Sunlight Exposure, Pigmentary Factors and Risk of Nonmelanocytic Skin Cancer

I. Basal Cell Carcinoma

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Background and Design
Basal cell carcinoma (BCC) of the skin is the most common neoplasm in white populations, and solar radiation is generally accepted to be the dominant environmental risk factor for this disease. However, little information is available on the nature of the relationship between BCC and sunlight. The purpose of this study was to evaluate the nature of the relationship between sunlight exposure, pigmentary factors, and BCC of the skin. A population-based case-control study of 226 male patients with BCC diagnosed from January 1, 1983, through December 31, 1984, and 406 randomly selected male control subjects was conducted in Alberta, Canada. The study was conducted using a standardized questionnaire, administered in person by trained interviewers. Data were analyzed using conditional logistic regression methods.

Results
After controlling for other host and pigmentary factors, the risk of BCC was increased in subjects with light skin color and those who freckled in childhood. A history of severe sunburn in childhood also increased risk. Subjects of southern European ethnic origin were at significantly lower risk of BCC. Surprisingly, no association was seen between mean annual cumulative summer sunlight exposure and risk of BCC. A significantly increased risk of BCC was seen in subjects with increased recreational sunlight exposure in adolescence and childhood (age, 0 to 19 years), although an inverse relationship was seen with lifetime recreation exposure. The relationship with childhood sun exposure was most pronounced among sun-sensitive subjects whose skin tended to burn rather than tan in the sun.

Conclusions
The lack of association between cumulative sun exposure and BCC contradicts conventional wisdom about the cause of this tumor, and the increased risk with sun exposure at age 0 to 1.9 years suggests that childhood and adolescence may be critical periods for establishing adult risk for BCC.

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Basal cell carcinoma (BCC) of the skin is the most common malignancy seen among white populations in Europe, North America, and Australia, and sunlight exposure is generally accepted to be the most important environmental factor accounting for individual risk of this tumour.[1-3] Interest in the relationship between skin cancer and solar UV radiation has increased in recent years due to the substantial increases in incidence seen in both cutaneous melanoma [4-5] and nonmelanocytic skin cancer.[6,7] Projections of further increases in incidence of skin cancer due to depletion of stratospheric ozone and consequent increases of ground-level UV radiation have served to heighten interest in this issue.[8] With the exception of the studies conducted on Maryland watermen, [9] however, relatively little work has been done to evaluate the character and timing of sunlight exposure that is responsible for BCC risk.

In 1983 and 1984, a case-control study of risk factors for BCC and squamous cell skin cancer was conducted in Alberta, Canada. In this article, we report on the results for pigmentation, constitutional factors, and sunlight exposure in BCC.

Materials and Methods

Pathology reports on all newly diagnosed cases of BCC occurring in males in the province of Alberta during the period January 1, 1983, through December 31, 1984, were obtained from the Alberta Cancer Registry. We selected males only for cost reasons and because males were thought to offer a better opportunity to study the contribution of occupational sunlight exposure to BCC risk than would females. A selected group of patients (one in four with head and neck cancers and one in two with tumors at other body sites) aged 25 through 79 years at the time of diagnosis were considered age eligible for the study and were invited to participate.

The sample consisted of 14 BCC cases selected from a total of 1052 male BCCs diagnosed in the province during the period of 1983 through 1984, and of the 314, 6% could not be located, 13% refused to participate, and 9%were either deceased, too ill to participate, or study

personnel were refused physician permission to approach the patient. Successful etiologic interviews were completed with 72% (226) of the eligible subjects.

A randomly chosen male control series was selected from the Alberta Health Care Insurance Plan list of subscribers. This insurance plan covers virtually every member of the adult population of the province, the only exceptions being individuals who have been residents of Alberta for less than 3 months. The controls had no prior diagnosis of skin cancer as determined through the cancer registry, and were frequency matched to the patients within 5-year age groups. A total of 573 age-eligible controls were ascertained and 406 of these subjects submitted to an interview (71%).

Each patient and control was interviewed in his home by a trained interviewer using a standardized questionnaire similar to that used in the Western Canada Melanoma Study conducted several years prior [10-12] to the present study. Interviewers were not informed of the disease status of the subject prior to interview and were not informed of any study hypotheses.

The questionnaire evaluated each subject's propensity to burn on first exposure to summer sun (skin type), as well as degree of freckling, childhood and adult sunburn history, tanning history, outdoor recreation and vacation activities, and occupational history. Data on the place of birth and the ethnic status of both the mother and the father of each subject were also collected. Skin color was evaluated on both a sun-exposed site (dorsum of hand) and an unexposed site (upper inner arm) by comparing with a range of skin colors from light to dark as in the Western Canada Melanoma Study[10] Hair color was evaluated by direct comparison with wig makers' samples and where hair had changed color with age, subjects were asked to match their hair color at age 30 years with the samples. Eye color was recorded by the interviewer as blue, gray, green, hazel, or brown from direct observation. Each interview lasted approximately 1.5 hours, and interviews of all cases and controls were completed by June 1985.

The sunlight exposure history of each subject was examined using responses to questions on occupational and recreational activities, including vacations. A lifetime occupational history was taken recording each job of 6 months duration or more. For each occupation, the usual number of hours per week of outdoor work in summer and in winter was recorded. Summer was considered to include the months April through September and winter, the months October through March. Subjects were asked to detail the usual clothing worn by season while on the job from a card listing preferences for head covering and upper body and lower body clothing.
Recreational activities were assessed separately for summer and winter, for age 0 to 19 years, and then by decade up to age 79 years. Study subjects were handed a card describing four groups of activities delineated by the type of clothing worn. Group A included activities for which a bathing suit was normally worn, such as swimming or sunbathing; group B activities included those for which light clothing would be worn such as summer gardening, tennis, soccer;
group C represented recreational pursuits in which normal weight or heavier clothing might be worn such as fishing,
walking, and horseback riding; and group D activities were those conducted in snow and ice such as skiing, mountaineering, and skating. Subjects were asked about the number of hours per week and months per year in both summer and winter that they spent in each activity by decade.

Sunlight indexes were devised for both occupational and recreational sun exposure. The recreational index was developed by multiplying mean exposure hours per activity type for childhood and adolescence (age, 0 to 19 years) and each succeeding decade of life by proportion of the body exposed from the clothing preference questions. Exposure proportions ranged from a high of 89% for a subject wearing a bathing suit to a low of 3% (face only) for subjects wearing clothing suited to a group D activity such as skiing. The index was calculated separately for both summer and winter. The resulting measure, whole-body equivalents (WBEs) of exposure calculated per year, allowed meaningful comparison over a range of outdoor activities. The occupational index was developed in the same fashion from data on outdoor exposure while on the job, coupled with clothing preferences. As start and finish dates were available for each job, exposure figures were available by decade of life as with recreational solar exposure.

Because of the direct relationship between age and risk of BCC, subjects were age stratified into single-year categories and odds ratios were calculated using conditional methods. Odds ratios were calculated first for host pigmentation and skin type factors (skin, eye, hair color, propensity to burn). Following this, we evaluated risk factors that combined personal susceptibility and

sunshine exposure (such as freckling, tanning, and sunburn history) controlling for significant host factors, using conditional logistic regression techniques.

Mean annual recreational solar exposure in WBEs was analyzed for childhood and adolescence (age, 0 to 19 years), for the decade prior to diagnosis, and finally over lifetime using approximate exposure quartiles within the control group with the lowest quartile as the index for calculating odds ratios. Mean annual occupational sunlight exposure in WBEs was evaluated for the 10 years prior to diagnosis and for the whole of each subject's lifetime. Mean annual cumulative solar exposure was calculated by combining the recreational and occupational exposure for the same periods as occupational sun exposure. Odds ratios were calculated adjusting for skin and hair color and mother's ethnic origin but not for freckling, sunburn history, or tanning history, which were considered to already incorporate a component of solar exposure.

Results

Age-adjusted crude odds ratios for pigmentary and constitutional factors (Table I) showed significantly elevated risks for BCC among men who had a light skin color, red hair, and who tended to burn and not tan after sun exposure.

Although data on both the father's and the mother's ethnic origin were sought on the questionnaire, the data on the mother's origin were available on all subjects while that for the father's origin were frequently missing, Hence the mother's origin was used in the analysis. By comparison with subjects whose mothers were of Celtic, English, and Scandinavian origin, those with mothers of southern European ancestry were at significantly reduced risk of BCC. Although Celts, English, and Scandinavians are genetically different from each other, they were combined because their risk of BCC was similar, and each group was relatively small numerically. When all constitutional factors were examined using a multivariate model with each factor adjusted for the effects of other pigmentary and phenotype factors, only the mothers' ethnic origin, and skin color remained statistically significant, although a high relative risk was still seen for subjects with red hair.

Risk factors shown in Table 2 combine facets of subjects' pigmentary and constitutional characteristics with solar UV exposure. These factors were evaluated with control for subject pigmentary characteristics known to be associated with risk of BCC (skin color, mother's ethnic origin, hair color [red vs; other]), but not for sunlight exposure as freckling, sunburn, or suntan may in themselves be "skin level UV light dosimeters." [13-14] The presence of freckling in childhood increased the risk of later BCC even after adjustment for skin color, hair color, and mother's ethnic origin. Subjects who had frequent or severe burns in childhood had somewhat increased risk of BCC by comparison with those who do not recall ever having been sunburned. Sunburn history as an adult (by decade of life from age 20 years) showed no association with risk of BCC. Very severe sunburn in childhood defined as causing pain for 2 or more days after the burn showed a strong relationship to adult risk of BCC, with children recalling two or more such burns per year having a 4.6-fold risk of BCC. No association with very severe sunburn was seen in later decades of life, or in the 10-year period prior to diagnosis.

A tanning score was calculated for each subject by summing the degree of tan (no tan or little tan, 1; mild tan, 2; and deep tan, 3) over each body site (hands and face, trunk, upper limbs, and lower limbs) for the ages 0 to 19 years and for each decade of adult life. No association was seen between tanning score and risk of BCC.

Sunlight exposure was evaluated in a number of ways (Table 3). Mean WBEs per year of recreational sun exposure were examined within each decade of life, in the 10-year period prior to diagnosis, and in childhood and adolescence (age, 0 to 19 years). After adjustment for host factors (mother's ethnic origin. hair color, and skin color) only childhood exposure was significantly positively related to risk of BCC. Men who recorded more than 333 annual WBEs of sun exposure as children and adolescents had 2.6 times the risk of BCC compared with subjects who were minimally exposed. Mean annual lifetime recreational exposure to time of diagnosis in patients and time of interview in controls showed an inverse relationship with BCC risk with subjects having the most exposure being at only 40% of the risk of those in the lowest category. Approximate summer hours per week of solar exposure in typical clothing were calculated and included in Table 3. This measure is slightly different from the VVBE measure in that all exposure is assumed to take place in summer. Since less than 5% of total solar exposure in this population actually occurs in the winter, ascribing all exposure to summer does not violate the exposure data in any significant way and results in more

meaningful figures relating BCC risk to actual outdoor sunlight hours.

No elevated risks of BCC from occupational solar exposure were seen for any decade of employment, from age 20 years. Mean annual lifetime occupational exposure showed a slight gradient of risk from lowest to highest exposure, although this was not statistically significant. Cumulative sun exposure (lifetime mean annual exposure), comprising recreational plus occupational exposure combined, demonstrated no association with BCC.

Finally, because prior research in melanoma has indicated that the effect of sun exposure may be different among individuals who are sun sensitive as opposed to those who are not," we separated study subjects into "tanners" and "nontanners." Tanners were defined as those who, when exposed to 2 hours per day of sunlight over a week, "got a brown suntan without burning" plus those who "got a brown suntan with the aid of sunscreens." Nontanners were defined as subjects who "usually got some degree of burn followed by a tan" as well as those who "only burned." Exposure to recreational sunlight in childhood and adolescence (age, 0 to 19 years) produced a strong increase in risk only among nontanners (Table 4). Similarly, the inverse relationship between risk of BCC and mean annual lifetime recreational sun exposure was much stronger in the nontanners than in the tanners.

Finally, separation of the sun-sensitive and sun-resistant subjects suggested a gradient of risk for BCC with mean lifetime cumulative sun exposure among the sun-resistant tanners. It should be noted, however, that this effect was not statistically significant. Separation of tanners and nontanners produced no findings of interest for occupational sun exposure.

Comment

Results of this study suggest that childhood sunlight exposure may be important in accounting for adult risk of BCC. The data, however, should be interpreted with caution. In a study in which older subjects were asked to recall events many years in the past, there was a potential for substantial exposure misclassification. This was particularly true for sunlight exposure, as it was not possible to use models and milestones to aid subjects in estimating exposure as can be done with, for instance, dietary or reproductive histories. On the other hand, provided the misclassification occurs with equal prevalence among patients and controls, the net effect is to make it more difficult to detect a relationship between sunlight and cancer. This should render the findings of the study relatively conservative by underestimating risks associated with exposure differences. There are good reasons for believing that the degree of misclassification does not differ between patients and controls. An elevated risk of BCC was seen only with childhood sun exposure and not with recreational activities in other decades of life. Furthermore, no association was seen overall with occupational solar exposure. It is extremely unlikely that patients would have misclassified their childhood recreational exposure and not misclassified exposure of other types and during other periods of life. Data for the study were collected from 1983 through 1985, before members of the general public and, especially, patients with skin cancer became highly sensitized to the potential effects of sunlight. In addition, interviewers were blinded to the disease status of study subjects to guard against the possibility of bias arising during questioning.

The final concern in interpreting findings is the use of the WBE measure for assessing sunshine exposure. This measure takes into consideration upper body, lower body, and head and neck clothing preferences of each subject. However, many BCCs occur on exposed sites and, hence, incorporating whole-body clothing preferences may actually provide a distorted assessment of solar exposure to the actual relevant anatomic site. Unfortunately, specific anatomic site information for BCCs was unavailable for cases, and site specific analyses could not be conducted. However, this same method of analysis was used in the Western Canada Melanoma study in which very good information was available on anatomic site of the melanoma. Analyses of clothing preferences for that study demonstrated that, by and large, for equivalent outdoor activities, individual subjects had historically very similar clothing preferences giving similar sunlight dosages to a given body site. Alberta was one of the four provinces participating in the Western Canada Melanoma study and, thus, for the present investigation, conducted only 3 years after the melanoma study, subjects would be most likely to again demonstrate relatively uniform clothing preferences for given outdoor activities.

The increased risk of BCC in subjects with light skin seen in the present study is similar in character to that shown in several previous studies.[16, 17] Southern European ancestry has been reported to be an independent factor protective against BCC,[18] and the results from the present investigation appear to confirm this. Light hair color has

been shown to increase risk in several investigations, with red-haired individuals being at highest risk.[18, 19] In the study of Kricker et al,[18] as in the present study, hair color did not remain an independent predictor of risk when other factors were accounted for.
The association with freckling is important not only because it has been seen in another study of BCC[18] but also because it is a well-established risk factor for melanoma [10,20] and may be a marker for UV light damage to the skin. The fact that sunburn in childhood and in particular severe sunburn substantially increased risk of later BCC and no such effect was seen for adult sunburn suggests that skin may be more sensitive in childhood to initiation events that eventually lead to malignancy. Again, a similar relationship has been detected for malignant melanoma .[21]

The most notable findings in this study were the association between BCC and recreational sunlight exposure in childhood and adolescence coupled with the lack of relationship between cumulative sunlight exposure and BCC. The lack of association with both mean annual occupational sunlight exposure and mean cumulative exposure is somewhat surprising as skin cancer surveys have consistently demonstrated increasing incidence rates of BCC with decreasing latitude among white populations. Although these studies could never assess more than potential exposure at the population level, conventional wisdom suggested that lifetime cumulative solar exposure was the measure of importance. In the present study this proved not to be the case. The study of Strickland et al[22] that assessed UVB exposure quantitatively among individual Maryland watermen also failed to detect an association with cumulative solar exposure, although it should be noted that some 25% of BCCs included in that study were not histologically confirmed.

The relationship between solar exposure in childhood and adolescence is broadly similar to that seen in the Geraldton2' investigation that showed that subjects who arrive in Australia after age 10 years (presumably from less sunny climates) have a significantly lower risk for BCC as adults. Of course, it is possible that, among these immigrants, late arrival simply delays onset of BCC until later in life due to lack of accumulation of sufficient UV insult; however, the Australian study also failed to detect a significant relationship between cumulative adult solar exposure among native-born Australians casting doubt on such an interpretation.

The inverse relationship between lifetime recreational solar exposure and risk of BCC is puzzling. Both the positive association with childhood exposure and the inverse association with lifetime exposure were seen primarily in the nontanners. This indicates that there may be confounding in the sunlight analyses that is not well controlled by the simple measures of pigmentation and ethnic origin used in our study. If this is so, the explanation for the inverse relationship may be that sun-sensitive case patients not identified by ethnic origin, hair, and skin color substantially decrease recreational sun exposure as adults due to unpleasant experience with sunburn early in life.
Separating the tanners from the nontanners suggested a gradient of BCC risk among tanners with increasing mean cumulative summer sun exposure. Although not statistically significant, this gradient indicates that even among those with sun-resistant skin, individual capacity to repair solar UV-induced damage may eventually be overwhelmed.

The findings from this study will require confirmation, but they suggest that, particularly among subjects with sun-sensitive skin, timing and character of solar exposure may be more important than cumulative dose in predicting adult BCC risk. By extension, among sensitive individuals, sun-avoidance behavior in adulthood may not markedly reduce risk for this tumor.

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

Factors	Category	No. of Cases	No. of Controls†	Odds Ratio		95% Confidence Interval
				Crude‡	Adjusted§	
Mother's ethnic origin	Celtic/English/Scandinavian	151	215	1.0	1.0	
	Northern European	67	165	0.6	0.5	0.3, 0.8
	Southern European	8	26	0.4	0.5	0.1, 2.2
				P=.004	P=.02	
Skin color	Dark	5	37	1.0	1.0	
	Medium	88	150	5.3	4.8	1.7, 13.6
	Light	133	219	5.1	4.0	1.4, 11.3
				P<.001	P<.005	
Eye color	Brown	36	88	1.0	1.0	
	Hazel	40	59	1.8	1.7	0.9, 3.1
	Green, gray	20	43	1.2	1.1	0.6, 2.3
	Blue	130	216	1.6	1.4	0.8, 2.4
				P=NS	P=NS	
Hair color	Black	13	25	1.0	1.0	
	Brown	88	174	0.8	0.6	0.3, 1.4
	Blond	102	198	0.9	0.6	0.3, 1.4
	Red	22	9	3.6	2.1	0.7, 2.2
				P=.04	P=NS	
Skin reaction to first sun exposure	Never burn	33	71	1.0	1.0	
	Burn after long exposure	56	125	0.9	0.7	0.4, 1.3
	Burn after short exposure	81	137	1.1	0.8	0.4, 1.5
	Usually burn	56	73	1.4	0.9	0.4, 1.9
				P=NS	P=NS	
Skin reaction to 1 wk of exposure	Tan without burning	72	155	1.0	1.0	
	Tan with protection	9	14	1.1	1.1	0.4, 3.3
	Burn, then tan	100	193	1.0	0.9	0.6, 1.5
	Burn, never tan	45	43	2.1	1.6	0.8, 3.2
				P=.03	P=NS	

*There were 226 male patients and 406 male controls.
†One control response missing for skin reaction to 1 week's sun exposure.
‡Crude odds ratios adjusted for age only.

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

Factor	Category	No. of Cases	No. of Controls	Adjusted Odds Ratio†	95% Confidence Interval
Freckling (age, 5-15 y)	Absent	100	274	1.0	
	Present	126	132	1.8	1.2, 2.5
				P=.002	
Sunburn (age, 5-15 y)	Never burned	77	175	1.0	
	Rare or mild burns	29	86	0.8	0.5, 1.4
	Moderate burns	68	92	1.3	0.8, 2.1
	Frequent or severe burns	25	53	1.6	1.0, 2.7
				P=.05	
Sunburn pain ≥2 d (age, 5-15 y)	Never	188	375	1.0	
	Once per year	22	24	1.7	0.9, 3.4
	2+ per year	16	7	4.5	1.7, 12.3
				P<.001	
Tanning (age, 0-19 y)	Little or no tan	67	122	1.0	
	Moderate tan	90	176	1.1	0.7, 1.7
	Dark tan	69	108	1.5	0.9, 2.4
				P=NS	
Sunburn pain ≥2 d (lifetime)	Never	160	291	1.0	
	Ever	66	115	0.9	0.6, 1.3
				P=NS	
Sunburn pain ≥2 d (last decade)	No	214	398	1.0	
	Yes	12	8	2.3	0.8, 6.6
				P=NS	
Mean lifetime tanning score (by decade over life)	Little or no tan	76	146	1.0	
	Moderate tan	95	170	1.2	0.8, 1.8
	Dark tan	55	90	1.4	0.9, 2.3
				P=NS	
Tanning score (last decade)	Little or no tan	106	163	1.0	
	Moderate tan	71	159	0.7	0.4, 1.0
	Dark tan	49	84	1.0	0.6, 1.7
				P=NS	

*There were 226 male patients and 406 male control patients.
†Odds ratios adjusted for effects of age, mother's ethnic origin, skin color, and hair color.

Table 3. Recreational, Occupational, and Cumulative Sunlight Exposure and Risk of Basal Cell Carcinoma*

Factor	Category: Annual WBE†	Category: Summer Hours‡	No. of Cases	No. of Controls§	Adjusted Odds Ratio‖	95% Confidence Interval
Mean recreational sun exposure per year (age, 0-19 y)	<100/y	<3.8 h/wk	49	97	1.0	
	100-199	3.8-7.4	56	113	1.1	0.6, 2.0
	200-332	7.5-12.4	54	101	1.4	0.7, 3.0
	333+	12.5+	57	76	2.6	1.1, 6.5
					P(trend)=.03	
Mean recreational sun exposure per year (lifetime)	<75/y	<2.8 h/wk	47	75	1.0	
	75-149	2.8-5.5	65	106	0.9	0.5, 1.7
	150-224	5.6-8.4	42	72	0.6	0.3, 1.3
	225+	8.5+	32	73	0.4	0.2, 1.0
					P(trend)=.03	
Mean occupational sun exposure per year (lifetime)	<15/y	<3.5 h/wk	56	87	1.0	
	15-59	3.5-13.9	56	105	1.0	0.6, 1.8
	60-104	14.0-24.9	46	86	1.3	0.8, 2.3
	105+	25+	68	128	1.4	0.8, 2.4
					P(trend)=NS	
Mean cumulative sun exposure per year (lifetime)	<120/y	<11.5 h/wk	45	85	1.0	
	120-189	11.5-18.9	51	84	1.3	0.8, 2.2
	190-279	19.0-27.9	52	90	1.2	0.7, 2.2
	280+	28+	38	67	1.3	0.7, 2.4
					P(trend)=NS	

**There were 226 male patients and 406 male controls.*

†One whole-body equivalent (WBE) represents 1 hour of sun exposure to the whole surface of the body.

‡Hours of exposure per week during the summer were calculated from the WBE values using typical clothing for summer beach (recreational) activities and for summer on-the-job (occupational) activities and for cumulative sun exposure as follows: (1) recreational, T-shirt, shorts, no head covering; (2) occupational, short-sleeve shirt, long pants, no head covering; and (3) cumulative, short-sleeve shirt, half-time long pants, half-time shorts, and no head covering.

§A total of 10 patients and 19 controls had missing values for childhood sun exposure. In addition, 30 patients and 61 controls were missing values for at least one decade of recreational exposure and thus were eliminated from the calculation of mean lifetime recreational sun exposure.

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

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