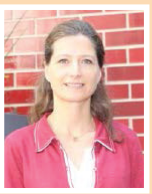
Research Review
EDUCATIONAL SERIES

Non-melanoma skin cancer, melanocytic naevi, and sunscreen use adherence

About the Experts



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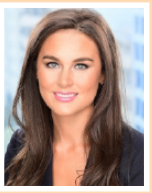

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Dr Louise Reiche is a New Zealand physician trained vocational specialist dermatologist. Experienced in a wide range of general clinical dermatology, she sees the impact of NZ sun exposure on her patients on a daily basis and pleasing results from sun protection interventions. Louise has served on the Vitamin D Working Group for the Cancer Society, is a member of Melnet NZ, Clinical advisor for Melanoma NZ and works alongside these groups and on behalf of the NZ Dermatological Society promoting holistic sun protection practices in an expert voluntary capacity.

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This review summarises recent findings on the skin cancer front pertaining to risk and prevalence and preventative efforts. Three diverse topics are discussed:

1. Consideration of non-melanoma skin cancer as an occupational disease.
2. Melanocytic naevi in children as a risk factor for melanoma later in life.
3. Enhancing skin cancer prevention through improvement of sunscreen use adherence.

Ultraviolet radiation (UVR) is classified by the International Agency for Research on Cancer as a Class 1 (definite) human carcinogen.[1] UVR received from the sun is the primary environmental risk factor for the development of melanoma, non-melanoma skin cancer, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and actinic keratosis (pre-cancerous lesions). In Australia, a conservatively estimated 63% of melanomas and almost all non-melanoma skin cancers are attributable to high UVR levels.[2] UVR exposure is also linked to the development of melanocytic naevi, which are key risk factors for melanoma.[3,4]

Exposure to UVR can be diminished through sun avoidance and various sun protective measures. Sunscreen is key in the armamentarium for sun protection and skin cancer prevention in addition to the use of protective clothing, hats, sunglasses, and seeking shade. There is strong evidence to support regular sunscreen use in the reduction of the development of non-melanoma skin cancer and melanoma.[5]

1. Non-melanoma skin cancer as an occupational disease

Non-melanoma skin cancer is the most common cancer in the world.[6] Two to three million people are diagnosed with non-melanoma skin cancer every year and, during the past 30 years, there has been an average yearly increase of 3–8% in white populations in Australia, Europe, the US, and Canada.

In Australia, the skin cancer capital of the world, a high burden of UVR exposure occurs in occupational settings. According to a 2014 analysis based on 2011–2012 data, 40.3% of Australians are potentially exposed to carcinogens in their workplace, with UVR being the most common exposure (37% of working males and 8% of working females).[7] An earlier study from 2006 estimated that 34,000 non-melanoma skin cancers per year are due to occupational exposures in Australia.[8] It is not possible to quantify risk in NZ because there is no routine recording of non-melanoma skin cancer incidence and occupational history, although it is well recognised that NZ outdoor workers are exposed to high levels of solar UVR.[9]

In 2016, a European working party was convened to review and discuss the literature and current clinical expert opinion on non-melanoma skin cancer as an occupational disease. The consensus report produced by the working party states the following:[6]

- There is increasing evidence linking UVR exposure in outdoor workers to non-melanoma skin cancer.
- Up to 90% of non-melanoma skin cancers may be due to UVR exposure.

A 2016 European multicentre case-control study showed that outdoor workers demonstrated more risk behaviour (with similar constitutional skin cancer risk factors) and more UVR exposure, used sunscreen less, and had lower levels of health literacy than indoor workers.[10] Consequently, outdoor workers were at significantly increased risk of developing BCC and SCC. These findings are supported by two earlier meta-analyses of epidemiological studies from the international literature that found that outdoor workers are at increased risk for the development of SCC and BCC,[11,12] although the effect for BCC may be of lesser magnitude.[13]

In Australia, male farm workers have a higher rate of mortality due to melanoma and non-melanoma skin cancer relative to the general male population.[14] This statistic is perhaps not surprising given surveys indicating general low levels of sunscreen use and sunscreen re-application among farmers.[15]

In summary, current research recognises non-melanoma skin cancer as an occupational disease. Hence, outdoor workers are in particular need of protection against UVR. Providing UV-protective equipment, promoting its use and that of other sun protection behaviours, instilling a sun-protective workplace culture, and use of customised sun protection plans are interventions that have the potential to improve the sun-protective practices of NZ and Australian outdoor workers,[9,16-18] and reduce skin cancer rates in Australia and NZ.

2. Naevi in children as a risk factor for melanoma

Melanocytic naevi are benign skin lesions caused by the focal proliferation of melanocytes (pigment-producing cells), more commonly known as moles.[19,20] Most people have at least one naevus with fair-skinned people having more naevi than darker-skinned people. Some naevi are present at birth (congenital naevi) but the majority develop during childhood and early adult life (acquired naevi).

Acquired naevi share genetic and environmental risk factors with melanoma.[21]

For example, individuals with fair skin are at an increased risk for malignant melanoma and their prevalence of naevi is higher than darker-skinned individuals. Epidemiological studies support the role of early-life UVR exposure in determining the prevalence of naevi in childhood.[22] Naevi have been demonstrated to be common at a very young age in children in Queensland, Australia and to be associated with sun exposure.[23]

In terms of molecular aetiology, naevi and melanoma have been demonstrated to share common driver mutations.[21] For example, acquired melanocytic naevi harbour oncogenic mutations in BRAF, which is the predominant oncogene associated with melanoma.

In their 2010 meta-analysis of epidemiological data on the magnitude of the relationship between naevus counts and melanoma risk, Olsen et al. estimated that 25% of melanoma cases are attributable to the presence of ≥1 atypical naevi and that high common naevus counts (≥50 naevi) account for 27% of melanoma cases whereas individuals with few common naevi (0-10) account for only 4% of melanoma cases (**Table 1**).

Number of melanocytic naevi	Proportion of melanoma cases
Atypical naevi:	
1 or more	≈25%
Common naevi:	
0-10	≈4%
11-24	≈7%
25-49	≈15%
50 or more	≈27%

Table 1. Relationship between melanocytic naevi exposure and melanoma risk based on estimates of the population attributable fraction (PAF) of melanoma associated with atypical naevi and common naevus counts.[24]

With Olsen et al having demonstrated naevi to be a risk factor for melanoma, with higher naevus counts being associated with the highest melanoma burden,[24] logic suggests that reducing the number of naevi acquired in childhood has the potential to reduce the risk of melanoma in adulthood.

A recently published cross-sectional study aimed to establish the relationship between sun exposure habits and constitutional factors and the number and distribution of naevi by assessing the presence, density, and regional distribution of acquired naevi in a paediatric population.[25] Data on the numbers and distributions of acquired naevi in the total study population of 369 children were collected and correlated with age, sex, and skin phototype. The data were also correlated with environmental factors including annual/lifetime intermittent and chronic sun exposure, sunburns, and sunscreen use.

As previously reported by others, analysis of the data identified several risk factors associated with naevus density and distribution:[25]

- The density of naevi increased with age.
- Boys had more naevi on the trunk and girls had more naevi on the legs.
- Children with light skin phototype had more naevi.
- A higher level of accumulated sun exposure was correlated with a higher number of naevi in children with non-adequate sunscreen use.

A comparison of the results of the study with those of other investigations supported an inverse association between latitude and naevus number and hence the concept that ambient sun exposure plays a key role in melanocytic proliferation in early childhood. Notably, the study results confirmed a protective role of sunscreen in the development of acquired melanocytic naevi.[26]

Indeed, sunscreen use has been demonstrated to attenuate the number of naevi in fair-skinned children by other researchers.[23,27,28] An attenuating effect of sunscreen on naevus prevalence does however assume that sunscreen use does not encourage longer sun exposure.

3. Sunscreen: Improving acceptability to improve user adherence

Poor adherence to regular sunscreen use compromises the effectiveness of sunscreen as an adjunctive modality for sun protection.[4,29]

The barriers to sunscreen adherence that are typically cited include cost, cosmesis, forgetfulness, societal influences, and confusing messages about efficacy and safety.[4,30] Without doubt, the aesthetic or cosmetic properties of sunscreen, such as texture and feel, also contribute to sub-optimal use. The opaque quality and greasiness of sunscreen are among the common complaints made by consumers.[31-33] In a survey of Australian dermatology clinic outpatients, greasiness was a barrier to sunscreen use,[34] and a survey of UK dermatology patients revealed a preference for lighter cream-based emollient rather than greasier emollients.[35] In addition, among outdoor workers in Germany, the cosmetic properties, sweat resistance, and usability of sunscreen (including non-irritation of the eyes) under outdoor working conditions were found to be key factors in the overall acceptance of daily sunscreen use in a randomised study.[36]

Formulating sunscreen products is a complex process, requiring careful selection of active sunscreen ingredients and vehicle components to control efficacy and aesthetics.[37] In terms of aesthetics, the primary contributor to greasiness is the quantity of UV filters in sunscreens. Higher SPF products may contain 20–30% active ingredients such as octocrylene (a UVB filter) and avobenzone (a photostabliser) that are inherently oily and viscous.[30,38] Film formers and emulsifiers also contribute to the nature of the physical film that forms on the skin surface. For example, polymers, such as polyvinylpyrrolidone, that are used in water-resistant formulations to retain the UV filters on the skin surface are naturally oily and contribute to the greasy feeling of many water-resistant sunscreen products. The opaqueness of inorganic sunscreens containing micro-sized titanium oxide (TiO_2) and zinc oxide (ZnO) is also considered cosmetically undesirable.[33]

Efforts to reduce the stickiness of sunscreens have involved the use of silicones, silica, and other slipping agents, as well as polymeric surfactants, such as acrylate cross polymers, which provide rapid emulsion-breaking (and water-resistance) characteristics that allow easier spread of sunscreen on the skin with reduced tackiness.[30,38] Water- or alcohol-based gels that provide less greasy aesthetics have also been developed, although these products are less substantive than oil-based formulations, which limits their durability.[38] Regarding the inherent opaqueness of micro-sized TiO_2 and ZnO, this can be reduced, without significantly compromising UVR-blocking efficacy, by replacing them with nano-sized TiO_2 and ZnO particles.[33] Despite these advances, further formulation improvements are needed to improve the experience of sunscreen application.

Initiatives to improve adherence to the use of existing sunscreen products should continue to be applied.[30] These include efforts by healthcare professionals using the scientific evidence base to dispel controversies about sunscreen use that drive negative patient and public concerns, ongoing education (e.g. that regular sunscreen use does not cause vitamin D deficiency), and information strategies to remind the public of the risks of prolonged UVR exposure and the appropriate use of sunscreen and other sun avoidance measures to prevent skin cancers. The use of technologies such as Australia's SunSmart App (which has an alert prompt as to the quantity of sunscreen to apply) and New Zealand's Sun Protection Alert App should also continue to be embraced.

In addition to promoting the benefits of regular sunscreen use in moderating the risk of developing melanoma and non-melanoma skin cancer to encourage sunscreen adherence, raising awareness of other potential benefits for the skin might also help to increase adherence. For example, there is evidence that daily use of sunscreen slows or even reverses photoageing and that sunscreen preserves skin barrier function during UVR exposure.[39-42]

EXPERT'S CONCLUDING COMMENTS – PASCALE GUITERA

Initiatives to increase usage of sun cream have been promoted by the industry. When manufacturers propose the use of sprays that deliver such a small layer of product that users should in theory re-apply every hour to maintain an appropriate "film" of product, there is a need for greater consumer awareness of how to correctly use sprays. The product label is still "4hr water resistant" as the regulator assesses sun cream in a standard g/cm2 amount. This amount is unlikely to be the "normal" amount used by "normal" users. So, while the sprays maybe easier to use on children, hairy areas, or the "dirty" skin of workers, it should be emphasized to users that enough of the product is applied and re-applied.

In Australia and NZ, public sun protection awareness and education campaigns have been quite efficient at promoting sun protection among children (and parents) but are still failing in the teenage group. The argument of better cosmetic outcomes with less ageing of the skin is often better received by this group than any health advice.

EXPERT'S CONCLUDING COMMENTS – ANNIKA SMITH

Sun exposure, without doubt, plays a major role in the development of non-melanoma (NMSC) and melanoma skin cancer.[1] Life-time risk of skin cancer is directly linked to both cumulative and intermittent sun exposure throughout life and intrinsically linked to sun exposure in childhood. There is direct evidence that sun exposure impacts on DNA integrity, inducing mutations and altering expression of critical tumour suppressor genes in basal cell carcinomas (BCC), squamous cell carcinomas (SCC) and melanoma, allowing initiation of tumour development.[2] Diminishing UV exposure through photoprotective methods has been shown to prevent the development of actinic keratoses, SCC, BCC, and melanoma, in addition to reduction of photoaging.

Skin cancer risk involves a complex interplay between genetic predisposition and environmental risk factors, with exposure to UV radiation being the largest modifiable risk factor, resting at the core of our public health efforts. Public health strategy addressing UV exposure minimisation must emphasize the need to employ the *full* complement of sun protective armamentarium including: appropriate use of sunscreen; wearing of hats, UV protective clothing, and sun protective eye wear; and avoidance of sun exposure.[3] The primary prevention message must be emphasized in key domains pertaining to education, workplace, and healthcare settings, with occupational UV exposure being a somewhat under-recognised contributor to skin cancer risk.

The foundations for preventative sun-safe behaviour begin in the formative years. There is ample evidence demonstrating that photoprotective strategies employed in childhood result in diminished acquisition of melanocytic naevi, with total naevus burden serving as a potent risk marker for melanoma development and sun exposure in early life key to determining lifetime skin cancer risk.[4,5]

Sunscreen is an important aspect of photoprotection and the most commonly employed; however, it should not be relied upon as the sole agent for sun protection. There is little high quality data assessing sunscreen's role in skin cancer prevention. The primary source of RCT evidence comes from the Nambour Skin Cancer Study,[6,7] which demonstrated a positive effect for sunscreen use in all skin cancers, along with reduced acquisition of melanocytic naevi. While the results did not reach statistical significance for a protective benefit with BCC, this was likely due to several confounders in the study design and there is ample evidence, direct and epidemiologic, to support UV exposure as a key risk factor in BCC development.[8]

Sunscreen's efficacy is determined by its SPF and broad spectrum potential, in addition to quality and quantity of application, factors that must be highlighted to patients. The quantity of sunscreen used in SPF photo-testing *in vivo*, 2mg/cm^2, equivalent to two tablespoons, is rarely applied in practice, with individuals applying as little as one quarter of this recommended dose, effectively reducing the SPF.[9]

Sunscreen aesthetics are crucial to enhancing consumer adherence, in part aided by nanoparticle technology and more elegant sunscreen formulations. The nanoparticle and vitamin D furore has served to interfere with the sun-safe message and sunscreen adherence. Reviews of the scientific literature have concluded that nanoparticulate titanium and zinc oxide pose no risk to human health.[10] Further, sunscreen use does not serve to contribute to vitamin D deficiency.[11]

The skin cancer preventative landscape continues to evolve with the adjuncts of oral and topical nicotinamide, the amide form of vitamin B3. Oral nicotinamide, in the context of those with an established history of NMSC, has been shown to reduce NMSC risk by 25% and actinic keratosis by 15%, by enhancing DNA repair of skin cells and providing protection against UV-induced immunosuppression.[12] Further sub-study analyses are awaited in the context of melanoma and immunosuppressed cohorts.

Skin cancer prevention requires a sustained, comprehensive, multifaceted public health strategy with a community-wide approach. Evidence demonstrates that multi-strategic health prevention approaches are fundamental to effecting behavioural and attitudinal changes that improve sun protective practice and ultimately diminish skin cancer risk. Maintained momentum on a primary prevention front is required for long lasting skin cancer control.[3]

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EXPERT'S CONCLUDING COMMENTS – LOUISE REICHE

Sunscreen is a *filter,* not a complete barrier to the sun. This means vitamin D will still be generated by the skin in outdoor physically-active individuals, wearing sunscreen. For fair skin individuals living in Australasia, where there is a high level of ambient UVR, providing a filter between exposed skin and the sun reaps benefits in both the short and long term at all ages. As melanoma risk increases with the number of naevi an individual has, reducing the development of sun-induced naevi early in life may have a long-term impact – reducing melanoma development later in life for individuals and populations as a whole. Regularly applying broad spectrum high-SPF sunscreen slowly *reverses* features of sun-induced ageing and reduces development of non-melanoma skin cancers, not only in academic studies but I witness this in clinical practice. So, it is never too late to start protecting the skin from the sun, seeking the shade, and wearing hats, sunglasses, protective clothing, and sunscreen. However, as evidence accumulates to suggest we should be recommending sunscreen application as routine skin care over a lifetime, it is important that the products are safe, are regulated to prove they meet the required standards of sun protection, are accurately labelled, easily affordable, and are optimal cosmetically.

Take-home messages:

- There is an inextricable link between UVR exposure and non-melanoma cancer.
- Non-melanoma cancer should be recognised as an occupational disease and continued effort on a preventative front is required to reduce UVR exposure in the workplace. This can be achieved through modification of workplace culture and behavioural patterns and provision of shade, UV protective clothing appropriate for work type and situation, hats, and sunscreen.
- Acquired melanocytic naevi share genetic and environmental risk factors with melanoma.
- The propensity to develop melanocytic naevi is an independent risk factor for melanoma; minimising the acquisition of naevi in childhood may reduce the risk of melanoma later in life.
- A recent study demonstrating that sunscreen protects against the acquisition of melanocytic naevi in children further supports the role of sunscreen as an effective adjuvant to covering up and sun avoidance.
- Sunscreen non-adherence due to poor sunscreen aesthetics is a barrier to the effectiveness of sunscreen in protecting against skin cancer.
- Sunscreen products with improved aesthetics are needed to improve sunscreen use adherence.
- Sunscreen aesthetics will continue to improve with technological advances in sunscreen production and formulation, which will enhance efficacy and cosmesis.

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