Use of host factors to identify people at high risk for cutaneous malignant melanoma

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Objective: To determine which host characteristics are risk factors for cutaneous malignant melanoma in order to aim prevention and early detection programs at people at high risk.
Design: Case-control study.
Setting: Southern Ontario.
Subjects: The 583 case subjects were aged 20 to 69 years and had had malignant melanoma newly diagnosed between Oct. 1, 1984, and Sept. 30, 1986. The 608 control subjects were randomly selected from a list of residents in the study area and were stratum matched for age, sex and municipality.
Intervention: Through in-person interviews the interviewer ascertained exposure to putative external risk factors and assessed skin colour and number of nevi on the arm, and the subject reported his or her natural hair colour at age 20 years, eye colour, skin reaction to repeated sun exposure, and freckle and whole-body nevus densities.
Results: Although all the host factors mentioned were significantly associated with melanoma risk when considered separately, only hair colour, skin reaction to repeated sun exposure, and self-reported freckle and nevus densities remained significant after backward logistic regression analysis. The odds ratio for melanoma was estimated to be 10.7 in people who had many nevi compared with those who had none (95% confidence interval [CI] 6.6 to 17.4), 4.0 in people who had red hair compared with those who had black hair (95% CI 1.9 to 8.2), 1.9 in people who had many freckles compared with those who had none or few (95% CI 1.3 to 2.8) and 1.8 in people who burned after repeated sun exposure compared with those who tanned (95% CI 1.3 to 2.5).
Conclusions: Four risk factors for malignant melanoma have been identified. Prospective evaluation of their predictive value should be done. In the meantime, however, these factors should be used to identify people apparently at high risk for malignant melanoma, who can then be targeted for early detection and prevention programs.

Objectif : Déterminer quelles caractéristiques des hôtes sont des facteurs de risque de mélanome malin de la peau afin d'axer les programmes de prévention et de dépistage hâtif sur les personnes à risque élevé.
Conception : Étude cas-témoins.
Contexte : Sud de l'Ontario.

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Sujets : Les 583 sujets étudiés étaient âgés de 20 à 69 ans, et ils étaient atteints de mélanome malin de diagnostic récent, c'est-à-dire entre le 1er octobre 1984 et le 30 septembre 1986. Les 608 sujets témoins ont été choisis au hasard à partir d'une liste de résidents dans la région étudiée, et on les a appareillés selon l'âge, le sexe et la municipalité.

Intervention : Au moyen d'entrevues personnelles, l'intervieweur a déterminé l'exposition à des facteurs externes de risque présumé, il a évalué la couleur de la peau et le nombre de naevi sur le bras; et le sujet a mentionné la couleur naturelle de ses cheveux à l'âge de 20 ans, la couleur de ses yeux, la réaction cutanée à des expositions répétées au soleil et les densités des taches de rousseur et des naevi sur le corps entier.

Résultats : Bien que tous les facteurs relatifs à l'hôte mentionnés soient reliés de façon significative au risque de mélanome lorsqu'on en tient compte séparément, seules la couleur des cheveux, la réaction cutanée à une exposition répétée au soleil et les densités des taches de rousseur et des naevi signalées par le sujet sont demeurées significatives après une analyse de régression logistique. Le risque relatif de mélanome était évalué à 10,7 chez les personnes qui avaient de nombreux naevi par comparaison avec celles qui n'en avaient aucun (intervalle de confiance [IC] de 95 %, 6,6 à 17,4), à 4,0 chez les personnes qui avaient les cheveux roux par comparaison avec celles qui avaient les cheveux noirs (IC de 95 %, 1,9 à 8,2), à 1,9 chez les personnes qui avaient de nombreuses taches de rousseur par comparaison avec celles qui n'en avaient pas ou peu (IC de 95 %, 1,3 à 2,8) et à 1,8 chez les personnes qui ont brûlé après des expositions répétées au soleil par comparaison avec celles qui ont bronzé (IC de 95 %, 1,3 à 2,5).

Conclusions : On a identifié quatre facteurs de risque de mélanome malin. Il faudrait faire une évaluation prospective de leur valeur prédictive. Entre-temps, on devrait toutefois utiliser ces facteurs pour identifier les personnes qui semblent courir un risque élevé de mélanome malin qu'on pourrait ensuite cibler pour un dépistage hâtif et des programmes de prévention.

Increases in the incidence rates of cutaneous malignant melanoma and the rates of death from this disease have been reported for both sexes in white populations around the world.[1-4] In Ontario the age-standardized incidence rate for both sexes has increased from 4.0 per 100 000 in 1969[5] to 11.1 per 100 000 in 1988,[6] a difference of 178% (Fig. 1). This represents an average annual increase of 6%, larger than that for any cancer site except the lung among women.[5,6]

The increased incidence rate and evidence that efforts at early diagnosis result in a higher proportion of thin tumours[7,8] with good prognosis[1,9] have directed interest toward prevention and early detection. In Ontario in 1988, 1160 cases of melanoma were newly diagnosed in a population of 9.4 million.[6] Therefore, early detection and prevention programs will have a low ratio of new cases to population covered unless specific high-risk groups are targeted.

This study was designed to analyse host characteristics as risk factors for cutaneous malignant melanoma documented in a study completed recently in southern Ontario. Subgroups of this population who are at increased risk are identified so that prevention and early detection programs can be focused appropriately.

Methods

Although the study design and methods have been reported in detail previously[10] they will be described in brief here. We used a case-control design with a population-based series of 583 case subjects and 608 randomly selected control subjects. All subjects were interviewed in person with the use of a standard questionnaire. The study procedures and instruments were approved by the human ethics review committees of the University of Toronto and McMaster University.

Eligible case subjects were people who (a) had histologically confirmed cutaneous melanoma (including Hutchinson's melanotic freckle, lentigo ma-

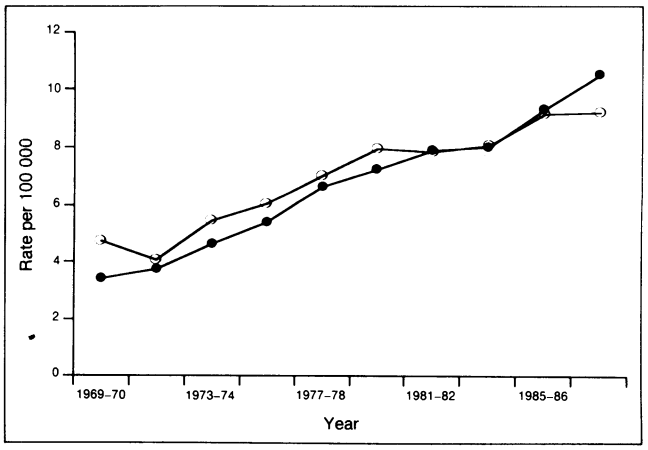

Fig. 1: Age-standardized incidence rates of cutaneous malignant melanoma among men (black circles) and women (open circles) in southern Ontario from 1969 to 1988. Rates were adjusted for age to the world standard population.

ligna and melanoma in situ) newly diagnosed between Oct. 1, 1984, and Sept. 30, 1986, (b) were 20 to 69 years of age at diagnosis, (c) resided in the southern Ontario regions of York, Metropolitan Toronto, Peel, Halton, Hamilton-Wentworth and Niagara, and (d) had melanoma diagnosed at one of the hospitals or private laboratories in the study area. Laboratories provided the study centre with a pathology report and slides for each eligible subject. Consent to contact each person was obtained from the treating physician identified from the pathology report. Slides were reviewed by one of us (L.F.), and those with ineligible diagnoses were eliminated. People with recurrent rather than new lesions were identified with the use of records from the Ontario Cancer Registry and were also excluded.

Control subjects were selected at random from the property tax assessment rolls of the 39 municipalities in the study area in an attempt to maintain the same distribution of age, sex and municipality of residence as that for the case subjects. Black people were excluded from the study, as were those who could not be interviewed because of language problems.

The interviews took about 30 minutes and included questions on such personal characteristics as natural hair colour at age 20 years, eye and skin colour, typical skin reaction to sun exposure and nevus density. Skin colour was assessed by the interviewer, who compared the skin on the subject's upper inner arm to a 15-colour prosthetic skin-tone panel.[11] Each panel was measured by means of reflectance spectrophotometry at three wavelengths in the visible light range (400, 500 and 600 nm); panels were ordered from dark to light on the basis of the average of these three reflectance values. Dark, medium and light skin classifications were obtained by dividing the control distribution of the reflectance values approximately into thirds.

Subjects were asked about their skin's reaction to strong sunlight after the first summer exposure (initial exposure) and after a few days of exposure (repeated exposure). Subjects were also asked whether they freckled after sun exposure; if so, they were shown photographs of lower arms representing different freckling densities and asked to select the one that most closely resembled their own skin in summer. Subjects were also asked to report whether they had ever had "big, splotchy freckles that appeared after a severe sunburn and that have not disappeared."

Nevus density was determined in two ways. First, the interviewer counted the number of raised pigmented moles on the subjects' left arm between 10 cm above and 10 cm below the elbow; moles greater than 5 mm in diameter were noted. Second, the subject was asked to select which of four whole-body diagrams[12] corresponded most closely to his or her nevus density (Fig. 2). The two diagrams representing the most moles were combined to form the highest exposure category.

The odds ratio, indicating the ratio of the odds of exposure among case subjects to the odds of exposure among control subjects, was used throughout this analysis as an estimate of relative risk. The relative risk for each characteristic was estimated separately, with adjustment only for age and sex. In addition, logistic regression analysis was used to estimate relative risks adjusted for all other factors.[13] Finally, a backward stepwise procedure was used to produce a model containing the risk factors with the most explanatory value, as well as age and sex. At each step the score test[14] was done to determine the significance of inclusion of each term in the model.

Results

Study populations

Of the 647 people who were eligible 64 (10%) did not complete the interview: 20 (3%) had died or were too ill, 20 (3%) refused, and 24 (4%) could not participate because their physicians refused to allow them to be contacted. Of the 751 control subjects who were invited to be interviewed 608 (81%) agreed.

Table 1 shows the distribution of cases by type of melanoma. This was determined by the review pathologist after examination of the slides in 91% of the cases and examination of the original pathology report in the other 9%. Most (72%) of the cases were of the superficial spreading type, nodular melanoma being the next most common (accounting for 12%).

The location of melanoma varied according to

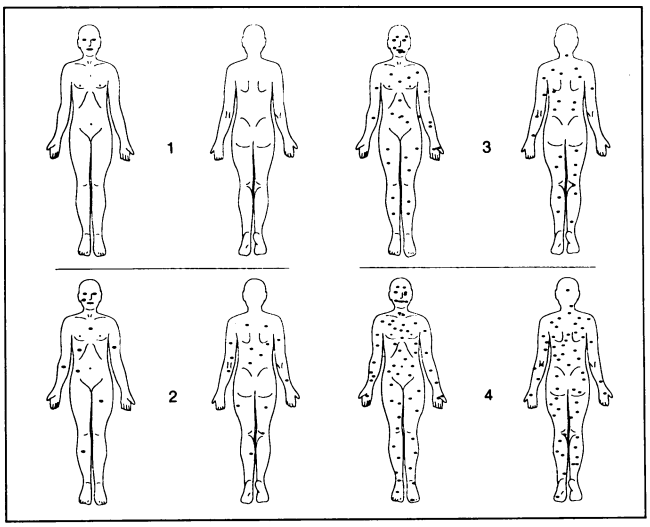

Fig. 2: Diagrams of whole-body nevus density used to elicit self-reports from respondents.

sex (Table 2). The most common site among the men was the trunk and among the women the legs. More of the women than of the men had melanoma on the arms; the reverse was true for melanoma on the face, head or neck. The distribution according to sex, histologic findings and body site was similar to that found in the Ontario Cancer Registry (unpublished data).

The study design ensured that case and control subjects were similar with respect to age and sex distributions. Women accounted for 53% of the case subjects and 54% of the control subjects. The average ages were 47.7 and 48.4 years respectively.

Relative risk estimates

Estimated relative risks for all potential risk factors are presented in Table 3. When taken individually each host factor under study was found to identify people at significantly elevated risk for melanoma. However, the factors tended to be closely associated with each other; therefore, the relative risks were not independent. This is evident from the general reduction in risk estimates that occurred after all factors were simultaneously controlled.

Subjects with light hair, eye and skin colour were at increased risk for melanoma. For example, people with blond or red hair had relative risks of 4.0 and 4.8 respectively, as compared with 2.4 for those with black hair (3.6 after adjustment for other factors). People with hazel, green or grey eyes were 1.7 times more likely than those with brown eyes to have melanoma; however, the risk decreased to a nonsignificant level after full adjustment. The risk of melanoma among the subjects with light skin was more than double the risk among those with dark skin; this difference also diminished after further adjustment. Thus, of the three pigmentation variables hair colour was the one most strongly related to melanoma risk.

Elevated risks were associated with having skin that tended to burn, regardless of whether the exposure was initial or repeated. Compared with the subjects whose skin reportedly tans without burning, the risk of melanoma was 2.3 times higher among those who said that their skin burns after initial exposure to strong summer sunlight without subsequent tanning. The relative risk was 2.6 times higher among subjects whose skin burns after repeated exposure with no increase in tan, as compared with those whose skin tans without burning. Although risk estimates for both of these factors were reduced after full adjustment they remained statistically significant.

Subjects who reported having freckles after sun exposure were at elevated risk for melanoma. The relative risk of melanoma was 2.6 times higher among those with many sun freckles than among those with none or few. Splotchy freckles that appeared after a sunburn were associated with a relative risk of 2.0. The estimates were less after adjustment but were still significant.

The largest relative risk for any factor (11.2) was found for the self-report of many nevi according to the whole-body diagrams. This risk estimate decreased slightly after adjustment to 10.4. Likewise, a significant elevation in the relative risk (3.0) was associated with an interviewer count of three or more raised nevi on one arm when this factor replaced the self-assessed nevus density in the model (not shown). This increased risk also persisted after adjustment for other factors. The number of raised nevi greater than 5 mm in diameter did not elevate the risk above that for nevus count alone. Once adjusted for age and sex the relative risk for three or more nevi, one or more being greater than 5 mm in diameter, was 2.9, whereas the risk for three or more nevi, none being greater than 5 mm, was 3.0 (not

Table 1: Distribution of 583 cases of cutaneous malignant melanoma in southern Ontario, newly diagnosed from 1984 to 1986, by subtype

Subtype	No. (and %) of cases
Nodular	72 (12)
Superficial spreading and in situ	420 (72)
Lentigo maligna	41 (7)
Unclassifiable, not otherwise specified and acral lentiginous	50 (9)

Table 2: Distribution of cases by location of melanoma and sex

Location	Sex; no. (and %) of cases		
	Male	Female	Total
Face, head or neck	45 (16)	26 (8)	71 (12)
Trunk (including shoulders)	161 (58)	93 (30)	254 (44)
Arm	33 (12)	56 (18)	89 (15)
Leg	33 (12)	122 (40)	155 (27)
Unknown	5 (2)	9 (3)	14 (2)
Total	277	306	583

shown). Since the self-report of nevus density was the strongest predictor of melanoma risk it was the only indicator of nevus density used in subsequent modelling.

Table 4 gives the risk estimates for the factors that remained in the final model after a stepwise backward elimination procedure; these factors were hair colour, skin reaction to repeated sun exposure, freckle density and nevus density. No other factors contributed significantly to the model. The logistic regression model assumes that the risk associated with having several risk factors is equal to the product of the risks associated with each factor. There is no evidence in these data of any departure from this multiplicative assumption. A comparison of observed versus expected values obtained from the model (data not presented) indicated a good fit over the range of risk subgroups.

Identification of high-risk subgroups

The four factors that constituted the final model were used to estimate risks in subgroups of the population defined by these variables. The referent for these estimates was the subgroup at lowest risk, namely those with black hair, a "tan, no burn" reaction to repeated sun exposure, no or few freckles after exposure to the sun and no nevi.

Fig. 3 displays the relative risks shown in Table 4 for various combinations of these four factors in a different format. The chart emphasizes the expected multiplicative nature of risks and helps one visualize

Table 3: Crude estimates of relative risk for malignant melanoma and estimates adjusted for all risk factors

Risk factor	Group; no. of subjects		RR (and 95% CI)*	
	Case	Control	Adjusted for age and sex	Adjusted for all factors†
Hair colour				
Black‡	26	67	1.0	1.0
Brown	180	253	1.9 (1.1–3.0)	1.5 (0.9–2.7)
Light brown	179	158	2.9 (1.8–4.9)	2.0 (1.1–3.6)
Blond or fair	123	81	4.0 (2.4–6.9)	2.4 (1.3–4.6)
Red	58	32	4.8 (2.6–9.0)	3.6 (1.7–7.6)
Eye colour				
Brown‡	139	208	1.0	1.0
Blue	209	191	1.6 (1.2–2.2)	1.0 (0.7–1.4)
Hazel, green or grey	230	205	1.7 (1.3–2.3)	1.2 (0.8–1.7)
Skin colour				
Dark‡	99	190	1.0	1.0
Medium	269	228	2.3 (1.7–3.0)	1.5 (1.0–2.1)
Light	211	189	2.1 (1.6–2.9)	1.4 (0.9–2.0)
Skin reaction to initial sun exposure				
Tan, no burn‡	100	196	1.0	1.0
No burn, no tan	107	72	2.9 (2.0–4.3)	1.6 (0.9–2.7)
Burn, then light tan	89	47	1.6 (1.0–2.6)	1.8 (1.0–3.2)
Burn, no tan	330	284	2.3 (1.7–3.0)	1.4 (1.0–2.1)
Skin reaction to repeated sun exposure				
Tan, no burn‡	320	444	1.0	1.0
No burn, no tan	57	44	1.8 (1.2–2.8)	1.2 (0.7–2.0)
Burn, no increase in tan	195	110	2.5 (1.9–3.3)	1.5 (1.1–2.2)
Freckle density				
None or few‡	300	413	1.0	1.0
Moderate	122	101	1.8 (1.3–2.4)	1.3 (1.0–1.9)
Many	145	82	2.6 (1.9–3.6)	1.7 (1.2–2.5)
Splotchy freckles				
No‡	493	556	1.0	1.0
Yes	68	38	2.0 (1.3–3.1)	1.6 (1.0–2.7)
Nevus density, self-report				
None‡	50	156	1.0	1.0
Few	338	372	3.1 (2.2–4.4)	3.5 (2.3–5.2)
Moderate or many	193	63	11.2 (7.2–17.5)	10.4 (6.3–17.0)

*RR = relative risk, CI = confidence interval.
†Estimates were adjusted for age and sex as well.
‡Referent group.

how a person's risk may be higher or lower depending on his or her particular constellation of risk factors. According to the model used here, hair colour, reaction to repeated sun exposure, sun-freckle density and nevus density define a person's risk subgroup. Risks associated with each level (value) of these risk factors are found under the appropriate heading in Fig. 3. The risk for any given subgroup defined by the values of these factors relative to the risk of the referent was estimated as the product of risk estimates for the given risk factor values. All such comparisons involved people of the same sex and age as the individual of interest. For example, people who have light brown hair, burn without an increase in tan after repeated sun exposure and have many sun freckles and a moderate number of nevi have a relative risk of 26.3 ($2.2 \times 1.8 \times 1.9 \times 3.5$) as compared with those who are in the low-risk referent group of the same sex and age.

Table 4: Estimates of relative risk for malignant melanoma adjusted for age, sex and significant risk factors*

Risk factor	RR (and 95% CI)
Hair colour	
Black†	1.0
Brown	1.6 (0.9–2.8)
Light brown	2.2 (1.3–3.9)
Blond or fair	2.7 (1.5–4.9)
Red	3.9 (1.9–8.2)
Skin reaction to repeated sun exposure	
Tan, no burn†	1.0
No burn, no tan	1.4 (0.8–2.4)
Burn, no increase in tan	1.8 (1.3–2.5)
Freckle density	
None or few†	1.0
Moderate	1.5 (1.0–2.1)
Many	1.9 (1.3–2.8)
Nevus density, self-report	
None†	1.0
Few	3.5 (2.3–5.2)
Moderate or many	10.7 (6.6–17.4)

*Estimates were calculated from a model obtained through a backward stepwise elimination procedure.
†Referent group.

Discussion

Although constitutional risk factors for malignant melanoma have been investigated previously[15-24] our study provided the opportunity to examine a number of these factors simultaneously and to estimate subgroup risks in a large, geographically defined population. Our results with respect to the relative importance of various constitutional risk factors generally agree with those of previous investigators and indicate that the number of nevi, freckling, hair colour and the skin's reaction to the sun are strong independent predictors of melanoma risk.

The estimated risks for the host factors identified as important for melanoma in southern Ontario may be applicable to a broad spectrum of Canadians.

Hair colour		×	Skin reaction to repeated sun exposure		×	Freckle density		×	Nevus density		=	Personal relative risk
Black	1.0		Tan, no burn	1.0		None or few	1.0		None	1.0		
Brown	1.6		No burn, no tan	1.4		Moderate	1.5		Few	3.5		
Light brown	2.2		Burn, no increase in tan	1.8		Many	1.9		Moderate or many	10.7		
Blond or fair	2.7											
Red	3.9											

Examples

Brown (1.6)	×	Tan, no burn (1.0)	×	None or few (1.0)	×	None (1.0)	=	1.6
Blond or fair (2.7)	×	Tan, no burn (1.0)	×	None or few (1.0)	×	Few (3.5)	=	9.5
Brown (1.6)	×	No burn, no tan (1.4)	×	None or few (1.0)	×	Moderate or many (10.7)	=	24.0
Light brown (2.2)	×	Burn, no increase in tan (1.8)	×	Many (1.9)	×	Few (3.5)	=	26.3

Fig. 3: Chart used to estimate personal relative risk.

A person or his or her physician can use the risk chart provided to determine the risk factor subgroup and its corresponding estimated risk of melanoma. Since there is evidence that campaigns aimed at early recognition of melanoma will result in increased detection of thin melanomas,[7,8] for which prognosis is good,[1,9] people found to be at high risk may appropriately be targeted for early detection, education and prevention programs.

There are several strategies that can be used to define high risk. By assuming that the control distribution represents the Ontario population in the same age range and by using 1988 Ontario incidence rates of melanoma and our subgroup estimates of relative risk, we can estimate the incidence rates for each risk subgroup (Appendix 1). Thus, the incidence rate in the referent group is about 1.35 per 100 000 population. A subgroup with a risk of 10 relative to the referent group would have an incidence rate of 13.5 per 100 000, which is slightly below the crude rate for Ontario residents aged 20 to 69 years (15.23 per 100 000).

We can also estimate both the number of people at risk in the population and the number of cases that will occur in each risk subgroup. If risk subgroups are ordered by size of relative risk from greatest to smallest, one can estimate the proportion of the population whose risk exceeds a specified value as well as the proportion of melanoma cases expected to have the same attributes (Fig. 4). For example, about 33% of the population has a relative risk of 10 or more, and people in these subgroups constitute 70% of all melanoma cases. Eleven percent of the population has a relative risk of 25 or more, and these subgroups account for 40% of all cases of melanoma. The 5% of the population at greatest risk has a relative risk that exceeds 36 and accounts for almost 25% of all melanoma cases.

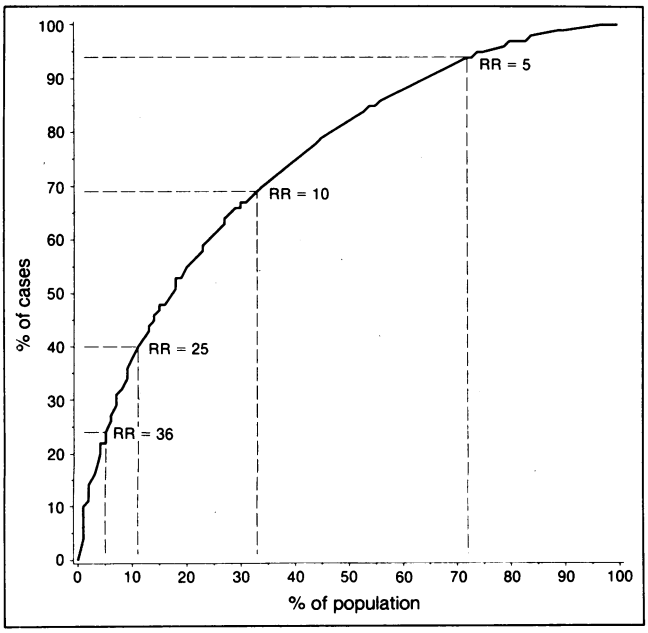

Fig. 4: Relation between proportion of population at risk for melanoma and occurrence of melanoma by relative risk (RR).

Because the subgroups at highest risk constitute only a small proportion of the general population, the number of melanoma cases occurring in those groups is also small. Although such subgroups should be targeted, the larger groups should not be excluded, because their risk may still be substantially elevated and they may account for more cases of malignant melanoma. For example, red hair is a stronger risk factor than blond hair, yet more people with blond hair will have melanoma in southern Ontario because there are more blond-haired people. Thus, any program for people at high risk must consider the trade-off of a higher yield of melanoma cases per 100 targeted people versus the absolute yield.

There are, of course, some limitations to the inferences that can be made from our findings. First, recall bias should be considered, since people with melanoma may give a more accurate or complete response than control subjects because of their experience with the disease. In our study we compared the responses of a subset of 43 patients interviewed at a skin lesion clinic before their diagnosis with those of the remaining 540 people in the group. Their responses concerning hair colour, skin reaction to repeated sun exposure and freckle density did not differ. However, their self-report of mole density did ($\chi^2 = 6.52$, 2 degrees of freedom, $p = 0.04$). Although the two groups reported "many and moderate" moles with similar frequency, the clinic patients reported "few" moles less often; this suggested a potential reporting bias. This difference may be real, perhaps related to the pattern of referral to the clinic.

A recent paper by Weinstock and associates[25] assessed recall bias in the ascertainment of two risk factors for melanoma: ability to tan and hair colour. In comparing responses before and after diagnosis they observed a shift toward reporting a reduced ability to tan after a diagnosis of melanoma. There was no evidence on reporting bias for hair colour.

If present, recall bias could give an overly optimistic impression of the potential utility of the diagrams as a tool for identifying people at high risk. It is also possible, though less likely, that the recall bias could produce a low estimate of risk. Nevertheless, the diagrams may be of considerable value because of their ease of use and their strong predictive value.

In addition, it is difficult to assess whether the multiplicative assumption inherent in the logistic model adequately represents risk in the subgroups.

Relative risk estimates in subgroups identified by two factors were found to be similar to estimates obtained from two-factor logistic models. This result suggests that there is no deviation from the multiplicative assumption in these data.

A third limitation is the size of the risk subgroups. Because of small numbers, estimates of the proportion of control subjects in some risk subgroups are highly unstable, and thus our estimates of the proportion of the population in aggregates of risk subgroups (Fig. 4) must be interpreted cautiously. Because of these limitations prospective evaluations should be conducted to determine the utility of our personal risk estimation strategy.

Conclusion

Our study identifies four host characteristics that are risk factors for cutaneous malignant melanoma. These factors could be easily integrated into screening, self-examination and education programs for high-risk groups. People with a large number of nevi appear to be at particularly high risk and can easily be identified through the use of a simple diagram. Those who have red or blond hair, have a history of freckling in response to sun exposure and burn with no tan after repeated sun exposure are also at high risk. These people should be candidates for surveillance programs and educated on the early recognition of suspicious skin lesions and on behaviour to reduce risk.

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Appendix 1: Estimation of the incidence rate of cutaneous malignant melanoma for subgroups at risk

Referent subgroup

The 1986 Ontario incidence rate (15.23 per 100 000) is equated to the weighted average of the rates for each subgroup.*

$$R = \sum_{i=1}^{135} r_i \times p_i$$

The rate for subgroup i (r_i) is replaced by the rate in the referent group (r_1) multiplied by the relative risk for subgroup i (RR_i), and the expression is solved to obtain r_1.

$$R = \sum_{i=1}^{135} RR_i \times r_1 \times p_i$$

$$R = r_1 \sum_{i=1}^{135} RR_i \times p_i$$

$$15.23 = r_1 \sum_{i=1}^{135} RR_i \times p_i$$

$$15.23 = r_1 (11.9)$$

$$1.35 = r_1$$

Risk subgroups

Using the incidence rate for the referent group (1.35) we can calculate the rates for each risk subgroup.

$$r_i = RR_i \times r_1$$

For example, the subgroup with brown hair, a reaction to repeated sun exposure of burn with no increase in tan, no or few freckles after exposure to the sun and a moderate number of nevi has a relative risk of 10 ($1.6 \times 1.8 \times 1.0 \times 3.5$) and an incidence rate of 13.5 (10×1.35) per 100 000.

*p_i = proportion of control subjects with the risk factors of subgroup i, and R = 1986 Ontario incidence rate of malignant melanoma among people aged 20 to 69 years.

Disease

Most men form an exaggerated estimate of the powers of medicine, founded on the common acceptance of the name, that medicine is the art of curing diseases. That this is false definition is evident from the fact that many diseases are incurable, and that one such disease must at last happen to every living man. A far more just definition would be that medicine is the art of understanding diseases, and of curing or relieving them when possible. Under this acceptation our science would, at least, be exonerated from reproach, and would stand on a basis capable of supporting a reasonable and durable system from the amelioration of human maladies.

— *Jacob Bigelow (1786–1879)*
Nature in Disease, *Ch. 2*