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Review

Non-Melanoma Skin Cancer Development and Environmental Factors

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Abstract

Multiple and interacting environmental factors are involved in the development of non-melanoma skin cancers (NMSC) in the Caucasian population. NMSC include basal cell carcinomas and squamous cell skin carcinoma. The aim of our paper was to present literature data on the etiopathogenesis of NMSC with special stress on environmental agents such as: ultraviolet radiation (including sunbathing), ozone depletion, smoking and occupational factors. The role of administered treatment with phototherapy and immunosuppresants is described as well. As skin cancer incidence has increased, the necessity of avoidance of NMSC risk factors is highlighted.

Keywords: non-melanoma skin cancers, basal cell carcinoma, squamous cell canrcinoma, ultraviolet radiation, occupational factors

Introduction

Non-melanoma skin cancers (NMSC), including basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), are the most common malignancies in the Caucasian population [1, 2]. Continuous increase in their numbers has been observed in the last few decades [3]. Literature data indicate that the lifetime risk for developing NMSC for a child born in 1994 in North America ranges from 28% to 33% for BCC and from 7% to 11% for SCC [4]. In South Wales, Holme et al. [5] showed a 16% increase in the number of SCC and 66% increase in BCC number over a 10-year period. The ratio of BCC to SCC has changed during last years and still the higher tendency for BCC development is noted. In 1998 it was estimated as 5:1 [5]. Despite the fact that BCC is more frequent, SCC has a greater metastatic potential and causes the majority of NMSC deaths [6]. Probably the number of NMSC is still underestimated because in some cases destructive treatment (cryotherapy, laser therapy, topical 5-fluorouracil ointment) without histological confirmation is performed. When surgical excision is performed, histological examination is always done [1].

Family history of skin tumors and the presence of BCC in some hereditary syndromes, like xeroderma pigmentosum or Gorlin's syndrome, may be proof of the significant role of genetic predisposition in their occurrence [7, 8]. However, in twins, according to Finnish studies, the total lack of concordance for skin cancer was observed [9], suggesting an important role of environmental factors in their development in a white population.

Multiple and interacting environmental agents play a potential role in skin cancer development. Lifestyles have changed rapidly in the last decades and it is fashionable to develop a "healthy" tan, generated by exposure to natural sunlight or to artificial sunlamps. Taking up outdoor sports like skiing or golf also contributes to BCC and SCC development [10]. Besides ozone depletion, exposure to certain occupational factors and phototherapy are known to be involved in carcinogenesis [1].

Therefore, the aim of this paper is to present literature data on environmental factors influencing the etiopathogenesis of non-melanoma skin cancers.

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Ultraviolet Radiation/Sunbathing

Ultraviolet radiation (UVR) is a well known etiologic agent for skin cancer in humans through DNA damage, damage repair and immunosuppression [11-13]. DNA photoproducts created after UV exposure can lead to mutations and skin cancers [14,15]. The most common photoproducts are cyclobutane pyrimidine dimmers, especially thymidine dimers and pyrimidine (6-4) pyrimidone photoproducts. UVR also activates p53 protein, which plays an important role in repair of DNA damage through up-regulations of genes involved in DNA repair and/or cell cycle arrest [16, 17]. The obtained data enabled the scientists to call p53 a "guardian of the genome" [18]. The presence of p53 mutations which are observed in 40-50% of BCC indicates its role in skin cancer development. Also, the increased frequency of mutations in *ras* family of proto-oncogenes, mutations in PTCH (human homologue of *Drosophilia* patched gene) tumor suppressor gene and elevated levels of IL-4 and IL-10 after UV exposure, reduce antitumor surveillance [12, 19, 20]. Besides experimental data, the highest frequency of BCC and SCC in people living in the area of the equator and often occurrence of skin cancers on UV-exposed sites like head, neck and hands prove UVR as a causative agent. Matta et al. [3] examined the population of Puerto Rico for NMSC and DNA repair capacity. They showed that patients with NMSC had statistically lower DNA repair capacity in comparison with the controls. In their study, a 1% decrease in DNA repair capacity increased the risk of NMSC developing by 21%.

Epidemiological studies have shown higher incidence of skin cancers in fair-skinned, red haired, and blue eyed populations. Many authors have revealed that burning easily, a history of sunburn in childhood and adolescence and the number of freckles in infancy, melanocytic nevi, solar lentigines and actinic keratosis are associated with the prevelance of BCC [8]. These results are consistent with the studies performed by Corona [21], Gallagher [22] and Vlajinac [23]. Corona et al. [21] found a 5-fold increase in the risk of BCC development after summer holiday exposure lasting longer than 8 weeks before the age of 20. Although Gallagher et al. [22] did not observe the association between cumulative sunlight exposure and BCC, however they also pointed out that the risk for BCC was increased in fair-skinned subjects. They concluded that the age from 0 to 19 years may be a critical period for establishing adult risk for BCC [21-23]. Multicentre South Europa study "Helios" showed that hair colour is more associated with NMSC occurrence than eye colour [24]. They also found that the number of sunburns and age of the first sunburn are risk factors for SCC, but not for BCC development. Odds ratio for BCC and SCC for I phototype subjects are 2.7 and 2.0, respectively.

Ozone Depletion

The ozone layer is a natural shield in the stratosphere which absorbs most of the harmful UV radiation before it reaches the earth's surface [25]. Ozone depletion, observed since 1985, is due to environmental pollutants like chlorofluorocarbons (CFCs) – long-lived chemicals used in coolants in refrigerators, air conditioners, foam-blowing agents and solvents [26]. The most evident ozone destruction is in Antarctica because of very cold conditions that transform ineffective substances into ozone-destroying forms. Literature data show that each 1% decrease in the ozone layer results in 1.7% and 3% annual increase in the incidence for BCC and SCC, respectively [25]. Madronich et al. [27] estimated that total ozone layer over the US decreased between 4.8%-7.4% in the period 1987-1992. These data and the fact that ozone depletion is expected to continue indicate that an increase in NMSC numbers will be noted over time. The next study confirming ozone depletion as an important factor in incidence of NMSC was performed by Moan et al. [28]. This data showed that in Northern Norway (located closer to the North Pole), where the population normally receives less sunlight when compared to its southern part, the related tumor density for skin sites frequently exposed to the sun is about 30 times higher for SCC and 60 for BCC than that on sites normally covered by clothes.

Tanning Beds

Over the last decades tanning has been assumed to be safe and healthy. Hence, the tanning industry is extremely large in America and Northern Europe. Epidemiological data show that in the US over 1 million people attend tanning salons every day. People are not aware of the hazardous effects of artificial UV radiation (sunbeds), especially the biological effects of tanning, molecular changes in the skin leading to carcinogenetic effects. UVR side effects depend on total dose received per year, and according to Western et al. [29] in Sweden adolescents attending tanning salons doubled doses considered "not harmful". Although Corona et al. [21] found no evidence of a positive association between BCC and the use of sunbeds, other studies show that repeated exposure to tanning beds might be a contributory factor [30]. Whitemore et al. [31] observed that short-term recreational tanning salon exposure causes cyclobutane pyrimide dimers in DNA and p53 protein expression, which are believed to be essential in the development of skin cancer. Diffey [32] estimated that the use of a UVA II (320-340 nm) device in a solarium 3 times a week for 30 minutes over a 20-year period would double the risk of developing SCC. Today scientists claim that clients of the tanning salons should be fully informed on side effects resulting from exposure to artificial UVR sources, especially in the aspects of photoaging and the increase in risk of skin cancers.

Immunosuppression

Although immunossupresion is not a real environmental factor, a wide spectrum of used drugs and therapeutic methods cause this biological effect and may provide NMSC development. This is the reason we decided to describe this problem more excessively. Prolonged immunosuppression caused by various diseases such as chronic lymphocytic leukemia, inflammatory disorders of the skin, connective tissue diseases, AIDS or administered treatment (transplant recipients, systemic corticosteroids, immunosuppresants) provide T- and B-cell depletion, dysfunction or dysregulation of immunological status and may result in NMSC development [33].

The most frequent group of malignancy in these patients is SCC and, in second place, BCC [34]. The exact number of NMSC in transplant recipients is difficult to estimate because many cancer registers do not record BCC and SCC. Furthermore, in some countries only the first episode of NMSC is recorded [34, 35].

Harvelt et al. [36] showed that an incidence of BCC in renal transplant recipients was 10 times higher than in the general population. In renal transplant recipients living in Queensland, Australia, an area of high ultraviolet light, the SCC/BCC ratio was reversed from 1:3.7 to 2:1 after transplantation. NMSC risk in immunosuppressed patients in the period over 20 years increases by 82% [35]. In the Netherlands 10% of renal transplant recipients developed skin cancer after 10-years, 40% after 20 years, and in the United Kingdom over 30% after a 10--year immunosuppression. In most studies, skin cancer rates are 2 to 3 times higher in the recipients of heart transplants when compared to age-matched kidney transplant recipients [34].

The most important risk factors of NMSC development in transplant recipients are immunosuppressive therapy, papilloma virus infection, solar radiation, arsenic exposure and phototype (skin type, eye and hair colour) and history of NMSC before transplantation [34, 37, 38]. Among commonly used immunosuppressants, azathioprine is believed to be a risk factor especially for SCC, cyclosporine for BCC and prednisolone for both. Literature data indicate that in the transplant recipients skin cancer may have both a more agressive course and the risk of local recurrence, regional and distant metastases, and increased mortality [33, 34]. In pediatric patients with solid organ transplants, skin cancer can be particularly aggressive [34].

Because of the special high risk of NMSC in the immunosuppressed patients, they should be educated about that problem and its prevention (sun avoidance, protective clothing and high factor UVA and UVB sunscreens application) and follow-up should be done [34].

The American Society of Transplantation recommends the in all renal transplant recipients careful skin examination should be performed by a physician (dermatologist) every year [39].

Photo- and Photochemotherapy (Psoralens and UVA, PUVA)

The association between the development of NMSC and photo- and photochemotherapy is still controversial [40]. These therapeutic methods are widely used in patients with various dermatoses such as psoriasis, atopic dermatitis, lichen planus, cutaneous T cell lymphoma, and others.

Although experimental studies (keratinocyte cultures, animal experiments) provide its mutagenicity and carcinogenicity, the exact influence of PUVA-therapy on NMSC occurrence in patients is not fully explained. The risk of development of SCC increases continuously with the cumulative UVA dose. A cumulative UVA dose higher than 1500-3000J/cm^2 and using potentially carcinogenic medications (arsenic, tar, ionizing radiation, UVB, metothrexate) increase the risk of PUVA therapy for NMSC, mainly SCC. The connection between PUVA and BCC is still unclear. Some authors suggest no association, or indicate the role of additional carcinogenic factors [40, 41]. Others observed more frequent occurrence of BCC in PUVA-treated patients [42, 43]. Seidl et al. [42] described that although psoralen and UVA are carcinogens and immunosuppressants they cause only minority of p53 mutations in PUVA-associated BCC.

Besides PUVA, UVB and UVA irradiations are commonly used in dermatology. It is known that UVB radiation (280-320 nm) is more carcinogenic than UVA radiation (320-400 nm). UVB radiation causes mutations in p53 which were found in human SCC and BCC. The UVA–carcinogenic effect is mediated through reactive oxygen species and largely without p53 mutations, but both sources of light (UVB, UVA) can raise genomic mutations, leading to NMSC development [44].

Smoking

Tobacco smoking is a risk factor for several cancers, but the association between smoking and NMSC development is not fully known. Hertog et al. [45] found statistically significant positive correlation between smoking and cutaneous SSC, with higher risk for current than for former smokers. These authors revealed a link between the number of cigarettes and pipes smoked and increase in cutaneous SCC development. However, in the study in Montreal region no-dose response relationship was found [46]. Also, it was observed that current smokers had a 50% increase in the risk of developing a cutaneous SCC compared with those who had never smoked [30]. The association between BCC and smoking also remains unclear. In some studies no increased risk of BCC was observed for subjects who smoked more than 6500 packs of cigarettes in a lifetime compared with non-smokers [21]. Similar results were noted by Van Dam et al. [47] Boyed et al.[30] found that BCC in young women is connected with past or current smoking. Also, Wojno

[48] noted a statistically significant correlation between BCC of the eyelid and smoking. Smith and Randle [49] described an increased prevalence of BCC larger than 1.0 cm in diameter among the smokers. Erbagci and Erkilic [50] suggest that smoking can play a key role in differentiation of BCC towards its sclerosing form, considered the most aggressive one.

Occupational Factors

Occupational factors including asphalt, tar, soot, crude paraffin, anthracene, pitch, organic and non-organic solvents, mineral oils, organophosphatic compounds, ionizing radiation, inorganic arsenic and solar exposure (outdoor workers) are known as risk agents for development of NMSC [23, 51, 52]. Also, contact with fibreglass dust and dry cleaning agents may be connected with an increased occurrence of BCC [53]. Moreover, the risk of developing BCC is higher among furriers and welders [51, 54]. For occupationally related skin malignancies the latency period usually lasts from several years to decades [52]. Letzel and Drexler [52] performed the study in tar refinery workers and they revealed that SCC was the most frequent skin malignancy and BCC was the second one, and the ratio of BCC to SCC was shifted towards SCC (1:1.7) when compared to 10:1 in general population.

Corona et al. [21] showed a tendency towards increased incidence of BCC only if an outdoor occupation had been carried out for more than 8 years while Vlajinac et al. [23] found this correlation only for summertime outdoor workers. On the contrary, Naldi et al.[8] observed no relation between BCC and occupational UV skin exposure. This is in line with the observation that an intermittent and intense sun exposure increases the risk of BCC while prolonged exposure to the sun, as in the case of outdoor occupations, is not associated with its development [13, 21].

Arsenic is a known carcinogen linked to skin cancer occurrence, particularly in regions with highly contaminated drinking water or in patients taking arsenic-containing medicines [55, 56]. In southwestern Taiwan, the concentration of arsenic in drinking water was as high as 1220μg/l. Tsend et al. [57] observed a dose-dependent relation between the arsenic level in drinking water and the prevalence of skin cancers. Arsenic contaminated drinking water also has been detected in Mexico, Argentina, Chile, India and Bangladesh [56]. In the USA, most of the epidemiological studies did not find any relation between skin cancers and arsenic concentrations in drinking water. Karagas et al.[56] described a higher incidence of NMSC in the individuals with the highest (above 97th percentile) toenail arsenic concentration (correlated with arsenic concentration in water) in the New Hampshire region, USA. Latency period for arsenic effects on the development of skin cancers is uncertain. Treatment of psoriasis with potassium arsenite (Fowler's solution) resulted in skin cancer development in the period of 3 to 40 years after drug administration [58]. Boonchai et al. [59] presented 36 patients with a history of another arsenic-containing medication (Bell's Asthma Medication) treatment in whom the first presentation of BCC was the mean age of 33 years old.

Ionizing radiation related with occupational exposure (mainly in the past) and prolonged therapeutic administration (tinea capitis, skin angioma, thymic enlargment in childhood) is associated with a subsequent NMSC occurrence, particularly BCC [60-62]. The results of the study performed in the Japanese atomic bomb survivors for the time period between 1958 and 1987 showed 54 BCC and 36 SCC in the irradiated group in comparison to 26 and 33, respectively, in the unirradiated one. There was a strong positive dose response association for BCC, but null dose response trend to SCC [63]. That excess risk of BCC has been related to the radiotherapy of inflammatory dermatoses as well as goiters, ankylosing spondilitis, acute lymphocytic leucaemia and astrocytoma [60]. Lichter et al. [60] found an increased risk for BCC which was confined to the site of radiation exposure. The correlation between NMSC and the age of the first radiation treatment was also observed. Steinert et al. [62] found that only one patient out of 99 who were exposed to radiation during the Chernobyl incident developed two BCC (15 years after exposure). It was also shown that young people and Caucasians are at highest risk of NMSC development after radiation exposure [60]. The latency period between first exposure and the development of skin cancer is estimated to be at least 20 years [60, 61].

According to the Skin Cancer Foundation, one in six Americans will develop skin cancer during their lifetime [64]. Modern populations consider themselves aware and well organized and they should realize dangers and benefits in their environment. It is extremely important to know how to avoid NMSC risk factors. The early diagnosis of skin cancers can prevent against any further complications (local invasion, destruction, metastases and death) and provide higher quality of life. The most common environmental factor is undoubtly exposure to UV radiation, so that using of sunscreens, protecting clothes and avoidance of acute seasonal exposure, especially in childhood and adolescence are of great importance in fighting against NMSC development. In light of literature data we would like to stress that in certain risk groups (transplant recipients, outdoor workers, people with I/II phototype) a regular skin check by dermatologists is strongly recommended.

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