Chapter 2
Photoprotection and Skin Cancer Prevention

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Key Points

- Ultraviolet radiation is a major risk factor for the development of skin cancer, the most common form of cancer in the United States.
- Ultraviolet radiation causes both direct and indirect damages to DNA, leading to mutations and malignant transformation if the damage is not repaired.
- Skin cancer can be prevented by reducing intentional exposure to ultraviolet radiation and using photoprotective strategies, including sunscreens.
- Daily sunscreen application protects against the development of actinic keratoses, squamous cell carcinoma, nevi formation, and melanoma.

2.1 Introduction

Environmental exposures to both natural and man-made substances are a major risk factor for the development of many types of cancers. Skin serves as the interface between the body and the environment and is frequently exposed to potentially hazardous environmental elements. Viral and bacterial infections, smoking, radiotherapy, immunosuppressant drugs, artificial ultraviolet sources for phototherapy and tanning, and chemical carcinogens have all been shown to predispose individuals to skin cancers [1].

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Ultraviolet radiation (UVR) from sunlight is a major risk factor for melanoma and non-melanoma skin cancer (NMSC) [2]. Epidermal cells accumulate UVR-induced DNA damage which can lead to DNA base mutations and malignant transformation. This chapter discusses the biologic impact of UVR on the skin and its role in the development of both NMSC and melanoma. In addition, the role of photoprotection to prevent cutaneous malignancies is reviewed.

2.2 UV Radiation

Solar radiation is divided into ultraviolet (200–400 nm), visible light (400–700 nm), and infrared radiation (>700 nm) [3]. UVR plays a major role in the development of photoaging and skin cancer [4]. Due to inherent differences in biologic effects, the UV spectrum is further subdivided into UVC (200–290 nm), UVB (290–320 nm), UVA2 (320–340 nm), and UVA1 (340–400 nm) [4, 5]. The subdivision of the UVA range is due to a change in the slope of the action spectrum for erythema occurring near 340 nm, with UVA2 having more erythemogenic activity than UVA1.

The different types of UVR vary in their intensity at the Earth's surface and their effects on human skin. Nearly all of the UVC radiation from the sun is absorbed by the ozone layer, effectively negating its effects on the human body [6]. Approximately 95 % of the solar radiation reaching the Earth's surface is UVA, with the remaining 5 % UVB [7]. The intensity of UVB has been shown to increase between 4 and 10 % with every 1000 ft of elevation and by approximately 3 % for every degree of latitude as approaching the equator [8]. UVB, being a shorter wavelength compared to UVA, is only capable of penetrating down to the basal layer of the epidermis and superficial dermis, while UVA can penetrate deeper into the reticular dermis [9]. Compared to UVA, the erythemogenic potential of UVB is 1000 times greater [10]. UVA is generally more closely associated with tanning and photoaging changes such as loss of skin elasticity and wrinkling, although UVB can also produce the same effects [4, 11]. Both UVB and UVA have been implicated in the development of skin cancers.

2.3 DNA Damage by UVR

2.3.1 UVB Effects

UVB directly damages the DNA of keratinocytes. UVB is absorbed by DNA molecules within the keratinocytes, leading to the formation of dimeric photoproducts between adjacent pyrimidine bases. The two most common photoproducts are the cyclobutane pyrimidine dimer (CPD) and the 6-4 photoproduct (6-4PP), formed at a ratio of about 3:1 [12, 13]. The presence of these molecules prevents the replicative DNA polymerases from passing through the template strand, thereby blocking DNA

synthesis [14]. Failure to repair these defects can lead to a collapse in the replication fork at the damaged site, causing a DNA double-strand breaks and ultimately cell death. Furthermore, the presence of UV-induced photoproducts can interfere with base pairing during DNA replication, leading to mutations.

Although normal cells maintain a high repair fidelity, errors in repair can lead to cytosine (C) → thymine (T) base substitution at dipyrimidine sites and CC → TT tandem base substitutions [14, 15]. These are known as "UV signature mutations," indicating damages from past UVR exposure [15]. While these mutations were once known as "UVB signature mutations," further studies have demonstrated that a high proportion of C → T transitions also occur with UVA-induced damage, but at a lower frequency (65 % for UVA vs. 85 % for UVB) [16, 17]. The rates of repair for 6-4PP and CPD photoproducts are different. Nearly 90 % of the 6-4PP lesions are repaired at 3 h post-UV exposure [12, 18]. In contrast, only 10 % of CPD lesions are repaired at 3 h and 50 % at 24 h after exposure [18]. Repair capacity diminishes with age, and there is a cumulative loss of 25 % in repair ability between the ages of 20 and 60 years; this difference may account for the increased risk of skin cancer that begins in middle age [19]. Individuals with defective nuclear excision repair pathways, such as patients with xeroderma pigmentosum, are exceptionally vulnerable to UV-induced cutaneous malignancies.

2.3.2 UVA Effects

UVA indirectly damages DNA via a free radical-mediated pathway [12]. UVA reacts with chromophores and photosensitizers, such as porphyrins, cytochromes, heme, riboflavin, and tryptophan, which generate free radicals [20–24]. In addition, UVA reacts with oxygen species and induces the formation of reactive oxygen species (ROS) [20]. Within 20 min of UVA exposure, expression of NADPH oxidase in human keratinocytes increases by 2-fold [25]. NADPH oxidase converts oxygen molecules to superoxide anions, which are ultimately converted to ROS such as hydrogen peroxide, superoxide anion ($\bullet O_2^-$), peroxide ($\bullet O_2^{-2}$), hydroxyl radical (•OH), hydroxyl ion (OH^-), and singlet oxygen ($^1O_2$) [26]. These short-lived free radicals damage DNA in a myriad of ways, including cross-linking DNA to proteins and forming single-strand and double-strand breaks [12, 27]. It is important to note that UVB can also trigger oxidative damage [20, 28, 29].

Aside from these forms of nonspecific DNA damage, UVA-induced oxidation leads to specific DNA base mutations. The molecule 8-hydroxyguanine (8OH-G) is a mutagenic base that results from ROS interaction with guanine [30]. 8OH-G is preferentially generated with UV wavelengths greater than 350 nm and hence is thought to be UVA signature mutation [28]. This particular lesion has been shown to create G:C → T:A transversions in DNA [31]. In addition, UVA generates CPD mutations at nearly five times that of 8OH-G mutations [32]. However, compared to CPD mutations from UVB, the overall number of UVA-generated DNA photoproducts is significantly lower [20].

2.4 DNA Base Mutations in Malignant Transformation

Upon DNA damage, cells can either repair the mutation or, if the damage is beyond repair, target the cell for apoptosis. The *p53* tumor suppressor gene plays a major role in regulation of cell cycle checkpoint activity, DNA repair, and apoptosis. However, if the *p53* gene becomes mutated, these protective cellular mechanisms may fail, leading to carcinogenesis. Clones of cells with UV signature mutations (e.g., C → T and CC → TT transitions) in the *p53* tumor suppressor gene have been found in sun-exposed skin, actinic keratoses, squamous cell carcinoma, basal cell carcinoma, and melanoma, supporting its role in photocarcinogenesis [33, 34].

Under normal circumstances, p53 responds to DNA damage by blocking the progression of the cell cycle. Immediately after UV irradiation, *p53* transcription is upregulated and DNA damage leads to the alteration of the p53 protein, allowing for phosphorylation by other protein kinases [35]. Elevated levels of p53 that occur after UV exposure lead to induction of *p21* (also known as WAF1 or CIP1), which is responsible for cell cycle arrest and inhibiting apoptosis [36]. The p21 protein is capable of competitively forming a complex with cyclin-dependent kinase (CDK), blocking its interaction with cyclin and effectively inhibiting cell entry to the S phase where DNA replication takes place [37, 38]. Cell cycle arrest may also occur at checkpoints during S phase or after G2 (before mitosis) to ensure DNA fidelity [39]. By inhibiting progression of the cell cycle, the cell is providing itself time to repair, to prevent passage of mutated DNA onto daughter cells.

Upon cell cycle arrest, DNA repair mechanisms are activated to correct the UV-induced lesions. Two major mechanisms for DNA repair include base excision repair (BER) and nucleotide excision repair (NER). BER is used to remove damaged bases, such as the oxidized form of guanine (8OH-G) [40]. In this pathway, DNA glycosylases remove specific damaged or inappropriate bases forming a single-strand break, which is then repaired with small fragments of 1–12 nucleotides [41]. NER is used to repair a variety of bulky DNA damages, including CPDs and 6-4PPs, that commonly result from UVB exposure [42]. NER involves single-strand incisions flanking the lesion, followed by DNA repair synthesis and ligation. As mentioned earlier, 6-4PPs are repaired much more quickly than CPDs. This is thought to be because 6-4PPs are more destabilizing and cause a greater degree of unwinding in the DNA helix than CPDs [4, 43, 44]. Repair of these UV-specific CPD and 6-4PP lesions significantly decreases the overall apoptotic response [45].

If the DNA damage is beyond repair, apoptotic pathways are activated to prevent passage of daughter cells carrying those mutations. The molecule p53 can induce apoptosis through two major pathways, either the intrinsic mitochondrial pathway or the extrinsic death receptor pathway [46]. In the mitochondrial pathway, p53 upregulates pro-apoptotic genes, such as *Bax* and *Bak*, or p53 represses transcription of antiapoptotic genes, such as *survivin*. Furthermore, p53 induces caspase activation and apoptosis [46, 47]. To a lesser extent, p53 activates the death receptor pathway by promoting *fas* transcription and its cell-surface expression [48, 49]. Additionally, p53 induces DDB2 (damaged-DNA binding protein 2) which promotes programmed cell death by

facilitating degradation of p21, an inhibitor of apoptosis [50]. Mutations in p53 can effectively inhibit these protective apoptotic pathways. The unregulated passage of DNA-carrying mutations to daughter cells during cell division leads to tumorigenesis.

Aside from the *p53* gene, there are other important genes affected by UVR. UV signature mutations have also been identified in the patched homologue (*PTCH*), smoothened (*SMO*) tumor suppressor genes, as well as the *ras* oncogene [12, 51–53]. Mutations in PTCH or SMO, two conducting proteins involved in the Hedgehog pathway, have been identified in up to 90 % of all BCCs [54]. As a result, molecules involved in this pathway represent an enticing target for novel treatment modalities. Inhibitors of this pathway, such as vismodegib, are now being employed to systemically treat locally advanced or metastatic BCCs. Other targeted therapies are sure to follow as the biological mechanisms and pathways underlying malignant transformation are further elucidated.

While *p53* mutations are commonly implicated in NMSC, they are not thought to play a major role in the development of melanoma. UVR has been shown to stimulate the clonal expansion of melanocytes expressing *BRAF* mutations in melanocytic nevi [55, 56]. The oncogenic BRAF V600E substitution has been shown to be an early event in melanomagenesis and is the most common somatic mutation identified in melanomas. Approximately 80 % of acquired human nevi and primary melanomas carry *BRAF* mutations [57]. A recent study using BRAF V600E mutant mice showed that UVR induced larger and more abundant nevi compared to non-UVR-exposed skin [55]. Additionally, all mutant mice developed melanomas within 7 months after UVR, whereas UVR did not induce melanoma in non-BRAF mutant mice. Finally, the application of broad-spectrum SPF 50 sunscreen blocked p53 induction, apoptosis, epidermal hypertrophy, and dermal thickening and also delayed the onset of UVR-driven melanoma. It should be noted that all sunscreen-protected mice did eventually develop tumors representing a significant increase over non-UVR-exposed mice, highlighting the damaging effects of UVR and need for enhanced photoprotection and UVR avoidance. Nevertheless, sunscreen did produce a significant reduction in tumors in those that were exposed to UVR and significantly prolonged the latency before tumor development, accentuating the role of sunscreen protection in addition to UVR avoidance for those at risk of melanoma.

2.5 Epidemiology of UV-Induced Cutaneous Malignancies

Skin cancer is the most common form of cancer in the United States [58–60]. Nearly five million people in the United States are treated for skin cancer every year with an estimated annual cost over $8 billion [61–63]. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) account for nearly 95 % of skin cancers, and melanoma makes up approximately 5 %. In the United States in 2014, it is estimated that there would be over 76,000 new cases of invasive melanoma and 9710 melanoma-related deaths [64]. The risk of skin cancers is governed by both genetic factors and exposure to UV radiation.

2.5.1 Genetic Factors

Incidence rates of BCC and SCC are 5–10 times greater in the Caucasians than in darker-skinned individuals [58]. Individuals with blue or green eyes, red or blond hair, and lighter skin type have higher risk for developing skin cancer [65, 66]. Those individuals tend to have MC1R mutation and generate more pheomelanin than eumelanin [67]. Pheomelanin is less effective in absorbing UV, and furthermore, upon UVA exposure, pheomelanin are pro-oxidative and generate free radicals that can damage DNA and nearby cellular organelles. Other phenotypic traits associated with increased risks for skin cancer include high nevus count, tendency to sunburn, inability to tan, and a history of sunburn at a young age [68–70]. Additionally, individuals with a personal or family history of skin cancer are at an increased risk, suggesting the presence of additional genetic factors increasing susceptibility that have not yet been phenotypically identified.

2.5.2 Relationship to Ambient UV Radiation

The incidence of NMSC increases with higher exposure to ambient solar radiation and is greater in individuals with higher mean daily UV radiation [71]. Ecologic studies have shown that the incidence of skin cancer is higher in regions of low latitude and high UV index [72, 73]. The Nurses' Health Study reported an increased risk of skin cancer in individuals who lived in areas with moderate or high UV index (greater than or equal to 6), with more pronounced effects seen for women who grew up in states with higher UV indices [74]. Further studies have demonstrated that early childhood exposure to high UV radiation increases the risk of skin cancer. A migration study from Western Australia demonstrated that immigrants from Great Britain who arrived before the age of 10 years had similar rates of melanoma compared with the native-born population, whereas the incidence was nearly a quarter of the native rate in those who arrived after the age of 15 years [75]. Similar findings in migrant populations have been documented in other countries, including the United States [76–78].

Although a strong relationship exists between ambient solar radiation and the incidence of skin cancer, patterns of sun exposure appear to have an impact on the type of skin cancers. Chronic UV exposure has been implicated in the development of both precancerous actinic keratoses (AK) and SCCs [79–81]. These lesions tend to occur on sun-exposed sites, such as the head, neck, and dorsal hands. The association between BCC and sun exposure is more complex, because a large percentage of BCCs are located on non-sun-exposed sites [82, 83]. As a result, it is postulated that BCC may result from intermittent UV exposure or exposure early in life rather than cumulative UV exposure.

Likewise, the overall risk of melanoma appears to also be associated with more intense and intermittent exposure to high levels of UVR, often stemming

from recreational activities or exposures occurring during childhood [66, 84, 85]. Melanoma is not often found on chronically sun-exposed sites, but rather is more common on locations that are sporadically exposed, such as the trunk in males and the legs in females [86]. However, certain subtypes of melanoma, such as lentigo maligna melanoma or desmoplastic melanoma, are more commonly found on chronically sun-exposed sites with a predilection for the head, neck, and upper extremities [87–90]. These lesions are often found on sun-damaged skin in older individuals [88, 91, 92]. These observations suggest that different subtypes of melanoma may result from either cumulative or intermittent sunlight exposure.

2.5.3 High-Risk Occupation and Behaviors

Aside from genetic traits, individuals with certain occupations and those who carry out high-risk behaviors have an increased probability of developing skin cancer. Outdoor workers tend to have extensive amounts of UV radiation. A systematic review and meta-analysis of 18 studies (6 cohort and 12 case–control) reported that 16 of the 18 studies (89 %) showed an increased risk of SCC in individuals with occupational UV exposure compared against individuals without UV exposure (OR = 1.77; 95 % CI = 1.40–2.22) [93]. As for BCC, a meta-analysis including 23 epidemiologic studies found a weaker, but still significant, association between occupational sun exposure and risk of BCC (OR = 1.43; 95 % CI = 1.23–1.66) [94]. The data on melanomas is mixed. While some studies have suggested that outdoor workers may not be at an increased risk of melanoma [95, 96], others have shown an increased risk among workers in UV-intense areas and a strong association between melanoma incidence and both intermittent and total UVR exposures [4, 97, 98]. These observations further emphasize the need for adequate protection for individuals who are exposed to the damaging effects of UVR in the workplace.

Individuals, especially young women, seeking indoor tanning are at high risk for developing skin cancer. A recent systematic review and meta-analysis concluded that there are an estimated 400,000 NMSCs and 6000 cases of melanoma annually in the United States attributable to indoor tanning [99]. In a study of tanning bed users, any use of tanning devices was associated with an increased risk of SCC (OR = 2.5; 95 % CI = 1.7–3.8) and BCC (OR = 1.5; 95 % CI = 1.1–2.1) [100]. A separate meta-analysis concluded that individuals with any history of indoor tanning had an increased risk of melanoma (OR = 1.16, 95 % CI = 1.05–1.28) [101]. The risk of skin cancer has a strong dose–response relationship with tanning, thought to be due to the accumulation of UV exposure [102]. Indoor tanning exposes users to elevated amounts of UV radiation, and in 2009, the World Health Organization (WHO) classified indoor tanning devices as group I human carcinogens due to numerous studies showing the link between tanning and increased cancer risk [103]. Furthermore, the FDA recently upgraded sunlamps to moderate-risk (class II)

devices, requiring enhanced product labeling detailing the potential health effects of use [104]. As such, use of these devices should be strongly discouraged due to the adverse effects they can have on the skin.

2.6 Photoprotection

Numerous studies have shown that skin cancers can be prevented by reducing intentional exposure to UV radiation and improving photoprotective strategies. Effective photoprotection involves seeking shade, wearing protective clothing, and applying sunscreen properly. Although sunscreen is less effective than other protective measures, it is by far the most widely used vehicle for sun protection. A large body of clinical research has demonstrated that sunscreens, when used appropriately, can prevent skin cancers and precursor lesions.

2.6.1 Actinic Keratoses (AK)

A number of studies have demonstrated the protective effects of sunscreens on the development of AK [105–107]. The largest randomized controlled trial was conducted in subtropical Nambour, Australia, where 1621 adults were randomly assigned to two groups: daily use sunscreen vs. discretionary use of sunscreen [107]. Individuals in the daily use group were provided with free sunscreen (SPF 16) and instructed to apply it to all sun-exposed sites of the head, neck, arms, and hands. No sunscreens were provided to individuals in the discretionary use (control) group, but they were permitted to use sunscreens if they chose. After the first 2.5 years of intervention, there was a 21 % reduction of AKs in the daily use group compared to the control group in sunscreen-treated locations. However, no significant reduction between the two groups was observed after a further 2 years of follow-up. The acquisition rate of new AKs in the control group markedly decreased in the second 2-year period of the trial, which the investigators suggest may have been caused by an increase in sunscreen use by the control group.

Similar results showing the protective effects of sunscreen on AK development were observed in two smaller randomized controlled trials. In the first, conducted in Victoria, Australia, investigators studied the protective effects of using daily broad-spectrum sunscreen (SPF 17) to prevent the formation of new AKs and induce remission [105]. A total of 431 white residents who had between 1 and 30 AKs at baseline were enrolled. Sunscreen was applied daily to sun-exposed sites and the number of new lesions was recorded over a 7 month period. Participants in the sunscreen group developed fewer new lesions (difference = 0.72, 95 % CI = 0.15–1.28) and had 25 % remission of their existing AKs, compared to 18 % remission in the control group (OR = 1.45: 95 % CI = 1.10–1.88). Overall,

participants in the vehicle control group had an average increase of one AK, while participants in the sunscreen group actually saw a decrease in the mean number of AKs by 0.6.

The last study was a randomized controlled trial in the United States assessing AK prevention by sunscreen use in 37 high-risk patients with a history of precancerous lesions or NMSC over a 2-year period [106]. The subjects in the sunscreen group were instructed to apply sunscreen (SPF 29) every day, while the control group applied the vehicle cream without active ingredients. After controlling for differences in risk factors, a 36 % decrease in the annual rate of new AKs was seen in the sunscreen group compared with the placebo group. These three studies demonstrate that daily use of sunscreen has protective benefits for AKs.

2.6.2 Non-melanoma Skin Cancer

The same population of Australian adults from the Nambour Trial was also observed over the same period from 1992 to 1996 to determine the effect of sunscreen use on the development of NMSC [108]. At enrollment, participants completed a survey and underwent a complete skin exam by a dermatologist. Any prevalent skin cancers were removed. Those randomized to the treatment group were instructed to apply a layer of SPF-16 sunscreen to all exposed sites on the head, neck, arms, and hands every morning, with reapplication after heavy sweating, bathing, or long sun exposure. The control group was permitted to use sunscreen at their discretion, and no sunscreen was provided. Compliance for the sunscreen group was assessed by weighing sunscreen bottles every 3 months. At follow-up clinics in 1994 and 1996, dermatologists blinded to treatment allocation reexamined all participants, with histologic confirmation of all clinically diagnosed skin cancers.

After 4.5 years of follow-up, the investigators observed that sunscreen use had no effect on either the incidence of BCC or in the total number of BCC tumors. However, the overall incidence of SCC, in terms of persons affected, was 12 % lower in the sunscreen treatment group ($n=22$) compared with the control group ($n=25$), but this difference was not statistically significant. The study found a 39 % reduction in the total number of SCC tumors among participants assigned to the daily sunscreen group, with 28 SCCs occurring in the sunscreen group compared with 46 SCCs in the control group (95 % CI = 0.46–0.81).

A follow-up study was published in 2006 to assess for potential latency of sunscreen use [109]. Participants were followed for an additional 8 years. There was a rate reduction of 35 % (95 % CI = 0.43–0.98) in the incidence of SCC, and there was a rate reduction of 38 % (95 % CI = 0.38–0.99) in the total number of SCCs diagnosed in the sunscreen group. When the analysis was limited to the late follow-up period (2001–2004), there was a rate reduction of 51 % for both the incidence SCC and total tumor number. In contrast, the prolonged follow-up failed to demonstrate a statistically significant reduction in the incidence of BCC (persons affected) or total number of BCCs occurring in the daily sunscreen group. However, there was a

25 % reduction in the total number of BCCs in the treatment group in the late follow-up period (2001–2004), although this difference is not statistically significant (rate ratio = 0.75, 95 % CI = 0.49–1.14).

2.6.3 Nevi

Having many nevi or having at least 1 atypical nevus is the strongest constitutional risk factors for melanoma. Studies have shown that UVR promotes the growth of nevi [110–112]. Currently, there is only one randomized controlled trial conducted in Vancouver, British Columbia, that demonstrated the protective effect of broad-spectrum sunscreen in reducing the development of nevi in children [113]. Schoolchildren, ages 6–10, were randomized to either a sunscreen group and provided with SPF 30 broad-spectrum sunscreen or control group which received no sunscreen and were given no advice about sunscreen use. Each child's nevi were counted at the beginning and end of the 3-year trial. Based on an initial questionnaire and dermatologic examination, the authors found that factors such as hair color, skin response to sun exposure, facial freckling, and sunburn score in the first 5 years of life were all associated with nevus counts. Analysis revealed regular use of sunscreen was associated with a significant reduction in new nevi (median counts 24 vs. 28; $p = 0.048$). Additionally, a greater effect was seen for sunscreen used in individuals with a higher degree of freckling, with models suggesting that freckled children using sunscreen would develop 30–40 % fewer new nevi than untreated freckled children. These data demonstrate the importance of regular sunscreen use on attenuating the development of new nevi which are a known risk factor for melanoma.

2.6.4 Melanoma

There have been controversies regarding the protective role of sunscreens against the development of melanoma. Some of the early case–control studies suggested an increased risk of melanoma with sunscreen use [114–116]. A meta-analysis of the literature published between 1966 and 1999 found no association between sunscreen use and increased risk of melanoma (relative risk = 1.01; 95 % CI = 0.46, 2.28) [117]. A second review also found a similar result (odds ratio 1.0; 95 % CI = 0.8–1.2) [118]. However, these early case–control studies failed to account for skin sensitivity. Specifically, individuals who are more susceptible to burning and developing melanoma were more likely to use sunscreen, and hence there could be uncontrolled confounding by indication. Other explanations are related to inappropriate application of sunscreen with low SPF and lack of UVA protection.

The controversy was largely put to rest with the results from Nambour Trial in Queensland, Australia [119]. The participants were observed after long-term

follow-up to assess whether application of sunscreen during the first 4.5 years had an effect on their risk of primary cutaneous melanoma. At the end of 10-year follow-up (nearly 15 years from the start of the trial), there were a total of 11 primary melanomas (3 invasive) in participants randomized to the sunscreen group and 22 primary melanomas (11 invasive) in the discretionary use (control) group. The study showed a 50 % reduction in the risk of overall melanomas in the sunscreen group ($p = 0.051$) and a 73 % reduction in the risk of invasive melanomas among the daily sunscreen group ($p = 0.045$). These results demonstrated that daily sunscreen use over a 4.5-year period appears to reduce the long-term melanoma incidence over a 10-year period, with the most pronounced effect seen for invasive melanoma.

It is important to note that the control group in the Nambour Trial for the AK, SCC, BCC, and melanoma studies was not given a placebo or inactive sunscreen, but rather was allowed to continue discretionary use of sunscreen. The design of the trial underestimates the full protective benefits of sunscreen against melanoma. Furthermore, the sunscreen used in the trial was SPF 16 and not UVA stable. Modern-day sunscreens have higher SPF values and are photostable, and theoretically they should offer superior protection.

2.7 Conclusion

UV radiation plays a key role in the development of both non-melanoma skin cancers and melanoma. It is imperative that clinicians continue to educate the general public regarding the benefit of ongoing photoprotection. The public message of photoprotection should encompass seeking shade when outdoor; wearing sun-protective clothing, hats, and sunglasses; and applying broad-spectrum sunscreens. Current scientific evidence demonstrates that sunscreens are safe and that daily application of sunscreen can prevent the incidence of AK, SCC, nevi, and melanoma.

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