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REVIEW

Exposome and Skin. Part 2. The Influential Role of the Exposome, Beyond UVR, in Actinic Keratosis, Bowen's Disease and Squamous Cell Carcinoma: A Proposal

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ABSTRACT

Actinic keratosis (AK) is the main risk factor for the development of cutaneous invasive squamous cell carcinoma (SCC). It represents the first sign of severe chronic ultraviolet radiation exposure, which has a clear significant effect. Nevertheless, the skin is exposed to many other exposome factors which should be thoroughly considered. Our aim was to assess the impact of exposome factors other than ultraviolet radiation (UVR) on the etiopathology of AK and Bowen's disease (BD) and progression of AK to SCC and to design tailored prevention strategies. We performed an exhaustive literature search in September 2021 through PubMed on the impact of exposome factors other than UVR on AK, BD and SCC. We conducted several parallel searches combining terms of the following topics: AK, BD, SCC and microbiome, hormones, nutrition, alcohol, tobacco, viral infections, chemical contaminants and air pollution. Notably, skin microbiome studies have shown how *Staphylococcus aureus* infections are associated with AK and AK-to-SCC progression by the production of chronic inflammation. Nutritional studies have demonstrated how a caloric restriction in fat intake, oral nicotinamide and moderate consumption of wine significantly reduce the number of premalignant keratoses and SCC. Regarding lifestyle factors, both alcohol and smoking are associated with the development of SCC in a dose-dependent manner. Relevant environmental factors are viral infections and chemical contaminants. Human papillomavirus infections induce deregulation of cellular proliferation and are associated with AK, BD and SCC. In addition to outdoor jobs, occupations such as industrial processing and farming also increase the risk of developing keratoses and SCC. The exposome of AK will undoubtedly help the understanding of its etiopathology and possible progression to

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SCC and will serve as a basis to design tailored prevention strategies.

Keywords: Actinic keratosis; Dermatology; Environmental factors; Exposome; Hormones; Microbiome; Nutrition; Pollution; Prevention strategies; Squamous cell carcinoma

Key Summary Points

The main environmental risk factor for Actinic keratosis (AK), Bowen's disease (BD) and squamous cell carcinoma (SCC) is ultraviolet radiation (UVR) and therefore photoprotection is always advisable.

Nevertheless, other host, environmental and lifestyle factors play a relevant role in the onset of AK and BD and progression to invasive SCC.

S. aureus infections, alcohol, tobacco, human papillomavirus, chemical contaminants and air pollution are clearly associated with AK and SCC development.

Bowen's disease is also associated with human papillomavirus infections and arsenic exposure.

Caloric restriction of fat intake, oral nicotinamide, moderate consumption of red wine and green leafy vegetables are beneficial to prevent AK and SCC.

INTRODUCTION

Actinic keratosis (AK) represents the first sign of severe solar skin damage. It is considered the most common precursor and the main risk factor for the development of invasive squamous cell carcinoma (SCC) [1]. There has been much controversy concerning its classification as a premalignant lesion or as an in situ carcinoma [2]. The European guidelines have defined it as an in situ carcinoma [3] and many dermatologists claim that it is the same lesion and that AK simply represents the initial lesion in a disease continuum that might progress, histologically and clinically, to invasive SCC [4, 5]. In fact, the term AK has been recently reclassified as "keratinocytic intraepidermal neoplasia I–III (KIN I–III)" [6, 7] or "in situ SCC type AK I–III" [8]. Bowen's disease (BD) is sometimes referred to as SCC in situ, characterized by a proliferation of atypical intraepidermal keratinocytes filling the entire epidermis, including the granular layer [9, 10]. AK progresses to invasive SCC in 10% of cases and several pathways have been proposed to explain this phenomenon such as the "classic" or the "differentiated pathway" [11, 12]. The risk of progression of BD to invasive SCC is generally considered to be about 3%, of which approximately one-third may metastasize [13]. Undoubtedly, AK constitutes a major public health concern because of its high worldwide prevalence of between 11% and 25% and its potential for malignant transformation [5, 14]. According to a systematic review, the rate of progression of single AK into SCC ranges between 0 and 0.53% per year with regression of single lesions between 15% and 63%. Although the progression rate per lesion per year is small, in individuals with multiple AK lesions for more than 1 year, the risk for SCC development may be higher [15, 16]. Cutaneous SCC, if left untreated, is a deadly threat owing to its ability to invade locally, spread via the lymphatic system, blood or by perineural invasion, metastasize to any organ in the body and eventually result in death [17, 18]. Treatment of these lesions is highly recommended [3], although unfortunately most of the current treatments have local and systemic adverse effects [14]. Clearly, the best clinical approach is to identify the risk factors associated with the malignant onset and progression of these lesions to design better preventive strategies [18]. It is generally well acknowledged that the highest incidence rates are seen in elderly fair-skinned individuals, with light-coloured eyes and hair, skin that is prone to sunburn [5, 11, 18–20] and especially those persons on immunosuppressive therapy [21–24]. A multicentre case–control study conducted in Europe showed how the risk for AK is seven times higher in persons with red hair, followed by those with white, blonde, dark

blonde and light brown hair. They also observed a 40% reduced risk for AK in brown-eyed compared with blue-eyed persons, and a lower risk for darker phototypes. Sun exposure and sunburns during childhood significantly increased the risk for AK [25]. Another multicentre case–control study showed that chronic sun exposure was strongly associated with SCC [26]. In addition, many other studies have also pointed to ultraviolet radiation (UVR), which has a clear significant effect [27], as the main environmental trigger of AK [28], underestimating other relevant exposome factors. BD is also associated with UVR and immunosuppression, although other exposome factors such as viral infections and chemical contaminants are also of importance [10]. As the very first barrier between our body and the environment, the skin is exposed to many environmental, lifestyle and host factors from conception onwards which have been defined as the exposome [29, 30]. Therefore, many exposome factors besides UVR could be playing an important role in the onset and progression of AK by the production of inflammation, oxidative stress, impaired apoptosis, mutagenesis, dysregulation of cell growth and proliferation, and tissue remodelling, which have all been described as the main mechanisms of AK formation [31]. Hence, the primary aim of this study was to assess the impact of exposome factors other than UVR and other than the well-known host factors (e.g. immunosuppression, gender, phototype) on the etiopathology of AK and BD, and in the progression to invasive SCC. The secondary aim was to serve as a basis for physicians to define the relevant medical history of patients, and design tailored prevention strategies which complement sunscreens and exposure reduction to sunlight.

METHODOLOGY

We performed a broad literature search on articles published until September 2021 through PubMed on the impact of exposome factors other than UVR on AK, BD and invasive SCC. We conducted several parallel searches combining related terms of the following topics: actinic keratosis, squamous cell carcinoma, Bowen's disease and microbiome, hormones, nutrition, alcohol, tobacco, viral infections, chemical contaminants and air pollution. Relevant articles including in vitro, in vivo, ex vivo, clinical and epidemiological studies were selected for review. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

INFLUENTIAL ROLE OF EXPOSOME FACTORS

The AK, BD and SCC exposome consists of environmental, lifestyle and other host factors (Fig. 1) and their interactions affecting an individual and producing a specific biological response influencing the onset and progression into a malignant lesion (Table 1).

Host Factors

Skin Microbiome

Our skin is home to beneficial microorganisms with essential roles such as protecting us against

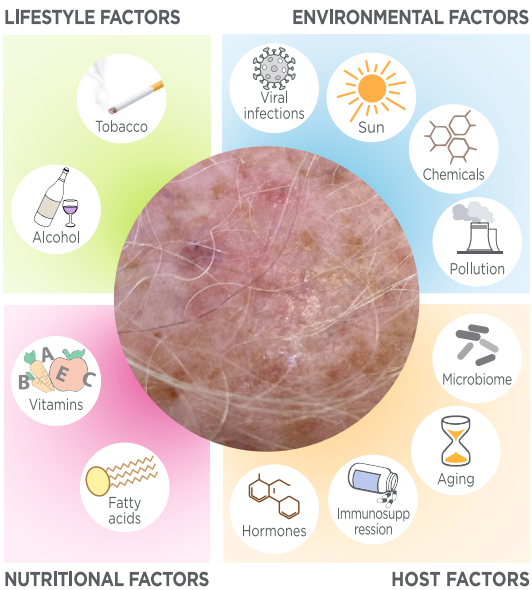

Fig. 1 Schematic map of the host, nutritional, lifestyle and environmental factors influencing AK, BD and SCC

Table 1 Summary of host, nutritional, lifestyle and environmental factors on AK, BD and invasive SCC

Exposome	Subclassification	Specific factors	Risk/association			References
			AK	BD	SCC	
Host	Microbiome	*S. aureus*	↑	–	↑	[33–35]
		Propionibacterium, Malasezzia	↓		↓	[34]
	Hormones	Higher serum vitamin D	–	–	↑	[47, 54–56]
			–	–	↓	[53]
		PPARα, PPARγ	↓	–	↓	[58]
		PPARδ	↑	–	↑	[58]
Nutritional	Fatty acids	Calorie restriction of fat	↓	–	↓	[65]
		High-fat diets	–	–	↑	[66–68]
		Oily fish (moderate intake)	↓	–	–	[74, 86]
	Vitamins & minerals	Green leafy vegetables	–	–	↓	[66, 67, 74, 86]
		Vitamin B_3	↓	–	↓	[82, 83]
		β-Carotene	–	–	↓	[86]
		Vitamin C	–	–	↓	[86]
		Retinol	–	–	↓	[91]
		Selenium	–	–	↑	[92]
Lifestyle	Alcohol & tobacco	Wine	↓	–	–	[74]
		Alcohol	↑	–	↑	[103, 104]
		Tobacco	–	–	↑	[107–112]
Environmental	Viral infections	HPV	↑	↑	↑	[116, 117, 120, 121, 125–130]
		Merkel cell polyomavirus	–	↑	–	[132]
	Chemical contaminants	Arsenic	↑	↑	↑	[133, 134, 136–139]
		Coal tar, soot	↑	–	↑	[140]
		Paraquat	↑	–	↑	[144, 145]
	Air pollution	PM	–	–	↑	[153]
		PAH	–	–	↑	[157, 158, 160]
		Ozone depletion	–	–	↑	[169]

AK actinic keratosis, *BD* Bowen's disease, *HPV* human papillomavirus, *PAH* polycyclic aromatic hydrocarbons, *PM* particulate matter, *PPAR* peroxisome proliferator-activated receptors, *SCC* squamous cell carcinoma

invading pathogens and educating our immune system. Nevertheless, any imbalance between commensals and pathogens may lead to skin disease progression [32]. Several studies have compared the skin microbiome between AK, seborrhoeic keratosis (SK), SCC, basal cell carcinoma (BCC) and healthy skin [33–35]. Nevertheless, we did not find any study evaluating the role of the microbiota in BD. In a hospital-based case–control study, *Staphylococcus aureus* DNA was strongly associated with SCC and there was also a trend for association with AK but no association was found for BCC or SK [33]. The study could not determine the possible causal or consequential relationship of the presence of *S. aureus* with AK and SCC although it is clear that acquisition of this bacteria was not due to mere protrusion of the lesions, since SK, a benign exophytic growth, did not show such association. A longitudinal, cross-sectional microbiome analysis conducted in immunocompetent men showed that *Propionibacterium* and *Malasezzia* organisms were relatively more abundant in non-lesional photodamaged skin than in AKs and SCCs. In contrast, *Staphylococcus* was most commonly associated with lesional skin, in particular, sequences most closely related to *S. aureus* [34]. Only some *S. aureus*-like operational taxonomic units (OTUs) were associated with SCC, which means that only particular strains of *S. aureus* are associated with SCC and could be used as possible biomarkers [34]. The distinction between the causal or the consequential role of *S. aureus* in the development of AK and AK-to-SCC progression is not clear, although both may be possible at the same time. The ulcerating growth characteristics and the reduced availability of sebum in both AK and SCC could partly explain the consequential *S. aureus* overabundance in these lesions. *Propionibacterium*, a common skin-colonizing bacterium, depends on sebum production to survive, and its decline may exacerbate lesion severity by disrupting the microbiome homeostasis and promoting *S. aureus* growth [34]. Conversely, *S. aureus* may be the cause of AK and AK-to-SCC progression by causing chronic inflammation, with the production of nitric oxide and cytokines which contribute to carcinogenesis [36–38]. Indeed, inflammation is a classical mechanism of carcinogenesis wherein oxidative stress and pro-inflammatory cytokines play a notorious role in oncogenesis, *Helicobacter pylori* and gastric adenocarcinoma being a clear example [39]. Interestingly, individuals with AK have shown a decline in RoxP concentration, an exogenous bacterial protein secreted by *Propionibacterium acnes* which modulates the redox status of the skin protecting the host from oxidative stress [40]. Furthermore, the staphylococcal alpha-toxin has been shown to activate several cytokines and nuclear factor-κB (NF-κB), supporting the hypothesis of the causative role of *S. aureus* in AK onset and progression to SCC [41]. Moreover, *S. aureus* overabundance has been significantly associated with human β-defensin 2 (hβD-2) expression, an endogenous antimicrobial peptide (AMP) with the ability to induce cell proliferation [35] and to stimulate keratinocyte migration and proliferation under the control of EGFR, STAT1, and STAT3 activation [42]. Overall, it would be of interest to develop biotherapeutics which stimulate the normal skin microbiota to the detriment of skin pathogen growth such as *S. aureus*. Curiously, *Staphylococcus epidermidis*, the antagonist of *S. aureus*, produces a molecule, 6-HAP (6-*N*-hydroxyaminopurine), which reduces UV-induced skin tumours in mice by inhibiting DNA polymerase activity [43]. Furthermore, it has been demonstrated how certain commensals secrete UV-absorbing compounds such as mycosporine-like amino acids (MAAs), and enzymes, including superoxide dismutases (SOD), with antioxidant activity [44]. Accordingly, people should be encouraged to take care of their skin microbiota in order to complement sunscreens. Urbanization and excessive hygiene with soaps decrease skin microbiota diversity [45] and therefore it would be of interest to demonstrate if soap-free shower gels may help in the prevention of skin dysbiosis. UVR influences the cutaneous microbiota with both positive and negative consequences [44] and the beneficial or detrimental effect of sunscreens on the skin microbiota remains to be demonstrated.

Hormones

Hormones (e.g. vitamin D, growth hormone or steroids) influence the development and function of human skin and cause a wide range of different biological responses through interaction with receptors [46]. Vitamin D is a clear example and is synthesized under the environmental influence of sun exposure, which is the main environmental risk factor for skin cancer [47]. Keratinocytes can convert vitamin D_3 to its hormonal form, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] (calcitriol), which in turn stimulates their differentiation, raising the hope to prevent skin cancer [48]. In fact, 1α,25-dihydroxyvitamin D_3, the active form of vitamin D_3, has potential antiproliferative, prodifferentiative, and immunomodulatory activities and thus potential therapeutic applications in the treatment of AK and SCC [49]. Studies in animals have demonstrated that vitamin D_3 hydroxyderivatives can attenuate chemically or UVB-induced epidermal carcinogenesis and inhibit growth of SCC and BCC [50]. Furthermore, vitamin D treatment decreases cell growth and metastasis in vitro [51, 52]. Nevertheless, the relationship in vivo between vitamin D and SCC is controversial and not well defined. The level of 25(OH)D, the major circulating form of vitamin D, is widely accepted as the best indicator of vitamin D status and vitamin D deficiency occurs if 25(OH)D levels are less than 20 ng/mL and insufficiency if less than 30 ng/mL. In a nested case–control study, higher serum 25(OH)D levels were associated with a decreased risk of non-melanoma skin cancer (NMSC) in older Caucasian men [53]. Conversely, other studies, including a systematic review and meta-analysis, a prospective study, and a cohort study, have found positive associations between circulating 25(OH)D level and risk of SCC [47, 54, 55]. This positive association could be explained by the confounding effect of sun exposure, which is responsible for both vitamin D synthesis and skin carcinogenesis. Indeed, in a case–control study, vitamin D and SCC risk were directly associated in the unadjusted model but after correcting for the effect of undesired variables (including age, sex and sunlight exposure) there was no significant association [56]. Perhaps, the association between high vitamin D levels and SCC suggests that UV exposure may have a predominant adverse influence that exceeds any putative benefit from the higher levels of vitamin D. What is clear is that sun protection should always be advised, especially for patients with skin cancer, while ensuring adequate levels of vitamin D [57]. Hormone receptors are also important in both AK and SCC. The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily that regulate important cellular functions in skin, including cell proliferation and differentiation, as well as inflammatory responses. It has been reported that PPARα immunoreactivity is reduced in human keratinocytes of SCC and AK, while PPARδ appears to be upregulated. PPARδ has been demonstrated to have an anti-apoptotic role and to maintain survival and differentiation of epithelial cells, whereas PPARα and PPARγ activators induce differentiation and inhibit proliferation and regulate apoptosis [58]. We did not find any study evaluating the potential role of hormones in the development of BD.

Nutritional Factors

Quality and Quantity of Free Fatty Acid Consumption

The first evidence that high-fat diets influence the development of ultraviolet radiation (UVR)-induced skin cancer in experimental animals was reported in 1939 [59]. It has been shown that high-fat diets markedly shorten the time between UV exposure and tumour appearance and increase tumour multiplicity [60, 61]. Interestingly, experimental studies have shown how caloric restriction inhibits the formation of skin tumours in animals [62–64]. One dietary-intervention trial clearly demonstrated how a large decrease in calories consumed as fat reduces the incidence of AK in humans. In this study, subjects who were assigned to the intervention group with a low-fat diet (20% of energy from fat) for 2 years developed 3 ± 7 (mean ± SD) AKs, which was significantly fewer than the 10 ± 13 AKs observed in the control group (40% of energy from fat) [65]. Indeed,

several studies have shown an increased SCC tumour risk in susceptible persons, with increasing consumption of high-fat diets and consumption of unmodified dairy products, such as whole milk, cheese and yoghurt [66–68]. Several explanations have been proposed for the underlying mechanisms of high-fat diets and skin cancer, such as lipid peroxidation of unsaturated fatty acids, which plays a role in at least part of the photocarcinogenic response [60, 69], and photochemical conversion of skin cholesterol into carcinogenic substances [70]. Although polyunsaturated fatty acids (PUFA) are a clear target of free radical attack, a clear distinction has to be made between the effect of omega-3 and omega-6 fatty acids [71]. It has been shown that ω-6 fatty acids significantly enhance carcinogenic expression and tumour multiplicity, especially in the post-initiation stage, while ω-3 fatty acids inhibit UV-carcinogenesis even at high dietary levels [72]. Since there exists a connection between inflammation and cancer [38] it is logical that ω-3 fatty acids have been shown to dramatically reduce the plasma and cutaneous pro-inflammatory and immunosuppressive prostaglandin E synthase type 2 (PGE_2) levels, while they increase the UVR-mediated erythema threshold in humans. Conversely, ω-6 fatty acids increase PGE_2, appear to act as tumour promoters, downregulate macrophage tumoricidal activities, inhibit interleukin-2 (IL-2) production, promote cellular hyperproliferation and tumour angiogenesis and suppress apoptosis [73]. Accordingly, in the dietary-intervention trial in which a large decrease in calories consumed as fat reduced the number of AK [65], there was also a reduction in levels of cholesterol and linoleic acid, an ω-6 fatty acid [61]. Additionally, a longitudinal study conducted in Australia using a validated food-frequency questionnaire showed how a moderate intake of oily fish (an average of one serving every 5 days) decreases the rate of AK by 26% and 28% among participants with intermediate and the highest intakes of oily fish, respectively [74]. The explanation of AK improvement with oily fish such as salmon, tuna and sardines probably relies on the high content of omega-3 fatty acids, especially if compared with other fish and seafood [75]. Overall, low-fat diets could play an important role in the clinical management of AK, as well as the prevention of SCC.

Antioxidant and Vitamin Intake

Antioxidants such as vitamin E or C are known to act as free radical scavengers and they can reduce lipid peroxidation damage. Indeed, nutritional studies have shown how antioxidants of the skin provide protection against the formation of UV-induced cholesterol α-oxide [76]. Animal studies have shown less frequent actinic lesions and SCCs when receiving antioxidants [77]. Oral nicotinamide (vitamin B_3) prevents UV radiation-induced immunosuppression which is triggered by DNA damage [78, 79]. The underlying mechanism may rely on its capacity to prevent ATP depletion, thereby boosting cellular energy and enhancing DNA repair [80, 81]. Several double-blind randomized controlled trials have shown how oral administration of nicotinamide effectively reduces AK count [82, 83]. A phase II placebo-controlled study with 500 mg of orally administered nicotinamide twice or once daily has shown a 35% and 29% relative reduction in AK count at 4 months respectively. What is more, the study showed lower odds of developing skin cancer when compared with placebo [82]. Later, a phase III randomized trial also demonstrated a lower rate of AK and NMSC among high-risk patients treated with 500 mg of nicotinamide twice daily for 12 months [83]. Clinical studies have also indicated that consumption of green leafy vegetables in individuals with history of skin cancer prevents SCC [66]. Green leafy vegetables contain a variety of vitamins, minerals and other bioactive substances that may protect against cancers, including the antioxidants lutein, vitamins C and E, flavonoids and folate, which is implicated in DNA synthesis and repair [84]. Nevertheless, the potential beneficial effect of many vitamins such as vitamin A, vitamin E, vitamin C and carotenoids and selenium has been assessed in many epidemiologic studies and the relationship with SCC has been, at best, weak [85] (Table 2). We did not find any study showing the relationship between nutritional factors and BD.

Table 2 Epidemiological studies evaluating the association between vitamins, minerals and NMSC

Reference	Type of study	No. of individuals	Vitamins and minerals analysed	Main outcome
Kune et al. [86]	Case–control study	88 cases + 88 controls	β-Carotene and vitamin C serum concentration	β-Carotene- and vitamin C-containing foods appear to be protective for both SCC and BCC. Cases had a lower mean serum level of β-carotene ($p < 0.001$) and vitamin A ($p = 0.02$)
Karagas et al. [87]	Nested case–control study	132 cases + 264 controls	Selenium, α-tocopherol, β-carotene and retinol serum concentration	No association was found between the concentrations of any of these nutrients and SCC
Frieling et al. [88]	Randomized, double-blind, placebo-controlled trial	22,071	12 years of 50 mg of β-carotene supplementation on alternate days	An average of 12 years of supplementation with β-carotene does not affect the development of both BCC and SCC
Green et al. [89]	Community-based randomized controlled trial	1621	30 mg of β-carotene supplementation per day	No beneficial or harmful effect on the rates of SCC and BCC as a result of β-carotene supplementation
Greenberg et al. [90]	Randomized clinical trial	1805	50 mg of β-carotene supplementation per day	In persons with a previous nonmelanoma skin cancer, treatment with β-carotene does not reduce the occurrence of new skin cancer over a 5-year period
Moon et al. [91]	Randomized, double-blind, controlled trial	2297	25,000 IU of oral retinol supplementation per day	Daily supplementation with 25,000 IU of retinol was effective in preventing SCC, although it did not prevent BCC
Duffield-Lillico et al. [92]	Double-blind, randomized, placebo-controlled clinical trial	1312	200 µg daily selenium supplementation	Selenium supplementation is ineffective at preventing BCC and it increases the risk of SCC and total NMSC

BCC basal cell carcinoma, *NMSC* non-melanoma skin cancer, *SCC* squamous cell carcinoma

Lifestyle Factors

Alcohol Consumption

A longitudinal study conducted in Australia in the 1990s, using a validated food-frequency questionnaire, showed that moderate consumption of wine (average of half a glass per day) significantly reduced the rate of acquisition of new AKs [74]. There are several classes of compounds on which polyphenols from wine could exert a biological effect. The most important polyphenols include flavonoids (quercetin, catechin, anthocyanins) and non-flavonoids (resveratrol), which are considered

powerful antioxidants and are bioavailable after wine consumption [93]. Nevertheless, there is more and more evidence that flavonoids are unlikely to act as major antioxidants but rather through modulation of signalling cascades such as the MAP kinase pathway [94]. Polyphenols, especially resveratrol, have demonstrated anti-inflammatory and also anticancer properties, including inhibition of tumorigenesis [95, 96], and they also inhibit UVR damage in human skin cells [97]. It should be considered that the concentration of *trans*-resveratrol varies depending on the quality and type of wine. Specifically, red wines have a concentration of between 0.1 and 14.3 mg/L while white wines rank much lower (< 0.1–2.1 mg/L) [98, 99]. Proprietary formulations with resveratrol have been developed for skin rejuvenation due to its antioxidant and anti-aging properties [100], but not for AK and SCC. Since resveratrol has been shown to inhibit the growth of human skin SCC A431 xenograft in nude mice by inducing apoptosis and suppressing survivin and the activation of caspase-3 [101], it would be of interest to test the potential beneficial effect of topical resveratrol in the treatment of AK and SCC. Nonetheless, the anticarcinogenic properties of wine should be considered carefully since acetaldehyde, the first ethanol metabolite, is a cancer-causing agent [102]. In fact, alcohol drinking is positively associated with SCC in a dose-dependent manner [103], and is an independent risk factor of AK according to a retrospective observational study [104]. Nevertheless, we did not find any study pointing to this association in BD.

Cigarette Smoking

Epidemiologic studies evaluating the effect of cigarette smoking in AK are scarce, and although several studies have assessed the possible positive association, statistical significance has never been reached [105, 106]. Nevertheless, it would be advisable for patients with AK to stop smoking since it has been reported to be associated with SCC in many studies [107–112], including prospective [107, 108] and case–control studies [109–112]. Some of them have also reported a dose–response relationship in SCC with number of cigarettes [110–112], years smoked and pack-years of smoking [112].

Environmental Factors

Viral Infections

Human papillomaviruses (HPV) are ubiquitous viruses that infect the skin [113] and have been reported to be responsible for cervical carcinoma [114] and oropharyngeal carcinoma [115] among others. Regarding actinic lesions and NMSC, a cross-sectional study of skin swabs demonstrated that HPV species 1 and 2 of the Betapapillomavirus genus were associated with the presence of AK. Indeed, a greater number of HPV types per sample was found in individuals with AK or SCC or AK alone than in healthy participants [116]. Other studies have also demonstrated the relationship between Betapapillomavirus species 2 with SCC, especially in sun-exposed sites [117]. The preferential finding of HPV DNA in sun-exposed sites might be due to increased promoter activity after UV irradiation [118], as well as decreased apoptosis [119]. Specifically, the inhibition of apoptosis in response to UV damage by the E6 protein from a range of cutaneous HPV types may play a key role in providing a survival advantage to genetically damaged keratinocytes, resulting in AK and SCC [120]. Epidermodysplasia verruciformis-associated HPV (EV-HPVs) are possibly involved in the development of AK, as has been demonstrated in serological studies, and may play a role in the pathogenesis of SCC [120, 121]. Interestingly, an observational report with 9-valent HPV vaccination as adjunctive, off-label management of AK showed AK regression beginning within months of the first injection, leading to the clearance of thousands of lesions before the vaccination protocol was completed [122]. Regarding the possible association with other viral infections, the literature is scarce and controversial. While one study suggested the association of human herpesvirus 8 (HHV-8) with proliferative skin lesions [123], another study suggested that both HHV-8 and Epstein-Barr virus do not play an etiological role in cutaneous oncogenesis [124]. BD has also been associated with HPV infections

in many epidemiological studies [125–130]. Several serotypes have been associated with BD including HPV-6 and HPV-18 co-infection [126], HPV-58 sub-lineage A1 [125], HPV-31 [130], HPV-11, -16 and -18 [128]. Prevalence of HPV infection in patients with BD varies greatly from 4.8% [130] to 68% [129], according to different studies. A retrospective study showed that HPV detection rate was significantly higher in pelvic BD compared to non-pelvic BD [127]. Conversely, one clinical study involving two cases of BD failed to detect evidence of HPV infection [131]. BD has also been associated with Merkel cell polyomavirus infection in a Brazilian population study [132].

Chemical Contaminants

A strong positive correlation has been established between arsenic and chromium concentration and AK and NMSC [133]. Most human arsenic exposure occurs from consumption of contaminated water. Skin lesions are the first signs of chronic arsenic exposure [134]. Several arsenic poisoning outbreaks have been reported in Bangladesh and India due to the introduction of deep tube-pumps to obtain drinking water from underground sources [135, 136]. A population study assessing water levels of arsenic and skin lesions in India showed that the age-adjusted prevalence of keratosis was strongly related to water arsenic levels, rising from zero for the lowest exposure level (< 0.05 mg/L) to 10.7 and 8.3 per 100 for male and female individuals, respectively, for the highest exposure level (> 0.8 mg/L) [136]. BD has also been associated with arsenic exposure in several case-report publications [137–139]. Water from areas of endemic arsenic poisoning clearly needs to be thoroughly analysed as a preventive measure. Other sources of exposure to chemical contaminants may arise during exposure in certain occupations. Aside from outdoor workers, keratoses and skin cancers can arise in other workers exposed to chemical carcinogens such as coal tar products and arsenic: tar keratoses or arsenical keratoses are a clear example. Tar keratoses may appear years after exposure to coal distillation products (e.g. coal tar, pitch, shale oil) [140]. Arsenical keratoses usually appear on the palms of the hands and soles of the feet after ingestion of arsenic and can progress to SCC [140]. Arsenic (As^{3+}) may induce large deletion mutations leading to genomic instability [141], which is a hallmark of cancer, and it is likely to act as a tumour promoter by stimulating Jun kinases (JNKs), AP-1, c-jun and c-fos [142]. Arsenic is used in many industrial processes, including the manufacture of semiconductors, glass and also insecticides and herbicides [140]. It is also produced as a by-product in the smelting of copper, lead and zinc. Workers may also be exposed to arsenic in its mining and smelting [140]. Farmers are exposed to arsenic pesticides and thereby exposed to increased risk of AK and SCC. There are other pesticides such as paraquat which have also been reported to be potentially carcinogenic [143]. The relationship between paraquat and keratosis, hyperkeratosis and SCC has been controversial. Some studies have reported an increased risk of developing these lesions in paraquat manufacturers, probably due to exposure to tarry by-products in the production process [144, 145]. Conversely, other studies have reported no significant association between paraquat and keratoses or other skin lesions [146–148]. SCC, the malignant progression of AK, may also result from polycyclic aromatic hydrocarbons (PAH), which are the main carcinogens present in tar, pitch, soot and raw paraffin [140]. To understand the risks of industrial processes thoroughly it is crucial to design better prevention strategies such as personal protective equipment (PPE), coupled with educational projects to encourage the early detection of premalignant lesions.

Air Pollution

Urban air pollution is a complex mixture of gases and particles with condensed organic matter. The major sources of airborne pollutants are mainly from incomplete burning of materials derived from fossil fuels, vegetative sources or mixtures of these materials (e.g. garbage, waste and coal) [149]. As the outermost organ, the skin is exposed to many air pollutants such as PAH, volatile organic compounds, oxides, particulate matter (PM) and ozone which have detrimental effects on the skin [150].

Particulate Matter PM consists of complex mixtures of particles suspended in the air which vary in size and composition. It is categorized according to the size of the particles: coarse particles larger than 1 μm diameter (e.g. $PM_{2.5}$ and PM_{10}), fine particles smaller than 1 μm, and ultrafine particles smaller than 0.1 μm. The major components are metals, organic compounds such as PAH and endotoxins, materials of biologic origin, ions and particle carbon core. They are produced in factories, power plants, refuse incinerators, motor vehicles, construction activity, fires and natural windblown dust [151]. PM penetrates into barrier-disrupted skin through hair follicles or across the stratum corneum, causing inflammation and increased levels of IL-8, matrix metalloproteinase-1 (MMP-1) and reactive oxygen species (ROS), which have detrimental effects in the skin. Indeed, PM leads to neutrophil infiltration in the deep dermis, as well as epidermal thickening. Most PM that penetrates into the skin consists of fine particles that are hazardous for human skin [152]. A semi-individual cohort study showed that an increase in PM_{10} of 10 μg/m^3 was associated with a 52% increase in relative risk of NMSC [153]. Another epidemiologic study demonstrated that urban PM_{10} air pollution in São Paulo was associated with incidence and mortality of skin cancer [154]. Accordingly, a higher residential green space level should have a protective effect for NMSC in areas with low to moderate UV intensity.

Polycyclic Aromatic Hydrocarbons PAH are the largest class of chemical compounds, ranked ninth most threatening and known to cause cancer. They are present ubiquitously in the environment as pollutants and are formed by the incomplete combustion of almost any fuel such as motor vehicle emissions, residential heating and pollution from industrial machines and are transported through the atmosphere in the vapour phase. Indoor air sources of PAH exposure include tobacco smoke, fumes from open fires, kerosene heaters and cooking. Humans are exposed to PAH by inhalation, ingestion and skin contact, which bioaccumulate in soft tissues, binding to DNA and causing mutations that result in cancer [149, 155, 156]. The PAH benzo[*a*]pyrene (BaP) and dibenzo[*def*,*p*]chrysene (DBC) both produced SCC in an FVB/N mouse skin tumour model [157]. The carcinogenic effect of PAH is mediated through the interaction with their receptor, the aryl hydrocarbon receptor (AhR), and subsequent activation of CYP1A1. This protein constitutes a member of the cytochrome P450 family, which is responsible for the degradation of PAH, resulting in the formation of highly carcinogenic diol-epoxide metabolites that form DNA adducts. Indeed, $AhR^{+/+}$ mice exposed to airborne PM developed SCCs while $AhR^{-/-}$ did not [158]. Interestingly, animal studies have demonstrated that resveratrol, a natural AhR antagonist, inhibits BaP-induced CYP1A1 expression and subsequent formation of DNA adducts [159]. It has also been demonstrated that UVA combined with BaP significantly increases the risk of skin cancer [160]. In cell culture, BaP synergistically increases the formation of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in combination with UVA [161]. BaP serves as a photosensitizer to generate massive ROS upon UVA irradiation which in turn causes oxidative damage and BaP–DNA binding (genetic effect), and potentiates the activation of signal transduction cascades (epigenetic effect), thereby leading to carcinogenesis. In fact, topical application in mice of BaP followed by UVA significantly increased the skin tumour incidence and multiplicity compared with UVA or BaP treatment alone [162]. Photoproducts resulting from UVB radiation are also able to activate AhR, which leads to subsequent activation of cytochrome P450 1A1 and EGF receptor internalization with activation of the EGF receptor downstream target ERK1/2 and subsequent induction of cyclooxygenase-2 (COX-2), which is involved in SCC development by generating pro-inflammatory and anti-apoptotic metabolites [163]. In addition, the UVB-sensitive transcription factor AhR attenuates the clearance of UVB-induced cyclobutene pyrimidine dimers in human HaCaT KC and skin from SKH-1 hairless mice by inhibition of p27 tumour suppressor protein [164]. Interestingly, the AhR has been identified as a locus significantly associated with SCC development in a genome-wide association study [165].

Regarding BD, we did not find any study evaluating the potential role of air pollution.

Ozone Ozone is an unstable toxic gas normally found in the stratosphere, where it plays a beneficial role in filtering out the short-wave spectrum of UV radiation. Unfortunately, growing emissions of chlorofluorocarbon molecules are causing a diminution in the ozone layer, resulting in more UVB reaching the Earth's surface [166]. Consequently, for every 1% decrease in ozone there is a 2% increase in UVB irradiance, and therefore a 2% increase in skin cancer is predicted [167]. Specifically, each percentage point degradation in the O_3 layer thickness would raise the incidence of SCC by 3% to 4.6% [168, 169]. Surprisingly, large reductions in UV irradiance have been observed in polluted urban areas when compared to pristine locations. While the cleaner atmosphere in Lauder, New Zealand is undoubtedly beneficial for health, its effect on UV may not be. During the summer, mean UVB irradiances in Tokyo are approximately 40% less than in Lauder for the same solar zenith angle. These differences are slightly smaller in the winter, and in the UVA region. The effects of pollution in Tokyo impose large reductions in UV irradiances compared with those at the pristine Lauder site. The reductions in UV in Tokyo become progressively larger as the wavelength decreases through the UVA and UVB regions [170]. While ozone in the upper atmosphere (stratosphere) occurs naturally and protects skin by filtering out harmful solar ultraviolet radiation, ozone at ground level (troposphere) is a noxious, highly reactive oxidant pollutant [171]. It is formed in photochemical smog reactions, with the interaction of sunlight (UVR) with hydrocarbons, VOCs, NOx, carbon monoxide (CO) and other pollutants [150]. Acute ozone exposure depletes skin vitamins C and E and induces lipid peroxidation in upper epidermal layers. The stratum corneum, as the penetration barrier of the body, appears to be particularly susceptible to ozone-induced oxidative stress. Such processes at superficial skin layers lead to barrier perturbations and could trigger inflammatory responses in adjacent skin layers [172]. Nevertheless, to the best of our knowledge there is no evidence claiming that tropospheric ozone causes SCC.

CONCLUSIONS

The main environmental risk factor for the development of AK, BD and SCC is UVR exposure, which has a clear significant effect, in combination with other host factors (e.g. phototype, gender, and light-coloured hair and eyes). Accordingly, photoprotection is clearly advisable, especially for patients with skin cancer and individuals prone to sunburn. Nevertheless, the exposome of AK, BD and SCC should not be restricted to UVR since many other exposome factors play a relevant role in the disease onset and progression. Historically, the exposome of AK, BD and SCC has mainly focused on UVR, and the interactions with other exposome factors are missed or poorly understood. Clearly, the independent effect of these other potential risk factors is difficult to quantify, and inconsistencies and controversial data are due to the confounding effect of sun exposure. However, many exposome factors interact with each other on a genetic background to produce a specific biological response. In addition to photoprotection it would be advisable to take care of the microbiota, by avoiding excessive hygiene, eating omega-3 fatty acids (e.g. salmon), avoiding excessive fatty acid meals, following a regular diet rich in antioxidants, stopping smoking and being aware of the potential occupational risk factors. Undoubtedly, the exposome of AK, BD and SCC presented here will help not only to understand AK and SCC etiopathology but also to understand the underlying mechanisms of malignant transformation and be able to design tailored prevention strategies which complement sunscreens and avoidance of sun exposure.

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