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# Risk Factors for Squamous Cell Carcinoma of the Skin with Two Illustrative Cases and Literature Review

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**SUMMARY** Non-melanoma skin cancers, including basal cell carcinoma and squamous cell carcinoma are most frequently observed neoplasms worldwide. Their incidence has steadily been growing. Cutaneous squamous cell carcinoma is more common than basal cell carcinoma in dark complexion individuals. Every year, more than one million new cases of non-melanoma skin cancers (NMSC) are identified in the United States, which is roughly estimated to account for 50% of all cancers in this country. In this article, two illustrative cases are presented, which demonstrate the risk factors for cutaneous squamous cell carcinoma development, emphasizing the relationships and synergistic interactions in the process of carcinogenesis.

**KEY WORDS:** squamous cell carcinoma, non-melanoma skin cancer, lip cancer, scar cancer, ultraviolet induced carcinogenesis

## INTRODUCTION

Non-melanoma skin cancers (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), belong to the most frequently observed neoplasms in the world, while their incidence has steadily been growing. Every year, more than one million new cases of NMSC are identified in the United States, roughly estimated to account for 50% of all carcinoma cases in this country (1). The risk of BCC and SCC during average life span in the American population has been estimated to 30% and 4%-14%, respectively, depending on sex (higher incidence rates are noted in men than in women) (2,3). Spinocellular squamous cancer, derived from keratinocytes of the epidermal prickle-cell layer, is diagnosed 5-10 times less frequently than BCC in European populations; however, due to its much higher malignancy, infiltration and risk of metastases, it is responsible for the majority of NMSC-related mortality rate (4). In addition, it is more common worldwide in non-European lineage populations.

Multiple studies have now demonstrated a relationship between ultraviolet exposure and an increased risk of developing skin cancer (5,6). Populations of Europe, North America and Australia may have a different level exposure to UV radiation in their growing susceptibility to BCC and SCC development. Exposure to UV radiation in childhood, as well as UV exposure episodes experienced later in life may lead to BCC, whereas SCC usually occurs in elderly subjects following multi-year, chronic, sometimes occupational exposure to sun radiation (7-10). Latitude is an important factor, inseparably associated with UV intensity.

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For example, UV dose *per* time unit at the equator is about twice as high as that in Europe or in the northern regions of the USA and by 30% higher than that in the southern parts of the USA. The incidence of SCC increases also with age, being approximately 35 times higher for subjects after 75 *vs*. those between 50 and 55 years of life. Men are twice as often affected than women (11). Other factors predisposing to SCC development include ionizing radiation, UVA radiation combined with psoralens (PUVA), chronic inflammatory (ulcerations, fistulas, decubital ulcers) and atrophic diseases (post-burning and post-irradiation scars), local and general immunosuppression, infection with oncogenic viruses such as HPV 16, HPV 18, and chemical agents including arsenic, asbestos, polycyclic aromatic carbohydrates, as well as tobacco smoking and alcohol use (11-13). Moreover, SCC develops on the basis of pre-neoplastic changes, which include solar (actinic) keratosis, actinic cheilitis, Bowen's disease, and erythroplasia of Queyrat. This report presents two cases of SCC with regard to factors that may have contributed to their development.

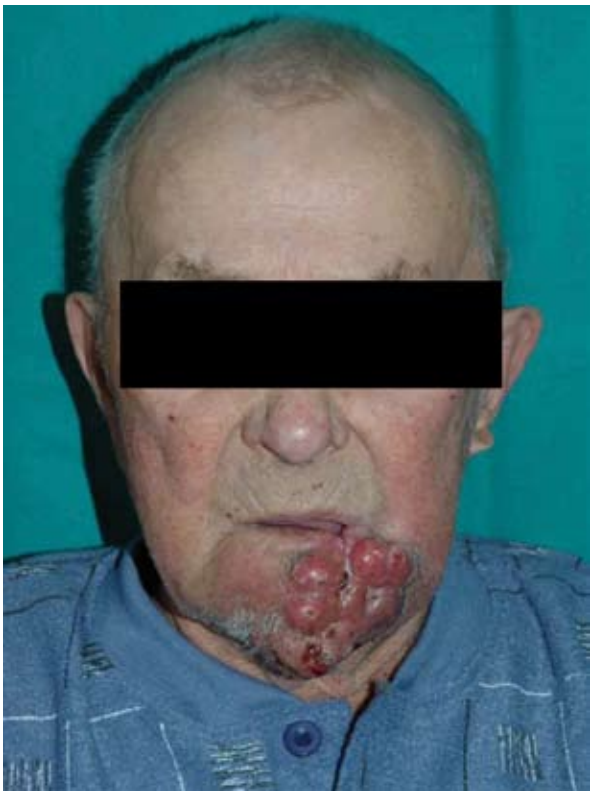

**Figure 1.** Squamous cell carcinoma involving the lower lip, oral mucosa and chin.

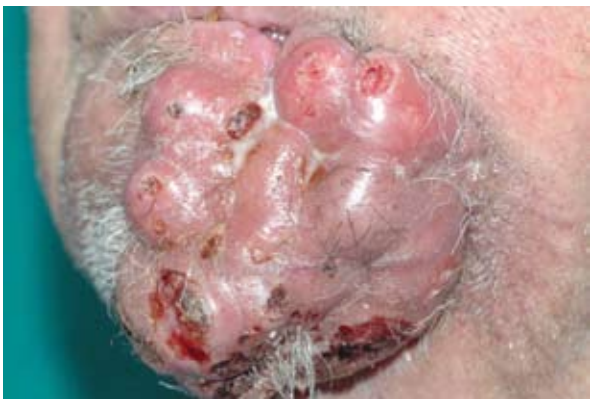

**Figure 2.** Squamous cell carcinoma on the lip and chin.

## CASE REPORTS

### Case 1

A 97-year-old man was seen for a tumor in the lower lip and chin area. Five years before, he had noted a small erosion in this region of his lip. It gradually enlarged to form an extensive tumor involving the entire area of the chin and lower lip mucosa. The tumor was neglected until pain and problems with difficult eating due to tumor size became intolerable. The patient was a farmer and exposed to solar/UV radiation in most of his outdoor activities. As he reported, he burned easily during outdoor activity. Since age 18, he used to smoke 20 cigarettes a day. For 25 years, he had received outpatient treatment for recurrent cheilitis, including protection and cryosurgery. However, he had last visited a dermatologist for this reason 12 years before. Now, an extensive tumor was identified, involving the lower lip, oral mucosa and chin (Figs. 1-3), together with enlarged submental, submandibular and cervical lymph nodes. Biopsy specimens showed a well-differentiated SCC (Figs. 4 and 5). Computed tomography (CT) scans of the head and neck revealed several enlarged lymph nodes of 8-10 mm in

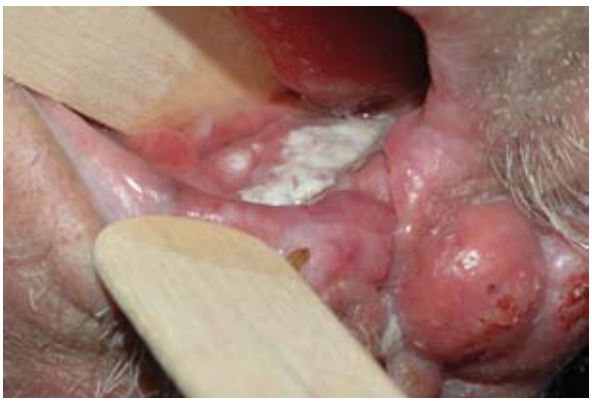

**Figure 3.** Squamous cell carcinoma infiltrating mucous membranes of the lower part of the oral cavity, in the lip area.

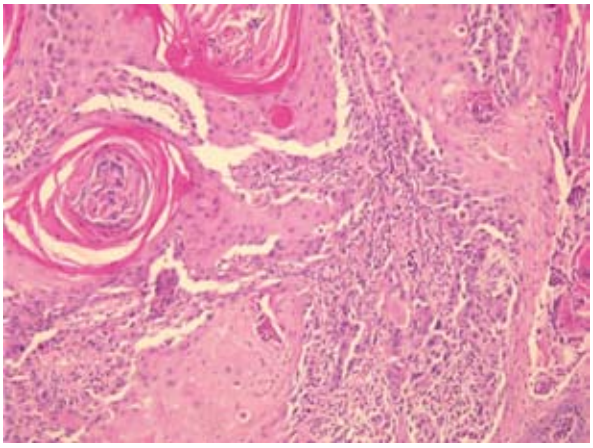

**Figure 4.** Squamous cell carcinoma: horn pearl visible in the central part. (HE; x100).

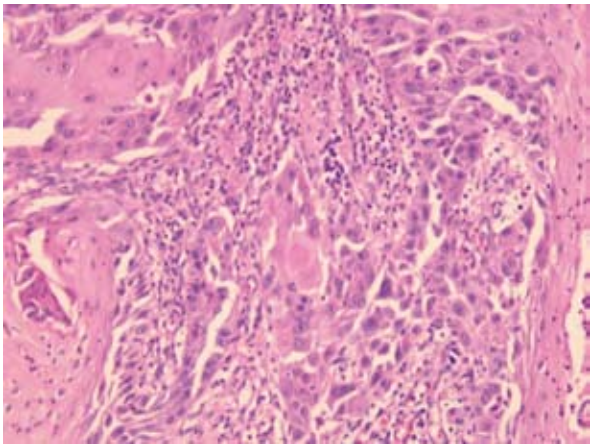

**Figure 5.** Well-differentiated squamous cell carcinoma with the horn pearl in the middle. (HE; x200)

size, localized in the submental region. An enlarged, changed lymph node of 10x9 mm in size was detected in the right submandibular region. An enlarged lymph node of 15x10 mm in size was found in the right cervical region and another one of 13.5x6 mm in the left cervical region. The tumor was assessed at T4, NX, MX. Because of the extent of the neoplastic process, the patient's age and multiple concurrent medical diseases, surgery was not considered and he was referred to a pain relief clinic.

### Case 2

A 53-year-old woman presented in 2008 with an ulcerated tumor localized in the sternal region of the chest. It began as a tiny erosion that appeared in the region 3 years before, then gradually enlarged and formed an extensive, disintegrating and bleeding tumor, occupying the entire surface of the sternum. At this site, she had suffered 2$^{nd}$ and 3$^{rd}$ degree burns from scalding hot water at age of 5. The burn injuries on sternal skin healed with formation of a hypertrophic, large scar. When the burn healed, the patient sought for many years dermatological and surgical aid to improve general cosmetic effect, including multiple injections of triamcinolone and x-ray irradiation.

The patient was evaluated for an extensive, disintegrating tumor localized in the sternal region (Figs. 6 and 7), with enlarged lymph nodes in both axillary fossae. A skin biopsy specimen showed a well-differentiated SCC (Figs. 8 and 9). Sternum CT scan showed ribs and clavicles free from infiltrative changes. Enlarged axillary lymph nodes, up to 17 mm on the right side and to 19 mm on the left side, were observed. The tumor was assessed as T4, NX, MX. The patient was referred for excision with a free split thickness skin graft; the axillary lymph nodes, both macroscopically changed and unchanged, were also removed. No neoplastic metastases were found to the lymph nodes of either axillary fossa.

## DISCUSSION

Skin carcinogenesis is a multistep process that includes initiation, promotion and progression, in which environmental as well as lifestyle dependent risk factors play a crucial role (14). Ultraviolet radiation, especially within the wavelengths between 290 and 320 nm (UVB), exerts a variety of biological effects including suppression of the immune system. The biological implications of photoimmunosuppression still remain mostly unclear. It certainly plays a crucial role in photocarcinogenesis since chronically immunosuppressed patients including transplant recipients have a dramatically increased risk to develop

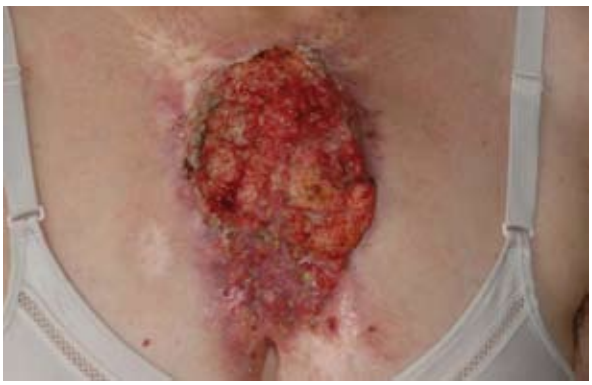

**Figure 6.** Squamous cell carcinoma on the chest, sternal region, infiltrating neighboring tissues.

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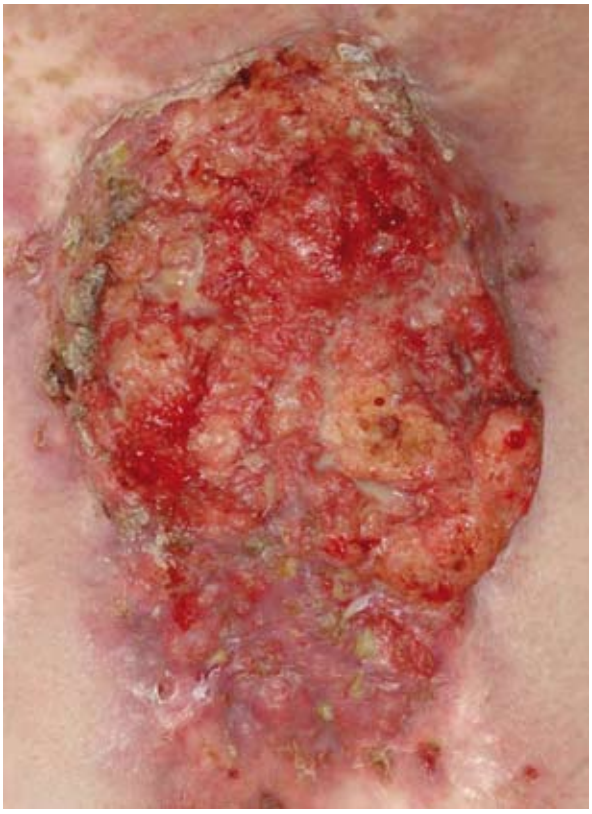

**Figure 7.** Squamous cell carcinoma on the chest infiltrating neighboring tissues.

skin cancer and it strongly correlates with cumulative UV radiation exposure (15). Therefore, UV radiation is considered as one of the major causative factors of NMSC, including SCC. This type of radiation also leads to premature skin aging, and induces immunosuppression, inflammatory reactions and cell death. The negative impact of UV radiation on host defense against skin tumors has been convincingly demonstrated in various experimental animal models. UV radiation induces immunosuppression, which enables the outgrowth of transplanted epithelial skin cancers and melanomas in mice (16,17). The key molecular event in UV-induced photoimmunosuppression and associated photocarcinogenesis is DNA alteration, manifested by the formation of characteristic structures such as cyclobutane pyrimidine dimers and 6-4 photoproducts (18,19). There is, however, a defensive mechanism protecting against UV detrimental effects, while most DNA is corrected by the activity of nucleotide excision repair (NER) (20). The significance of this mechanism is most characteristic in patients with xeroderma pigmentosum, in whom the lack of genetic material repairing enzymes increases the susceptibility to skin neoplasms. These phenomena have

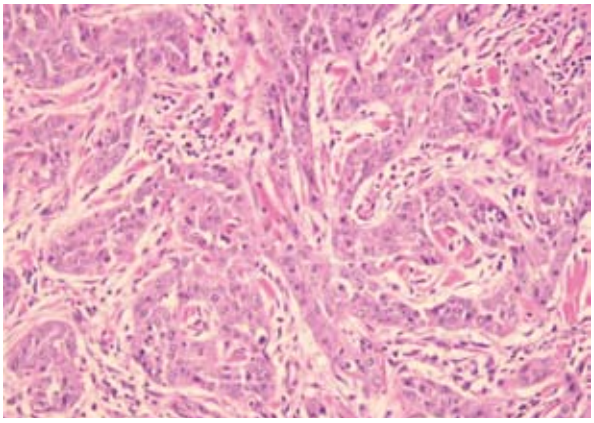

**Figure 8.** Well-differentiated squamous cell carcinoma. (HE; x200)

been very clearly explained on an animal model designed by Vries *et al.* (21).

For SCC, the risk of development of malignant formation is higher in male patients, especially above 60 years old, with a history of severe actinic skin damage and who burned easily on sun exposure (22). The history of sunburn linked with agricultural occupation as important risk factors for SCC are well presented in the wide study by Hogan *et al.* (23). Our patient no. 1, being a farmer, was by occupation exposed to multi-year effects of solar/UV radiation. According to reported statistical data, the prevalence rates of SCC are usually higher in Caucasian men, being usually localized in the lower lip area (24). The patient also had the anticipated precursor neoplasms, solar keratosis and actinic cheilitis. Actinic keratosis and actinic cheilitis are analogous (25,26). Abreu *et*

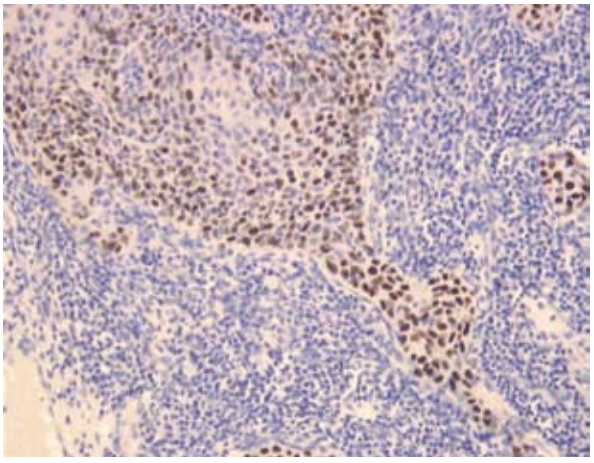

**Figure 9.** Immunochemistry staining showing overexpression of p53 protein in tumor cells (brown stained cells). (original magnification X200)

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*al.* confirmed the relationship of actinic cheilitis with SCC of the lip, while the rate of metastases was lower in patients with SCC with concurrent actinic cheilitis in comparison to those with SCC but without actinic cheilitis (27). Thus, the coexistence of actinic cheilitis may be a favorable prognostic factor in the course of SCC of the lip. Moreover, this patient was a long-term tobacco smoker. Kargas *et al*. showed that the rate of SCC was significantly higher among current and former smokers in comparison to persons that never smoked, and increased with the duration and amount of cigarettes smoked (22). Tobacco smoking is globally the most preventable cause of death in developed countries, and a great public health concern. Despite the negative effect on cardiovascular and pulmonary systems, smoking leads to a variety of cutaneous manifestations. Tobacco smoking is clearly associated with poor wound healing (28), wrinkling and premature skin aging (29), psoriasis (30), and exacerbation of cutaneous manifestations of autoimmune diseases such as systemic lupus erythematosus (SLE), where smoking patients were less responsive to antimalarial treatment (31). Most importantly, it induces carcinogenesis. More than 40 mutagenic and carcinogenic substances have so far been identified in tobacco smoke, including heterocyclic amines, aromatic hydrocarbons and various nitrosamines, with the main risk of cancer for the organs directly affected by tobacco smoke, such as oral cavity, esophagus, lungs and pharynx. In addition, although in a smaller degree, other organs also demonstrate indirect consequences of tobacco smoke, such as uterine cervix, pancreas, kidneys and stomach (32).

Most studies worldwide confirm an association between tobacco smoking and cutaneous SCC (33). According to recent reports, cigarette smoking is one of the key factors for the development of SCC of the lip, as presented data estimate 80% of patients with SCC of the lip to have been or being tobacco smokers (34). What is interesting, the relation between smoking and the development of BCC remains a point of controversy. Since the number of smokers is fairly high in the US population, as well as in the populations of other countries in the world, and lesions of SCC type develop only in a very small portion of smokers, concurrent risk factors have been postulated, which may additionally stimulate cancer development in this particular area.

These factors include mainly chronic exposure to UV radiation (discussed above), as well as alcohol intake (35). The goal of current studies is to analyze these factors not only as separate risk factors for NMSC, but also their synergistic carcinogenic effects.

Recent data confirm a higher prevalence of NMSC as well as melanoma in alcoholics in comparison to non-drinking subjects (36-38). The mechanism by which alcohol promotes carcinogenesis has not yet been well understood; however, a number of possible pathways for alcohol-dependent carcinogenesis are postulated, including, among others, alcohol (ethanol) transformation into acetaldehyde (AcH) and formation of free radicals. It is AcH, an alcohol metabolite, which is classified as the main carcinogen. Saladi *et al.* describe a hypothetical concept of alcohol (ethanol) effects, with simultaneous exposure to UV radiation, of cell damage, leading to skin cancer development. The postulated theory given considerable credence is that the products of alcohol metabolism behave as photosensitizers, increasing the degree of DNA and cell damage (39), thus increasing the risk of carcinogenesis. Moreover, alcohol consumption seems to be a behavioral risk factor of the higher prevalence of sunburns (13) and therefore an indirect pathway to the development of SCC.

Scars from skin burning represent a pivotal risk factor for NMSC development, especially SCC (12,40). Skin burnings, especially those experienced in childhood, used to be a common denominator and factor, frequently mentioned as highly significant for NMSC development. Our patient no. 2 suffered from severe burning at 5 years of age. In consequence of thermal skin injury, hypertrophic, spread scars developed and have remained. The initial treatment protocol of the patient included injections of steroids, including triamcinolone. Considering the locally immunosuppressive effects of those drugs, as well as their long-term use, they can also be regarded as co-factors, additionally increasing the risk of carcinogenesis. Apart from scar injections with triamcinolone, the patient was also treated by locally applied x-ray irradiation, a well-established skin cancer promoting factor.

## CONCLUSION

The two illustrative cases demonstrate risk factors for the cutaneous SCC development, emphasizing the relationships and synergistic interactions in the process of carcinogenesis.

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By rain, wind and snow use Nivea cream; year 1935.
(from the collection of Mr. Zlatko Puntijar)