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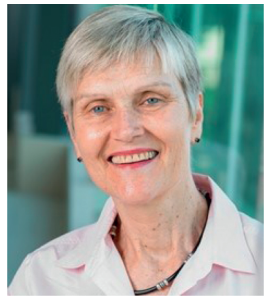

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Regular Application of Sunscreen Can Prevent Skin Cancer

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Synopsis

This review summarizes the evidence on the protection against skin cancer afforded by sunscreen. Solid evidence can come only from randomized controlled trials, despite a multitude of case–control and cohort studies that have addressed the issue, because observational evidence is intractably confounded since those at highest risk of skin cancer are naturally the highest users of sunscreen. Findings of the single human trial conducted in subtropical Australia during 1992–1996 with follow-up to 2014 showed that the application of a broad-spectrum, sun protection factor 16 sunscreen to exposed skin of the head and neck and upper limbs at least 3–4 days per week in adulthood can reduce the risk of developing cutaneous squamous cell carcinoma and melanoma but does not appear to reduce the risk of basal cell carcinoma (BCC) overall, although it may reduce the occurrence of multiple BCCs over time.

Skin cancers constitute the most common types of cancer in predominantly white-skinned populations. There are three major types of skin cancer—the most common is basal cell carcinoma (BCC), with squamous cell carcinoma (SCC) the second most common and more serious because of its propensity to metastasize, and the least common but potentially fatal if not treated early is melanoma. Together, these cancers impose a costly burden on affected populations because of the extensive healthcare resources needed to treat them. Personal costs are also substantial and include cosmetic as well as out-of-pocket costs because skin cancer affects the face most frequently followed by other body sites that are often or occasionally exposed (1).

High exposure to solar ultraviolet (UV) radiation, the shortest wavelength component of sunlight on earth, is a cause of all three types of skin cancer (2), although the exact pattern and total amount of sun exposure required differs for each type (1,2). Thus, mainly white-skinned populations are most susceptible to skin cancer, likely because they lack the UV-shielding melanin skin pigment possessed by dark-skinned populations (see the article by Antony Young in this issue). High UV levels also explain why the continually exposed skin of the face, head and neck in general, and forearms and hands are the body sites most

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affected. The most straightforward way to prevent skin cancer is to avoid intense sun exposure of the skin. Measures include staying indoors in the middle part of the day when ambient UV levels peak or seeking shade and wearing protective clothing, such as hats and long sleeves, when outdoors (3). The application of sunscreen that shields the skin by reflecting or filtering UV radiation is another popular measure. This article reviews the available evidence regarding the use of sunscreens for skin cancer prevention.

EVIDENCE FROM OBSERVATIONAL STUDIES

One of the most extensive reviews of relevant observational studies was a recent systematic review of the evidence in humans (available to February 2018) regarding the use of sunscreens for melanoma prevention (4). The authors identified 23 case–control, one ecological, and three cohort studies, and their evidence was deemed weak and heterogeneous because of the challenges of controlling for "confounding by indication" (4). This confounding occurs because factors such as sunburn susceptibility, high occupational or recreational sun exposure, or previous skin cancer determine both sunscreen use and skin cancer risk (5), so *a priori* people who use sunscreen are naturally the people most likely to develop skin cancer, and this cannot be adjusted for in analysis of observational studies. Randomized controlled trials (RCTs) are the only kind of study that avoid this confounding through the random allocation of sunscreen use irrespective of the risk of skin cancer and, therefore, the only kind of study that can properly evaluate the long-term effectiveness of sunscreen in preventing skin cancer (5).

EVIDENCE FROM RCTS

There has been only one RCT that has assessed the effects of using sunscreen on skin cancer occurrence. It was conducted in Nambour, a township in subtropical Queensland, Australia (6). The participants were initially selected at random from a community register (the electoral roll: voting is compulsory in Australia) in 1986 when they were aged 20–69 years, for a study of skin cancer prevalence followed by incidence studies (7). Of the 2,095 people in the original prevalence study, 1,621 consented to take part in the field trial that evaluated daily application of sunscreen (and daily oral supplements of beta-carotene) to prevent skin cancer, from 1992 to 1996 (6). At baseline in 1992, they completed self-administered questionnaires recording personal characteristics such as education, smoking, medical conditions, and medications, and skin cancer risk factors, namely, skin color, sunburn tendency and past sunburns, and occupational (weekday) and recreational (weekend and holidays) sun exposure (6). All received full-body skin examinations for skin cancer and other signs of sun damage by dermatologists at trial baseline. Using a computer-generated random assignment sequence, trial participants were allocated to one of four intervention groups: daily application of a standard sunscreen (details in the following paragraph) and a 30-mg beta-carotene tablet each day, daily sunscreen and placebo tablet, beta-carotene only, and placebo only (8). (The beta-carotene intervention had no effect on skin cancer and is not discussed further.) Participants not assigned to daily application of sunscreen were not assigned placebo sunscreen for ethical reasons and were asked to continue the use of sunscreen at their discretion, which was mostly recreational use or no use.

Those allocated to daily sunscreen received unlimited free supplies of the study sunscreen, a water-resistant, broad-spectrum, sun protection factor (SPF) 16 sunscreen (Ross Cosmetics, Melbourne, Australia). They were asked to apply it every morning to all exposed skin on the head, neck, arms, and hands, with reapplication after heavy sweating, bathing, or prolonged sun exposure. To estimate compliance with trial protocol, participants answered questionnaires in 1994 and at the end of the trial about frequency of sunscreen use on average each week and attended study clinics quarterly when they returned sunscreen bottles for weighing.

Incident skin cancers were monitored in several ways to ensure complete capture. At the quarterly study clinics, participants reported new skin cancers; they carried wallet-sized treatment cards which doctors completed if a skin cancer was treated, and they had full skin examinations by dermatologists in 1994 and 1996. Histological confirmation was sought for all clinically diagnosed skin cancers.

The Nambour Trial ceased in 1996, and the participants were followed up for another decade with regular questionnaires about habits of sun exposure and protection and about treatment of new skin cancers, all of which were confirmed by review of medical records. All major regional and state pathology laboratories provided pathology reports for any skin cancers diagnosed among trial participants resulting in virtually complete ascertainment of all skin cancers confirmed histologically (9,10). *A priori*, all new cancers diagnosed in the first year of the trial were excluded from analyses of the preventive effect of sunscreen (8).

At the end of the trial, 75% of those allocated to daily sunscreen use were regular users (defined as applying sunscreen >3–4 d per week), and 74% of those allocated to discretionary sunscreen were either not using it at all or applying it at most 1–2 d per week (8). Sun exposure among those in the daily and discretionary sunscreen groups remained similar throughout the trial, as shown by measured UVB radiation exposure in a subsample, and by 79% and 77%, respectively, reporting that in the previous summer, they had spent <50% of their time outdoors in the sun on weekends at the trial's end; proportions of hat-wearing and shade-seeking people were also similar in each treatment group (11). After trial cessation, a large proportion of those allocated to daily sunscreen use continued to apply sunscreen to their skin regularly: 35% of pretrial regular users and 20% of those who were irregular or never users before the trial (12).

BCC

The incidence of BCC was not reduced by daily sunscreen use during the trial period [rate ratio (RR) = 1.03] (8) or at the end of the follow-up in 2004 (RR = 1.02) compared with controls (9). However, there was evidence that sunscreen application delayed the appearance of subsequent BCCs in those who developed multiple BCCs during follow-up (13).

SCC

At the end of the trial, new SCC tumors diagnosed clinically or histologically were reduced by 40% in the intervention group (RR = 0.61; 95% confidence interval (CI) 0.46–0.81) and by more than 50% based on only histologically confirmed SCCs (RR = 0.48; 95% CI 0.35–0.64) (8). By 2004, incidence rates of SCC were significantly reduced in

terms of both people newly affected (RR = 0.65; 95% CI 0.45–0.94) and new SCC tumor development (RR = 0.62; 95% CI 0.38–0.90) in those allocated to daily sunscreen versus discretionary users (9).

MELANOMA

The effect of regular application of sunscreen in the trial on subsequent occurrence of primary melanoma was evaluated 15 years post-trial. Diagnostic pathology slides of all first primary melanomas (*in situ* and invasive) that occurred (confirmed in the Queensland Cancer Registry) in participants between 1993 and 2006 were obtained and were reviewed by two expert dermatopathologists who were unaware of sunscreen allocation status of the 33 persons affected (19 in situ, 14 invasive, and 0 metastatic). A borderline-significant 50% reduction in risk of melanoma across all sites was observed in people who had been randomly assigned to the sunscreen intervention compared with controls [hazard ratio (HR) = 0.50; 95% CI 0.24–1.02], with the estimated risk reduction slightly more on the head, neck, and upper limbs although this was not statistically significant because of the small number of cases involved (HR = 0.46, 95% CI 0.17–1.20) (10). There was no difference between treatment groups in the risk of *in situ* melanomas (HR = 0.73; 95% CI 0.29–1.81), but the risk of invasive melanoma in the intervention group was reduced by more than 70% (HR = 0.27; 95% CI = 0.08–0.97) (10).

SAFETY

In the short-term, some in the intervention group complained of skin irritation (n = 25), skin greasiness (n = 10), and stinging eyes on facial perspiration (n = 6), and most of these were resolved by switching to another sunscreen of similar SPF (8). At the end of the trial, there was no difference in serum vitamin D status between those randomized to daily sunscreen versus discretionary use (14). On long-term follow-up in 2014, there was no difference in deaths in the sunscreen intervention group (n = 160, 59 of which were due to cardiovascular disease) and the control group (n = 170, 76 of which were due to cardiovascular disease) with an overall HR = 0.94 and 0.77, respectively, for deaths from cardiovascular disease (15).

LIMITATIONS

Evidence about sunscreen's ability to protect against skin cancer is limited to this single Nambour Trial conducted in a subtropical population, so there is uncertainty about both the repeatability of the findings and their applicability in populations living in temperate climates. Trial participants in the intervention group applied the sunscreen too thinly on average i.e., at far less that the thickness of 2 mg/cm^2 recommended for maximum effectiveness (16). In addition, the intervention sunscreen had an SPF 16 rating, whereas many sunscreens today have higher SPF ratings, so the size of protective effects may have been underestimated. Finally, the actual trial period was only 5 years, which is relatively short for the assessment of cancer prevention, and moreover it was conducted among adults, so the effectiveness of a sunscreen intervention earlier in life, carried out for longer, is unknown but potentially greater. The longer term effects of the trial were estimated by intention-to-treat analyses (9,10), so although post-trial sunscreen use lessened after the

trial ceased, this would not have introduced bias but would have diluted the strength of the findings.

DISCUSSION AND CONCLUSIONS

Although there was evidence that sunscreen may prevent the occurrence of multiple BCCs over time, the apparent lack of protective effect of sunscreen use on BCC occurrence overall may be partly explained by the dispersed anatomic site distribution of BCC, where around one-third occur on sites other than the specified trial application sites [although 25% of the intervention group were applying sunscreen regularly to other sites, namely, the trunk and lower limbs, at the end of the trial (16)]. It could also mean that regular sunscreen use for a limited period in adulthood is "too little, too late" to prevent BCC development if BCCs are initiated early in life and are promoted not only by solar UV radiation but by other factors as well.

On the other hand, the large reductions in risk of SCC and melanoma with regular sunscreen use are consistent with other trials (17–20) that have shown regular sunscreen use can prevent development of actinic keratosis [the common benign tumors caused by cumulative sun exposure that are strongly associated with both SCC and melanoma (21)] and melanocytic naevi [common pigmented lesions that are the strongest known predictors of melanoma risk (22)], respectively. The protective effect of sunscreen on skin cancer is also supported by experimental evidence that consistently shows that application of sunscreen prevents DNA damage in human skin (23).

In summary, based on the evidence from a single randomized controlled trial conducted in an Australian community, regular sunscreen use by adults does not appear to protect against BCC but does appear to reduce the risk of developing cutaneous SCC and melanoma, consistent with other findings. Sunscreen use is but one of a suite of sun protection measures, however, and it is important for healthcare agencies and practitioners to encourage the use of clothing cover and shade in addition to promoting sunscreen (3). Users also need clear instructions on the proper application and reapplication of sunscreen to achieve optimal protection (16).

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