Non-melanoma skin cancer: The hygiene hypothesis
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A B S T R A C T
Protection against ultraviolet radiation-induced DNA-damage in the skin is not only provided by the pigmen-
tary system. The epidermal barrier consisting of stratum corneum keratinocytes, filaggrin and other pro-
teins is an additional component of the UV-shield. Disruption of the epidermal barrier through fre-
quent body cleansing with soaps and cosmetics may increase the risk of non-melanoma skin cancer.

Introduction
Since the 1950s it is known that excessive exposure to ultravi-
iolet radiation (UVR) is associated with an increased risk of non-
melanoma skin cancer [1]. Non-melanoma skin cancer is the term
which covers basal cell carcinoma (BCC) and squamous cell carci-
mona (SCC). UVB and UVA are both oncogenic and immunosup-
pressant, but UVB mostly acts through direct mutagenic onco-
genesis while UVA's effects mainly impair the immunosurveil-
lane. The current leading theory, fuelled by overwhelming epide-
iologic evidence is that epidermal protection against skin cancers is solely provided by the pigmentary system. This barrier of melanin produced by melanocytes in the basal layer of the skin is transferred to the keratinocytes via melanosomes. The mismatch between skin phototype (degree of pigmentation) and UVR-exposure has become a truism to explain the rise in incidence of non-melanoma skin cancer. This mismatch is the single most important risk factor for non-melanoma skin cancer which has left little room for research on alternative risk factors. The currently failing prevention programs necessitate the analysis of preventable causes [2]. Here, we propose epidermal barrier dysfunction through personal hygiene habits as a new risk factor for the development of non-melanoma skin cancers.

Why pigmentation only does not suffice
Melanin is thought to protect the skin from the DNA-damaging effects of UVR-light. The lower prevalence of non-melanoma skin cancer in dark skinned individuals underscores this. Nevertheless, the existence of DNA-repair mechanisms in the skin indicate that pigment only may not suffice to protect us. The rare cases of African patients with xeroderma pigmentosum illustrate this in vivo. These patients develop squamous cell carcinomas in the typical photodistributed locations very early in their lives [3]. While a darker skin type in healthy Africans does offer protection against non-melanoma skin cancer, facultative pigmentation as seen in people of European ancestry offers no protection against development of UV-induced pyrimidine dimers [4]. Pheomelanin even induces apoptosis of keratinocytes as it acts as a photosensitizer after exposure to UVB [5]. Although the pigmentary system protects us from acute sunburn, the development of non-melanoma skin cancer does not threaten the survival of individuals before reproductive age. In the anogenital area, the squamous cell cancer arises without significant, previous UVB-exposure. This is explained by the oncogenic-effects of human papilloma virus and indicates the existence of alternative and complementary routes of pathogenesis from which melanin offers no protection.

Stratum corneum as UVR-barrier
There is more in the epidermis than pigment only to block the UVR. The most outer layer of the skin, stratum corneum, is the first component of the skin to absorb the photons. It is known that low doses of UVR from the ambient spectrum may not even penetrate stratum corneum [6]. Thickening of the stratum corneum is the most important adaptation to acute UV-exposure in humans [7]. In a study with vitiligo patients, the skin stripped of stratum corneum was significantly more sensitive to UVB in terms of mean erythema dose than non-stripped skin [8]. Besides the dead keratinocytes and their contents the photons from UVR also encounter a barrier of many proteins, amino acids, ceramids and lipids in stratum corneum. Stratum corneum, together with all these components is also referred to as the epidermal barrier. This barrier is held in place by a scaffold of filaggrin. Filaggrin is a protein which contributes to compaction of stratum corneum and cohesion between its constituents [9]. Impairments in the functioning of filaggrin, its precursors or derivatives have been linked to inflammatory skin disorders like atopic dermatitis but may also lead to a disrupted epidermal UVR-barrier. A study with a human...
skin model showed increased UVB-induced apoptosis after knockdown of filaggrin expression [10]. Conversely, in response to UVB-exposure filaggrin expression is upregulated together with other components of the epidermal barrier [11]. Derivatives of the filaggrin metabolism also may provide protection against UVB induced effects. Filaggrin cleavage by caspase-14 is required for its proper functioning. A major derivative of the cleavage process of filaggrin by caspase-14 is urocanic acid. Urocanic acid provides protection against dehydration and low-level protection against UVB-induced DNA-damage [12]. The skin of caspase-14-deficient mice is highly sensitive to the formation of pyrimidine dimers after exposure to UVB compared to wild type mice [13]. These data strongly suggest that the stratum corneum provides an additional component for the total UVR barrier.

**Epidermal barrier dysfunction and skin cancer**

Previously mentioned studies have demonstrated increased sensitivity to UVR in dysfunctional stratum corneum but there is also circumstantial evidence that defects in the stratum corneum may actually lead to non-melanoma skin cancer. Patients with skin disorders primarily related to epidermal barrier dysfunction have been of particular interest. In a Danish cohort of 31,330 patients with atopic dermatitis, a common disorder of the epidermal barrier the standardized incidence ratios for BCC and SCC were 1.41 [95% CI 1.07-1.83] and 2.48 [95% CI 1.00-5.11] respectively [14]. Patients with epidermal barrier dysfunction are also frequently sensitised to various allergens because of the more permeable epidermis. They develop antibodies of the IgE-type. Patients who have multiple squamous cell carcinomas have these antibodies more often (odds ratio 3.82 [95% CI 1.05-13.88]) [15]. This suggests that patients with an impaired epidermal barrier, which is indicated by the presence of sensitisation to common allergens, are at higher risk of developing non-melanoma skin cancer. Same results can be found in non-vulgars itchosis and Netherton syndrome. These rare disorders are extreme examples of epidermal barrier dysfunction. Patients with these disorders show an increased susceptibility to squamous cell carcinoma [16]. In Netherton syndrome a mutation in SPINK5 leads to impaired function of a serine protease inhibitor. The proteases which it inhibits are involved in desquamation and remodelling of the stratum corneum and processing of filaggrin. These patients often have an atopic dermatitis-like phenotype and exhibit high serum-levels of IgE. Therefore, even exposure to only water during washing may rinse of significant amounts of the epidermal scaffolding which takes some time to replace. We postulate that frequent exposure to showering and detergents in soaps and cosmetics, as habitually used in modern times, lowers epidermal UVR-blocking capacities and increases the risk of non-melanoma skin cancer.

**Testing the hypothesis**

Future studies may encounter some problems. It will be difficult for the fundamental scientist to define hygienic behaviour in animal models and dysfunctional skin barrier. This makes the results hard to interpret and to extrapolate to humans and clinically relevant endpoints. Genetic studies may reveal polymorphisms influencing the epidermal barrier and the development of non-melanoma skin cancer but the practice of hygiene is obviously a cultural phenomenon which cannot be taken into account within these studies. Functional testing with measuring of the epidermal barrier function is not feasible in large groups of patients and the time until the development of skin cancer may blur the results. Also, the amount of damage to the skin barrier through external factors needs defining especially in longitudinal cohort studies. The testing of our hypothesis therefore necessitates research involving different areas. In vitro studies should focus on how stratum corneum and filaggrin protect us against UVR-induced DNA-damage and how this may be impaired by environmental factors. Genetic studies are needed to help form new hypotheses. Epidemiologic studies may show or dispute associations between diseases of the epidermal barrier such as atopic dermatitis and non-melanoma skin cancer. This is a cumbersome field because of many potential confounders such as use of immunosuppressant medication and treatment with UVR. The role of hygiene and cosmetics as well as exposure to yet unknown environmental factors should be explored. After the identification of relevant epidemiologic, genetic and biologic parameters interventional studies can be initiated. Though randomising patients into “hygienic” and “less hygienic” groups may be unthinkable for longer periods of time, it is feasible to have two groups of individuals practising different hygiene behaviours during holidays when disproportionate exposure to UVR takes place. Finally, the gained knowledge can be implemented through prevention studies.

**Conflict of interest statement**

None declared.

**References**


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