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PREDICTORS FOR CUTANEOUS BASAL- AND SQUAMOUS-CELL CARCINOMA AMONG ACTINICALLY DAMAGED ADULTS

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Abstract

Risk factors for non-melanoma skin cancer among populations with evidence of precursor damage are not well described. We examined and compared risk factors associated with the development of cutaneous basal-cell (BCC) or squamous-cell (SCC) carcinoma amonga group of 918 adults with significant sun damage (≥10 clinically assessable actinic keratoses) but no prior history of skin cancer. These adults were participants in a 5-year skin chemoprevention trial between 1985 and 1992, who had been randomized to the placebo group and followed for occurrence of skin cancer. During the study, a total of 129 first SCC and 164 first BCC lesions were diagnosed. The overall BCC and SCC incidence rates for this group of men and women, mean age 61 years, were 4,106 and 3,198 per 100,000 person-years, respectively. Different constitutional and exposure factors were independently associated with BCC compared to SCC. Only increased age independently predicted BCC occurrence among this population. In contrast, older age along with male gender, natural red hair color and adult residence in Arizona for 10 or more years independently predicted SCC occurrence. The substantial incidence of skin cancer found among this population confirms the need for active dermatological monitoring among individuals with multiple visible actinic lesions.

Keywords

non-melanoma skin cancer; basal-cell carcinoma; squamous-cell carcinoma; skin cancer; risk factors; epidemiology

High rates of basal-cell carcinoma (BCC) and squamous-cell carcinoma (SCC) have been documented among light-skinned populations residing in lower-latitude locations, such as Australia and the southwestern United States.[1-5] Data from several countries suggest that the incidence of these non-melanoma skin cancers (NMSCs) is increasing, though the relative rate of change of BCC compared with SCC differs by country.[5,6] The risk of NMSC is much higher after an incident skin cancer.[7,8] BCC and SCC are not typically associated with mortality; however, increases in cancer mortality and incidence of other invasive cancers following NMSC have been reported.[9-12] In addition, increased health-care burden and morbidity have been associated with the incidence of NMSC.[8,13-17]

Actinic keratoses (AKs), pre-malignant lesions which are indicative of photodamage, are highly associated with an increased risk of both BCC and SCC.[18-22] AKs, however, are

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considered precursors, or an early form of the lesion, only for SCC.[18,20,21,23-27] Estimations of the rate at which specific AK lesions may progress to SCC vary from 0.025% to 16% per year.[24,25] AKs on sun-exposed body surfaces indicate previous exposure to sufficient UV radiation to initiate epidermal cells.[21,28] The prevalence of AKs, just as for BCC and SCC, is increased in sun-intensive regions.[18-22] Currently, the factors associated with AK progression to SCC are not known.

A phase III vitamin A chemoprevention trial has investigated and compared factors associated with development of the first BCC or SCC among persons with multiple AKs but no prior history of skin cancer.[29,30] The present analysis identifies and compares factors associated with an incident BCC or SCC among participants randomized to the placebo arm of this trial.

MATERIAL AND METHODS

Subjects

Healthy adults (aged 21 to 85 years) living in Arizona were eligible for the 5-year double-blind trial of the efficacy of oral vitamin A (25,000 I.U. daily) *vs.* placebo as an NMSC chemopreventive agent. The design and results of this trial have been previously published.[29,30] At baseline, study dermatologists determined if potential participants qualified as "moderately sun-damaged", defined as having 10 or more AKs on the forearms. Exclusion criteria included <10 clinically diagnosed AKs on the forearms, >2 prior NMSCs, any other cancer or treatment for cancer within the past 5 years, supplementation of vitamin A exceeding 10,000 I.U. daily [more than twice the U.S. recommended dietary allowances (RDA)] and clinical chemistry values (serum assessments typically included in clinical chemistry analyses are albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, carbon dioxide, creatinine, direct bilirubin, γ-glutamyl transpeptidase, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, cholesterol, protein, and uric acid) outside of normal limits.

Between 1985 and 1989, 2,297 participants were randomized into the 5-year study. The current analyses were limited to those eligible volunteers with no prior history of a skin cancer at baseline or within the first 3 months who were randomized to the placebo-control group, a total of 918 participants. Study volunteers were followed for 57 ± 12.7 months (mean ± SD) for NMSC occurrence.

Initial and follow-up dermatological information

Clinical assessments by study dermatologists determined the eligibility and presence of lesions requiring pathological diagnoses. Chart reviews verified the participants' reports of dermatological treatments. For participants with a biopsy or lesion removal, pathology reports and slides were obtained. A single study dermatopathologist reviewed all available slides to provide the final diagnoses. This centralized diagnosis was available in more than 93% of the cases. For specimens not reviewed, the diagnosis of the community pathologist was used.

Several methods were used to ensure completeness of the dermatological end points. At the 6-month clinic visits, participants completed questionnaires and interviews about dermatological treatments. Between visits, contact postcards prompted event reports. Yearly clinic visits included an assessment by the study dermatologist regardless of whether the individual was being followed by a private dermatologist. Finally, charts were reviewed in the offices of all physicians from whom the participant reported receiving dermatological treatment or by mail for those participants who lived outside the region.

Other measurements

Extensive questionnaires collected information about participant characteristics, skin-cancer risk factors and medical history. This background included self-report of weight and height, data that were utilized to calculate body mass index (BMI = kg/m^2).

Analyses

Data management included extensive quality-assurance procedures throughout the study. Skin-cancer incidence rates within the study population were calculated as the number of events (BCC or SCC) divided by the total person-years at risk. Similarly, age group-specific rates were calculated as the number of cases divided by person-years at risk for each gender-specific category and expressed per 100,000. Since the length of follow-up varied among participants, the Cox proportional hazards model was used to model the hazard of development of skin cancer.[31,32] This approach adjusted for staggered entry into the study and variable follow-up periods. Separate models were run for each outcome: diagnosis of the first skin BCC and diagnosis of the first skin SCC. Participants were right-censored at the time of the first NMSC, study attrition (illness, death or lost to follow-up) or end of the trial. If a case developed both BCC and SCC during follow-up (n = 48), the participant was included in the analysis of the first NMSC and censored from the analysis of the other type of NMSC. Twenty persons were censored from the BCC model at the date of SCC diagnosis, and 23 persons were censored in the SCC model at the date of their first BCC. Five individuals were diagnosed with both BCC and SCC on the same date and counted for each model. Analyses were also run where all subjects were included and not censored if the different type of skin cancer occurred first. Neither the fit of the models nor the factors independently associated with BCC or SCC differed for the uncensored model compared to the censored model.

Univariate and age-adjusted proportional hazard analyses with each potential risk factor were completed separately for BCC and SCC incidence. Age was entered as a continuous variable for the age-adjusted models. Categorical variables included current (asked at study baseline) skin reaction to sun exposure (rarely/never burn, burn minimally, burn moderately, always/usually burn), eye color (brown, blue/green/gray), natural hair color as a young adult (dark brown/black, blond/light brown, red), self-reported count of current moles (0, 1 or >2) or freckles (0, 1−4, 5−9, >10), usual sun exposure (0−5, 6−10, 11−20, >21 hr/week), history of occupational arsenic exposure (no, yes), history of x-ray treatment for skin ailments (no, yes) and quartiles of BMI. Categorical variables were created to examine youth and adult solar exposure. Participants who reported spending at least 1 decade in their first 20 years in Arizona were considered to have high youth exposure. Participants who reported residing in Arizona 10 years or longer after the age of 30 years were considered to have high adult solar exposure. Linear trends for continuous variables were examined. Stepwise, backward iterative modeling followed. Likelihood ratio tests were used to evaluate 2-factor interactions. The fit of each model was assessed by examining the Cox-Snell residuals, the deviance residuals and the assumption that the hazard ratio was constant over time.

RESULTS

The majority of adults participating in the study were male, 69% (n = 629 of 918) (Table I). This southwestern population was primarily married and well educated, with a mean (± SEM) age of 60.5 ± 0.3 years. The distribution of marital status differed between men and women, and follow-up was longer for female compared to male study participants, 58.2 ± 0.7 *vs.* 57.0 ± 0.5 months. There were no other gender differences in sociodemographic characteristics.

A total of 164 first BCCs and 129 first SCCs were diagnosed in the 5 years. Incidence rates of BCC and SCC among this cohort of individuals with substantial photodamage were 4,106 and

3,198 per 100,000 person-years, respectively, both being higher for men than women (Table II). BCC incidence increased with age for both men and women ($p = 0.06$ and $p = 0.04$, respectively), while SCC incidence significantly increased with age only among men ($p = 0.004$). In general, the ratio of BCC to SCC incidence decreased with age among men and women. However, SCC incidence was disproportionately high among women aged 50 to 59 years.

Different factors were associated with the development of BCC compared to SCC in this sample (Table III). After adjustment for age, no additional variables were significant predictors of BCC. In contrast, SCC incidence was associated with residence in Arizona for 10 or more years after the age of 30 and increased BMI. Participants who reported residence in Arizona for 10 or more years after the age of 30 were almost 1.9 times more likely to develop SCC compared to participants reporting fewer years of residence in Arizona. However, adult residence in Arizona did not significantly influence the likelihood of developing BCC.

In the simultaneous examination of multiple risk factors, only age was independently associated with both BCC and SCC incidence (Table IV). After adjustment for multiple risk factors, each year of life was associated with an increased risk of 2% and 4% for BCC and SCC, respectively. Male gender, having naturally red hair and living 10 or more recent adult years in Arizona independently predicted SCC incidence in this sample.

DISCUSSION

In this cohort of participants with 10 or more AKs, the age-adjusted incidence rates for cutaneous BCC and SCC are among the highest reported. There is considerable world-wide variability in NMSC rates among populations at increased risk (*e.g.*, a white population with high UV radiation exposure). The highest NMSC rates are associated with lower-latitude regions, such as Arizona and Australia.[2,33] These areas report rates more than 40-fold higher than those reported in higher-latitude regions, such as Finland.[34] The high incidence rates of NMSC found among this actinically damaged population verify reports that UV-induced AK lesions are indicative of an epidermis promoted for skin cancer.[18,21,22,27,28]

High incidence rates for both BCC and SCC were expected among these sun-damaged adults. However, based on general population estimates, a greater differential between the 2 skin-cancer types would have been expected. The ratio of BCC to SCC among our study participants was 1.3 compared to population-based estimates of 3.2 and 3.4 among whites in Albuquerque, New Mexico, and southeastern Arizona.[2,34] The ratio of BCC to SCC incidence world-wide varies from 1.5 to more than 10, with the lowest ratios found in the higher NMSC incidence areas.[5,35] The low BCC to SCC ratio indicates that the study population was at higher risk for SCC compared to the general population residing in the same geographical location. Furthermore, this low ratio suggests that multiple AKs explain a greater proportion of SCC incidence than BCC incidence.

BCCs are not thought to arise from AKs, whereas AKs can be an early form of SCC.[18,19,23,25-27] Estimations of the rate per annum at which a specific AK lesion may become SCC vary from 0.025% to 16%. As evident in the world-wide variability in SCC incidence, solar exposure along with cutaneous and genetic differences may be important factors in the wide range of estimated rates of lesion progression.

Our investigation highlights important epidemiological differences in the development of BCC and SCC of the skin. The only variable that predicted both NMSC types was increasing age, with year of age associated with a 2% and 4% rise in the hazard of developing BCC and SCC, respectively. No other variables significantly predicted BCC occurrence. However, prolonged adulthood residence in a region of high UV radiation levels, male gender and red hair also

independently predicted SCC incidence. Unlike findings from other studies, prolonged sun exposure during the first 2 decades of life was not significantly associated with BCC or SCC incidence among our population.[36-40]

Our analyses examined associations among a highly promoted subgroup of the general population. Participants were selected for the presence of NMSC risk factors and evidence of prior skin carcinogenesis promotion, *i.e.*, multiple AK lesions. Study eligibility required at least 10 clinically assessable lesions; however, since actual enumeration of the forearm AKs was not done, the number may have been higher. Study participants disproportionately reported light eye and hair color, skin types that burned with sun exposure and having at least 1 parent of northern European ancestry.[30] Hence, the study was designed to capture high incidence rates of both BCC and SCC and represents the portion of the general population known to be at higher risk. Future chemoprevention studies should be focused on this unusually high-risk population. Of note, none of the usual risk factors for NMSC continued to significantly predict BCC occurrence and men were not at significantly higher risk for BCC.

Missing information limited the analyses. Mole and freckle count surveys, administered separately from other study questionnaires, were not completed by 26% of the participants. Additionally, although questions were included with baseline habit surveys, almost 10% of women and 14% of men did not respond to questions regarding sunscreen use. The questions also did not ask for seasonal use or repeated applications of sunscreen. Past and recent use, skin type, sun exposure hours and sun protection ability may confound the potential effect of sunscreen.[41,42] A more thorough assessment of sunscreen use would allow examination of the independent association with prevention or risk of BCC or SCC.

Additionally, the present study was not designed to quantify AK lesions and cellular factors associated with transformation to SCC skin cancer. Histopathological verification of the qualifying actinic lesions and procurement of epithelial tissue samples for examination of cellular alterations would have been highly informative.

Extremely high rates of both BCC and SCC incidence (4,106 and 3,198 per 100,000 person-years, respectively) among adults with current multiple AKs indicates that these lesions are important predictors of skin carcinogenesis. However, even among adults with substantial evidence of sun damage, other factors continued to confer an increased risk of NMSC, though cutaneous BCC and SCC did not share identical sets of risk factors. Older age independently predicted BCC and SCC occurrence, while gender was significantly related only to development of SCC. Persons at highest risk for SCC were older, male and red-haired and reported prolonged residence as an adult in a sunny region.

Further research is needed to understand the significance of multiple AKs for subsequent BCC and SCC incidence. The high incidence of SCCs among adults with numerous AKs suggests that periodic monitoring and treatment are important within this subgroup. Adult years of residence in Arizona independently predicted SCC incidence, a finding that warrants further exploration and suggests that sun-exposure behavior as an adult can significantly affect skin-cancer occurrence. The potential for prevention during the years in which one is at increasing risk for discernible NMSC should be investigated along with examination of age cohort differences in NMSC incidence.

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TABLE I

BASELINE SOCIODEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION, BY GENDER

Characteristic	Overall (n = 918)	Males (n = 629)	Females (n = 289)
	Number (%)	Number (%)	Number (%)
Age (years)			
<50	143 (15.6)	88 (14.0)	55 (19.0)
50−59	220 (24.0)	148 (23.5)	72 (24.9)
60−69	374 (40.7)	265 (42.1)	109 (37.7)
≥70	181 (19.7)	128 (20.4)	53 (18.3)
Marital status			
Single, never married	39 (4.3)	23 (3.7)	16 (5.5)
Married	732 (79.7)	543 (86.3)	189 (65.4)
Widowed/divorced	147 (16.0)	63 (10.0)	84 (29.1)
Education			
Less than high school	55 (6.0)	40 (6.4)	15 (5.2)
High school graduate	160 (17.4)	103 (16.4)	57 (19.7)
Some post-high school	310 (33.8)	202 (32.1)	108 (37.4)
College graduate	188 (20.5)	139 (22.1)	49 (17.0)
Graduate school	205 (22.3)	145 (23.1)	60 (20.8)
Occupation			
Employed	257 (28.0)	185 (29.4)	72 (24.9)
Retired/disabled	532 (58.0)	350 (55.6)	182 (63.0)
Homemaker/other	16 (1.7)	9 (1.4)	7 (2.4)
No response	113 (12.3)	85 (13.5)	28 (9.7)
Follow-up			
Months (±sd)	57.4 (12.7)	57.0 (13.1)	58.2 (11.8)

TABLE II

INCIDENCE PER 100,000 PERSON-YEARS OF SKIN BCC AND SCC AMONG PERSONS WITH MULTIPLE AKS BUT NO SKIN CANCER HISTORY

	Number	BCC cases	BCC incidence rate	RR[1] (95% CI)	SCC cases	SCC incidence rate	RR[1] (95% CI)	BCC/SCC
Overall	918	164	4,106.0		129	3,197.6		1.3
Males	629	120	4,449.8		95	3,491.6		1.3
Females	289	44	3,391.4		34	2,588.7		1.3
Age group-specific rates								
Males								
<50 years	88	14	3,352.9	1.00	4	931.3	1.00	3.5
50−59 years	148	24	3,744.0	1.06 (0.55−2.09)	18	2,754.7	3.97 (1.16−13.62)	1.3
60−69 years	265	49	4,393.9	1.11 (0.60−2.05)	44	3,899.1	4.77 (1.47−15.55)	1.1
≥70 years	128	33	6,310.0	1.61 (0.84−3.08)	29	5,692.3	7.18 (2.15−24.02)	1.1
p for trend				0.06			0.004	
Females								
<50 years	55	6	2,446.5	1.00	3	1,207.6	1.00	2.0
50−59 years	72	9	2,608.9	0.94 (0.32−2.69)	13	3,881.6	8.27 (1.07−64.04)	0.7
60−69	109	18	3,726.6	1.44 (0.57−3.65)	11	2,211.9	3.97 (0.50−31.78)	1.6
≥70 years	53	11	4,906.6	1.77 (0.64−4.87)	7	3,007.9	6.37 (0.77−52.87)	1.6
p for trend				0.04			0.58	

[1] RR estimated from hazard ratio with age entered as a covariate.

TABLE III

AGE-ADJUSTED RR FOR INCIDENT BCC AND SCC BY POTENTIAL SKIN-CANCER RISK FACTORS

Factor	Number	BCC cases number (%)	ARR[1] (95% CI)	SCC cases number (%)	ARR[1] (95% CI)
Gender					
Females	289	41 (14.2)	1.00	26	1.00
Males	629	103 (16.4)	1.18 (0.82−1.69)	80	1.40 (0.90−2.19)
BMI					
<23.3	221	31 (14.0)	1.00	15 (6.8)	1.00
23.3−25.6	223	42 (18.8)	1.43 (0.90−2.27)	24 (10.8)	1.70 (0.89−3.24)
25.7−28.5	222	38 (17.1)	1.32 (0.82−2.13)	30 (13.5)	2.14 (1.15−3.98)
≥28.5	252	33 (13.1)	1.01 (0.62−1.66)	37 (14.7)	2.64 (1.45−4.83)
p for trend			0.73		0.004
Eye color					
Brown	202	28 (13.9)	1.00	24 (11.9)	1.00
Blue/green/gray	715	116 (16.2)	1.18 (0.78−1.78)	82 (11.5)	0.99 (0.63−1.57)
Natural hair color					
Dark brown/black	240	46 (15.8)	1.00	32 (11.0)	1.00
Blond/light brown	523	84 (16.1)	0.99 (0.69−1.42)	57 (10.9)	1.00 (0.65−1.55)
Red	103	14 (13.6)	0.91 (0.50−1.67)	17 (16.5)	1.79 (0.99−3.24)
Skin reaction to first 30 to 45 min exposure to summer sun					
Rarely burn	70	8 (11.4)	1.00	7 (10.0)	1.00
Burn minimally	87	9 (10.3)	1.02 (0.39−2.64)	13 (14.9)	1.77 (0.70−4.43)
Burn moderately	376	69 (18.4)	1.91 (0.92−3.98)	43 (11.4)	1.40 (0.63−3.11)
Always burn	384	58 (15.1)	1.62 (0.77−3.41)	43 (11.2)	1.50 (0.67−3.36)
Total palpable moles (n = 681)					
0	448	71 (15.9)	1.00	50 (11.2)	1.00
1	118	20 (17.0)	1.16 (0.71−1.90)	16 (13.6)	1.33 (0.75−2.33)
2 or more	115	22 (19.1)	1.18 (0.73−1.90)	10 (8.7)	0.77 (0.39−1.52)
p for trend			0.82		0.68
Total non-palpable moles (n = 681)					
0	192	31 (16.2)	1.00	16 (8.3)	1.00
1−4	192	31 (16.2)	1.03 (0.62−1.70)	22 (11.5)	1.29 (0.67−2.49)

Factor	Number	BCC cases number (%)	ARR[1] (95% CI)	SCC cases number (%)	ARR[1] (95% CI)
5−9	125	22 (17.6)	1.05 (0.60−1.84)	13 (10.4)	1.10 (0.52−2.30)
10 +	172	29 (16.9)	0.96 (0.57−1.63)	25 (14.5)	1.40 (0.73−2.70)
p for trend			0.98		0.13
Usual sun hr/week					
0−5	154	26 (16.9)	1.00	11 (7.1)	1.00
6−10	208	26 (12.5)	0.71 (0.41−1.23)	29 (13.9)	1.91 (0.96−3.83)
11−20	267	49 (18.4)	1.11 (0.69−1.79)	30 (11.2)	1.60 (0.80−3.19)
21 +	289	43 (14.9)	0.87 (0.54−1.42)	36 (12.5)	1.69 (0.86−3.32)
p for trend			0.29		0.10
Smoking history					
Never	352	64 (18.2)	1.00	38 (10.8)	1.00
Former	458	66 (14.4)	0.77 (0.55−1.09)	54 (11.8)	1.08 (0.71−1.64)
Current	108	14 (13.0)	0.74 (0.41−1.32)	14 (13.0)	1.33 (0.72−2.47)
Take supplements					
Daily	392	65 (16.6)	1.00	48 (12.2)	1.00
Sometimes	268	31 (11.6)	0.71 (0.46−1.09)	26 (9.7)	0.88 (0.54−1.42)
Never	258	48 (18.6)	1.13 (0.78−1.64)	32 (12.4)	1.02 (0.65−1.60)
Lived in Arizona as a youth					
No	761	123 (16.2)	1.00	90 (11.8)	1.00
Yes	157	21 (13.4)	0.92 (0.56−1.50)	16 (10.2)	1.26 (0.72−2.21)
Adults years (after age 30) in Arizona					
<10 years	355	63 (17.8)	1.00	28 (7.9)	1.00
≥10 years	563	81 (14.4)	0.81 (0.59−1.13)	78 (13.9)	1.87 (1.21−2.87)
p for trend			0.12		0.001
Ever had severe sunburn that blistered					
No	401	59 (14.7)	1.00	53 (13.2)	1.00
Yes	508	83 (16.3)	1.26 (0.90−1.77)	50 (9.8)	0.86 (0.58−1.27)
Year-around tan					
No	193	31 (16.1)	1.00	24 (12.4)	1.00
Yes	612	100 (16.3)	1.23 (0.85−1.76)	71 (11.6)	1.10 (0.72−1.67)
Sunscreen use (n = 804)					

Factor	Number	BCC cases number (%)	ARR[1] (95% CI)	SCC cases number (%)	ARR[1] (95% CI)
Do not use	166	24 (14.5)	1.00	18 (10.8)	1.00
<Half the time	236	49 (20.8)	0.92 (0.52−1.61)	32 (13.6)	1.18 (0.63−2.21)
>Half the time	206	32 (15.5)	1.14 (0.67−1.95)	23 (11.2)	1.23 (0.66−2.29)
Always	196	25 (12.8)	1.55 (0.94−2.54)	22 (11.2)	1.42 (0.79−2.55)
Physical exercise					
Never	258	43 (16.7)	1.00	29 (11.2)	1.00
Sometimes	389	59 (15.2)	0.95 (0.64−1.41)	39 (10.0)	1.01 (0.62−1.65)
Often	266	42 (15.8)	0.96 (0.63−1.48)	37 (13.9)	1.40 (0.86−2.29)
Average number of alcoholic beverages (beer, wine and liquor) per week					
None	196	22 (11.2)	1.00	19 (9.7)	1.00
<1	78	11 (14.1)	1.23 (0.60−2.54)	4(5.1)	0.51 (0.17−1.50)
1−2	305	56 (18.4)	1.70 (1.04−2.78)	40 (13.1)	1.35 (0.78−2.33)
≥3	337	55 (16.3)	1.47 (0.90−2.41)	43 (12.8)	1.31 (0.76−2.25)
p for trend			0.52		0.44
Either biological parent ever diagnosed with skin cancer					
No	760	121 (15.9)	1.00	87 (11.5)	1.00
Yes	158	23 (14.6)	0.95 (0.60−1.50)	19 (12.0)	1.25 (0.75−2.07)

[1] ARR, age-adjusted relative risk.

TABLE IV

INDEPENDENT PREDICTORS OF INCIDENT SKIN BCC AND SCC AMONG ADULTS WITH A HISTORY OF AKS

Predictors	**BCC RR (95% CI)**	**SCC RR (95% CI)**
Age	1.02 (1.00−1.04)	1.04 (1.02−1.07)
Gender		
Female	N.S.[1]	1.00
Male		1.63 (1.04−2.55)
Hair color		
Dark brown/black	N.S.	1.00
Light brown blond		0.97 (0.63−1.50)
Red		1.82 (1.01−3.31)
Adult residence in Arizona (years after age 30)	N.S.	
<10 years		1.00
≥10 years		1.96 (1.27−3.04)

[1] N.S., not significant.