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EPIDEMIOLOGY (R DELLAVALLE, SECTION EDITOR)

Epidemiology of Keratinocyte Carcinoma

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Abstract
Purpose of the Review The study aimed to provide a synopsis of recent research advances in the epidemiology of keratinocyte carcinoma (KC), with a focus on indoor tanning and known risk factors for other forms of cancer such as cigarette smoking and alcohol drinking.
Recent Findings The evidence is strong enough to infer that use of ultraviolet radiation (UVR)-emitting indoor tanning devices causes KC. Epidemiologic studies of cigarette smoking, alcohol drinking, and menopausal hormone therapy tend to show some suggestion for increased risk of KC but the evidence is not yet strong enough to determine if there is a true etiologic role. Body mass index is clearly inversely associated with KC risk, but this is more likely to be due to lower UVR exposure in overweight and obese individuals than it is due to a true etiologic role.
Summary The epidemic of KC continues unabated, and the causal role of indoor tanning is contributing to this unfavorable trend in KC incidence rates. Advances in understanding the etiology of KC should not divert attention away from the fact that the primary public health strategy to prevent KC is known: minimize population exposure to UVR from the sun and from UVR-emitting indoor tanning devices, particularly among those with sun-sensitive phenotypes.

Keywords Non-melanoma skin cancer · Epidemiology · Indoor tanning · Cigarette smoking · Alcohol drinking · Obesity · Body mass index · Estrogen

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Introduction

The primary reason keratinocyte carcinoma (KC) is such an important public health problem is because of its high prevalence: it is far and away the most common human malignancy. KC is predominantly comprised of two major histologic types, basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC), with BCC more common than SCC. Estimates indicate that in 2012 approximately 3.3 million individuals had been diagnosed with KC in the US population with a total of 5.4 million KC lesions diagnosed per year [1]. Despite its high incidence, KC has a low mortality rate of 0.7 deaths per 100,000 people per year [2] but nevertheless causes approximately 3000 deaths per year in the USA [3]. These KC deaths are almost exclusively due to SCC which has a 2% case fatality rate [4].

As the most common form of cancer in the world, KC presents a global health problem of great magnitude. Not only is the current magnitude of the global public health problem posed by KC formidable, but the increasing trends in the KC incidence rates in regions such as North America, Europe, and Australia indicate the growing scope of this global epidemic. For example, in Norway between 1963 and 2011, the incidence of SCC increased sixfold in males and ninefold in

females [5]. Increases were evident even in younger age populations, which foreshadow future population-level increases because the risk of KC increases with age. In the USA, a 35% increase in the estimated number of persons diagnosed with KC between 2006 and 2012 was noted by Rogers and colleagues [1]. This degree of increase was replicated in an analysis of US data from the Medical Expenditure Panel Survey from 2002 to 2011 that documented a 39% increase in the number of adults treated for KC between 2002–2006 and 2007–2011 [6]. In addition to the substantial morbidity and mortality caused by KC, enormous economic costs are associated with treating patients with a diagnosis of KC; in the same study, the estimated average annual medical care costs were $4.7 billion annually in the 2007–2011 period, a 74% increase from 2002 to 2006 [6]. This set of circumstances underscores the need for implementing comprehensive primary prevention strategies.

The major determinants of KC at both the population-level and individual-level are well-established. The predominant environmental cause of KC is epidermal exposure to solar ultraviolet radiation (UVR). The risk of both BCC and SCC associated with solar UVR is dose-dependent, with risk increasing the greater the duration and intensity of exposure. For example, using global data, even an area-level measure of mean daily ambient solar UVR exposure accounted for 40% of the variability in SCC incidence rates and 37% of the variability in BCC incidence rates [7]. Thus, in Caucasian populations, the geographic patterns in the occurrence of KC show that rates are highest at latitudes closer to the equator and hence high ambient solar UVR levels, with associations between decreasing latitude and increasing rates of KC [7]. In a meta-analysis of outdoor work and BCC risk, the summary odds ratio (OR) was 1.43 (95% CI 1.23–1.66) [8]. An even stronger association was observed in a meta-analysis of outdoor work in relation to risk of SCC (summary OR 1.77; 95% CI 1.40–2.22) [9].

The risk of KC associated with solar UVR exposure is asymmetrical across populations, with individuals with sun-sensitive skin phenotypes exhibiting the greatest susceptibility to solar UVR-caused KC [10]. The risk of UVR exposure is primarily concentrated among individuals with sun-sensitive skin phenotypes. Sun-sensitive phenotypic characteristics include red hair, fair complexion, freckling, and blue eye color, but the major driving characteristic is how the skin responds to prolonged periods of sun exposure such as burn/peel, no impact, or tan. Skin types that are particularly sensitive to UVR, and therefore at an increased risk of developing KC, are the Fitzpatrick skin types I, II, and III. These fair skin types lack the ability to tan and have a propensity to sunburn and freckle when exposed to UVR. Approximately 98% of all KCs occur in individuals with sun-sensitive skin types as defined by Fitzpatrick skin types I, II, and III [11]. In a population-based study in the USA, the majority of individuals with a personal history of KC had a sunburn-prone skin type, with a distribution of skin types that were 15% "blistering sunburn," 38% "sunburn without blistering," and 34% "mild sunburn that turns tan" [12].

The patterns of KC occurrence at the population-level as well as the risk of KC at the individual-level are largely a function of these two factors: solar UVR exposure dosage combined with degree of the skin's sensitivity to solar UVR. Against this backdrop with solar UVR as the predominant environmental cause and sun-sensitive phenotype as the predominant susceptibility factor, continual refinements are being made in the understanding of the contribution of other factors to the etiology of KC. In recent years, in addition to identifying and characterizing other factors that influence susceptibility to KC, a major source of manmade population exposure to UVR has emerged: intentional UVR exposure from indoor tanning devices. Characterizing the association between indoor tanning and risk of KC is thus a public health priority, as is characterizing the individual characteristics associated with indoor tanning. Below first evidence on the association between indoor tanning and KC risk is reviewed before going on to review the results of recent studies with respect to well-established risk factors for other forms of cancer: cigarette smoking, alcohol drinking, obesity, and exogenous hormone use. A concluding section provides an update on KC as a marker of other adverse health effects, including risk of noncutaneous malignancies and fatal outcomes.

Indoor Tanning

Indoor Tanning and KC Risk

Building on the foundation of a relatively sparse body of prior evidence, the more recent studies have firmly established the link between indoor tanning and both BCC and SCC. The results of a clinic-based case-control study of early onset (≤40 years) BCC comprised of 376 cases and 390 controls showed a significantly increased BCC risk for ever-versus-never use (OR 1.69; 95% CI 1.15–2.48) of indoor tanning devices [13]. These findings were closely replicated in a population-based case-control study (657 cases, 452 controls) of BCC diagnosed among those ≤50 years of age with an ever-versus-never use of indoor tanning devices (OR 1.6; 95% CI 1.3–2.1); early age of initiation of indoor tanning was even more strongly associated with BCC risk and the risks were consistently observed across device types [14•]. With respect to SCC, in a large-scale prospective cohort study with long-term follow-up, a strong dose-response association was observed between indoor tanning during the ages of 10–49 years and subsequent SCC risk (highest-versus-lowest exposure relative risk (RR) 2.38; 95% CI 1.33–4.25) [15•]. In a prospective cohort study of nurses in the USA, significant dose-

response trends were observed between indoor tanning use and both BCC and SCC [16]. Combined with the results of earlier studies [17], there is now a substantial body of epidemiologic evidence documenting a strong and consistent association between UV-emitting indoor tanning devices and risk of both BCC and SCC. "Strength of the association" and "consistency of the association" are both epidemiologic criteria for inferring causality. Further, UVR is a well-established cause of KC via known mechanistic pathways, so the causal criteria of "coherence of the association" and "biologic plausibility" are also met. The evidence base on this topic is now sufficiently strong to confidently infer that UVR exposure delivered via UV-emitting indoor tanning devices causes KC.

Prevalence and Correlates of Indoor Tanning

The established risk of KC associated with UVR-emitting indoor tanning devices poses a major threat to skin cancer prevention. This makes it important to characterize the prevalence of indoor tanning and factors associated with this behavior. In the USA, a national survey of high school students in 2013 found that 20% of females had used indoor tanning and 10% engaged in frequent indoor tanning; when limited to the highest prevalence group of non-Hispanic white females, the prevalence was 31% users and 17% frequent users [18]. By comparison, the prevalence of indoor tanning among males was 5% for any use and 2% for frequent use [18]. Despite the high prevalence of indoor tanning among high school students, propitious trends have been observed with notable declines observed in overall prevalence of indoor tanning from 16% in 2009 to 7% in 2015 [19]. This includes a major decline in non-Hispanic white females, from 37% in 2009 to 15% in 2015 [19]. Indoor tanning was also significantly associated with sunburns in high school students [19], in accord with associations observed in adults that indoor tanning is correlated with high prevalence of sunburns and low prevalence of sun-protective behavior [20].

The concept of "tanning dependence," akin to substance use dependence, has been steadily evolving. Evidence indicates that indoor tanning is associated with measures of tanning dependence [21, 22]. As tools to screen for and treat tanning dependence emerge, this will have important implications for translation into the clinical setting.

Policy Implications for Indoor Tanning

From the public health perspective, when the cause of a disease has been identified as is the case for UV-emitting indoor tanning devices and KC risk, any policy intervention that either eliminates or reduces the exposure in the population is a step in a positive direction toward reducing the population burden of KC. That is, the greater the reduction in exposure to UVR-emitting indoor tanning devices, the greater the reduction in KC rates that will be achieved.

Borrowing from tobacco control, which also has an industry that manufactures and promotes a harmful product, there are many potential policy options. With respect to directly limiting access, these include options ranging from outright prohibition of usage in minors to restricting the minimum age of legal use to requiring parental consent [23–25]. Examples of additional strategies include increasing taxes, limiting the UVR dose emitted by indoor tanning devices, and consumer warnings [23–25]. Clearly, the most extreme policies will yield the greatest public health benefit by reducing population-level exposures to UVR emitted from indoor tanning devices.

Individual Lifestyle Risk Factors

Cigarette Smoking

Cigarette smoking is an established cause of 13 different types of cancer [26], so it is logical to test the hypothesis that smoking is associated with KC. In the Women's Health Initiative cohort study, current smoking compared with never smoking was inversely associated with KC risk (RR 0.86; 95% CI 0.77–0.96) [27].

So far, the totality of the evidence clearly shows that cigarette smoking is not associated with increased risk of BCC. In a well-designed cohort study in Australia, the risk of BCC was reduced in current-versus-never smokers (RR 0.69; 95% CI 0.45–1.05) [28]. These results were consistent with the results of a meta-analysis that for BCC estimated a summary OR of 0.95 (95% CI 0.82–1.09) in smokers compared with non-smokers across 17 studies [29].

In contrast, the evidence points more strongly toward smoking being a risk factor for SCC. In the same meta-analysis by Leonardi-Bee, smoking was significantly associated with SCC risk although only seven studies contributed data (summary OR 1.52; 95% CI 1.15–2.01) [29]. However, in a cohort study of smoking in relation to SCC risk carried out in Australia that was specifically designed to study skin cancer and thus had excellently characterized sun exposure and skin type data, the comparison of current smokers with never smokers yielded a relative risk that was weak and not statistically significant (RR 1.12; 95% CI 0.82–1.50); further, there was no evidence of a dose-response relationship [30]. Despite numerous studies in which smoking has been investigated as a potential risk factor for KC, the current body of evidence indicates that cigarette smoking has yet to emerge as a clear risk factor.

Alcohol Drinking

The relationship between drinking alcohol and cancer risk has been extensively evaluated in epidemiologic case-control and

cohort studies, and the International Agency for Research on Cancer (IARC) [31] has assessed the evidence and judged that alcohol is a cause of cancers of the oral cavity, pharynx, larynx, esophagus, colorectum, liver, and female breast. Cohort studies published in 2012 and beyond have generated results to suggest that alcohol drinking may be weakly associated with KC risk [32–34]. In the Women's Health Initiative cohort study of almost 60,000 women, KC showed a highest-versus-lowest category RR of 1.23 (95% CI 1.11–1.36) [33]. In a large cohort study of BCC, a similar magnitude of association was observed (highest-versus-lowest category RR 1.22; 95% CI 1.15–1.30) [32]. In the Danish "Diet, Cancer, and Health Study," results were presented separately for both BCC and SCC; the level of alcohol drinking was much higher than the other cohorts and the 30–50 g/day category yielded RRs of 1.26 (95% CI 1.12–1.41) for BCC and 1.41 (95% CI 0.93–2.16) for SCC [34]. In contrast, some other studies have observed little or no association between alcohol drinking and KC risk [35, 36]. Overall, several recent studies provide some indication that alcohol drinking could be weakly associated with KC risk but the evidence as a whole is not clear-cut.

Anthropometric Factors: Body Mass Index and Height

The past few decades have seen obesity emerge as a robust risk factor for several malignancies, including postmenopausal breast cancer and cancers of the esophagus, pancreas, colorectum, endometrium, gallbladder, and kidney [37]. Several high quality prospective cohort studies have reported on the potential association between anthropometric factors such as BMI and height in relation to the risk of KC [38–42]. The pattern of findings has been relatively consistent across these studies, providing evidence of an inverse association between BMI and KC. In an all-female cohort, BMI was inversely associated with KC; compared to those of normal weight, the relative risks were 0.93 (95% CI 0.89–0.99) and 0.86 (95% CI 0.80–0.91) for the categories of overweight and obese, respectively [38]. Specific to BCC, in women, other cohort studies have also tended to generate even stronger inverse associations [39–41]; in the study of Lahmann et al. [42], the RRs were not statistically significant but were still in the inverse direction (RRs 0.90–0.96). In men, strong inverse associations were sometimes observed for the associations between BMI and BCC [39, 40] but this was not true in all studies [41, 42]. For SCC, strong inverse associations were also seen among women [40, 42] and sometimes [40] but not always [42] in men.

In contrast to what has been observed for most malignancies, the emerging evidence for KC reveals a trend toward higher BMI being associated with reduced KC risk. The inverse associations between BMI and KC tend to be stronger and more consistent in women than men. The precise reasons for this observation are not known. In the absence of the identification of a clear-cut physiologic mechanistic pathway, the explanation most compatible with an inverse association between BMI and KC risk is that it is attributable to overweight and obesity being associated with reduced time outdoors and hence reduced exposure to solar UVR. This example typifies the challenges inherent in attempting to identify and characterize new risk factors for KC in the presence of such a predominant risk factor as solar UVR. The associations reviewed above were often observed after statistically adjusting for sun exposure variables but truly disentangling two such interrelated factors poses a formidable methodological obstacle; thus, overweight and obesity acting as a marker of reduced solar UVR exposure is still the most likely explanation that is compatible with the observed data.

Hormones: Estrogen-Related Factors

The role of female reproductive characteristics and lifetime use of exogenous estrogens have been well-characterized in relation to breast cancer risk and cancers of the female reproductive tract. Epidemiologists have investigated whether these characteristics may be associated with KC, with one postulated hypothetical mechanism that estrogen may act to sensitize the epidermis to the damaging effects of UVR [43•].

Reproductive characteristics and exogenous estrogen use were examined in relation to BCC risk in a prospective cohort study of more than 46,000 women [43•]. Among the primary findings were the associations of increased BCC risk with later age at menopause (RR 1.50; 95% CI 1.04–2.17 for ≥55 versus 50–54 years) and menopausal hormone therapy (ever-versus-never use RR 1.16; 95% CL 1.03–1.30) [43•]. The findings for oral contraceptive use were null [43•]. In another cohort study, a similar association between menopausal hormonal therapy and BCC (ever-versus-never use RR 1.15; 95% CL 1.02–1.29) was observed [44]. Results such as these raise the notion that menopausal estrogen exposures may have at least a modest deleterious impact on KC risk, but the evidence base needs to be strengthened before firm conclusions can be reached.

Keratinocyte Carcinoma and Risk of Other Cancers and Fatal Outcomes

This section shifts from considering risk factors for KC to the topic of KC as a marker for increased risk of other adverse health effects. The results of numerous epidemiologic studies consistently indicate that a personal history of KC is significantly associated with an overall elevated risk of noncutaneous malignancies [45–47]. In a systematic review and meta-analysis, compared to individuals without a personal history of KC, those with a prior KC diagnosis had a 1.5-fold elevated risk (summary RR 1.49; 95% CI 1.12–1.98) of

developing another type of cancer in prospective cohort studies with individual-level data [47]. This excess cancer risk associated with KC was observed in both males and females and for both BCC and SCC [47]. Since the systematic review was published, the evidence characterizing KC as a marker of increased risk of noncutaneous malignancies has strengthened considerably [45, 46]. Two notable prospective cohort studies with individual-level data, one carried out in Taiwan [48] and the other in the USA [49], were published that provide further evidence of a strong association between NMSC and risk of other cancers. In the study in Taiwan, the entire study population was examined by dermatologists [48]. This is a unique study design feature not seen in previous studies on this topic; a skin examination would be expected to substantially improve classification of KC status. This is one a possible reason for the stronger association observed in this study compared with other studies; individuals with KC had more than double the risk of a subsequent internal malignancy compared to those with no KC history [48].

A cohort study of notable size (approximately 9.3 million) was a record-linkage study carried out in the UK [50•]; the large study population permitted the association between KC and risk of other cancers to be assessed with many different specific types of cancer with adequate statistical precision. The results clearly demonstrated the cross-cutting nature of the association between KC and cancer risk, as 97% (28/29) of the cancer site-specific RRs were in the direction of increased risk; 90% (26/29) of the RRs were statistically significant [50•]. The results also revealed that the risk of other cancers was stronger the younger the age of onset of KC; the relative risks of other cancers were 3.52 (95% CI 3.30–3.75), 1.74 (95% CI 1.70–1.79), and 1.32 (95% CI 1.30–1.33) in ages 25–44 years, 45–59 years, and ages ≥60 years of age, respectively [50•]. The results of this large study thus reinforce two important themes that have emerged from previous studies: (1) the association between KC and risk of other cancers is not limited to just a few malignancies but rather applies to a broad spectrum of malignancies and (2) the risk of other cancers seems to be even stronger in those with younger compared with older age-of-onset of KC [51]. Thus, this association exhibits many intriguing features and has now been consistently observed in many prospective studies, suggesting that KC may be a marker of a high cancer risk phenotype. The reasons for this association remain to be characterized, but the fact that this association applies to so many different types of cancer suggests that uncovering the mechanistic basis of this association has the potential to yield insights into susceptibility to cancer in humans.

In a separate line of inquiry, some studies suggest that a personal history of KC may be associated with increased mortality. In a cohort study with individual-level data that adjusted for several cancer risk factors, a personal history of SCC was associated with significantly increased risk of all-cause mortality (RR 1.29; 95% CI 1.01–1.54), whereas BCC was not associated with excess mortality [52]. In a systematic review of this topic, this pattern was consistent across all three studies, and SCC was more strongly associated than BCC with cancer-specific mortality in the lone study to report on this association [53]. Further, the systematic review found that both BCC and SCC were associated with worse survival after a diagnosis with a noncutaneous cancer [53]. The evidence base on the relationship between a personal history of KC and fatal outcomes is still sparse and therefore awaits more intensive investigation. The associations observed thus far are intriguing and suggest further research is warranted.

Conclusions

A review focused on recent epidemiologic research in KC highlights a few key themes. The understanding of the potential role of lifestyle behaviors other than sun exposure/sun protection continues to be refined. The results of epidemiologic studies of cigarette smoking, alcohol drinking, overweight/obesity, and hormonal therapy in relation to risk of KC have yielded interesting results with the trends in the results indicating some signal of increased risk in at least some subgroups for cigarette smoking, alcohol drinking, and hormonal therapy and signal of decreased risk with being overweight/obese. However, all of these examples highlight the challenges inherent in attempting to discern a genuine association from associations that might be attributable to confounding by UVR exposure.

Advances in understanding the etiology of KC should not divert attention away from some fundamental principles in KC prevention and control. First, the KC epidemic continues unabated in most regions with a high prevalence of KC. On top of rates that were already extraordinarily high, the incidence rates of KC continue to increase. Second, the primary public health strategy to prevent KC is known: minimize population exposure to solar UVR and UVR from UVR-emitting indoor tanning devices, particularly among those with sun-sensitive phenotypes. Minimizing unprotected solar UVR exposure entails either sun avoidance strategies or engaging in sun-protective behaviors, such as use of sunscreens on sun-exposed skin and use of sun-protective clothing, hats, and sunglasses. UVR exposure from indoor tanning causes KC and continues to evolve as a challenge to KC prevention efforts. Prevention strategies need to emphasize avoiding exposure to ultraviolet radiation via indoor tanning devices.

At the policy-level, preventive strategies include the regulation of tanning beds and media campaigns. The built environment is important, such as ensuring that playgrounds and school yards have shaded areas where children can be out of the sun. Further, educational interventions are needed at the individual-level. For all ages, the physician-patient interaction

represents an important opportunity to address skin cancer prevention behaviors. The associations between UVR exposure and KC are dose-dependent, meaning that skin cancer prevention behaviors are relevant to all age groups. The critical role of early life interventions for children and adolescents is clear, accentuating the importance of visits to the pediatrician as an opportunity to educate new parents about sun protection behaviors for their children. Further, school-based interventions offer an important opportunity to educate young people about the causes of skin cancer and immediate steps they can take to prevent it. The implementation of a comprehensive framework of skin cancer prevention strategies at the policy and individual levels are needed to curtail the KC epidemic.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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types of cancer; 2) the risk of other cancers is stronger the younger the age of onset of KC.

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