

Sunlight Exposure, Pigmentation Factors and Risk of Nonmelanocytic Skin Cancer

II. Squamous Cell Carcinoma

Richard P. Gallagher, MA; Gerry B. Hill, MB, ChB, MSc, FRCPC; Chris D. Bajdik, MSc; Andrew J. Coldman, PhD; Shirley Fincham, PhD; David L McLean, MD, FRCPQ William J. Threlfall, MSc

Introduction and Design

Squamous cell carcinoma of the skin (SCC), a common cancer in white populations, is related to sunshine exposure; however, relatively little information is available on how timing and character of exposure affect the relationship. The purpose of this study was to investigate the nature of the relationship of SCC to individual solar UV exposure after control for phenotype and pigmentary factors. All newly diagnosed cases of SCC were in men aged 25 through 79 years, ascertained in the province of Alberta from January 1, 1983, through December 31, 1984, who were approached for participation; 80% completed a standardized etiologic interview that was conducted in their homes by a trained interviewer. Control subjects were chosen at random from the Alberta Health Care Insurance Plan subscribers list, matched only by sex (male) and age (within a 5-year age group). The response rate among controls was 71%.

Results

Subjects with pale skin and red hair had an elevated risk of SCC. Subjects whose mother was of southern European ancestry had a reduced risk of SCC. After accounting for pigmentary factors, no association was seen between risk of SCC and cumulative lifetime sun exposure. However, a strong trend toward increasing risk was seen with increasing chronic occupational sun exposure in the 10 years prior to diagnosis.

Conclusion

The results suggest that recent sun exposure (in the 10 years prior to diagnosis) may be important in accounting for individual risk of SCC.

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Squamous cell carcinoma (SCC) of the skin is a common malignancy in white populations, and its incidence appears to be increasing.^{1,2} Solar UV irradiation is thought to be the most important environmental risk factor for the disease,³ but the nature of the relationship between SCC and solar UV irradiation is not well understood. While a number of studies have shown an association with sun exposure,⁴⁻⁶ the categorization of the

exposure has generally been relatively crude and it has not been possible to evaluate the character, duration, and timing of exposure in relationship to risk. A case-control study of SCC was conducted in the Canadian Province of Alberta in 1983 and 1984. This article reports on the relationship of pigmentation and phenotype factors, as well as individual sun exposure patterns, to the risk of SCC.

Materials and Methods

Pathology reports on all newly diagnosed cases of SCC of the skin in males from January 1, 1983, through December 31, 1984, were obtained from the Alberta Cancer Registry, a population-based registry covering the entire province. A total of 225 male subjects with SCC aged 25 through 79 years were eligible for the study and were invited to participate. Of these, 80% (180) agreed to participate and undergo the full etiologic interview. Of the 225 subjects, 15 (7%) could not be located, 25 (11%) refused to participate, and five (2%) were too ill to interview. Only male subjects were studied for both cost reasons and because males were thought to offer a better opportunity to study the contribution of occupational sunlight to risk of SCC than were females.

The study of SCC was conducted in conjunction with a companion investigation of basal cell carcinoma of the skin,⁷ and, because the age distribution of cases for the 2 types of skin cancer was very similar, a common control series was selected from the subscriber file of the Alberta Health Care Insurance Plan. This insurance plan covers virtually the entire population of Alberta, the major exception being individuals who have resided in Alberta less than 3 months. Controls were checked against the cancer registry to ensure no previous diagnosis of nonmelanocytic skin cancer. Control subjects were matched to case subjects by sex (males only) and age (within 5-year group). A total of 573 age-eligible controls were approached for the study, and 406 (71%) were interviewed.

Each case subject and control subject was interviewed in his home by a trained interviewer, using a standardized

questionnaire that was very similar to that used in the Western Canada Melanoma Study⁸⁻¹⁰ conducted in the same region 3 years earlier. Interviewers were blinded to the disease status of the subjects prior to interview. Pigmentation and constitutional factors evaluated on the questionnaire included propensity to burn rather than to tan in the sun (skin type), freckling, childhood and adult sunburn history, and ethnic background. Data on the national origin and ethnic status of both the mother and the father of each subject were also collected. Skin color was evaluated by comparing each subject's upper inner arm (non-sun exposed) with a series of flexible latex color samples designed by a prosthetist to mimic human skin. A sun-exposed site (dorsum of the hand) was also evaluated. Hair color was recorded by comparison with wig maker samples, and where hair had grayed with age, subjects were asked to select the color that most closely matched their hair color at age 30 years. Eye color was recorded by the interviewer as blue, gray, green, hazel, or brown from direct observation during administration of the etiologic questionnaire.

The sunlight exposure history of each subject was evaluated using responses to questions on occupational and recreational outdoor activities, including vacations. A lifetime occupational history was obtained detailing each job of at least a 6-month duration. For each occupation, the usual number of hours spent outdoors per week was recorded for summer and winter, along with typical upper and lower body clothing and hat preferences while working. Summer was defined to be the months of April through September, and winter as October through March.

Recreational activities were assessed separately for summer and winter during childhood and adolescence (age 0 through 19 years) and then by decade of adult life up to the date of diagnosis (case subjects) or date of interview (control subjects). Subjects reviewed a card describing four groups of recreational activities categorized by type of clothing worn. Group A activities included those in which a bathing suit was normally worn, such as swimming or sunbathing. Group B activities were those in which light clothing (shorts, T-shirts) were worn, such as outdoor tennis, soccer, and summer gardening. Group C included recreational activities in which normal weight clothing might be worn, such as hiking, fishing, and horseback riding. Finally, group D activities were defined as those conducted in snow and ice, such as skiing, mountaineering. Subjects were asked the approximate

number of hours per week and months per year that they were involved in each of these groups of activities by decade of life.

Indexes were developed for occupational and recreational sunlight exposure. The recreational index was calculated by multiplying sun exposure hours for childhood and adolescence (age 0 through 19 years) and each succeeding decade of life by proportion of the body exposed in each activity from the clothing preference data. Body exposure proportions ranged from a high of 89% for a subject wearing a bathing suit (group A) to a low of 3% (face only) for subjects wearing clothing suited to group D activities, such as skiing. The index was calculated separately for both summer and winter. The measure resulting from the calculation, called *whole body equivalents* (WBEs) of exposure per year allowed comparisons between subjects over a wide range of outdoor activities and clothing preferences. The occupational index was developed in a similar fashion from hours of outdoor work per season in each occupation, coupled with clothing preferences. Because start and finish dates were available for each occupation, WBEs were again calculated by decade of life in the same fashion as recreational solar exposure.

Risk of SCC is strongly related to age, and hence we stratified all analyses on single year of age and calculated odds ratios using conditional methods. Pigmentation and phenotype factors were analyzed first on a univariate or crude basis controlling only for age followed by use of conditional logistic methods to determine which of the host factors were most important in determining SCC risk. Next, the risk factors that combined personal susceptibility and sunshine exposure, such as freckling, tanning history, and sunburn history, were evaluated controlling for significant host factors (skin, hair color, and mothers' ethnic origin), using conditional logistic methods.

Mean annual recreational solar exposure, expressed in WBEs during childhood and adolescence, in the decade prior to diagnosis, and over each subject's lifetime, was analyzed using approximate exposure quartiles within the control group, with the lowest quartile as the index for calculation of odds ratios. Mean annual occupational sun exposure after age 20 years was evaluated for the 10 years prior to diagnosis, and for the whole of each subject's lifetime. No subject had significant occupational exposure prior to age 20 years, and so a separate analysis for the period prior to this age was unnecessary. Finally,

mean annual cumulative solar exposure, combining the recreational and occupational components, was calculated for lifetime and for the 10 years prior to diagnosis. All odds ratios for solar exposure were calculated adjusting for skin color, hair color, and mother's ethnic origin, but not for freckling, sunburn history, or tanning history, which were considered to already incorporate at least some degree of sun exposure.

Results

Age-adjusted crude odds ratios for phenotype and pigmentary factors demonstrate an increased risk of SCC for subjects with light skin color and red hair who burn rather than tan when first exposed to the sun and who are unable to develop a tan even after a week or more of exposure to sunshine (**Table 1**). Subjects whose mothers were of southern European extraction (Italian, Portuguese, Spanish, or Greek) had a reduced risk of SCC by comparison with those with mothers of English, Celtic, and Scandinavian origin. Although data on both mother's and father's origin were collected, those for subjects' mothers were more complete than for fathers and were used to define ethnic origin. It should be noted that although Celts, Scandinavians, and English are of different genetic origin, they were combined because their risk of SCC was similar.

When host and pigmentary factors were entered into a conditional logistic model, only the mother's ethnic origin and hair color remained statistically significant; although skin color continued to exhibit a regular increase in risk with lightening of skin color, it was no longer statistically significant. Nevertheless, because of the regularity of the increase in risk it was retained as an adjustment factor in modeling the effects of sunlight exposure.

Freckling and sunburn history (**Table 2**) combine aspects of individual pigmentation and skin susceptibility with solar UV exposure. The presence of freckling in childhood appears to increase the risk of SCC (odds ratio, 1.6; 95% confidence interval, 1.0 to 2.4), although the association is on the margin of statistical significance. Assessment of sunburn in childhood and adolescence showed no increase in risk of SCC, with increasing frequency or severity of burns when all sunburns combined were assessed. However, when very severe burns (defined as those causing pain for 2 days or more) were analyzed separately, the presence of two or more such burns per year in childhood markedly increased the risk of SCC after control for host and pigmentary factors. Sunburn frequency for all sunburns and for very severe

sunburns by intermediate decades of adult life (age, 20 through 29, 30 through 39, and so on) for all of lifetime showed no association with SCC, although the presence of very severe burns once or more per year in the 10 years prior to diagnosis appeared to confer excess risk.

A tanning score was calculated for each subject by summing the value for degree of tan (1, no tan or little tan; 2, mild tan; 3, deep tan) over four major body sites (hands and face, trunk, and upper limbs and lower limbs). The score was assessed separately for childhood and adolescence for each decade of life after age 20 (ie, 20 through 29, 30 through 39, and so on) and for the 10 years prior to diagnosis or interview. No relationship was seen between tanning score and risk of SCC.

The relationship between solar irradiation and risk of SCC was examined using the WBE indexes for recreational exposure, occupational exposure, and cumulative exposure (**Table 3**). Analysis revealed that over 95% of solar exposure for the case and control subjects occurred in the summer, hence typical hours of exposure figures that are provided in Table 3 were calculated assuming all solar exposure took place in the summer. After adjustment for the mother's ethnic origin, hair color, and skin color, no association was seen with recreational sun exposure during childhood and adolescence (**Table 3**). An overall suggestion of decreased risk of SCC with increasing lifetime recreational sun exposure was seen, although the trend was not statistically significant ($P=.09$). A similar relationship was seen for recreational summer sun exposure over the 10 years prior to diagnosis, again with a marginal value for the test of trend $W=.06$). Mean annual lifetime occupational sun exposure was not significantly related to risk of SCC; however, occupational exposure over the 10 years prior to diagnosis showed a strong relationship to SCC risk, with an odds ratio of 4.0 in the highest exposure group. No association was seen between lifetime cumulative sun exposure and SCC, nor was any association seen with cumulative exposure over the 10 years prior to diagnosis, likely due to the fact that the trends for occupational and recreational exposure tend to cancel each other out when the two are combined.

Finally, sun-sensitive individuals were separated from sun-resistant subjects (nontanners vs tanners) using questions about propensity to burn. Tanners were defined as those who "got a brown suntan without burning" when exposed to sunlight for 2 hours per day over a week plus

those who "got a brown suntan with the aid of sunscreens." Nontanners were those who "usually got some degree of burn followed by a tan" and those who "only burned and never tanned." Reanalysis of the relationship of sun exposure to risk of SCC among tanners vs nontanners was uninformative.

Comments

Findings for host and pigmentation factors reflect those of previous studies and suggest that subjects with SCC have light skin,^{4,6,11,12} blonde or red hair^{4,6,11} and tend to burn rather than tan in the sun.^{4,11,12} In addition, propensity to freckle has also been reported to be more common in individuals with SCC.^{11,13} Similarly, a history of severe sunburn is also characteristic of patients with SCC and has been reported in at least one study conducted in Australia.⁶ Southern European origin has been reported to place subjects at lower risk of SCC in another Australian study.¹¹

Interpretation of the sunlight exposure results requires caution, in part due to the potential for misclassification in the interview data. In this study, older subjects (average age, 62 years) were asked to recall leisure participation patterns and outdoor job exposures that happened many years in the past. Thus, there is likely to be a good deal of misclassification in the sun exposure data. However, provided the misclassification occurs with equal prevalence among case subjects and control subjects, the effect will be to make it more difficult to detect an association should a real relationship exist. This should render the study findings conservative by underestimating the strength of relationships between solar exposure and SCC. There is some evidence within the data itself to indicate that the misclassification is, in fact, similar in magnitude in both the case subjects and the control subjects. First of all, elevated risks for SCC were seen only for occupational sun exposure 10 years prior to diagnosis and not for lifetime occupational exposure. Similarly, no elevated risks were seen with any aspect of recreational exposure. It seems unlikely that case subjects would have misclassified only their recent occupational exposure and not misclassified other types of solar exposure. Data for the study were collected during the period 1983 through 1985, before the general public was sensitized to the relationship between solar UV light and skin cancer. As well, since nonmelanocytic skin cancer is not regarded as life threatening, it seems likely that ruminant bias will be less pronounced than in other more fatal tumors. Finally, interviewers were blinded to the disease status of study

subjects to guard against the possibility that bias might arise during completion of the standardized etiologic interview.

The final concern is that the use of WBEs as the measure of exposure may itself alter the perceived relationship between solar exposure and SCC. Since most SCCs occur on constantly exposed anatomic sites, it is possible that incorporating whole-body clothing preferences may distort assessment of actual hours of solar exposure to the relevant tumor site. Data on specific anatomic locations of SCCs in this data set are lacking, however, and hence it was not possible to conduct sitespecific analyses.

It is noteworthy that, in the present study, no association was seen with lifetime cumulative solar exposure. Descriptive surveys have found an increase in the incidence of SCC with decreasing latitude, at least among North American populations¹³ suggesting that cumulative lifetime UV exposure was the etiologic factor of importance. In our data, the focus of effects seems to be on recent events in solar exposure history. Sunburn data also support the importance of recent solar exposure in that severe sunburn in the 10 years prior to diagnosis conferred a 2.5-fold increased risk of SCC. It is, of course, possible that the relationships with recent sunburn and solar exposure are due to more acute memory among case subjects than among control subjects of events just to diagnosis. However, no such similar relationships were seen in our study of basal cell carcinoma,¹ suggesting that these relationships with squamous cell carcinoma are not artifactual.

Early events, however, cannot be dismissed, particularly as the presence of two or more severe sunburns per year during childhood and adolescence appears to confer a 10-fold elevated risk of SCC.

Interestingly, for both recent (within the past 10 years) and lifetime recreational sun exposure, there is a suggestion of an inverse relationship with SCC. It is possible that this observed relationship may reflect the tendency of sun-sensitive individuals to avoid voluntary sun exposure. Such residual confounding may exist despite the control for host factors in the analysis of recreational sun exposure. However, subjects with outdoor jobs appear to be unable to avoid sun exposure and in the 10 years prior to diagnosis have significantly higher exposure than do subjects who do not develop SCC.

Evidence from other sources also implies that the appearance of SCC may be related to sunlight exposure just prior to diagnosis. Some actinic keratoses are known to be precursors of SCC.¹⁴ It has been demonstrated that recent sun exposure is important in the development of actinic keratoses,¹⁵ and that solar keratoses may themselves disappear without treatment in subjects who limit solar exposure.¹⁶ This suggests that the retention and progression of solar keratoses to malignancy requires continued exposure to relatively high doses of UV light. If this is true, it would be expected that subjects with SCC would demonstrate higher solar UV exposure in the years immediately prior to diagnosis than would subjects without SCC, as was the case in our data.

Finally, the quantitative study of nonmelanocytic skin cancer conducted by Strickland et al¹⁷ showed a relationship between predominantly occupational solar exposure and risk of SCC, although it must be noted that a significant proportion of the SCCs in that study were not histologically confirmed.¹⁸ Thus, it might be hypothesized that subjects at risk of SCC are those who are phenotypically sensitive to the sun (fair skin, red hair,

propensity to burn rather than tan in the sun), develop severe sunburns in childhood as initiating events in the sequence of development of a malignancy, and, finally, in the 10 years prior to diagnosis are under continuous chronic (occupational) sun exposure, which brings about malignant transformation, with or without the intermediate step of development of solar keratoses.

Results presented herein will require confirmation in other detailed studies, but they suggest that late-stage solar exposure may be important in accounting for SCC.

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Table 1. Pigmentary and Constitutional Factors and Risk of Squamous Cell Carcinoma*

Factors	No. of		OR		95% CI
	Case Subjects	Control Subjects†	Crude‡	Adjusted§	
Mother's ethnic origin					
Celtic/English/Scandinavian	122	215	1.0	1.0
Northern European	51	165	0.5	0.4	0.2-0.8
Southern European	7	26	0.5	0.4	0.1-1.9
			<i>P</i> =.002	<i>P</i> =.03	
Skin color					
Dark	8	37	1.0	1.0
Medium	49	150	1.4	1.2	0.5-3.0
Light	123	219	2.2	1.6	0.7-3.8
			<i>P</i> =.01	<i>P</i> =NS	
Hair color					
Black	12	25	1.0	1.0
Brown	69	174	0.9	0.8	0.3-1.8
Blond	79	198	0.8	0.6	0.3-1.5
Red	20	9	7.1	4.1	1.1-15.5
			<i>P</i> <.001	<i>P</i> =.005	
Skin reaction to first sun exposure					
Never burn	29	71	1.0	1.0
Burn after long exposure	37	125	0.7	0.7	0.4-1.2
Burn after short exposure	76	137	1.4	1.1	0.6-2.2
Usually burn	38	73	1.3	0.7	0.3-1.6
			<i>P</i> =.06	<i>P</i> =NS	
Skin reaction to 1-week sun exposure					
Tan without burning	58	155	1.0	1.0
Tan with protection	6	14	0.9	0.8	0.2-2.8
Burn then tan	77	193	1.1	0.9	0.5-1.5
Burn, never tan	39	43	2.3	1.6	0.8-3.5
			<i>P</i> =.02	<i>P</i> =NS	

*There were 180 male case subjects and 406 male control subjects. OR indicates odds ratios; CI, confidence interval; and NS, not significant.

†One control response missing for skin reaction to 1-week sun exposure.

‡Crude OR adjusted for age only.

§Odds ratios are adjusted for age and other pigmentary and phenotypic factors.

Table 2. Factors Combining Pigmentation, Sun Sensitivity, and Sun Exposure With Risk of Squamous Cell Carcinoma*

Factors	No. of		Adjusted OR†	95% CI
	Case Subjects	Control Subjects		
Freckling				
Absent	92	274	1.0
Present	88	132	1.6	1.0-2.4
			<i>P</i> =.06	
Sunburn history, age, 5-15 y				
Never burned	66	175	1.0
Rare or mild burns	27	86	0.8	0.5-1.6
Moderate burns	52	92	1.3	0.7-2.2
Frequent or severe burns	35	53	0.6	0.6-1.4
			<i>P</i> =NS	
Sunburn pain \geq 2 d; age, 5-15 y				
Never	150	375	1.0
Once per year	14	24	1.9	0.8-4.4
Twice or more per year	16	7	10.5	2.9-38.0
			<i>P</i> =.001	
Sunburn pain \geq 2 d; lifetime				
Never	121	291	1.0
Ever	59	115	1.2	0.8-1.8
			<i>P</i> =NS	
Sunburn pain \geq 2 d; last decade				
Never	172	393	1.0
Once or more per year	8	13	2.5	0.9-7.1
			<i>P</i> =.08	

*There were 180 male case subjects and 406 male control subjects; OR indicates odds ratios; CI, confidence interval; and NS, not significant.
 †Odds ratios adjusted for the effects of age, mother's ethnic origin, hair color, and skin color.

Table 3. Recreational, Occupational, and Cumulative Sunlight Exposure and Risk of Squamous Cell Carcinoma: 180 Male Case Subjects and 406 Male Control Subjects*

Factor	Category		No. of		Adjusted OR \ddagger	95% CI
	Annual WBE \dagger	Summer Hours \ddagger	Case Subjects	Control Subjects		
Mean recreational sun exposure per year (age, 0-19 y)	<100/y	<3.8 h/wk	52	97	1.0	...
	100-199	3.8-7.4	49	113	1.2	0.6-2.5
	200-332	7.5-12.4	36	101	1.1	0.5-2.6
	333+	12.5+	25	76	1.6	0.6-4.5
					<i>P</i> (trend)=NS	
Mean recreational sun exposure per year (lifetime)	<75/y	<2.8 h/wk	38	75	1.0	...
	75-149	2.8-5.5	43	106	0.6	0.3-1.1
	150-224	5.6-8.4	32	72	0.8	0.3-1.8
	225+	8.5+	23	73	0.3	0.1-0.9
					<i>P</i> (trend)=.09	
Mean recreational sun exposure per year (last 10 y)	<65/y	<2.4 h/wk	53	76	1.0	...
	65-119	2.4-4.4	29	99	0.4	0.2-0.7
	120-199	4.5-7.4	60	115	0.7	0.4-1.2
	200+	7.5+	25	83	0.4	0.2-0.7
					<i>P</i> (trend)=.06	
Mean occupational sun exposure per year (lifetime)	<15/y	3.5 h/wk	26	87	1.0	...
	15-59	3.5-13.9	36	105	0.8	0.3-2.0
	60-104	14.0-24.9	42	86	1.5	0.6-4.2
	105+	25.0+	76	128	1.4	0.4-4.3
					<i>P</i> (trend)=NS	
Mean occupational sun exposure per year (last 10 y)	0/y	0 h/wk	61	161	1.0	...
	1-29	<7.0	18	45	1.9	0.6-5.6
	30-99	7.0-22.9	46	113	2.2	0.8-6.4
	100+	23+	55	87	4.0	1.2-13.1
					<i>P</i> (trend)<.05	
Mean cumulative sun exposure per year (lifetime)	<120/y	<11.5 h/wk	32	85	1.0	...
	120-189	11.5-18.9	47	84	1.8	0.9-3.3
	190-279	19.0-27.9	35	90	1.2	0.6-2.3
	280+	28+	22	67	1.0	0.4-2.1
					<i>P</i> (trend)=NS	
Mean cumulative sun exposure per year (last 10 y)	<100/y	9.5 h/wk	41	107	1.0	...
	100-159	9.5-15.9	45	88	1.5	0.9-2.7
	160-239	16.0-23.9	43	78	1.7	0.9-3.1
	240+	24+	38	98	1.1	0.6-2.1
					<i>P</i> (trend)=NS	

*A total of 18 cases and 19 controls had missing values for childhood sun exposure. In addition, a further 26 cases and 61 controls were missing at least one decade of adult recreational exposure information and thus were excluded from the analysis of lifetime recreational sun exposure and lifetime cumulative exposure. WBE indicates whole-body equivalent; OR, odds ratios; CI, confidence interval; and NS, not significant.

\dagger One whole-body equivalent represents 1 h of sun exposure to the whole surface of the body.

\ddagger Typical hours of exposure per week during summer to achieve the WBE values shown were calculated using typical clothing for summer recreational activities and for summer occupational activities and for cumulative sun exposure as follows: recreational, T-shirt, shorts, no head covering; occupational, short sleeve shirt, half the time long pants, half the time shorts, no head covering; and cumulative, short sleeve shirt, half the time long pants, half the time shorts, no head covering.

\S Odds ratios adjusted for the effects of mother's ethnic origin, hair color, and skin color.

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