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Pigmentation and skin reaction to sun as risk factors for cutaneous melanoma: Western Canada Melanoma Study

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Abstract

Between 1 April 1979 and 31 March 1981, 904 residents of the four western provinces of Canada (population 6.5 million), were diagnosed as suffering from primary cutaneous malignant melanoma. Of 801 patients aged 20-79 years, 665 (83%) were interviewed along with control subjects chosen at random from the general population and matched for age, sex, and province. After exclusion of 70 subjects with lentigo maligna or acral lentiginous melanoma, comparisons of the 595 case-control pairs showed that light hair, skin, and eye colour, a history of heavy freckling in adolescence, and a tendency to burn readily and tan poorly in the sun were significant risk factors for melanoma. The strongest primary associations were with blond hair (relative risk 7.1 compared with black hair), light colour of unexposed skin (relative risk 2.4), and severe freckling (relative risk 2.1). These associations were independent of ethnic origin and of recorded amount of exposure to the sun and were somewhat stronger for superficial spreading than for nodular melanoma.

This study is the largest and most detailed of an incident series of melanomas to be published to date. The results were consistent with other studies reporting associations between melanoma and poor tanning ability, a tendency to burn easily, and a history of sunburn and showed that light hair colour was the strongest risk factor for the disease.

Introduction

Malignant melanoma is of concern because of the rapid increases in incidence and mortality rates which have been seen in almost all white populations with available data, including Canada, the United States, Australia, the United Kingdom, and several other European countries.¹⁻⁵ In Canada mortality rates doubled in a recent 15 year period, making melanoma one of the most rapidly increasing tumours.¹ The incidence of melanoma and mortality of the disease increase with decreasing latitude in Australia, in the North American continent, and within England and Wales, although in Europe the geographical pattern is more complex because of ethnic and social factors.^{4 6-9} Patients with melanoma reportedly tend to have lighter complexion, hair, and eye colour,¹⁰⁻¹³ although the early studies that documented these features were limited in that the groups of subjects with whom patients with melanoma were compared were either undefined or included patients with other skin complaints and non-melanomatous skin cancer. While two more recent case-control studies showed such differences in pigmentation,^{14 15} two others showed no major differences.^{16 17}

Our report is the first from the Western Canada Melanoma Study; 904 incident cases of primary cutaneous melanoma were ascertained, representing all new diagnoses for a continuous geographical area with a population of 6.5 million. Each subject interviewed was matched with a control subject chosen from the general population, and a detailed interview was carried out in the subject's home. This report is based on 595 subjects aged 20-79 years with superficial spreading or nodular melanoma and their matched controls and examines the characteristics of pigmentation and reaction of the skin to sun.

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Subjects and methods

Reports on all histologically confirmed cases of malignant melanoma newly diagnosed in Western Canada (Manitoba, Saskatchewan, Alberta, and British Columbia) during 1 April 1979 to 31 March 1981 were obtained through the treatment centres and cancer registries of each of the four provinces and patients aged 20-79 years interviewed. Each eligible patient was matched for sex and age (± 2 years) and by province of residence with a control subject. Controls were selected at random from medical insurance plan lists of subscribers, which include virtually the entire adult population of each province. Patients and controls were interviewed in their homes by trained interviewers using a standardised questionnaire. Information was obtained concerning host factors, history of places of residence, occupation, recreational and vocational habits with specific reference to outdoor exposure, medical history, chronic drug use, family history, certain aspects of diet, and, for women, reproductive history and use of oral contraceptives and oestrogenic drugs.

Colour of skin and hair was determined by direct comparison with samples made up specially for the project. Skin colour was evaluated twice, on an area not exposed to the sun (upper inner arms) and an area exposed to the sun (dorsum of hands). Eye colour was recorded directly by the interviewer from observation. Sensitivity to sunburning and tanning as an adult and in childhood was recorded, as well as the amount of freckling in childhood. Patients were also asked to indicate the colour of their hair during childhood using the hair samples.

For each patient a standardised abstract of the medical record was made and pathological slides reviewed in a standardised manner by one of two pathologists (Dr A Worth, Dr W S Wood) at the Cancer Control Agency of British Columbia. Material for review could not be obtained for 121 (20%) of the patients, and for these the original pathology report was used.

In the two year period 904 patients with newly diagnosed first primary cutaneous melanomas were registered, of whom 801 were aged 20-79 years. Of these, 665 (83%) were interviewed along with a matched control. Of those not interviewed, 21 had died and 40 were not located. In 21 cases the patient's physician thought that an interview would be inappropriate, and the remaining 54 subjects declined to take part. Of the 665 subjects who were interviewed, 56 had lentigo maligna melanoma and 14 acral lentiginous melanoma. Since the clinical and epidemiological features of these subtypes are apparently quite different from other melanomas,^{18,19} this analysis is restricted to the remaining 595 subjects; of these, 415 had superficial spreading melanoma, 128 nodular melanoma, 23 unclassified melanomas, and 29 borderline melanomas.

In Manitoba, Saskatchewan, and Alberta the study coordinators were allowed access to the provincial microfiche listing of medical plan subscribers, and subjects selected as potential controls were then telephoned to request their cooperation; 59% of those contacted agreed to participate. In British Columbia a letter requesting participation was sent out by the government Medical Services Commission and subjects had to send back a completed consent form; no telephone contact was used. This gave a response rate of 48%.

The present report deals primarily with host factors. For hair colour, subjects whose hair had changed colour gave information on their hair colour in childhood, and this information was used after an adjustment based on the usual trend to dark hair colour in adult life compared with childhood seen in the data for all subjects with a natural adult hair colour. Crude associations were based on matched pair odds ratios as an estimate of relative risk. To adjust for other factors a multiple logistic model based on matched pairs was fitted using the generalised linear interactive modelling procedure.^{20,21} Statistically significant results were those where the two sided p value was less than 0.05, based on the change in log likelihood for the multivariate model.

Differences in risks for different subgroups were investigated by extending the model using interaction terms between risk and subgroup factors. This provided risk estimates for the subgroups, and the significance of the gain in precision of this extended model compared with the simple model with common risks for all subgroups was assessed from the change in log likelihood.

Results

Pigmentation—Significant differences were seen between cases and controls for hair colour, colour of unexposed skin on the inner aspect of the upper arm, and for eye colour, the patients with melanoma having lighter colouring. The relative risks were 9.7 for blond compared with black hair, 3.4 for light compared with dark skin, and 1.6 for blue compared with brown eyes (table I); each of these factors considered alone was statistically significant. After adjustment of each factor for the others and for other factors to be described, blond hair was associated with a relative risk of 7.1 compared with black hair, with a regular trend in risk over intermediate colours being seen ($p < 0.001$). Light inner arm skin colour compared with dark had a relative risk of 2.4 ($p < 0.05$). The increased risk in blue eyed compared with brown eyed subjects was small and non-significant after adjustment for hair and skin colour (relative risk 1.2).

TABLE I—Associations between pigmentation factors, sun reaction and sunburn, and ethnic origin and risk of malignant melanoma; 595 patients* with cutaneous melanoma, excluding lentigo maligna, and population based matched controls

Factor	Category	Cases (%)	Controls (%)	Relative risk, crude†	Relative risk, adjusted (95% limits)‡
Hair colour	Black	3	8	1.0(R)§	1.0(R)
	Dark brown	39	44	2.6	2.5 (2.0, 3.0)
	Brown	41	38	3.4	2.8 (1.5, 5.2)
	Light brown and red	13	8	5.0	3.7 (1.8, 7.7)
	Blond	5	2	9.7	7.1 (2.6, 19.2)
			$\chi^2 = 36.1$; $p < 0.001$	$\chi^2 = 20.3$; $p < 0.001$	
Skin colour	Dark	2	6	1.0(R)	1.0(R)
	Medium	28	35	2.2	1.9 (0.9, 4.2)
	Light	70	60	3.4	2.4 (1.1, 5.2)
			$\chi^2 = 20.4$; $p < 0.001$	$\chi^2 = 6.8$; $p < 0.05$	
Eye colour	Brown	19	27	1.0(R)	1.0(R)
	Grey, green, hazel	27	27	1.4	1.1 (0.8, 1.6)
	Blue	54	46	1.6	1.2 (0.9, 1.7)
			$\chi^2 = 11.2$; $p < 0.01$	$\chi^2 = 4.3$; NS	
Freckles in adolescence	None	45	60	1.0(R)	1.0(R)
	Few	13	13	1.3	1.3 (0.9, 1.9)
	Some	21	18	1.6	1.4 (1.0, 1.9)
	Many	21	10	2.6	2.1 (1.4, 3.1)
				$\chi^2 = 34.4$; $p < 0.001$	$\chi^2 = 25.1$; $p < 0.001$
Sun reaction	Tan, no burn	31	47	1.0(R)	1.0(R)
	Tan with protection	13	10	2.0	1.8 (1.2, 2.7)
	Burn then tan	42	34	1.9	1.5 (1.1, 2.0)
	Burn only	14	10	2.3	1.7 (1.0, 2.6)
			$\chi^2 = 31.3$; $p < 0.001$	$\chi^2 = 12.4$; $p < 0.01$	
Childhood sunburn	Rare or mild	24	15	1.0(R)	1.0(R)
	Moderate or infrequent	27	25	1.4	1.1 (0.8, 1.6)
	Severe or frequent	49	60	1.9	1.3 (0.9, 1.8)
			$\chi^2 = 17.4$; $p < 0.001$	$\chi^2 = 1.8$; NS	
Ethnic origin	English	40	33	1.0(R)	1.0(R)
	Celt, Scandinavian	19	19	0.9	0.7 (0.5, 1.1)
	West European	14	18	0.7	0.7 (0.5, 1.0)
	East or south European	5	10	0.5	0.6 (0.4, 1.0)
	Other	21	20	0.9	1.1 (0.7, 1.5)
			$\chi^2 = 13.7$; $p < 0.01$	$\chi^2 = 9.5$; $p < 0.05$	

* Of the 595 case-control pairs, 12 were excluded from multivariate analysis because of missing information.

† Unadjusted relative risk, based on matched pairs, and p value.

‡ Relative risk, adjusted for other factors shown by matched logistic analysis, and p value.

§ R = Reference group.

Freckles in adolescence—Subjects who reported that in childhood and adolescence (age 5-15) they had had a "great many obvious freckles, noticed by most people" on the face showed a crude relative risk of 2.6 and a relative risk of 2.1 ($p < 0.001$) after adjustment for other factors, while lesser degrees of freckling were associated with lower risks.

Reaction to sun and sunburn—Subjects were asked how they tended to react to strong sunlight (a) for the first time each summer and (b) after a few days' exposure. The results for the two questions were similar, with those for a few days' exposure being the stronger. Compared with subjects who would "usually get a brown suntan without burning," those who would "only get sunburn and rarely get a tan" showed a crude relative risk of 2.3; however, after adjustment for pigmentation characteristics this fell to 1.7 ($p < 0.01$). A history of severe or frequent sunburns in childhood showed a crude relative risk of 1.9, but this became smaller (1.3) and non-significant after adjustment for pigmentation factors.

Ethnic origin—Questions on ethnic origin were included, as this is related to pigmentation. The strongest association was the low risk (0.5) in subjects of east or south European origin compared with those of English origin. The associations were, however, little changed by adjustment for other factors, the differences remaining significant ($p < 0.05$). Inclusion of ethnic origin did not substantially change the associations seen with pigmentation factors or freckling.

Discussion

These results apply to four sets of variables that are important in melanoma—pigmentation, freckles, reaction to sun, and ethnic origin.

Of the pigmentation variables, hair colour showed the strongest associations, while light colouring of usually unexposed skin had a small additional risk. These associations were somewhat stronger for patients with superficial spreading melanoma. The greater risk in fair haired and fair skinned subjects seen in this white population accorded with the large differences between white populations and black and oriental populations in risk of melanoma²²; subjects with less melanocyte based pigmentation had a higher risk of melanoma. Blue eyes was a substantial risk factor considered alone, but the association was almost completely explained by colour of hair and skin. Several early studies gave results consistent with these, although those studies used undefined or unsatisfactory groups for comparison—for example, patients with other skin cancers or diseases.¹⁰⁻¹³ Two more recent studies used population based controls and gave similar results,^{14 15} while two other studies showed no differences in pigmentation—namely, a Norwegian study

TABLE II—Relative risks for pigmentation and sun reaction after adjustment for other factors listed for subjects with melanoma classified by subtype and primary site

Subgroup	Subtype*		Subsite†				
	Superficial spreading melanoma	Nodular melanoma	Head and neck	Trunk	Arm	Leg	
No of cases	412	127	83	191	132	175	
Hair colour	Black	1.0	1.0	1.0	1.0	1.0	
	Dark brown	2.9	1.4	1.1	3.8	2.1	2.7
	Brown	3.3	1.3	1.4	3.0	2.9	2.7
	Light brown and red	4.1	2.6	0.6	6.8	3.2	3.6
	Blond	9.3	3.7	1.3	6.9	†	8.5
Skin colour	Dark	1.0	1.0	1.0	1.0	1.0	1.0
	Medium	2.2	1.1	2.2	3.9	1.1	1.0
	Light	2.4	1.9	3.0	3.1	1.2	1.9
Freckles	None	1.0	1.0	1.0	1.0	1.0	1.0
	Few	1.3	0.6	0.4	1.9	1.9	1.0
	Some	1.5	1.1	1.8	1.4	1.7	1.0
	Many	2.1	1.9	2.9	2.2	2.1	1.9
Sun reaction	Tan, no burn	1.0	1.0	1.0	1.0	1.0	1.0
	Tan, if protected	1.6	2.0	0.9	1.6	1.7	2.1
	Burn then tan	1.4	1.5	1.4	1.1	1.9	1.8
	Burn only	1.4	1.3	7.6	0.6	1.4	2.1

* Excluded are four cases with missing data and 46 with unclassified or borderline melanoma.

† Excluded are four cases with missing data, four axillary and three subungual tumours, and three with no precise site recorded.

‡ Insufficient data.

Type of tumour, primary site, sex, age, and province—Analyses were performed separately for the 415 subjects with superficial spreading melanoma and 128 subjects with nodular melanoma (table II). While the associations with hair and skin colour appeared to be weaker for nodular than for superficial spreading melanoma, the differences between the risks for the two subtypes were not statistically significant for any variable. This analysis was repeated using only subjects on whom pathological review had been completed, with no substantial differences in the results. Analysis by primary site similarly showed no statistically significant differences between sites in their associations with any of the factors studied, although tumours of the head and neck showed a weaker relation with hair colour and a stronger one with sun reaction compared with tumours of other sites. Analyses subdivided by sex, age, and province of residence showed no significant or substantial differences.

Adjustment for recorded exposure to sun—The questionnaire included extensive questions on occupation, regular recreational activities, and vacations, with particular attention given to outdoor exposure in terms of time, place, activities, and clothing. Estimates of ultraviolet exposure over the last decade and at each decade of life were made, which will be reported in detail elsewhere. The analyses for host factors were repeated, including the ultraviolet estimates in the model, thus adjusting for differences in estimated ultraviolet exposure, and also within broad categories of extent of exposure. The factors described were not substantially changed in terms of risk or statistical significance by these adjustments.

comparing 78 patients suffering from melanoma with 131 controls with cancers of sites other than skin,¹⁶ and a study in Scotland comparing 113 patients with melanoma with an undefined control group.¹⁷ These negative results may have been due to a combination of small numbers and the degree of homogeneity of the source populations.

An association with freckling would be expected, as freckles and light skin colour occur together.²³ The risk associated with heavy freckling in adolescence, however, changed little when adjusted for other pigmentation factors and so was an independent risk factor. No other studies have used this question, but Beral *et al* found that women in Sydney, Australia, with melanoma reported more naevi currently present than did comparison subjects and reported a greater tendency to develop visible naevi after exposure to sunlight.¹⁶ In Norway, Klepp and Magnus also reported that their patients developed freckles more easily than did the controls.¹⁵ This direct relation between melanoma and freckling suggests that freckles, or naevi, have an important role in pathogenesis. The ultrastructure of nodular and superficial spreading melanoma is similar to that of naevus cells, while that of lentigo maligna melanoma more closely resembles normal melanocytes.²⁴ Our results are consistent with the hypothesis that superficial spreading and nodular melanomas

develop from naevi^{25 26} and suggest that superficial spreading and nodular melanoma have similar relations to characteristics of pigmentation.

Our data are consistent with other studies showing associations between melanoma and poor tanning ability, a tendency to burn easily on unaccustomed exposure, and a history of sunburn.^{10 16 17 27} Most of the association with poor tanning ability is indirect and due to the primary associations of risk of melanoma with pigmentation and freckles, these characteristics themselves being linked to poor tolerance of the sun. In terms of sunburn history in childhood, this suggests that rather than the occurrence of sunburn itself increasing the risk of melanoma, the risk is due to the characteristics of pigmentation associated with poor sun tolerance.

The Canadian population comprised mainly European immigrants of diverse ethnic origins. The data show no evidence that subjects of Irish, Scottish, or Welsh origin had a higher risk than those of English origin, while they do show a lower risk in those of east or south European origin; the main countries represented were Czechoslovakia, Hungary, Poland, and Italy.^{5 9} This accords with the relatively low incidence and mortality rates reported in those countries.

In further analyses we shall explore in more detail the relations of melanoma to reported exposure to sunlight, to occupational factors, to ethnic origin and family history, and to other factors such as drugs and diet. Plainly, however, the strong relations with these host factors reported here are not substantially changed by including measures of sun exposure or ethnic origin in the analysis.

Our study is the largest and most detailed analytical study of an incident series of melanomas published to date and uses a general population comparison group of subjects. This first report shows that light pigmentation, a history of obvious freckles in adolescence, a tendency to burn easily and tan poorly, and a history of frequent sunburn in childhood are all risk factors for melanoma in white subjects and are independent of ethnic origin. Light hair pigmentation is the strongest of these factors.

This paper was prepared on behalf of the Western Canada Melanoma Study. Participants in the study include: (co-ordinators) J Birdsell, M Grace, S Kemel, M Leinweber, and D Robson; (pathologists) W S Wood and A Worth; (consultants) A J Coldman, M L Jerry, J A H Lee, D McLean, A B Miller, P Rebbeck, and H K B Silver; (analysis) J Moody and I D Turner; and (secretaries) K Anderson and J Gilbert.

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ONE HUNDRED YEARS AGO The following authenticated particulars of the case of the man named Pugh, who, whilst out with a hunting-party, encamped near Alexandretta, Syria, was bitten by a panther, and died a few weeks after his return to England, has been forwarded to us by Dr. Druce J. Slater. It appears that on January 17th, whilst the party was out after small game, one of the spaniels was heard to cry, as though held by a thorn. Pugh, who was in charge of the dogs, advanced towards the dog, when a panther, which had probably fascinated the little animal, sprang from some long grass upon Pugh, bit him severely in the left arm, near the elbow, inflicting four ugly lacerated wounds and a fracture of the radius, and throwing him to the ground. One of the beaters attacked the brute with his stick, and the spaniel, having overcome his fear also sprang at him, whereupon the panther made off, receiving in his retreat a charge of No. 7 shot in his shoulder, which, unfortunately, was not enough to stop him. Dr. Slater, as the doctor of the party, conveyed Pugh back to camp, and dressed his wounds with carbolic lotion. Inflammation set in, but was subdued by linseed-poultices. Some days later he had to enlarge one of the wounds, which was in the bend of the elbow, to allow the sloughs to escape. The patient went on well, and by March 18th, when he arrived in England, the wounds had healed, the bone united, and passive motion had improved the mobility of the joint. As there was still considerable stiffness, Mr. Willett saw the patient, and offered to take him into St. Bartholomew's, and break down the adhesions by manipulation. Pugh went to his home near Canterbury, and a day or two afterwards took cold. In the following week, Dr. Slater found him suffering from acute pneumonia. He was being attended by Mr. Hamilton of Chilham, but, in spite of that gentleman's care, he died on April 8th. The pneumonia was accompanied by delirium, and both Dr. Slater and Mr. Hamilton concur that the cause of death was not hydrophobia, as has been stated. But, interesting pathologically as such a case of hydrophobic poisoning would have been, the facts of the case do not, Dr. Slater says, warrant any association of the bite with the death. (*British Medical Journal* 1884;**ii**:917.)