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ANALYSIS OF RISK FACTORS AND THERAPEUTIC APPROACHES IN CUTANEOUS SQUAMOUS CELL CARCINOMA: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: The aim of this study is to explore scientific advances related to cutaneous squamous cell carcinoma (cSCC), with emphasis on risk factors, diagnostic methods, and therapeutic approaches, as well as prevention strategies for this pathology. Methodology: This systematic review was based on the following guiding question: What are the recent advances in the diagnosis, prevention, and treatment of cutaneous squamous cell carcinoma, considering the associated risk factors? To this end, searches were performed in the PubMed database, using specific descriptors combined with the Boolean term "AND". The process resulted in the selection of 8 relevant articles, which were analyzed in detail for this review. Results: Cutaneous squamous cell carcinoma (cSCC), a type of non-melanoma skin cancer, is characterized by varied risk factors, including exposure to ultraviolet (UV) radiation, smoking, and obesity. Diagnosis is largely guided by staging systems such as AJCC-8 and BWH, which help stratify cases according to risk. Molecular advances have revealed important epigenetic and genetic mechanisms, such as mutations in TP53 and

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CDKN2A genes, as well as the use of hyaluronic acid as a potential therapeutic tool. Immunotherapy and new targeted therapies, such as immune checkpoint inhibitors, have shown promising results in the management of advanced cases. In prevention, strategies such as systemic photoprotection, with the use of nicotinamide and Polypodium leucotomos, in addition to healthy eating habits, have been shown to be effective in reducing the risk of developing cSCC. Conclusion: The study emphasizes the importance of future research to deepen the understanding of the molecular mechanisms of cSCC and to evaluate the efficacy of new therapeutic and preventive approaches in the long term. Such advances have the potential to reduce mortality and significantly improve the quality of life of patients.

Keywords: Cutaneous Squamous Cell Carcinoma. Risk Factors. Diagnosis. Prevention. Molecular Therapies.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is one of the most prevalent non-melanoma skin cancers in the world, presenting a considerable burden on public health due to its high incidence, potential for metastasis, and associated mortality in advanced cases (Desai et al., 2023). This malignancy derives from the keratinocytes of the epidermis and is widely associated with risk factors such as cumulative exposure to ultraviolet (UV) radiation, immunosuppression, smoking, and genetic predispositions (Sawada & Nakamura, 2021). In recent years, scientific advances have elucidated the molecular and epigenetic mechanisms underlying the pathogenesis of cSCC, paving the way for new strategies for diagnosis, prevention, and treatment (Cozma et al., 2023).

The importance of photoprotection as a preventive measure has been widely recognized, with the use of compounds such as nicotinamide and Polypodium leucotomos showing promise for reducing UV-induced skin damage (Hyeraci et al., 2023). In addition, prognostic indicators, such as the Rate of Growth (ROG), emerge as valuable tools in risk stratification, allowing for more personalized and effective therapeutic interventions (Giuffrida et al., 2020). The integrated approach between prevention, diagnosis, and therapeutic advances, including targeted immunotherapies, has shown promising results to improve clinical outcomes in patients with advanced cSCC (Maubec, 2020).

This article systematically addresses risk factors, diagnostic methods, preventive strategies, and therapeutic advances in the management of cSCC, based on a rigorous selection of scientific literature. The investigation aims to contribute to a deeper understanding of the disease, highlighting the mechanisms that support its progression, and to evaluate the impact of clinical and molecular interventions on the treatment and prevention of cSCC (Roel et al., 2020).

The objective of this article is to explore and synthesize the most recent scientific evidence on cutaneous squamous cell carcinoma (cSCC), covering risk factors, diagnostic advances, preventive strategies, and innovative therapies. It seeks to understand the interaction between external and internal factors that contribute to the pathogenesis of cSCC, as well as to evaluate the efficacy of clinical and molecular approaches to the management of the disease. Cutaneous squamous cell carcinoma is one of the most prevalent forms of non-melanoma skin cancer, with high morbidity and potential for metastasis, especially in advanced cases. Despite its clinical relevance, many aspects related to early diagnosis, effective prevention, and targeted treatments still require further investigation. Advances in molecular research have provided significant insights into the mechanisms underlying carcinogenesis, revealing new therapeutic possibilities, such as

immunotherapies and systemic photoprotection strategies. However, there is a need to consolidate these findings into a comprehensive analysis that contributes to clinical practice and education on the best approaches to the prevention and treatment of cSCC. This article is justified by the urgency of translating scientific evidence into practical recommendations that can reduce the incidence, improve outcomes, and increase the quality of life of patients.

METHODOLOGY

This is a systematic review that seeks to analyze the main advances related to cutaneous squamous cell carcinoma (cSCC), highlighting the associated risk factors, diagnostic methods, and therapeutic and preventive approaches employed in the management of this pathology. For the development of the research, a guiding question was elaborated using the PVO (population, variable and objective) strategy: *What are the recent advances in the diagnosis, prevention and treatment of cutaneous squamous cell carcinoma, considering the associated risk factors?*

The searches were carried out in the PubMed Central (PMC) database. Five descriptors were used in combination with the Boolean term "AND": *Squamous cell carcinoma*, *Risk factors*, *Skin neoplasms*, *Skin cancer prevention* and *Ultraviolet radiation*. The search strategy applied was: *Squamous cell carcinoma AND Risk factors AND Skin neoplasms*, *Squamous cell carcinoma AND Skin cancer prevention*, and *Squamous cell carcinoma AND Ultraviolet radiation*. With this approach, 45 articles were identified, which were submitted to the selection criteria.

The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2020 to 2025 and that addressed topics compatible with the guiding question; in addition, review, observational and experimental studies, as long as they are available in full. Exclusion criteria included: duplicate articles, presented as abstracts, that did not directly address the proposed theme or that did not meet the inclusion criteria.

After applying the descriptors and selection filters in the searched databases, a total of 45 articles were identified. Of these, 15 articles met all the inclusion and exclusion criteria, and 8 studies were used to compose the review and support the discussions.

DISCUSSION

Cutaneous squamous cell carcinoma (cSCC) is a keratinocyte-derived malignancy of the spinous layer of the epidermis, whose etiology is intrinsically related to multiple factors affecting genetic integrity and cellular functionality. A detailed understanding of the

processes involved in the emergence and development of cSCC is crucial for effective diagnosis, prevention, and treatment.

The carcinogenesis of cSCC is a complex process that involves genetic and epigenetic changes in keratinocytes, resulting in a high mutational burden. These changes include mutations in tumor suppressor genes, such as **TP53**, and in genes involved in DNA repair, such as **CDKN2A**. These mutations compromise cell cycle regulation and apoptosis, allowing uncontrolled cell proliferation and the formation of malignant tumors (Cozma et al., 2023).

In addition to genetic alterations, epigenetic mechanisms play a significant role in the progression of cSCC. Aberrant DNA methylation and histone modifications are examples of epigenetic alterations that result in dysregulated expression of genes involved in tumorigenesis. These epigenetic changes can silence tumor suppressor genes or activate oncogenes, contributing to the malignant transformation of keratinocytes (Cozma et al., 2023).

Advances in understanding these molecular and epigenetic mechanisms have led to the development of new targeted therapies. For example, immune checkpoint inhibitors, such as anti-PD-1 antibodies, have shown efficacy in the treatment of advanced cSCC by restoring the immune system's ability to recognize and eliminate tumor cells (Cozma et al., 2023).

UV radiation is the main etiological factor in the development of cSCC, being responsible for causing direct damage to the DNA of skin cells. The formation of pyrimidine dimers, especially in tumor suppressor genes such as **TP53**, results in point mutations that compromise cell repair mechanisms and cell cycle regulation. This exposure is cumulative and more prevalent in fair-skinned people who have a lower ability to protect against UV damage due to the low amount of melanin (Ansary et al., 2022; Desai et al., 2023).

In addition, UV radiation causes local immune changes, reducing the effectiveness of cutaneous immune surveillance. This creates a permissive environment for the proliferation of mutated cells and facilitates the emergence of cancer. Type B ultraviolet (UVB) radiation is more carcinogenic than UVA, being the main responsible for genotoxic and epigenetic changes in keratinocytes (Desai et al., 2023).

Immunosuppression is another central factor in the etiology of cSCC. Transplant patients, who require immunosuppressive drugs such as cyclosporine or tacrolimus, have a significantly higher risk of developing cSCC. These drugs not only suppress the immune ability to eliminate emerging cancer cells, but also favor genetic changes that stimulate tumor growth (Ansary et al., 2022; Desai et al., 2023). Immunosuppressed individuals have

a higher rate of metastasis and recurrence, which reflects the critical role of the immune system in preventing the development of malignancies. In these populations, cSCC is more aggressive and is often associated with worse clinical outcomes (Desai et al., 2023).

Genetic mutations play a crucial role in the origin of cSCC. The **TP53** gene, which regulates apoptosis and DNA repair, is often altered in cases of cSCC. These mutations prevent proper cell cycle control, allowing uncontrolled proliferation of keratinocytic cells. In addition, mutations in the **CDKN2A** gene, which encodes the p16 and p14 proteins, are also common and contribute to malignant cell growth (Ansary et al., 2022; Giuffrida et al., 2020). Another important genetic marker is **tumor growth rate (ROG),** an emerging measure in the assessment of cSCC aggressiveness. Tumors with a GBR greater than 4 mm/month have a high probability of progression and metastasis, indicating an accelerated pathogenesis associated with aggressive genetic alterations (Giuffrida et al., 2020).

Exposure to carcinogenic compounds such as arsenic, pesticides, and solvents is also associated with the emergence of cSCC. These chemicals cause direct DNA damage and increase UV-induced genotoxicity, promoting cellular changes that culminate in malignant transformation (Ansary et al., 2022). Arsenic, in particular, is related to the development of cSCC due to its ability to interfere with DNA repair mechanisms and to increase oxidative damage, especially in sun-exposed areas of the skin. These characteristics reinforce the importance of identifying and mitigating environmental and occupational exposures as part of primary prevention (Ansary et al., 2022).

Certain genetic syndromes and skin conditions predispose to the development of cSCC due to defects in DNA repair or cell growth regulation. Among these conditions are:

Genetic conditions, such as Xeroderma Pigmentosum, related to deficiency in the repair of damage caused by UV radiation, and Epidermodysplasia Verruciformis, associated with persistent high-risk human papillomavirus (HPV) infections, which contribute to malignant transformation, increase the predisposition to cutaneous squamous cell carcinoma (cSCC). In addition, Oculocutaneous Albinism, due to the lack of pigmentation, severely reduces protection against UV radiation, increasing susceptibility to cSCC (Desai et al., 2023; Giuffrida et al., 2020).

Human papillomavirus (HPV), especially its high-risk strains, plays a significant role in the etiology of cSCC, particularly in mucosal and head and neck regions. HPV interferes with cell cycle regulation mechanisms by inactivating proteins such as **p53** and **RB,** promoting uncontrolled cell proliferation and carcinogenesis (Glastonbury, 2020).

Although these etiological factors are often described separately, they interact in complex ways. For example, UV radiation can potentiate the carcinogenic effects of

arsenic, while immunosuppression aggravates genetic damage and allows viral infections like HPV to have a deeper impact. These multifactorial mechanisms reinforce the need for an integrated approach in the assessment and management of cSCC (Ansary et al., 2022; Desai et al., 2023).

RISK FACTORS

Cumulative exposure to UV radiation is the main risk factor for the development of cSCC. UVB radiation has greater carcinogenic potential compared to UVA, as it causes direct mutations in the DNA of keratinocytes, mainly by the formation of pyrimidine dimers. These genetic alterations result in mutations in tumor suppressor genes, such as **TP53**, promoting uncontrolled cell growth. People with fair skin are particularly vulnerable due to melanin's lower natural protection against UV damage. In addition, the use of tanning beds significantly increases the risk, considering the concentrated emission of UVA radiation, amplifying DNA damage (Ansary et al., 2022; Desai et al., 2023).

Several genetic disorders increase the predisposition to cSCC, often associated with mutations in genes involved in DNA repair or cell regulation. Genetic conditions such as Xeroderma Pigmentosum, which causes deficiency in the repair of UV-induced DNA damage, resulting in high susceptibility to skin cancer; Oculocutaneous Albinism, due to the lack or reduction of melanin, which drastically decreases UV protection; and Epidermodysplasia Verruciformis, characterized by susceptibility to human papillomavirus (HPV) infections and a higher risk of cSCC, are important factors in the etiology of cutaneous squamous cell carcinoma (cSCC) (Ansary et al., 2022; Giuffrida et al., 2020; Desai et al., 2023).

Immunocompromised patients, such as organ transplant recipients and individuals with HIV, are at increased risk of developing cSCC. Compromised immunity reduces the immune system's ability to identify and eliminate emerging cancer cells. In addition, transplant recipients who use immunosuppressive drugs, such as cyclosporine and tacrolimus, have a 65-fold increased risk of developing cSCC. In immunosuppressed patients, the lesions are usually more aggressive, with a higher probability of metastasis and a worse prognosis (Desai et al., 2023).

Smoking is a risk factor for head and neck cSCC (cSCCHN). The chemical compounds in tobacco damage DNA and promote chronic inflammation, favoring carcinogenesis. Although smoking is negatively associated with melanoma, it correlates positively with cSCC, especially with regional lymph node metastases and tumor ulceration. Alcohol consumption is also linked to greater tumor aggressiveness and the development of

lesions in the oral cavity and pharynx, especially when combined with sun exposure (Glastonbury, 2020; Desai et al., 2023).

Smoking is a recognized risk factor for several malignancies, including skin cancer. Although it is negatively associated with melanoma incidence, it is not related to specific mortality or sentinel lymph node metastasis. However, in cSCC, smoking increases sentinel lymph node metastasis and tumor ulceration. Tobacco chemicals damage DNA and promote chronic inflammation, creating conditions for malignant transformation of keratinocytes (Sawada; Nakamura, 2021).

Human papillomavirus (HPV) infection, especially by high-risk strains, is directly linked to the development of cSCC, especially in anogenital and head and neck areas. Oncogenic HPV interferes with tumor suppressor proteins, such as **p53** and **RB,** promoting uncontrolled cell proliferation and malignant transformation (Glastonbury, 2020).

The circadian rhythm, also known as the "biological clock," regulates several physiological processes, including sleep, body temperature, and hormone secretion. Disruption of this rhythm, as occurs in night shift workers or people exposed to irregular hours, is associated with an increased risk of developing skin cancers. Studies indicate that chronic exposure to irregular schedules can lead to alterations in cell cycle regulation and immune response, favoring carcinogenesis. This dysregulation can compromise the body's ability to repair DNA damage induced by ultraviolet (UV) radiation, increasing susceptibility to melanoma and cSCC (Sawada; Nakamura, 2021).

Alcohol consumption is another lifestyle factor that influences the risk of skin cancer. Although the studies present controversial results, a meta-analysis revealed an increased relative risk of malignant melanoma in individuals who consume alcohol regularly. In addition, alcohol consumption is associated with an increased risk of basal cell carcinoma and cSCC in a dose-dependent manner. Alcohol can act as a tumor promoter, increasing the skin's susceptibility to damage caused by UV radiation and compromising DNA repair mechanisms (Sawada; Nakamura, 2021).

Obesity is a significant risk factor for several diseases, including skin cancers. Studies indicate that obesity is associated with an increased risk of melanoma in younger individuals and greater tumor thickness in cases of malignant melanoma. In the case of cSCC, obesity can contribute to tumor progression through mechanisms such as chronic inflammation, insulin resistance, and changes in the tumor microenvironment. These factors create favorable conditions for the growth and spread of cancer cells (Sawada; Nakamura, 2021).

Diet plays a crucial role in modulating the risk of skin cancer. Intake of dietary fiber, vegetables, and fruits is associated with protective effects against melanoma and cSCC. These foods are rich in antioxidants and bioactive compounds that help neutralize free radicals generated by UV radiation exposure, protecting skin cells from oxidative damage. On the other hand, the consumption of certain compounds present in citrus fruits, such as furocoumarins, may increase the risk of basal cell carcinoma due to their ability to sensitize the skin to UV radiation (Sawada; Nakamura, 2021).

In addition, omega-3 fatty acids, found in fish and seeds, have been shown to have protective effects against melanoma and cSCC, while omega-6 fatty acids, present in vegetable oils and processed foods, are associated with an increased risk of basal cell carcinoma and cSCC. Balanced intake of these nutrients is essential for maintaining skin health and reducing the risk of skin malignancies (Sawada; Nakamura, 2021).

Daily lifestyle has a significant impact on the development of skin cancers such as malignant melanoma and cSCC. Factors such as circadian rhythm, smoking, alcohol consumption, obesity, and diet have a complex influence on the risk of cutaneous carcinogenesis. Understanding these relationships is essential for developing more effective prevention and treatment strategies. Promoting healthy habits, such as maintaining a balanced diet, avoiding smoking and excessive alcohol consumption, and adopting protective measures against UV radiation, can significantly reduce the incidence of these malignancies (Sawada; Nakamura, 2021).

Specific histological subtypes of cSCC, such as desmoplastic, adenosquamous, and acantholytic, are at higher risk of recurrence and metastasis. Perineural invasion, characteristic of more aggressive tumors, is associated with a worse prognosis. Studies show that lesions with perineural invasion are more likely to have local recurrence and regional spread, negatively impacting patient survival (Desai et al., 2023).

Exposure to chemicals such as arsenic and hexavalent chromium increases the risk of cSCC. Professions that involve outdoor work, such as agriculture and construction, expose individuals to high levels of UV radiation, as well as potential carcinogenic chemical agents. Occupations that deal with solvents and pesticides also show increased risk due to long-term exposure to mutagens (Ansary et al., 2022).

cSCC is more prevalent in males and over 65 years of age, attributable to higher cumulative exposure to risk factors throughout life. Fair-skinned people (Fitzpatrick phenotype I and II) are more susceptible to cSCC due to the lower protection conferred by melanin against UV radiation damage (Ansary et al., 2022; Desai et al., 2023).

AGGRESSIVE CHARACTERISTICS AND PATHOGENESIS

cSCCHN, a more aggressive variant of cSCC, exhibits specific characteristics such as a diameter greater than 2 cm, depth of invasion greater than 5 mm, and a high recurrence rate. These tumors often invade deep structures and nerves, characterizing perineural invasion, which is associated with a worse prognosis and a higher risk of locoregional dissemination. In addition, histological subtypes, such as desmoplastic and acantholytic, are at higher risk of metastasis (Desai et al., 2023).

Genetic mutations play a central role in the pathogenesis of cSCC. The TP53 gene, which regulates the cell cycle and apoptosis, is often mutated in cases of cSCC. Other common mutations include CDKN2A, which encodes the tumor suppressor proteins p16 and p14, directly affecting cell cycle control. These genetic alterations promote cell growth dysregulation, resulting in tumorigenesis (Ansary et al., 2022).

Tumor growth rate (ROG) is also an emerging biological marker to assess the potential for cSCC metastasis. Recent studies suggest that a GBR greater than 4 mm/month may be associated with more unfavorable clinical outcomes, justifying immediate interventions in cases of rapid growth (Giuffrida et al., 2020).

The etiology, risk factors, and pathogenesis of cSCC reflect its complexity as a multifactorial disease. While environmental factors, such as UV radiation, smoking, and HPV infections, play crucial roles, genetic and immunological characteristics are determinants of tumor progression and aggressiveness. Understanding these interactions is key to improving strategies for prevention, early diagnosis, and therapeutic management of cSCC (Ansary et al., 2022; Desai et al., 2023; Giuffrida et al., 2020; Glastonbury, 2020).

The diagnosis and prognosis of cutaneous squamous cell carcinoma (cSCC) and its variants, such as cutaneous head and neck squamous cell carcinoma (cSCCHN), are fundamental aspects for clinical management and the definition of therapeutic strategies. Below, I present a detailed and in-depth analysis, based on the aforementioned articles, addressing staging systems, prognostic criteria, and the implications of incomplete excision.

DIAGNOSIS AND STAGING

The diagnosis of cSCC and cSCCHN involves a detailed clinical evaluation, complemented by histopathological and imaging tests. Staging is essential to determine the extent of disease, predict prognosis, and guide treatment.

The American Joint Committee on Cancer (AJCC-8) 8th edition staging system is widely used to classify cSCC tumors, especially in the head and neck region. It considers three main parameters: the size of the primary tumor (T), the involvement of regional lymph

nodes (N), and the presence of distant metastases (M). These criteria are combined to determine the overall tumor stage, which ranges from 0 to IV. Tumors larger than 2 cm, with deep invasion beyond the dermis, or with aggressive histological features, such as perineural invasion, are classified as high risk (Maubec, 2020). The AJCC-8 introduced significant changes from the previous edition, including consideration of extranodal extension (ENE) in category N. This inclusion reflects the prognostic importance of invasion beyond the lymph node capsule, which is associated with a worse clinical outcome (Maubec, 2020).

The Brigham and Women's Hospital (BWH) staging system is an alternative to AJCC-8, focusing on four main risk factors: tumor diameter (>2 cm), invasion beyond subcutaneous tissue, perineural invasion, and compromised surgical margins. Tumors classified as T3 in the BWH system account for only 5% of cases, but are responsible for 70% of lymph node metastases and 83% of disease-specific deaths. This system is particularly useful for identifying patients at high risk of recurrence and metastasis (Maubec, 2020).

PROGNOSTIC FACTORS IN THE CSCCHN

Cutaneous head and neck squamous cell carcinoma (cSCCHN) has specific prognostic features that directly influence recurrence and survival rates.

Tumours with a diameter greater than 2 cm and depth of invasion greater than 5 mm are associated with a significantly higher risk of metastasis and recurrence. Tumor depth reflects the extent of invasion into underlying tissues, and is one of the most important factors in determining prognosis (Desai et al., 2023).

Perineural invasion is a marker of tumor aggressiveness, indicating that the cancer is spreading along the nerves. This feature is associated with an increased risk of local recurrence, regional metastasis, and disease-specific death. Studies show that the presence of perineural invasion in cSCCHN tumors significantly increases the likelihood of locoregional spread (Desai et al., 2023).

Tumors located in high-risk areas, such as the lips, ears, and scalp, are more likely to recur and metastasize. These regions are often exposed to UV radiation and have complex lymphatic drainage, which facilitates the spread of cancer (Desai et al., 2023).

Incomplete excision of cSCC is a significant problem, associated with an elevated risk of local recurrence, tumor progression, and metastasis. Studies show that compromised surgical margins are present in up to 6.6% of cSCC cases, being more

common in tumors located in complex anatomical areas, such as the head and neck (Roel et al., 2020).

The presence of positive margins after the initial surgery increases the need for reexcisions, adjuvant radiotherapy, or even chemotherapy, which can increase patient morbidity. In addition, incomplete excision is associated with a worse prognosis, with significantly higher regional metastasis rates compared to completely resected tumors (Roel et al., 2020).

To minimize the risk of incomplete excision, it is essential to adopt strategies such as ensuring that surgery is performed by experienced professionals, such as dermatologists or plastic surgeons, utilizing safety margins of 5 mm for low-risk tumors and 10 mm for high-risk tumors, and employing Mohs micrographic surgery, which allows for precise removal of the tumor, layer by layer, with real-time histological analysis, ensuring tumor-free margins (Roel et al., 2020).

The diagnosis and prognosis of cSCC and cSCCHN depend on a detailed evaluation of clinical, histological, and anatomical factors. Staging systems such as AJCC-8 and BWH are valuable tools for stratifying risk and guiding clinical management. In addition, identifying prognostic factors such as tumor size, depth of invasion, and perineural invasion is crucial to predict outcomes and personalize treatment. Finally, strategies to avoid incomplete excision are key to improving clinical outcomes and reducing recurrence and metastasis rates (Maubec, 2020; Desai et al., 2023; Roel et al., 2020).

The impact of lifestyle on the development of skin cancers, such as cutaneous squamous cell carcinoma (cSCC) and malignant melanoma, is a topic of increasing relevance in medicine and public health. Factors such as circadian rhythm, smoking, alcohol consumption, obesity, and diet play significant roles in modulating the risk of developing these skin malignancies. Below, I present a detailed and in-depth analysis of how these factors influence cutaneous carcinogenesis, based on the aforementioned article.

Systemic photoprotection is an innovative approach to preventing the harmful effects of UV radiation, which goes beyond topical sunscreens. This approach involves the oral administration of substances that act as antioxidants, anti-inflammatories, or immunomodulators, protecting the skin against UV-induced cellular damage (Hyeraci et al., 2023).

Nicotinamide, also known as vitamin B3, is one of the most studied substances in systemic photoprotection. It has proven photoprotective properties, acting to prevent ATP depletion induced by UV radiation and promoting the restoration of cellular energy. In

addition, nicotinamide increases the ability of DNA to repair keratinocytes, reducing the risk of genetic mutations and skin tumor formation. Clinical trials have shown that nicotinamide supplementation significantly reduces the incidence of actinic keratoses and non-melanoma skin cancers, especially in high-risk populations (Hyeraci et al., 2023).

Vitamin D, particularly its active form, 1,25-dihydroxyvitamin D3, exerts protective effects on the skin. It is produced in the epidermis in response to UVB radiation, but, paradoxically, its deficiency may be associated with a higher risk of skin cancer. Preclinical studies indicate that vitamin D regulates the expression of genes involved in the cell cycle and apoptosis, inhibiting the growth of malignant cells. These effects suggest a potential therapeutic role of vitamin D in the prevention and treatment of cSCC and malignant melanoma (Hyeraci et al., 2023).

Polypodium leucotomos (PLE) extract, derived from a tropical fern, has been widely used as a photoprotective agent. It has high antioxidant activity, protecting skin cells against oxidative damage induced by UV radiation. In vitro studies show that PLE reduces the formation of pyrimidine dimers in DNA, one of the main mechanisms of mutation induced by UV radiation. In addition, PLE has anti-inflammatory properties that help minimize the local immunosuppressive effects of UV radiation on the skin (Hyeraci et al., 2023).

Retinoids, natural or synthetic derivatives of vitamin A, also play a crucial role in systemic photoprotection. They promote cell differentiation and maturation, in addition to regulating the cell cycle. Clinical trials suggest that retinoids may reduce the incidence of cSCC in high-risk patients, such as those immunosuppressed after organ transplantation (Hyeraci et al., 2023).

Diet has a significant impact on the prevention of skin cancer. Diets rich in antioxidants and bioactive compounds help counteract the deleterious effects of UV radiation and protect the DNA integrity of skin cells (Sawada; Nakamura, 2021). The consumption of dietary fiber, vegetables, and fruits is widely recognized for their skin health benefits. These foods are rich in antioxidants, such as vitamins C and E, and phenolic compounds, which neutralize free radicals generated by UV radiation. In addition, these nutrients help repair DNA and prevent mutations that could lead to the development of skin tumors (Sawada; Nakamura, 2021). Omega-3 fatty acids, found in fish and seeds, have been shown to have protective effects against cSCC and malignant melanoma. They have anti-inflammatory properties that help mitigate the immunosuppressive effects of UV radiation. On the other hand, omega-6 fatty acids, present in vegetable oils and processed foods, are associated with an increased risk of skin cancer, highlighting the importance of balancing these two types of fatty acids in the diet (Sawada; Nakamura, 2021).

Certain foods, such as citrus fruits, contain compounds such as furocoumarins, which can sensitize the skin to UV radiation, increasing the risk of skin cancer in some populations. This relationship reinforces the need for a balanced and conscious consumption of these foods, especially for individuals with high sun exposure (Sawada; Nakamura, 2021).

Skin cancer prevention does not depend only on individual interventions, but also on collective and educational efforts. Encouraging the use of sunscreens, both topical and systemic, and promoting healthy eating habits are key steps to reduce the incidence of skin malignancies. In addition, it is essential to raise awareness about the risks of unprotected sun exposure and the importance of regular dermatological visits, especially for high-risk populations, such as immunosuppressed individuals and those with a family history of skin cancer (Hyeraci et al., 2023; Sawada; Nakamura, 2021).

Systemic photoprotection and healthy eating habits represent fundamental pillars in the prevention of skin cancer, complementing conventional topical measures. Substances such as nicotinamide, vitamin D, Polypodium leucotomes and retinoids, associated with a diet rich in antioxidants and balanced in fatty acids, offer a multifaceted approach to protect the skin against the harmful effects of UV radiation. Promoting preventive measures and educating about lifestyle-associated risks are essential to address the growing challenges posed by these skin malignancies (Hyeraci et al., 2023; Sawada; Nakamura, 2021).

Advances in molecular research have played a crucial role in understanding the carcinogenesis of cutaneous squamous cell carcinoma (cSCC), identifying prognostic markers, and developing new therapeutic approaches. Below, I present a detailed and in-depth analysis on the molecular and epigenetic mechanisms, the impact of growth rates (ROG) as a prognostic marker, and the role of hyaluronic acid in cancer resistance and cSCC progression, based on the aforementioned articles.

Tumor growth rate (ROG) is an emerging biological marker that has been associated with the potential for metastasis and aggressiveness of cSCC. GBR is defined as the increase in tumor volume per unit of time and reflects the speed at which the tumor grows and invades surrounding tissues. Recent studies suggest that a GBR greater than 4 mm/month is associated with a significantly higher risk of metastasis and worse prognosis (Giuffrida et al., 2020).

Evaluation of GBR can be particularly useful for identifying high-risk tumors that require immediate therapeutic interventions. Fast-growing tumors tend to have aggressive histological features, such as perineural invasion and compromised surgical margins, which

reinforces the importance of monitoring this marker during clinical follow-up (Giuffrida et al., 2020).

In addition, ROG can be used to stratify patients into risk groups and personalize treatment strategies. For example, patients with fast-growing tumors may benefit from more aggressive therapies, such as surgery combined with adjuvant radiation therapy, to improve clinical outcomes (Giuffrida et al., 2020).

Hyaluronic acid (HA) is a glycosaminoglycan polysaccharide widely distributed in human tissues, known for its tissue repair and tumor microenvironment regulation properties. Recent studies have highlighted the role of high molecular weight HA (HMWHA) in cancer resistance, especially in long-lived species such as the naked mole rat (Heterocephalus glaber). These animals have a high concentration of HMWHA in the epidermis, mediated by interaction with the CD44 receptor, which contributes to their resistance to cancer (Damps et al., 2021).

In the context of cSCC, HA plays a dual role. On the one hand, HMWHA can induce apoptosis in cancer cells and restrict cell cycle progression by functioning as a cancer resistance mechanism. On the other hand, alterations in HA synthesis and degradation can create a microenvironment favorable to tumor progression, promoting invasion and metastasis (Damps et al., 2021).

These findings suggest that HA can be explored as a therapeutic approach in the treatment of cSCC. HA-based therapies, such as HMWHA administration or modulation of the HMWHA/CD44 interaction, have the potential to improve clinical outcomes, especially in patients with high-risk tumors or who are not candidates for surgery (Damps et al., 2021).

Advances in molecular research have provided a deeper understanding of the mechanisms underlying cSCC carcinogenesis, allowing the development of new therapeutic and prognostic approaches. Genetic and epigenetic alterations, such as **TP53** mutations and histone modifications, play central roles in the malignant transformation of keratinocytes. Tumor growth rate (ROG) emerges as a valuable prognostic marker, while hyaluronic acid offers new perspectives for cancer resistance and cSCC treatment. These advances highlight the importance of ongoing research to address the challenges associated with this cutaneous malignancy (Cozma et al., 2023; Giuffrida et al., 2020; Damps et al., 2021).

The prevention of skin cancer, including cutaneous squamous cell carcinoma (cSCC) and malignant melanoma, is a central theme in dermatology, especially due to the global increase in the incidence of these malignancies. Cumulative exposure to ultraviolet (UV) radiation remains the main risk factor for the development of these skin tumors. In this

context, preventive measures, such as topical and systemic photoprotection, as well as healthy eating habits, stand out as effective strategies to reduce the impacts of UV radiation and the risk of skin cancer.

CONCLUSION

Cutaneous squamous cell carcinoma (cSCC) is one of the most prevalent cutaneous malignancies, presenting a multifactorial etiology that combines environmental, genetic, epigenetic factors, and lifestyle habits. This article highlighted how advances in molecular research, the impact of external and internal factors, and the development of preventive and therapeutic strategies have contributed to the understanding and management of this disease.

The diagnosis and prognosis of cSCC are areas of prominence, where staging systems such as AJCC-8 and BWH play crucial roles in identifying high-risk tumors and guiding treatments. In addition, the study of markers such as tumor growth rate (ROG) enables a more accurate and personalized prognostic evaluation. At the same time, the consequences of incomplete excision reinforce the importance of advanced surgical techniques, such as Mohs micrographic surgery, to ensure tumor-free margins and minimize the risk of recurrence.

The growing understanding of molecular and epigenetic mechanisms has revealed critical pathways in the carcinogenesis of cSCC, including the role of hyaluronic acid in the tumor microenvironment and the relevance of mutations in genes such as TP53 and CDKN2A. These findings have paved the way for targeted therapies and immunotherapies that have shown promising results in advanced tumors, offering new hope for patients facing aggressive and metastatic forms of the disease.

In addition, the relevance of lifestyle habits in the prevention of cSCC and other skin cancers was highlighted. Factors such as protection against ultraviolet radiation, a diet rich in antioxidants, and supplementation with compounds such as nicotinamide and vitamin D have been shown to be effective in reducing the risk of skin malignancies. Ongoing education and awareness of preventive practices is critical to mitigating the impacts of cSCC at the population level.

Thus, the integration of preventive, diagnostic and therapeutic approaches, supported by scientific and technological advances, represents the way to significantly improve the clinical outcomes of cSCC. With continuous research and interdisciplinary collaboration, it is possible not only to reduce the burden of this disease, but also to raise the standards of care and quality of life for patients.

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