Trends in the treatment and prevention of keratinocyte carcinoma (non-melanoma skin cancer)

Alexander Zink

Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany

and

Clinical Unit Allergology, Helmholtz Zentrum München, German Research Center for Environmental Health GmbH, Neuherberg, Germany

Corresponding author:

Dr. Alexander Zink, MD, MPH

Department of Dermatology and Allergy, Technical University of Munich

Biedersteiner Str. 29, 80802 Munich, Germany

Telephone: +49.89.4140-3038

Fax: +49.89.41 40-3572

Email: alexander.zink@tum.de

Abstract

Keratinocyte carcinoma (KC), previously also known as non-melanoma skin cancer, is the most common malignancy worldwide. It comprises basal cell carcinoma, squamous cell carcinoma (SCC), and actinic keratoses as carcinoma in situ or precursors of SCC. With solar ultraviolet radiation being the main risk factor, several countries have accepted KC as an occupational disease of outdoor professions. The prevalence in these high-risk groups is substantial, but awareness and preventive behavior remains inadequate. Parallel to the development of improved treatments, such as daylight photodynamic therapy and PD1 inhibitors for progressive KC, target-oriented prevention strategies are requisite if the global burden of KC is to be lowered. Health-related communication, internet search analysis, and telemedicine could be the key to addressing this issue.

Keywords: keratinocyte carcinoma, non-melanoma skin cancer (NMSC), prevention, treatment

Introduction

Keratinocyte carcinoma (KC), previously known as non-melanoma skin cancer (NMSC), is the most common malignancy in fair-skinned populations worldwide; it includes basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and in a broader sense actinic keratosis (AK), which is inconsistently described in the literature as KC in situ due to dysplastic keratinocytes similar to SCC, as precursor of SCC or even as premalignant lesion [1,2]. NMSC includes not only BCC, SCC, and occasionally AK but also all malignant tumors of the skin other than melanoma, such as cutaneous lymphomas, Kaposi's sarcoma, and angiosarcoma [3]. Despite its very high cure rate, KC causes many deaths annually, worldwide, and a higher level of impairment as measured using the Disability-Adjusted Life Years (DALY) than does melanoma [1]. The health economic burden of KC remains immense; it is estimated at 4% of all expenditures for all malignant tumor in the USA alone [4]. Within the next few decades, KC incidence is likely to increase further and, in Germany, is predicted to double by 2030 [5]. Therefore, up-to-date knowledge about KC treatment and particularly prevention are of great interest to many, including healthcare and public health professionals, as well as scientists and authorities. This review aims to provide an update on the current trends in KC, with a particular focus on epidemiology, treatment, and prevention, based on reports published from 2016 to 2018.

From “Noli me tangere” to “keratinocyte carcinoma”

For several centuries, *Noli me tangere*, the biblical Latin expression for *Do not touch me*, was the medical term for all slow-growing destructive skin lesions. In the absence of an understanding of the etiology and pathogenesis of carcinomas, this term was used in the belief that these skin lesions are incurable and should not be touched or treated under any circumstances, as this would lead to acute exacerbation and death. With technological and scientific progress in medicine over the last century, a classification of malignant tumors based

on the cell of origin has evolved. For skin tumors, however, a second classification into melanoma and non-melanoma skin cancer (for all other skin tumors) has prevailed. In order to label AK, SCC, and BCC according to what they are, rather than what they are not, the term NMSC has been replaced by the term KC, given that these carcinomas are of keratinocytic origin [1,2].

Pathogenesis

In addition to the constitutional risk factor of skin type, the most important risk factor for KC is solar ultraviolet radiation (UVR) [1]. Therefore, KC is recognized as an occupational disease for outdoor professions in Germany and other countries [6]. In recent years, the possible association of KC with human papillomavirus (HPV) has increasingly been reported: HPV DNA can be detected in up to 90% of all KC in immunocompromised and in up to 50% of that in immunocompetent individuals [7]. Concurrently, recent publications have reported a successful HPV vaccine for prophylaxis and therapy in patients with multiple KC [8]. However, in contrast to cervical carcinoma, no specific HPV subtypes have yet been associated with KC overall, although some subtypes can typically be found in specific tumor locations, such as HPV 16 in head and neck KC [9].

Epidemiology

Registration of KC in, for example, tumor registries, is not uniform or compulsory globally, which makes it difficult to obtain accurate incidence data and hinders comparisons [10]. In Germany, with a population of about 82.6 million, the annual incidence of BCC and SCC is 180,000, and that of AK is 1.7 million [5]. In comparison, in Australia, with its 24.1 million inhabitants, the annual incidence is estimated at around 1 million [11]. However, the global incidence is predicted to increase further within the next years in most countries, and even to

double in Germany by 2030 [5]. Due to the lack of uniform registration, the actual number of annual cases might even significantly exceed these numbers [11].

With convincing evidence for solar UV radiation being the main risk factor for KC, several countries worldwide, including Germany in 2015, have recognized KC as an occupational disease [6,12]. Typical outdoor workers with substantial KC risk are farmers, gardeners, construction site workers, and professional mountain guides, who suffer from KC in up to 40% in some age groups, but demonstrate low overall awareness and protective behavior [13-17]. Significant risk differences for KC have been shown for various outdoor professions with severe UV exposure, as compared to indoor workers [17]. These findings suggest that prevention efforts have to be tailored to the specific everyday needs of different professions.

Indoor workers or other workers with in general low work UVR exposure naturally have a lower KC risk, as shown, for example, for sewage workers in Munich, Germany [18]. Nevertheless, individuals with low-UVR-exposure occupations can also carry a high risk for KC, comparable to that of outdoor workers, if they have hobbies or other regular leisure activities involving intensive UVR exposure. One example involves glider pilots in Southern Germany, who have been shown to have a KC risk comparable to that of farmers [19].

Thus, different professions and populations have different risks for KC, based on their individual UVR exposure. This highlights the importance of a meticulous assessment of cumulative UVR exposure related to both occupation and leisure activities, to identify high-risk groups for KC in order to promote prevention and early treatment [3].

Treatment

The treatment of choice remains complete surgical excision, wherever possible, with histological control of the margins. For inoperable BCC, radiotherapy or the use of the drug vismodegib is used. For inoperable and/or metastatic SCC, immunocheckpoint inhibitors, such as nivolumab and pembrolizumab, and recently, PD-1 blockade with cemiplimab, have been shown to be effective in advanced cutaneous SCC, with response in about half of all patients [20]. Local treatment options have not markedly changed in the last few years and imiquimod, ingenolmebutate, diclofenac-hyaluronic acid, and 5-fluorouracil, as well as photodynamic therapy (PDT), are used for early and superficial forms. Recently, 5-fluorouracil was shown to be more effective than imiquimod for preventing subsequent AK, although only in the short-term [21].

Daylight photodynamic therapy

PDT is a non-invasive and widely used approved treatment for AK, although the pain involved and the need for specialized equipment limits its use. Advancements in PDT have led to the development of daylight PDT (DL-PDT), which has similar efficacy as conventional PDT for treatment of AK, but is more convenient and tolerated by patients because it is nearly painless and requires sunshine, rather than special light sources [22,23].

Actinic Keratosis Area Severity Index

Evaluation of the severity of KC and of AK in particular is usually based on subjective assessment by a healthcare professional. Recently, the actinic keratosis area and severity index (AKASI) was proposed as a new and valuable tool for the quantitative assessment of AK. The AKASI score ranges from 0 (no AK) to 18 (severest possible degree) and is calculated by summing subscores for areas affected by sun-damage, distribution of AK, intensity of erythema, and thickness of worst visible AK on scalp, forehead, and left and right face, multiplied by an

area coefficient [24]. As a proven, reproducible score associated with the incidence of SCC [25,26], the AKASI can be useful for evaluating different AK treatment options, as shown for PDT [27].

Prevention

The main preventative recommendation for KC is limiting UVR exposure by “avoiding sun exposure” and “seeking shade,” and using UV protective clothes and topically applied sunscreen products. Recently, there has been increased focus on sun protection beyond the historically defined sun protection factor (SPF), which mainly focuses on UV-B radiation. To protect against light-induced skin damage, however, current sunscreen products also aim to protect against UV-A radiation and several other wavelengths of visible light, such as "high-energy blue light" [28].

Furthermore, secondary chemo-prevention of KC with systemic agents such as nicotinamide, COX-inhibitors or Polypodium leucotomas extracts is evolving especially for high-risk populations such as organ transplant recipients, although evidence for efficacy is limited [29].

However, it remains difficult to compare the efficacy of different prevention measures; e.g., it remains unclear whether wearing a hat or using sunscreen is "more" protective. Considering the variety of different types of photo-induced skin damage, this issue is likely to persist. The only reasonable comparison seems to be in relation to the acute UVR effects: erythema and sunburn. A US working group recently investigated whether staying in the shade under a beach umbrella or using sunscreen with SPF100 was "better" to protect against sunburn on a typical beach day. Interestingly, they found significantly fewer cases of sunburn in the sunscreen group than in the umbrella group. Nevertheless, the sunburn rate was so high in both groups (25% of all participants in the sunscreen and 78% of those in the umbrella group) that neither of the two methods were considered adequate, suggesting that different prevention measures should be

combined for the best possible protection [30]. Sunlight reflected from the ocean could be an explanation, but a recent study estimating the contribution of UVR from the ocean and beaches to erythema, using a numerical model, postulated that sunburn sustained at the seaside is more likely due to the absence of shade rather than to reflected sunlight [31].

Environmental impact of sunscreen

With the global increase in sun protection recommendations and the associated increase in the use of topically applicable sunscreen products, environmental aspects also require consideration. Various ingredients and decomposition products of sunscreen are detected and accumulate in lakes and oceans, with increasingly negative influences on various organisms. Ingredients commonly used in sunscreens poison corals (especially oxybenzone) [32], interfere with the endocrinological system and sexual development of fish (especially benzophenone) [33], influence gene regulation in mosquitoes [34], are toxic to marine crustaceans [35], and may even be endocrinologically active in humans by interfering with the hypothalamic–pituitary–gonadal axis [36]. Accordingly, there is a need to regulate the composition of sunscreens in terms of increasing ecological concerns, and the use of biodegradable substances should be promoted.

Health communication

A major challenge of KC prevention is the limited knowledge and awareness among high-risk groups. Several recent studies had shown that outdoor workers generally demonstrate poor sun protective behavior and have low awareness of KC [37,38]. A recent study focusing on farmers, gardeners, and roofers even found that two-thirds of participants had never undergone skin cancer screening and one-third had never even heard about it [16]. This raises the question about

how outdoor workers can be motivated in terms of KC prevention. A recent study explored the impact of sun protection messages in special interest magazines distributed to 1.45 million agricultural households. With a response rate of less than 0.01%, this approach was declared by the authors to have failed to reach a meaningful proportion of the agricultural population [39]. A possible effective solution could be teledermatology and teledermoscopy, combined with smart phone apps or text messages [40-43].

Internet search analysis

Within the last few years, several peer-reviewed medical publications have analyzed the volume of specific search terms on Google [44]. In dermato-oncology, these data of population-based internet search behavior were used to estimate the incidence and mortality rates of different types of skin cancers, and demonstrated a statistically significant correlation of the relative Google search volume and cancer incidence as well as mortality rates for melanoma [45]. However, Google data can also be used to identify fields of interest of a population related to KC, as well as temporal trends, which could then be used for the development and implementation of target-oriented awareness and prevention strategies [46].

Conclusion

KC remains the most common malignancy of fair-skinned populations globally. The main risk factor for KC is solar UVR, which poses different risks to individuals according to their levels of UV exposure in both work and leisure. Topical treatment and excision, where possible, remain the treatment of choice, but several new drugs for treatment of progressive KC have been developed. Preventive behavior remains inadequate and sustainable prevention and awareness strategies are needed. The environmental impacts of sunscreen products need to be considered. New teledermatologic approaches and online search volume analysis could provide a bases for population-based prevention. Coupled with big data, artificial intelligence [47,48],

nudging [49], and wearables [50,51] could potentially sustainably reduce the individual, national, and global health economic burdens of KC by novel and improved preventive measures.

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