to the development of specific histological subtypes of BCCs: a recent study highlighted that not all epidermal cells across the body are equally sensitive to oncogenic transformation and stressed the role of the extracellular matrix in the development of BCC. It showed that the composition of the extracellular matrix regulates how susceptible different regions of the body are to tumor initiation and invasion. Whereas the ear epidermis is susceptible to oncogenic transformation, the back skin proved to be profoundly resistant. More precisely, increased stiffness and a denser collagen I network e.g., in the back skin, provides natural resistance

against dermal invasion and tumor formation of BCC. Reducing collagen I expression in the back skin overcomes this natural resistance to tumor initiation [66].

In addition to natural UV radiation, the use of artificial radiation sources also poses a risk. Ever exposure to indoor tanning devices increases the risk of BCC by 29 % (RR: 1.29, 95% CI: 1.08–1.53). Furthermore, the age at first exposure is crucial: Indoor tanning before the age of 25 is associated with a 40 % increased risk of BCC (RR: 1.40, 95% CI: 1.29–1.52) [67]. Sunbed use not only increases the overall risk of developing BCC but also contributes to its occurrence at a young age, particularly before 40 years, which is known as early-onset BCC. Indoor tanning has been associated with a 69% increased risk of early onset BCC (95% CI: 1.15–2.48). Through population attributable risk calculations, it is estimated that around 27% of early-onset BCC cases could be averted by abstaining from indoor tanning. Particularly among women under the age of 40, the proportion of preventable cases is even more significant, with 43% of BCCs potentially avoided if females refrained from indoor tanning [68]. This gender-specific observation can be attributed to the higher frequency of tanning bed visits among women across Europe compared with men [69][70].

In addition to intentional, self-selected sources of radiation, medical treatment options also come with inherent side effects. Radiotherapy is a long-known risk factor for BCC. Exposure to radiation during childhood is linked to a substantial 6.3-fold risk (95% CI: 3.5–11.3) of developing NMSC, predominantly BCC (97%). Most of these tumors (90%) occurred within the radiotherapy field. The OR for subjects diagnosed with cancer requiring radiotherapy ≤21 years or younger, and receiving ≥35 Gray or more to the skin site compared with no radiation therapy was 39.8 (95% CI: 8.6–185) [71][72][73]. Not only patients, but also medical staff, are exposed to potentially harmful radiation, particularly those who worked in the more distant past. The relative risk of BCC is elevated in technicians who began their work in the 1950s (RR: 1.42, 95% CI: 1.12–1.80). The risk further increases, when work was initiated in the 1940s (RR: 2.04, 95% CI: 1.44–2.88), and even doubles when the occupation started before 1940 (RR: 2.16; 95% CI: 1.14–4.09), an era characterized by high ionizing radiation exposure, compared with those who commenced work after 1960 [74].

Individual lifestyle also has an influence on the development of BCC. Alcohol consumption, for example, is a risk factor for cutaneous BCC in both women and men. Regarding the different alcoholic beverages, wine and spirits were shown to be significantly associated with BCC development [25][75][76]. One possible explanation is that alcohol consumption has been associated with a higher number and severity of sunburns, indicating that the correlation is primarily due to more risky sun exposure habits [77][78]. Furthermore, it has been hypothesized that the combination of alcohol consumption and UV radiation can potentiate the skin carcinogenicity through the intermediate byproducts or metabolites of alcohol (e.g., acetaldehyde), which can serve as photosensitizers [79].

Conversely, certain lifestyle factors have a protective effect against the development of BCC. Various studies have shown that a high body mass index (BMI) is inversely associated with BCC risk. The substantial reduction in risk associated with a high BMI is noteworthy, as individuals with a BMI over 35 have up to a fourfold lower risk of developing BCC [80][81]. An explanation for this might be a different UV exposure behavior. Individuals with a greater body weight may be less inclined to expose their bodies to UV light in public places and tend to use solariums less than slim people [82].

A significant association between BCC and diseases related to iatrogenic or non-iatrogenic immunosuppression has been observed, for example in the context of organ transplantation or autoimmune diseases [83]. In comparison with the general population, the relative risk of BCC is increased sixfold in OTRs (standardized incidence ratio (SIR): 6.1, 95% CI: 5.4–6.9). The risk is higher in kidney and heart/lung recipients compared with liver recipients (SIR kidney 7.2, 95% CI: 6.3–8.3; SIR heart/lung 5.8, 95% CI: 4.0–8.2; SIR liver 2.6, 1.7–4.0), and it increases over time since transplantation [84].

Furthermore, the use of immunosuppressives, such as methotrexate, is associated with an increased risk of BCC (OR: 1.29, 95% CI: 1.20–1.38), with a linear dose–response effect [85].

3.2. Intrinsic Risk Factors for BCC

Apart from external factors, inherited genetic susceptibility also contributes to the risk of BCC development. Several phenotypic characteristics, in particular light complexion or low Fitzpatrick phototypes, modulate susceptibility to BCC: phototypes I, II and III have been shown to be independent risk factors for the development of BCC compared with phototypes IV–VI. A linear risk progression can be seen, with corresponding ORs of 17.5 (95% CI: 3.29–113.7), 15.6 (95% CI: 7.5–34.3) and 10.4 (95% CI: 5.1–22.4) for phototypes I, II and III, respectively [86]. The ORs of BCC is significantly increased in individuals with blonde (OR: 2.2, 95% CI: 1.27–3.91)) and light blonde to red hair (OR: 2.3, 95% CI: 1.15–4.49). Beyond hair color, the importance of eye color is noteworthy. Having light blue eyes show 1.8 increased odds for BCC (95% CI: 0.94–3.66), with green eyes even associated with a 3.4-fold increase in the odds (95% CI: 1.92–6.22) [61]. Another phenotypic risk factor for BCC are freckles in childhood (OR: 1.57, 95% CI: 1.29–1.92) [87][88].

Furthermore, genome-wide association studies have identified over 30 loci associated with BCC susceptibility [89]. Individuals carrying any MC1R variant have a significantly increased risk of BCC compared with subjects without MC1R variant. Carrying at least one MC1R variant is significantly associated with BCC (OR: 1.48, 95% CI: 1.24–1.76). Carriers of two or more MC1R variants have an even higher chance for developing BCC (OR: 1.70, 95% CI: 1.36–2.12) compared with carriers of one MC1R variant. It is important to notice that the MC1R-associated BCC risk was observed only for subjects without red hair, while in subjects with red hair, MC1R seemed not to have an effect in addition to phenotype. MC1R may therefore contribute to skin tumorigenesis through mechanisms distinct from pigmentation [90].

Other gene mutations associated with BCC are PTCH1, PTCH2, SUFU, and Smoothed (SMO). Especially PTCH1, but also PTCH2 and SUFU pathogenic variants, are associated with the hereditary or sporadic basal cell nevus syndrome (Gorlin-Goltz syndrome), which is characterized by numerous BCC, along with skeletal, ophthalmologic, and neurologic abnormalities. In this particular patient group age, number of sunburns and a history of radiation exposure are significantly associated with the severity of lifetime BCC [91][92].

Previous NMSC increases the risk of developing BCC. The 3-year cumulative risk for developing a subsequent BCC after the first one varies between studies, with a mean of 44% (33–70%). This represents an at least 10-fold increase in incidence compared with the rate in a comparable general population. The risk of developing BCC in patients with a prior cutaneous squamous cell carcinoma (cSCC) is approximately equal to the risk observed among individuals with a prior BCC [93].

For BCC development, gender-specific differences can be observed: male sex is an inherent risk factor for BCC. Being more frequent among females until the age of 40, it preferentially affects older males (>60 years old), leading to men having a higher aggregate risk than women. Age and male sex are two main, nonmodifiable, constitutive risk factors of BCC susceptibility [83][94]. Furthermore, there is a statistically significant association between site and sex. BCCs of the face, lower limb, lip and eyelid were more common in female patients, whereas BCCs of the ear/external auditory canal, scalp/neck, trunk, and upper limb were more common in male patients [95].

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