Early Life UV and Risk of Basal and Squamous Cell Carcinoma in New South Wales, Australia

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ABSTRACT

Sun exposure is the main cause of squamous (SCC) and basal cell carcinoma (BCC) although pattern and amount differ by cancer type, and sun sensitivity is the major host risk factor. Our study investigated risk factors and residential ambient UV in a population-based sample of Australian 45 and Up Study participants: 916 BCC cases, 433 SCC cases, 1224 controls. Unconditional logistic regression models adjusting for key covariates demonstrated 60% increased BCC risk and 2-fold increased SCC risk with sun sensitivity, and 3- and 4-fold increased risk respectively with solar keratoses. BCC but not SCC risk increased with higher early-life residential UV in all participants (odds ratio (OR) = 1.54; 95%CI 1.22-1.96 for intermediate; OR = 1.31; 95%CI 1.03-1.68 for high UV at birthplace) and similarly in Australian-born participants (*P*-values<0.05). Risk of SCC but not BCC increased with long-term cumulative sun exposure assessed by self-reported outdoor work (OR 1.74, 95%CI 1.21-2.49). In conclusion, sun sensitivity is important for both cancers, early life UV but not cumulative UV appears to increase BCC risk, the former an apparently novel finding, and SCC risk appears only to be related to long-term cumulative sun exposure.

INTRODUCTION

Basal cell (BCC) and squamous cell (SCC) carcinoma of the skin, the keratinocyte cancers, are the most common cancers and entail an increasing health and economic burden (1-3). Prevention offers the potential for savings but has required setting aside funding for national prevention campaigns (1-3). Due to their very large numbers (1, 2) the keratinocyte cancers are generally not registered by cancer registries.

Sun exposure is well recognized as a cause of BCC and SCC in populations of European origin (4-6), consistent with the strong association of high mean daily levels of ambient ultraviolet radiation (UV) with higher population-based incidence rates (7). Sun sensitivity, variously measured, is the major constitutional risk factor (6, 8-10).

Based on relatively limited epidemiological research, SCC has consistently been associated with cumulative sun exposure unlike BCC for which studies of personal sun exposure suggest a more intermittent exposure pattern (5, 8, 11, 12). Current understanding of ambient UV at residential locations, used as a surrogate for personal ambient UV exposure, is that locations with medium or high UV index or high cumulative UV flux increase keratinocyte cancer risk, more strongly for SCC than BCC (10). The life period of greatest risk for sun exposure is uncertain, apart from the greater risk for each cancer with early vs later childhood migration from low to high UV regions (13, 14) and greater risk of SCC than BCC from sustained sun exposure (10). The importance of early life ambient UV to BCC or SCC risk however, while suggested (6, 15, 16), is yet to be demonstrated.

Sampling from the Sax Institute's 45 and Up study, a large population based cohort of residents (https://www.saxinstitute.org.au/our-work/45-up-study/) in the Australian state of New South Wales (NSW; latitude 28^{o}S—36^{o}S), the Skin Health Study (SHS) recruited BCC and SCC cases and matched controls, minimizing selection bias by sourcing all participants from the one population. The SHS was designed to add greater definition to the relationships of BCC and SCC with

sun exposure and host factors, including examining body site of the cancer. No study has yet examined the association between constitutional risk factors and the occurrence of SCC by body site. In this report we analyze ambient UV and host factors, taking a comprehensive approach and focusing on early life ambient UV in personal residence histories and its relationship with risk of BCC and SCC.

MATERIALS AND METHODS

The NSW population-based 45 and Up Study asked participants for their history of keratinocyte cancer (skin cancer not melanoma) in a baseline questionnaire and for their consent to be approached for future research. The SHS (2010-2012) is a case-control study of NSW residents aged 45-84 years, nested within the 45 and Up Study cohort. Potentially eligible cases enrolled in the cohort in 2008-2009 and in the prior 3 years had a first primary BCC or SCC diagnosed, i.e. they responded positively to 'Has a doctor ever told you that you have skin cancer (not melanoma)' or 'Have you ever had any of the following operations? Removal of skin cancer', and gave an age at diagnosis or operation within the 3 years before their baseline questionnaire, a specification included to facilitate medical record confirmation. Participants who reported melanoma were excluded. Controls were a random selection of people who gave no history of skin cancer and were frequency-matched to cases by sex and by age in 5 year age groups.

The 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee and the Skin Health Study by the Cancer Council New South Wales Ethics Committee.

Participants. The 45 and Up Study coordinating center mailed to potentially eligible participants an SHS invitation letter, information pamphlet, consent form to sign and a skin cancer record. The letter to cases stated that study records indicated they had skin cancer diagnosed for the first time at a specified age (within the 3 year timeframe), and if they confirmed this statement, requested information for confirmation with the treating doctor: age when diagnosed, where living, doctor's contact details and tick boxes to indicate whether only one or more than one skin cancer was diagnosed at the specified age, skin cancer type for the first skin cancer diagnosed at that age (squamous cell carcinoma or SCC, basal cell carcinoma or BCC, melanoma, other), and its body location (head, neck, upper arms, forearms, hands, upper legs, lower legs, feet, trunk). Controls were mailed the study information, consent form and a letter inviting them to participate and return their signed consent. After receiving all documents including signed consent, the 45 and Up Study team forwarded these to the SHS to confirm participant eligibility and send the SHS questionnaire to all those eligible.

A total of 10,830 45 and Up participants were invited of whom 6,426 (59.3%) did not respond, 162 (1.5%) had died or were uncontactable and 4,242 (39.2%) consented to participate. Adequate documentation was received for confirming SHS eligibility as a case or as a control from 3,808 people, 2,478 potential cases (36% of invited cases) and 1,330 potential controls (34% of invited controls). Of the potential controls 1,224 participated (92%) and 97 did not respond, withdrew or died. After the relevant medical professional confirmed the skin cancer and its location there were 1,349 cases (54% of 2,478; 916 BCC, 433 SCC) and after excluding participants receiving immunosuppressive therapy or with unknown residential location or missing skin color the total available to the analysis was 1,174 controls, 891 BCC and 419 SCC cases.

Data collection. The SHS was conducted in 2010-2012. Self-reported questionnaire data items included hair and eye color, density of childhood face freckling and current nevi on the whole body (using illustrations), ever told by a doctor they had sunspots or solar keratoses and, if so, number

and times removed, skin screening history in 2004 or earlier assessed by 'did a doctor check the skin on your whole body for early signs of skin cancer?', or 'did someone who is not a doctor deliberately check any of your skin?', ever having an organ transplant, and ever told by a doctor that they had breast, prostate or other cancer (if yes, type requested). They also recorded their personal residence history in a calendar format against each year of age and calendar year from birth to 74 years of age. Items recorded in the 45 and Up questionnaire and available to this analysis included age, place of birth, ancestry, education, physical activity (frequency and duration of walking, moderate activity and vigorous activity of any kind in the last week), current work status, type of work, skin color in 6 categories from very fair to black and ability to tan on repeated exposure to summer sunlight without protection in 4 categories from 'get very tanned' to 'never tan'.

Sun exposure variables. Ambient UV at residential locations is an acceptable surrogate for personal UV exposure (15). It is estimated that around 2-4% of the total annual ambient UV is available for exposure of indoor- and 10% for outdoor-working adults and that this percentage varies with latitude (15, 17-19). Individual life histories of annual ambient UV irradiance (UVR) were constructed for each participant's residential locations from birth to 74 years of age.

Worldwide mean daily ambient UV irradiance levels at noontime were downloaded from the Total Ozone Mapping Spectrometer (TOMS) database (http://toms.gsfc.nasa.gov/) (accessed June 2011) maintained by the National Aeronautics and Space Administration (NASA). The data were downloaded in wavelengths from 305 to 380 nm in a 1^{o} latitude by 1^{o} longitude grid for 3 calendar year periods, 1979 to 1983, 1984-1997, 1998-2002. Daily ambient erythemal UV irradiance was calculated as an average of the wavelength-specific energy in the range downloaded, weighted to the McKinlay-Diffey erythemal action spectrum (20). This estimate, expressed in mJ/cm^2, is the basis of 'ambient UV' in this report.

Each residential location was geocoded, assigned to a point on the location grid and the relevant UV value at the closest grid point extracted. Annual values within each of the 3 calendar periods downloaded were taken as the average of the whole period. Yearly UV values were required from 1923 to 2012; the average for 1979-1983 was assigned to each year in 1923-1978, and that for 1997-2002 assigned post-2002 and up to 2010-12, the years of data collection. To calculate lifetime totals, the estimated UVR at each residential location was multiplied by the duration of residence and the product summed for each location to the date of SHS data collection. Average annual lifetime ambient UVR was calculated as the lifetime total divided by age.

A brief job history assessed total years of outdoor occupational exposure by asking for age at first regular full or part-time job since age 15, at retirement from a regular job and when first working in 'any job for one year or more in which you usually worked outdoors for more than one hour between 9am and 5pm' and the total years worked in each such job.

Statistical analysis. Age at baseline questionnaire was used as the age variable in these analyses. Ambient UV cut-points were based on the distribution in the controls selected for specific analyses, e.g. analyses restricted to Australian-born participants (to reduce confounding by sun exposure) used cut-points based on Australian-born controls. Additionally to reduce confounding by ethnic origin these latter analyses also excluded people with ancestry recorded as Southern European or Asian, because they have greatly reduced odds of keratinocyte cancers, and those whose ancestry was recorded simply as 'other' (N=61). Conventional methods for analysis of case-control studies were followed. Odds ratios (ORs) and accompanying 95% confidence intervals (CIs) were calculated in unconditional logistic regression models in SAS (SAS Institute, Cary NC., 1989) with adjustment for age in 5 year age groups, sex, skin color and age at arrival in Australia as appropriate because risk of BCC and SCC is reduced for people migrating to Australia after 15 years of age from a low sun

environment (13, 14). Socioeconomic status, based on education, did not confound the association between sun exposure variables and BCC or SCC in our data and was not included in analyses. All significance tests in this paper were 2-sided tests and a *P* value of 0.05 was considered statistically significant.

RESULTS

Body site and demographic characteristics

Most of the BCCs were on the head and neck (68%), 16% were on the trunk (males 19%, females 14%), 8% on the arms in both males and females and 8% on the legs (males 6%, females 9%). SCCs occurred less frequently than BCCs on the head and neck (45%) and the trunk (10%) and more often than BCC on the arms (28%) and legs (17%).

More BCC than SCC cases were 45 to 69 years of age (BCC 83%, SCC 77%) and reported Northern European ancestry (BCC 70%, SCC 65%) and more SCC than BCC cases were born in Australia (BCC 82%, SCC 88%). Controls were frequency matched to cases by age and sex and had a slightly lower proportion of females (56%) than the cases (BCC 59%, SCC 57%). ORs for both BCC and SCC were reduced substantially for Southern European or Asian ancestry, relative to Northern European ancestry, and relative to Australian-born participants ORs were less for SCC with migration to Australia at 15 years or older (OR = 0.34; 95% CI 0.23-0.50) than for BCC (OR = 0.63; 95% CI 0.49-0.80) (Table 1).

Very fair skin color and an inability to tan, each relative to the least sun-sensitive phenotype, increased the ORs for BCC and SCC (Table 1). Skin color was an independent predictor for SCC and for BCC when fitted with ability to tan in the same model. Freckling and nevi are personal characteristics that combine genetic traits *and* sun exposure. Freckling on the face as a child was

positively associated with BCC and SCC and whole body nevus density with BCC but not SCC. When both were fitted in one model for BCC the ORs for freckling fell by <10% and nevi were no longer statistically significant. When we examined these phenotype variables in models restricted to skin cancers on each of 4 body sites, ORs increased with moderate or severe face freckling: head and neck cancers for BCC (OR = 1.49; 95% CI 1.11-2.00) and SCC (OR = 2.03, 95% CI 1.31-3.16), the legs for BCC (OR = 2.24; 95% CI 1.19-4.21) and arms for SCC (OR = 3.64; 95% CI 2.19-6.05) (see Supporting Information, Table S1). Higher current nevus density on the whole body increased risk for BCC on the head and neck (moderate or high OR = 2.00; 95% CI 1.08-3.69).

Solar keratoses, an indicator of cutaneous sun damage, were the strongest predictor of risk of both keratinocyte cancer types. BCC had 3-fold and SCC had 4-fold increased ORs for greater numbers of lesions and 4- and 8-fold increased ORs respectively for reported excisions versus no excision (Table 1) with similarly increased risks for each cancer at each body site (Table S1). Skin checks with a doctor were associated with BCC and SCC risk (ORs of 1.5-1.7) and ever given a cancer diagnosis other than skin cancer increased the odds 4-fold for BCC and 5-fold for SCC (Table 1).

Ambient UV and outdoor exposure

BCC was positively associated with average annual ambient UV at birth, age 0-15 and 16-20 years in models adjusted for age, sex, skin color and age at migration (age 0 for those born in Australia). The ORs at each age interval appeared to be greater for the intermediate tertile (49.99mJ ORs of 1.4-1.6), the UV value for the Sydney region, than the highest tertile (>49.99mJ ORs of 1.1-1.3) (Table 2). In a model that excluded migrants (22% of all participants), Australian-born participants had similar ORs for ambient UV at these ages (age 0: 49.99mJ OR = 1.51; 95% CI 1.16-1.95; >49.99mJ OR = 1.24; 95% CI 0.95-1.61). Most migrants (88%) came from much less sunny environments than NSW. A

borderline positive association was apparent for UV above the baseline in the last 10 years (highest UV OR = 1.22; 95% CI 0.98-1.54). There was no association between SCC and ambient UV at any age, over the lifetime or in the last 10 years in the fully adjusted models of Table 2.

Outdoor work for 30 or more years increased SCC risk in both sexes combined (OR = 1.84, 95% CI 1.21-2.49) but had no positive association with BCC risk (Table 3). Total physical activity in the week prior to study enrolment had no apparent association with either skin cancer (Table 3).

ORs for BCC on the head and neck and on the trunk were increased for higher ambient UV at birth, to 15 years of age and at 16-20 years. There was no evidence of an association between ambient UV and SCC on each of the head and neck, trunk, arms, legs (Table S2).

DISCUSSION

We confirmed that the head and neck was the most common site of BCCs and that SCCs occurred on these sites but were diagnosed as often on the limbs. A very fair skin and a history of solar keratoses were independent risk factors for each skin cancer. Early life UV in residential locations at birth and up to 20 years of age contributed to BCC risk but there was no evidence of any association with SCC within the relatively limited ambient UV range of SHS participants. Many years of outdoor work increased SCC risk.

Body site

A predominance of BCC on the head and neck and SCC on both the head and neck and the limbs is common in Australia's high UV environment (21-24). SCC in lower UV populations of Northern Europe and the USA occurs most often on the face and neck although incidence on the trunk and limbs has been increasing and may reflect changing sun exposure habits (25, 26).

Host factors

Very fair skin color was a determinant of both BCC and SCC. Most skin cancer patients, 90% in one estimate (27), have a UV-sensitive phenotype (28) that exhibits modest but consistent associations for BCC (5, 9, 13, 29) and SCC, whether examined as tanning or burning (13, 14, 16, 30), sunburns (31, 32), freckling (14, 29) or a score (8). Severe sunburn as a result of excessive exposure depends on sun sensitivity and marks risk for BCC and SCC (5, 14, 28, 32-35). It is unclear whether sun sensitivity and sunburn have independent effects on skin cancer risk. We did not ask about sunburn history.

Nevi and freckling are part of the high risk phenotype and both are genetically determined and influenced by sun exposure (36). Our findings were consistent with other reports of increased risks for BCC with each (9) and for SCC with greater freckling (14, 29) but not nevi (13, 14, 29, 31, 37, 38). Nevi have an uncertain relationship with heavy sun damage (39). The bodysite associations of adult nevi with BCC on the head and neck, but not the trunk, and any solar keratoses with BCC on all body sites supports similar Queensland findings (40, 41). Childhood freckling too was a risk factor at all bodysites. The distinctive BCC subtypes on the trunk (superficial) and head (nodular) may implicate host and genetic factors as others have discussed (40, 42) or UV exposure differences (40, 42). Having any solar keratosis on the whole body increased SCC risk at each site and childhood

freckling increased risk for head and neck and arm lesions; no previous SCC study has examined these factors by site.

Solar keratoses are the strongest personal solar-related risk factor for each of BCC and SCC (5, 13, 14, 43, 44). They are attributed to high sun exposure levels (5, 13, 45, 46), especially occupational exposure (11, 47), but not to acute or intense exposures like sunburn (45), and their occurrence mainly after age 45 (46) further supports long-term exposure as a cause. Sun sensitive individuals are most at risk (46-48), especially immunosuppressed patients with particular patterns of actinic damage (49, 50). This risk profile for solar keratoses suggests an underlying individual susceptibility in the response to excessive sun exposure.

Although self-reported sun sensitivity predicts skin cancer risk, the expression of individual sensitivity depends on local UV levels: in Australia's high UV more people report peeling and blistering (41–44% (13, 14)) than in New Hampshire (30% (51)) or readily develop a tan (Australia 30-36% (13, 14)) than in the US Nurses Health Study (14% (8)). Presumably identification of additional genetic factors for phenotypes (see (5, 10)) will assist in refining 'sun sensitivity' and our understanding of its contribution.

Ambient UV

We found that higher early life ambient UV increased BCC risk modestly in adulthood, similarly to UV in state of residence at birth and at age 15 in the USA (52), self-reported early life intermittent exposure in Australia (53) and Canadian recreational exposure (54). Compared to being born in Australia, the lower risk with migration after 10 years of age from a low sun environment (5, 6, 13) and a 67% reduced BCC risk in SHS participants who migrated at mid-teen years clearly suggests an influence of early life UV on BCC risk. Early life sun exposure is strongly associated with sun-related skin damage later in life (39, 45). We were unable to confirm whether or not recent ambient UV

influences risk of a first BCC despite positive reports of an association between BCC and recent personal sun exposure (53) or the outdoor exposure implicit in physical activity (55); the epidemiological data are too limited (5, 56).

The link between BCC and solar keratoses suggests a background of high long-term ambient UV as supported by: 50% higher BCC incidence in higher UV regions of Australia than NSW (3), 20-fold greater BCC incidence in Australia (high UV) than Finland (minimal UV) (57), and worldwide correlation of high BCC incidence with low latitude (7). Such observations though cannot address whether lifetime or early life UV may dominate or interact to influence skin cancer occurrence.

The head and neck are heavily exposed in self-reported sun exposure (12, 58) and observed solar UV measurements (59), and exhibit high BCC incidence rates at low Australian latitudes (23, 60), all features coherent with the positive relationship we observed with higher residential ambient UV. Despite the trunk having much less exposure (12, 58), ambient UV increased risk for trunk BCC, consistent with findings for personal exposure hours (12) and sunburns (40) and for ambient UV in our study. Behavior and surveillance changes probably contribute to causing (61-63) the increasing incidence of trunk BCC (5, 61, 62, 64) and may blur observation of causative sun exposure (61-63), in particular the relative importance of intermittent and cumulative exposure (5, 40, 43).

Most studies have failed to demonstrate a clear link between BCC and cumulative personal UV or sun exposure, as others have discussed (see (5, 40, 65)). The overall increase in BCC risk with increasing ambient UV in early life is modest, in our study around 50% within any one latitude or UV band which was consistent with the 50% higher incidence in higher UV regions of Australia than NSW (3).

Most (73%) of the SCC in NSW occurred on the arms, head and neck, as in Western Australia (75% (21)), in line with the high solar UV measured at these bodysites in Australia (59). We found no association with residential ambient UV levels however contrary to positive US reports for UV index at current residence (52), average lifetime UV from TOMS data (66), and 'warmer' than 'cooler'

locations (31). Our participants though all lived in a high UV area which limited exposure heterogeneity and potentially the ability to detect differences by UV level. Birthplaces for those born locally were within 6 degrees of latitude, corresponding to the single 'high UV' category of US studies (52, 66). High UV regions internationally are linked to increased SCC incidence (7, 67) and in Australia essentially all SCCs were attributed to locally extreme ambient UVR compared with northern Europe (67) and its 10-fold lower skin cancer rates than Australia (7, 67). In our study migration after mid-teens, mostly from Northern Europe, greatly reduced SCC risk compared to a local birthplace, as in Western Australia (14). The potential exposure in long years of outdoor work, and possibly an accompanying but unmeasured preference for outdoor leisure activities (68), increased SCC risk by 70% both in our study and a meta-analysis of 18 case-control and cohort studies (69) and up to 3-fold in Europe (70). Australian outdoor workers may receive a UV dose of 10% and up to 30% of ambient UV (17). Available evidence thus supports a definitive role for continuing exposure to a high-level UV environment in causing SCCs.

To our knowledge no other study explored residence history and ambient UV at precise residence locations and calculated total UV from birth and throughout life, including a separate examination at early ages. The US skin cancer studies that reported ambient UV had collected state of residence only and did not record exposure before 25 years of age (8, 16, 71), labelling exposure as 'chronic' (8, 71) and 'not account[ing] for sun exposure in early life' (16), except one study which examined UV at 3 discrete ages, 0, 15 and 30 years (52). Neither adult nor lifetime ambient UV apparently conferred an increased BCC risk in our study.

Australian studies only attempted to elucidate the potential dose-response relationship within one UV band and account for migration from outside that band, ie from very low UV environments relative to Australia's high UV. In brief, our study supports that sun exposure

associated with BCC risk in later life is accrued mainly in childhood and adolescence but for SCC risk, points to longer-term cumulative sun exposure. The plateau in BCC risk at intermediate and high UV levels, observed in other populations, may be due to measurement error (72).

Study factors

The SHS design helped to minimize selection bias by recruiting cases with a first BCC or SCC and controls from the same population, the 45 and Up Study, which enrolled participants from a randomly selected NSW population sample (73). Similar proportions of cases (36%) and controls (34%) consented to participate. Host factors were self-reported, as in many studies, as were solar keratoses; we found the latter influenced skin cancer risk in NSW similarly to other high (40) and low (51) ambient UV environments. Individual past sun exposure is almost impossible to measure accurately (15, 17). Ambient UV however clearly determines skin cancer risk (7) and when estimated from residential history, which is regarded as more reliable and less subject to recall bias, is an acceptable surrogate for personal exposure (15, 16).

Variations in personal UV exposure by latitude and temperature (15, 18, 19) suggest study-based differences in sun-related behavior due to geography and climate that would operate in our study. Internationally the rise in keratinocyte cancer incidence per unit of ambient UV increase varies by latitude range, highlighting dose differences or complexity in exposure patterns (7). In our study BCC and SCC risk peaked at the Sydney region (49.99mJ, 33^{o} S) and a previous cancer diagnosis and skin cancer checks by a doctor increased risk of a diagnosis of keratinocyte cancer, possibly because of the greater health awareness they engender and the easier access to care in Sydney. Ready access to health checks in metro areas is suggested as possibly accounting for increased BCC incidence rates in higher SES individuals and in urban than rural workers in Europe (62, 74) and

anomalies in Australian melanoma incidence (23). An increased local skin cancer incidence caused by the Sydney metro region's greater health facilities could distort the true relationship with ambient UV levels.

Skin cancer prevention programs stressing sun protection, a feature of Australia from 1980 on, probably helped stabilize population rates of BCC by reducing childhood and teenage sun exposure (3) but not in the adolescence of adults in our study: the youngest participants were 45 years in 2008-29 at entry to the 45 and Up Study and 15 years old by 1978-79. Increasing skin health awareness and the proliferation of skin cancer medicine and clinics (22) however could add to incidence rates of diagnosed cancer.

CONCLUSION

There is convincing evidence, particularly from studies of migrants, that childhood sun exposure influences risk of BCC and SCC in adulthood; our exploration of ambient UV and BCC accords with this evidence. Our findings for SCC are consistent with evidence that lengthy outdoor employment and thus long-term cumulative exposure increases SCC risk. The occurrence of solar keratoses is a personal indicator of skin cancer risk but whether due chiefly to an underlying susceptibility or excessive exposure or both is an open question. Our results reinforce the need for ongoing sun protection programs, especially in early life and sun-sensitive people.

The analysis of the sun exposure component of studies could be more informative, we suggest, if focused on a limited latitude and UV range and able to control for extreme early life UV environments outside the selected range. Future studies will also increase our understanding of the basis of skin cancer risk when they can incorporate more refined indicators of susceptibility.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Tables S1 and S2. Tables presenting odds ratios and 95% confidence intervals by body site for BCC and SCC associated with cutaneous factors (childhood freckling, adult nevus density, solar keratoses) and average annual ambient UV (mJ/cm^2) at 0, 0-15 and 16-20 years of age.

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Table 1. ORs and 95% CI* for BCC and SCC for demographic and pigmentary factors and health indicators.

Predictor variable	Controls n	BCC n	BCC OR (95% CI)	SCC n	SCC OR (95% CI)
Demographic					
Sex					
Male	534	370	1.0	186	1.0
Female	688	543	1.10 (0.92-1.31)	243	1.05 (0.84-1.31)
P-value			0.29		0.67
Age at arrival					
Australian born	919	748	1.0	376	1.0
<15 years	55	41	0.92 (0.60-1.39)	15	0.67 (0.37-1.21)
≥15 years	237	119	0.63 (0.49-0.80)	36	0.34 (0.23-0.50)
P-value			<0.001		<0.001
Country of Birth					
Australia	919	748	1.0	376	1.0
UK/Ireland/North America	199	129	0.83 (0.65-1.05)	34	0.39 (0.27-0.58)
Europe	62	20	0.40 (0.24-0.67)	14	0.50 (0.27-0.90)
Other	42	16	0.44 (0.24-0.79)	5	0.29 (0.11-0.73)
P-value			<0.001		<0.001
Ancestry†					
Northern Europe	801	635	1.0	276	1.0
Australia	299	238	0.97 (0.79-1.19)	132	1.31 (1.02-1.68)

Southern Europe	55	17	0.40 (0.23-0.69)	13	0.72 (0.39-1.35)
Asia	16	4	0.28 (0.09-0.85)	1	0.20 (0.03-1.52)
Other	40	15	0.45 (0.25-0.83)	6	0.43 (0.18-1.04)
P-value			<0.001		0.01
Pigmentary, cutaneous factors					
Hair colour					
Black	85	50	1.0	24	1.0
Dark brown	427	279	1.08 (0.73-1.59)	131	1.11 (0.67-1.84)
Light brown	420	350	1.39 (0.94-2.04)	148	1.30 (0.79-2.14)
Blonde/Fair	250	194	1.30 (0.87-1.95)	100	1.46 (0.87-2.46)
Red	35	35	1.71 (0.94-3.09)	26	2.78 (1.39-5.55)
P-value			0.06		0.01
Eye colour					
Brown	268	152	1.0	74	1.0
Hazel	284	235	1.44 (1.10-1.88)	113	1.43 (1.02-2.02)
Green	154	106	1.16 (0.84-1.59)	46	1.10 (0.72-1.68)
Blue	418	357	1.52 (1.19-1.94)	166	1.43 (1.05-1.97)
Grey	73	48	1.13 (0.74-1.72)	21	1.02 (0.59-1.77)
P-value			0.008		0.11
Skin colour					
Dark	344	209	1.0	72	1.0
Fair	688	525	1.27 (1.03-1.56)	267	1.84 (1.37-2.46)
Very fair	173	171	1.62 (1.23-2.14)	84	2.35 (1.63-3.39)
P-value			0.002		<0.001
Ability to tan					

Very	343	203	1.0	83	1.0
Moderate	498	385	1.29 (1.04-1.61)	182	1.50 (1.11-2.01)
Mild	257	209	1.33 (1.03-1.72)	107	1.75 (1.25-2.45)
No tan	106	103	1.61 (1.16-2.23)	50	1.98 (1.30-3.02)
P-value			0.02		0.002
Freckles					
None	769	493	1.0	208	1.0
Mild	288	253	1.34 (1.09-1.65)	126	1.69 (1.30-2.20)
Moderate	86	82	1.42 (1.02-1.97)	60	2.78 (1.91-4.04)
Severe	67	78	1.83 (1.29-2.61)	29	1.79 (1.12-2.87)
P-value			<0.001		<0.001
Nevi					
None	644	440	1.0	232	1.0
Mild	510	413	1.14 (0.95-1.37)	163	0.91 (0.72-1.15)
Moderate/Severe	24	29	1.85 (1.06-3.23)	13	1.70 (0.84-3.42)
P-value			0.05		0.19
Solar keratoses (SK)					
None	624	258	1.0	86	1.0
Any	527	593	2.81 (2.32-3.40)	312	4.22 (3.23-5.51)
Missing	71	62	2.20 (1.51-3.20)	31	3.03 (1.87-4.90)
P-value			<0.001		<0.001
Total SKs removed					
None	624	258	1.0	86	1.0

0-2	170	152	2.11 (1.62-2.76)	60	2.54 (1.75-3.68)
3-5	103	106	2.58 (1.89-3.53)	51	3.50 (2.33-5.27)
6-11	91	107	2.99 (2.17-4.11)	56	4.44 (2.96-6.65)
>11	112	154	3.51 (2.63-4.68)	100	6.32 (4.44-9.02)
Missing	122	136	2.91 (2.18-3.89)	76	4.40 (3.04-6.38)
P-value			<0.001		<0.001
Times SKs removed					
None	624	258	1.0	86	1.0
0-1 times	149	118	1.84 (1.38-2.45)	43	2.06 (1.37-3.11)
2-3	177	197	2.78 (2.16-3.58)	77	3.14 (2.21-4.46)
4-5	85	90	2.74 (1.96-3.83)	59	5.01 (3.34-7.53)
>5	99	152	3.98 (2.96-5.37)	112	8.03 (5.63-11.45)
Missing	88	98	2.95 (2.12-4.10)	52	4.14 (2.73-6.29)
P-value			<0.001		<0.001
Health indicators					
Skin check by doctor					
No	620	375	1.0	154	1.0
Yes	547	496	1.49 (1.25-1.78)	251	1.83 (1.45-2.31)
Don't know	42	31	1.26 (0.78-2.06)	18	1.71 (0.96-3.07)
P-value			<0.001		<0.001

Ever told you have other cancer					
No	1087	603	1.0	260	1.0
Yes	135	310	4.37 (3.47-5.49)	169	5.22 (4.00-6.81)
P-value			<0.001		<0.001

*ORs and 95% CIs estimated in models adjusted for age and sex.

† Tick boxes given for Ancestry in the 45 and Up Study questionnaire used labels for 15 European and Asian countries, Australian, Other.

Table 2. Average annual ambient UV at place of residence: ORs and 95% CI* for BCC and SCC.

Average annual UV (mJ/cm^2)	Controls n	BCC n	OR (95% CI)	SCC n	OR (95% CI)
Birth					
<49.99	514	303	1.0	139	1.0
49.99	359	347	1.54 (1.22-1.96)	156	1.15 (0.85-1.56)
>49.99	292	237	1.31 (1.03-1.68)	122	1.22 (0.89-1.67)
P-value			0.002		0.44
Age 0-15					
<49.99	548	330	1.0	169	1.0
49.99	258	265	1.61 (1.26-2.06)	105	0.99 (0.73-1.35)
>49.99	363	291	1.27 (1.01-1.59)	145	1.06 (0.80-1.40)

P-value			<0.001		0.90
Age 16-20					
<49.99	479	302	1.0	153	1.0
49.99	328	315	1.39 (1.10-1.76)	128	0.90 (0.67-1.21)
>49.99	362	269	1.09 (0.87-1.37)	138	1.00 (0.75-1.33)
P-value			0.01		0.73
Age 21-30					
<=49.5	385	281	1.0	143	1.0
49.6-52.3	384	284	0.83 (0.66-1.05)	142	0.74 (0.56-0.99)
>52.3	400	321	0.91 (0.71-1.17)	134	0.85 (0.62-1.16)
P-value			0.32		0.14
Age 31-40					
<=51.0	386	255	1.0	161	1.0
51.1-55.5	402	321	1.06 (0.82-1.36)	136	0.82 (0.59-1.12)
>55.5	381	310	1.06 (0.81-1.39)	122	0.87 (0.62-1.23)
P-value			0.90		0.46
Lifetime					
<=51.1)	382	249	1.0	120	1.0

51.1-53.6	392	328	1.05 (0.81-1.35)	158	0.92 (0.67-1.26)
>53.6	395	312	1.01 (0.79-1.31)	141	0.87 (0.63-1.19)
P-value			0.93		0.67
Last 10 years†					
<=54.9	346	235	1.0	127	1.0
55.0-56.3	323	261	1.21 (0.95-1.53)	100	0.87 (0.63-1.18)
>56.3	376	312	1.22 (0.98-1.54)	136	0.99 (0.74-1.32)
P-value			0.16		0.62

*ORs and 95% CIs estimated in models adjusted for age, sex, skin colour, age at arrival in Australia.

†Ambient UV accumulated to 74 years of age only

Table 3. ORs and 95% CI for BCC and SCC for years of outdoor work and frequency of outdoor physical activity.

	Controls	BCC		SCC	
	n	n	OR (95% CI)	n	OR (95% CI)
Outdoor work*					
None	736	565	1.0	236	1.0
1-9 years	150	111	1.06 (0.80-1.40)	49	1.15 (0.79-1.68)
10-29 years	135	83	0.84 (0.62-1.15)	48	1.17 (0.80-1.72)
30+ years	152	126	1.18 (0.89-1.58)	80	1.74 (1.21-2.49)
P-value			0.35		0.03
Outdoor physical activity (times per week)†					
None	226	141	1.0	77	1.0
<6	256	221	1.39 (1.05-1.83)	91	1.01 (0.70-1.44)
6-9	263	194	1.23 (0.93-1.64)	83	0.95 (0.66-1.37)
15-19	110	96	1.48 (1.04-2.10)	43	1.13 (0.72-1.77)
20+	124	88	1.16 (0.82-1.65)	48	1.11 (0.72-1.71)
P-value			0.13		0.92

* Estimates adjusted for age, sex, age at arrival, skin colour.

† Estimates adjusted for age, sex, age at arrival. Total activities a week was summed from frequencies for walking, moderate and vigorous activity.