Review of the Literature on Cutaneous Squamous Cell Carcinoma

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Writer's Comment: I have never enjoyed writing as much as I did in UWP 104F; for an aspiring physician, the health science-centered theme of the course was especially engaging. When I learned that we would be writing a literature review, I immediately knew I wanted to cover cutaneous squamous cell carcinoma. My aspirations to become a medical doctor, innate love of scientific research, and having a close family member with this prevalent cancer compelled me to become thoroughly involved in the assignment. Becoming intimate with intricacies of a disease as well as learning how to format a professional, scientific journal-caliber review has given me a more profound appreciation of the medical community's dedication to excellence. The journey of composing the literature review satisfied my love of learning and discovery. Furthermore, it nurtured my drive to pursue a healthcare career where I can spread awareness to others.

Instructor's Comment: In my UWP 104F classes, students compose in a variety of genres. As part of the process, they spend a significant amount of time analyzing published examples of each genre before and during their writing process. Yet, despite the extensive analysis, even the strongest of writers may struggle from time to time. Not Helena. Entering class with strong writing skills, she negotiated the genres with ease. Such is the case with the literature review presented here. When she brought her first draft to conference, it had essentially assumed its finished form, requiring just minor revision. It possesses the characteristics I look for in medical review articles: strong synthesis of sources, little to no space devoted to study details (e.g., methods),

appropriate sentence subjects, strategic use of passive and active voice. In short, it is just one example of the level of writing produced by Helena during the quarter.

—William Sewell, University Writing Program

Abstract

Cutaneous squamous cell carcinoma (cSCC) is among the most commonly diagnosed cancers and is the second most common skin cancer in the United States, following basal cell carcinoma. cSCC is most frequently induced by UV radiation-invoked damage to DNA in regions naturally responsible for preventing tumor development and ensuring appropriate repair of DNA in the event of mutation. cSCC is most common among Caucasians and is especially prevalent in the aging Baby Boomer population, born from 1945 to 1965 in the post-World War II United States. In the general population, heightened sun exposure through increased involvement in outdoor recreational and occupational activities over the past several decades suggests a continued rise in diagnosis of cSCC in the future. Fortunately, cSCC has a fairly positive prognosis as both pre-cancer and clinical cSCC lesions are easy to detect, treat, and when deemed necessary, excise by minimally invasive surgical procedures. Metastasis is uncommon, but usually fatal when it occurs.

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most commonly diagnosed skin cancer in the United States, and is especially prevalent among Caucasian individuals.[1-7] With approximately 200,000 new cases arising each year, this cancer's rate of occurrence shows no signs of decreasing in the near future.[2] Furthermore, non-melanoma skin cancers (cSCC and basal cell carcinoma) are the most commonly diagnosed cancers, with combined incidence rates exceeding the frequency of any other form of cancer fivefold.[4,8] The increasing occurrence of cSCC in the United States is suspected to be due, in part, to the aging of the "sun seeking" Baby Boomers,[8] a generation produced by a post-World War II surge in birthrate from 1945 to 1965. Given that approximately 90% of skin cancers are diagnosed over the age of 45, it is by no coincidence that

the increasing rate of cSCC incidence over the past three decades occurs alongside the arrival of this Baby Boomer generation into middle and late-middle age.[8]

Research into the implications of genetics, the influence of environmental factors, and how the interactions of these two components can lead to progression of cSCC are of particular interest in studies of this skin cancer. The most significant factor correlated to acquisition of cSCC is cumulative exposure to UV radiation from the sun.[1-4,6,7,9-12] Coinciding with this phenomenon, levels of skin pigmentation related to one's ethnicity can either help protect against UV damage, as is the case with increased pigment production in individuals with darker skin, or it can be conducive to the development of cSCC, such as in Caucasian individuals who produce less pigment.[3,8]

Clinical conditions that may predispose individuals to the development of cSCC include Xeroderma Pigmentosum (XP), Actinic Keratosis (AK), Human Papilloma Virus (HPV), acute host immunosuppression, and other recognized precancerous conditions.[1-4,11,13-15] Though highly prevalent and often affecting multiple areas of the body, most cases of cSCC are easily and effectively addressed by either one or a combination of treatments with great success; selection of a particular treatment chiefly depends on the stage, severity, and quantity of the tumor(s) present. The following review serves to discuss the etiology, diagnosis, classification of treatments, and prognosis for this common skin cancer.

Etiology

As is the case with many types of cancer, a number of intrinsic and extrinsic risk factors contribute to future contraction of cSCC. Among such factors, the most prevalent are genetic conditions such as the inheritance or environmental acquisition of mutated genes that, in their altered state, hinder the body's innate ability to prevent tumor formation or repair DNA. The element of lifetime exposure to UV radiation is of particular importance in the acquisition of environmentally induced mutations. It is accepted that there exists a linear correlation between lifetime sunlight derived UV radiation exposure and incidence of cSCC; thus, UV radiation is the largest environmental carcinogen for cSCC due to its short wavelength and consequential highly penetrative, damaging

energy.[1-4,6-12,15,16] Furthermore, the majority of cSCC neoplasms occur on regions of the body most commonly exposed to the sun, including the dorsal surfaces of the hands, shoulders, ears, face, and head.[2-4,6,7,10,15,17]

Similar to all forms of radiation from the sun, UV radiation exists on a spectrum. UVB radiation is the most potent carcinogenic ray with a wavelength of 290 to 320 nm, followed by UVA radiation with a wavelength of 320 to 400 nm.[1-4,8,10,12,15] UVA is about 10,000 times less damaging than UVB radiation, and primarily acts to enhance the effects of UVB radiation.[1,3-8,10,12,15,16] There exists a third form of UV radiation, UVC, with a wavelength of 200 to 280 nm, but this form is effectively absorbed by the ozone layer and, therefore, poses minimal risk for acting as a skin carcinogen.[2,3,8,12,16] Repeated instances of penetration by UV radiation on skin cells elicits mutations in DNA, primarily in the formation of CC to TT double base changes, production of cyclobutane pyrimidine dimers, or generation of pyrimidine-pyrimidone (6-4) photoproducts, in skin cells.[1,2,4,6-8,10-12,16] If mutations accumulate beyond the healing capabilities of the body's intrinsic DNA repair mechanisms, cSCC results.

Every somatic cell contains the same set of genes in an identical copy of each individual's genetic code. If mutations occur in areas of the body with lower gene expression (or a lack of effective gene expression altogether) of mutated genes, this genetic damage poses little to no harm. Within skin cells, a critical tumor suppressor gene called *p53* is actively expressed as part of the body's innate ability to prevent the development of cancer. When both genetic copies of *p53* are damaged in multiple skin cells, as would occur from repeated and prolonged UV exposure, cSCC ensues.[2-4,6,7,10-12,16] About one half of UV damaged cells die via apoptosis, therefore posing no threat of future tumor development.[4] However, the remaining abnormal cells clonally expand and continue to grow and replicate, passing on their acquired mutations more rapidly than the restorative abilities of DNA repair pathways. This results in the formation of lesions called Actinic Keratoses, which are characteristic of the cSCC precursor condition Actinic Keratosis (AK).[1-4,6,7,10,11,15-19] AK lesions and clinical cSCC lesions look very similar, usually appearing 2 to 6 mm in diameter and often presenting as either skin-toned, pink, or brown papules or plaques.[4,7,18] cSCC lesions are also frequently described as itchy, callous-like, or painful, non-healing wounds that bleed upon traumatization and irritation.[4,7,18] It is generally understood that when

pre-carcinoma AK lesions go untreated, clinical cSCC follows.

While *p53* mutation is accepted to have a role in the development of both cSCC and several other cancers, one of its paralogs, *p63*, has also been speculated to influence cSCC. *p63* gene expression is critical for normal epidermal development, and it has also been reported to serve a role in DNA repair systems within skin cells.[6,11] Thus, it is likely that a loss of function in *p63* in the protective outer layer of epidermal cells may also contribute to DNA repair defects and subsequent carcinogenesis in the skin.[6,11]

Development of cSCC also depends on the degree of pigment in the patient's skin. cSCC's differential racial prevalence is due to the level of photo-protective pigment production that varies by race. Skin pigmentation is determined by the amount of melanin produced in one's skin and plays a partial role in natural protection from damaging UV radiation.[1-3,6,8,17] Caucasians display a lower amount of pigment-producing melanin than most other races. Related to this is the finding that cSCC occurs almost exclusively on the sun-exposed skin of Caucasian individuals.[2,6,8,10,15-17] Furthermore, people with congenital Albinism, who lack pigment production altogether, are especially at risk of developing cSCC.[2-4,7,17] In a study comparing the incidence of skin cancer in Caucasian versus African American individuals, increased pigment production in African Americans showed a 500-fold increase in protection against UV radiation.[8]

Though it is the cumulative number of mutations that chiefly contributes to developing cSCC, defects in DNA repair pathways, effectively termed "nuclear excision repair," can also lead to cSCC[11,12,16]; in individuals born with Xeroderma Pigmentosum (XP), this is exactly the case. To a large extent, the body's intrinsic mechanisms of nuclear excision repair serve to reverse DNA damage and preserve homeostasis of the skin. In individuals with XP, however, inherited mutations in DNA repair pathways prevent them from combatting the effects of UV-induced mutation.[1-4,7,11,12,14] With a median age of 8 years old for cSCC onset, contraction of cSCC in patients with XP occurs much earlier in life than that of skin cancer patients without XP.[1,2,11,14]

Other medical ailments related to cSCC but less commonly so than causes previously mentioned include iatrogenic immunosuppression, Human Papillomavirus (HPV), Ferguson-Smith Disease, and Bloom Syndrome. Immunosuppression most commonly occurs in patients

who receive organ transplants and who must take immune-suppressant drugs to promote acceptance of the transplanted tissue.[1,3,4,15,19] These immune-suppressants promote susceptibility of the body to viral infection, particularly HPV (also linked to cSCC), and likely depress the body's inherent ability to recognize and destroy malignant tumors.[1,3,15,19] Individuals who receive renal transplants are especially subject to this occurrence as a result of the nature of this transplant and the heightened susceptibility to HPV genital warts and subsequent development of cSCC.[19] Amplified HPV risk in patients with Epidermolysis Verruciformis leads to infections characterized by wart-like genital skin lesions that develop into cSCC in approximately half of all cases; this is due to congenital defects in cell-mediated immunity and immune response against certain viruses.[1,3,4,15,19] Prior research on HPV as a carcinogenic precursor for cSCC chiefly indicates that traces of HPV viral DNA are found in malignant cSCC tumors, but the exact oncogenic mechanisms of HPV are still unknown.[1,15,19] In Ferguson-Smith Disease, patients suffer from inherited mutations in genes involved in regulating various cellular differentiation processes. Defects in these genes results in the development of multiple locally destructive cSCC lesions in UV-sensitive sun-exposed regions; however, they usually regress, leaving scars as remnants of the tumors.[3] Patients with Bloom Syndrome (BS) experience severe growth retardation, diabetes, and predisposition to malignancies as a result of mutations in genes involved in DNA replication and repair pathways.[3] Tumors in BS patients are classified as cSCC in roughly 14% of cases.[3]

Additional sources of correlated influence on cSCC include age, sex, and family history. With the exception of individuals with XP, skin cancers rarely affect people < 20 years old, and the incidence of cSCC increases positively and linearly with increased age.[7,17] This finding coincides with the premise that cumulative, lifetime exposure to the sun is the largest risk factor for developing cSCC. Rates of cSCC occurrence in men have been found to exceed that of women.[1-4,7,15,17] This finding is not entirely understood, but social history pertaining to different realms of work for men and women in the mid to late twentieth century may serve some explanation.[1-4,7,15,17] Family history also bears notable effects. It has been observed that individuals whose parents were diagnosed with cSCC at < 40 years old are at a twofold increased risk for cSCC contraction than those whose parents are not diagnosed at < 40 years old.[3] Risk for

developing cSCC in general is higher for individuals whose parents were diagnosed at any age than those whose parents never developed cSCC.[3]

Diagnosis

It is important that lifestyle factors, medical history, and family (genetic) history be considered when determining if skin abnormalities are cSCC lesions. Even if a lesion seems to be alone, or several seem to be localized to one anatomical region, a full body screening and histopathological examination of all speculated lesions is protocol for proper diagnosis.[4,7]

As a result of the various precancerous conditions and carcinogenic sources of cSCC, the latency period of this cancer spans from 7 weeks to 60 years depending on host characteristics, with an average of 21 years.[1] cSCC lesions are often visually distinguishable from other skin cancers, except from their precancerous Actinic Keratosis (AK) precursor, and are confirmed diagnostically to be distinct from AK lesions exclusively by biopsy.[1,4,7,18,20] The appearance of cSCC lesions is described as skin-colored, pink, red, or brown, callous-like or scaly, and often slightly raised.[4,7,18] Reported symptoms of AK lesions and cSCC lesions are similar and consist of redness, itchiness, tenderness, and bleeding upon irritation.[4,7,18]

Treatment

Since exposure to carcinogens for cSCC is difficult to control, and some extent of genetic predisposition is nearly inevitable, the most important factor for controlling cSCC development and preventing metastasis is effective treatment. Remedy selection generally depends on the severity of the lesions and how successfully they can be treated by a particular mode of therapy. It is markedly difficult to follow each individual AK pre-cSCC lesion, and as previously noted they are often histologically indistinguishable from active cSCC lesions; thus, often all lesions are treated whether or not they are confirmed to be active cSCCs.[2,4,18,20] Most cases are effectually managed by either surgical excision or other more conservative modalities such as cryotherapy, topical treatment (Fluorouracil or Imiquimod), photodynamic therapy, or through various combinations of these treatment forms.[1-4,13,21,22]

For treating smaller AK and cSCC lesions, there exist three commonly

used remedies: Fluorouracil, Imiquimod, and Methyl Aminolevulinate Photodynamic Therapy (PDT). Fluorouracil is applied topically and functions as an anti-neoplastic anti-metabolite that interferes with the synthesis of DNA and RNA in order to provoke unbalanced cell growth and subsequent cell death in radically proliferating cells.[6,7,20] Fluorouracil topical treatment often invokes local irritation, swelling, desquamation, and tenderness at the site of application; however, these conditions are temporary and are usually followed by decreased severity or complete disappearance of the lesions.[6,7,20] Half of patients using Fluorouracil experience complete clearance of lesions, while an 80% reduction in lesion count is reasonably expected, and a 90% reduction in lesion count is considered likely.[20] Reported negative effects of Fluorouracil treatment include local irritation, inflammation, risks of ulceration, and scarring.[6,7,20] Topical treatment with Imiquimod functions by activating innate immune responses to combat lesion progression and to reduce their presence.[6,7,22] In a study to investigate the process of its effect, it was found that treatment with Imiquimod increases the number of AK lesions in the early stages of treatment; however, this is likely due to its efficacy at exposing subclinical AK lesions in addition to prominent ones.[22] Imiquimod-treated patients also report bouts of irritation and inflammation, but to a lesser extent than those receiving Fluorouracil treatment.[6,7,22] Imiquimod and Fluorouracil are most effective at treating AK lesions as opposed to active cSCC lesions.[21,22] In some cases, either Fluorouracil or Imiquimod are applied in conjunction with extreme cold-induced destruction and excision by liquid-nitrogen cryosurgery with great effectiveness[7]; this is often the recommended treatment modality when intervention that is less invasive than surgical excision is preferred. Methyl Aminolevulinate PDT works through the topical application of Methyl Aminolevulinate cream and its subsequent activation by light stimulation.[7,21] This activation is followed by the release of reactive oxygen species that induce local tissue destruction, thereby destroying proliferating AK and cSCC cells.[7,21] Methyl Aminolevulinate PDT is reportedly less irritating and requires a shorter treatment duration than Fluorouracil, and is less painful than cryotherapy.[21] Methyl Aminolevulinate PDT has not been frequently compared to Imiquimod regarding preferential use or efficacy.

By far the most successful technique for treating larger AK lesions as well as active cSCC lesions is surgical excision. In the past three decades,

extensive research has been conducted in order to best define surgical excision margins for cSCC tumors. Historically, recommended margins were 2 mm to more than 2 cm around lesions, an extremely broad range of excision with little definition on distinguishing exactly where to excise.[5] Often, tumors extend sub-clinically past the visible area of exposure on the skin. In a study conducted by Brodland and Zitelli,[5] a guideline for determining surgical excision margins with tumor clearance rates of 95% was delineated with the following findings: the minimal margin required for significant tumor clearance was found to be 4 mm around the tumor border in all directions, the relationship between tumor size and minimum tumor clearance margin was defined, and the effects of tumor histologic grade on excision margins were determined. Though actual excision margins depend on tumor-specific factors, the conclusions of this study serve to better define guidelines for such parameters with the utmost success, while preserving as much tissue at the surgical site as possible. In other treatment reviews, Mohs microsurgery is regarded as having the lowest rate of cSCC recurrence following treatment.[1,3-5,7] Mohs microsurgery has also been suggested to provide the best clearance of lesions in regions where sparing of tissues is particularly important.[5]

Prognosis

Altogether, cSCC bears a positive prognosis and is largely preventable through treatment of pre-cancerous AK lesions. These lesions are important markers of high UV exposure and increased risk of non-melanoma skin cancer.[1,4,6,7,9] Using this marker as an identifier of risk for future incidence of cSCC is critical in prevention of invasive cSCC and metastasis.

Recurrence and Metastasis

In general, rates of recurrence and metastasis for cSCC are relatively low at 8% and 5%, respectively.[4] The main factors involved in determining case-by-case risk of recurrence and metastasis include tumor size, tumor location, level of depth, treatment type, prior mode of treatment and response, histologic differentiation, precipitating factors beyond UV light, and host immune-ability.[1-4,6,7,13,15]

There exists a subset of cSCC cases termed “high risk cSCC,” for which individuals with this particular diagnosis have an elevated risk

of metastasis and death.[2-4,9] Though previously poorly defined, high-risk cSCC tumors are now described as those that have a diameter ≥ 2 cm, display poorly differentiated histology, depth beyond the level of the hypodermis, and perineural invasion ≥ 0.1 mm.[2-4,9] If AK lesions go untreated, develop into high risk cSCC lesions, and are allowed to persist, this metastatic cSCC occurs and is likely fatal.[1-4,9,13,18] Metastatic cSCC is highly preventable through proactive diagnosis and treatment of both the pre-cSCC AK lesions and clinical, pre-metastatic cSCC tumors.

Conclusion

The purpose of this review was to elucidate the prevalence, causes, prognostic factors, and treatments for cutaneous squamous cell carcinoma published over the last three decades. It is evident from the reviewed literature that cSCC is extremely common, and contraction chiefly depends on lifetime exposure to UV radiation, which causes DNA mutations in genes important for regulation of tumor suppression pathways. While other genetic diseases and predisposing conditions also add to cSCC incidence, UV radiation is the largest risk factor. cSCC bears a relatively positive prognosis when compared to melanoma skin cancers, with low rates of metastasis and effective treatments available. Future studies will likely aim to further progress treatment techniques to ensure that a most efficacious mode of remediation is administered to patients with cSCC, and to promote proactive behaviors to better prevent this condition in present and future generations.

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