Pigmentary Traits, Modalities of Sun Reaction, History of Sunburns, and Melanocytic Nevi as Risk Factors for Cutaneous Malignant Melanoma in the Italian Population

Results of a Collaborative Case-Control Study

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BACKGROUND. To the authors' knowledge, limited data are available from Mediterranean populations concerning risk factors for malignant melanoma. A few Italian case–control studies have produced conflicting results regarding the association between malignant melanoma and pigmentary traits, sunburns, and melanocytic nevi.
METHODS. A case–control study was conducted within the framework of the Italian Group for Epidemiologic Research in Dermatology (GISED). Twenty-seven centers in the north and south of Italy participated. A total of 542 cases and 538 controls were entered onto the study. A standardized questionnaire was administered to cases and controls. Cases and controls also were examined by trained dermatologists who were required to count the number of melanocytic nevi (those measuring $\geq$ 2 mm and $>$ 6 mm in greatest dimension, separately) and to make judgments regarding pigmentary traits.
RESULTS. In the multivariate analysis, eye and skin color, propensity to sunburn, history of sunburns before age 15 years, and solar lentigines all were associated with malignant melanoma. In addition, the risk of melanoma increased with the number of melanocytic nevi $\geq$ 2 mm. Nevi $>$ 6 mm in greatest dimension had effects on risk that appeared to be independent from the effects of smaller nevi (2–6 mm).
CONCLUSIONS. The results of the current study largely are similar to those obtained in northern European countries, the U.S., and Australia and provide further evidence of the importance of selected pigmentary traits, sun exposure, and the number of melanocytic nevi in the risk of cutaneous malignant melanoma. ***Cancer* 2000;88:2703–10.** © *2000 American Cancer Society.*

KEYWORDS: cutaneous malignant melanoma, risk factors, case–control study, Mediterranean populations, pigmentary traits, sunburns, melanocytic nevi.

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Over the past few years, considerable effort has been directed toward the identification of risk factors associated with the increasing incidence of cutaneous malignant melanoma in white populations worldwide. Among the array of factors considered are pigmentary traits and melanocytic nevi.[1–11] A fairly large body of evidence suggests that the number of melanocytic nevi represents the best predictor for cutaneous malignant melanoma and that large atypical nevi may play an independent role.[1–9,12]

In Italy, as in most countries with a predominantly white population, there has been a considerable increase in the incidence and mortality from cutaneous malignant melanoma.[13,14] In 1990–94 as compared with 1970–74, the standardized mortality rates rose from 0.6 to 1.5 per 100,000 among men and from 0.4 to 1.1 among women. In 1990, incidence rates of 3.6 per 100,000 among men and 4.1 among women were calculated. These figures were lower than the average estimates for the whole European community but were higher than those documented, among the others, for Spain, Portugal, and Greece.[14] Of note, at variance with other countries of the Northern Hemisphere where north–south gradients in skin carcinoma mortality rates are observed, in Italy, higher rates have been documented in the north than in the south.[15]

By and large, limited data are available from Mediterranean populations concerning risk factors for malignant melanoma, and, as far as we know, only three case–control studies from Italy have been published.[16–18] However, the results of these studies are inconclusive about the role of pigmentary traits, sunburns, and number of melanocytic nevi.

In view of the uncertainties concerning risk factors for malignant melanoma in the Italian population, we decided to perform a large collaborative case–control study, involving hospital centers in northern and southern Italy.

STUDY POPULATION AND METHODS

The study was conducted within the framework of the Italian Group for Epidemiologic Research in Dermatology (GISED). This is a collaborative network of hospital-based dermatology and oncology centers in Italy. Twenty-seven centers, 16 in the north and 11 in the south of the country, participated. During the period June 1992 through June 1994, consecutive patients with a first diagnosis of invasive cutaneous malignant melanoma were invited to take part in the study. Patients were classified according to the American Joint Committee on Cancer staging procedures.[19] Cases with in situ melanoma (Clark's Level I) as well as cases with a previous diagnosis of malignant melanoma were excluded. approximately 1% of cases were excluded because of a previous diagnosis of a primary malignant melanoma. We selected as controls patients admitted to the same hospitals with newly diagnosed nondermatologic diseases, including acute conditions not suspected to be related to neoplastic diseases, e.g., traumatic injuries, or for an elective procedure that was not related to neoplastic diseases.[20,21] Controls were age and gender matched to cases. Even if controls were not individually matched to cases on geographic origin, their distribution according to this variable was very similar to the case distribution. Oral informed consent was obtained from each subject, and fewer than 1% of cases and controls refused to participate. There were no important differences between participants and nonparticipants in terms of geographic origin, diagnoses, and age and gender distribution.

A total of 542 cases and 538 controls entered the study. Some general characteristics of the case group are reported in Table 1. The median age in the case as well as the control group was 54 years. This figure is similar to the median age at diagnosis reported in other series.[22] The mean tumor thickness increased from 1.4 mm in the age group 30 years old or younger to 2.0 mm in the age group older than 60. Of the

TABLE 1
Distribution of 542 Cases According to Gender, Age, Tumor Pathologic Variant, Thickness, and Anatomic Site

Characteristic	No. of males (%)	No. of females (%)
Age (yrs)		
≤ 30	21 (9.3)	34 (10.8)
31–60	117 (51.8)	172 (54.4)
> 60	88 (38.9)	110 (34.8)
Clinicopathologic variants		
Superficial spreading	156 (69.0)	235 (74.4)
Nodular	40 (17.7)	32 (10.1)
Lentigo maligna	15 (6.6)	24 (7.6)
Acral lentiginous	7 (3.1)	15 (4.7)
Unclassified	8 (3.5)	10 (3.2)
Tumor thickness (mm)		
< 0.76	69 (30.5)	114 (36.1)
0.76–1.50	49 (21.7)	55 (17.4)
1.51–3.99	54 (23.9)	67 (21.2)
≥ 4.00	26 (11.5)	23 (7.3)
Data not available	28 (12.4)	57 (18.0)
Anatomic site		
Head/neck	36 (15.9)	45 (14.2)
Trunk	139 (61.5)	80 (25.3)
Upper limbs	14 (6.2)	34 (10.8)
Lower limbs	32 (14.2)	151 (47.8)
Unspecified	5 (2.2)	6 (1.9)

[a] n = 226.
[b] n = 316.

control series, 30% were admitted for acute surgical and gynecologic conditions, 23% had acute medical disorders, 12% had traumatic or other orthopedic conditions (approximately one-third had traumatic injuries due to traffic accidents, one-third traumatic injuries due to other recreational or job activities, and one-third miscellaneous orthopedic disorders), and 35% had other illnesses, such as disorders of the ear, nose, throat, or teeth.

A standardized questionnaire was administered to cases and controls by trained interviewers. Questions centered on the lifetime history of sun exposure including the usual pattern of reaction to first sun exposure and history of sunburns with number and severity, past dermatologic reports, and excision of skin lesions. Sunburns were defined as episodes of intense erythema with or without blisters causing pain and discomfort for more than 2 days. Cases and controls also were examined by trained dermatologists who had to count the number of melanocytic nevi and make judgments on pigmentary traits according to standardized criteria. Nevi $\geq$ 2 mm and $>$ 6 mm in diameter were counted over the whole body surface excluding the genitalia and scalp area. These areas of the body were excluded because of the anticipated difficulties in assessing the number of nevi in areas of dense hair growth and to avoid unnecessary embarrassment during the examination. A simple instrument, called a "nevometer" was used to rapidly assess the diameter (2 and 6 mm).[23] The dermatologists also were provided with a photographic atlas of nevi to facilitate judgments.[24] Nevi of 2 to 6 mm in diameter were calculated as the difference between the counts of nevi $\geq$ 2 mm and $>$ 6 mm. Concordance of nevus counts among assessors and within each assessor in two independent trials was evaluated and judged to be satisfactory with both intra and interobserver intraclass correlation values not lower than 0.75 (unpublished data). Both total and area specific counts were made. Skin color was evaluated using a three-grade scale (light, medium, and dark) based on the examiner's judgment and comparison with representative sample photographs. The inner aspect of upper arms was selected for the evaluation of skin color. Judgment on eye color was made on a seven-category scale, and judgment on hair color was made on a six-category scale. Freckles (or ephelides) were defined as multiple pinpoint pale-brown macular lesions with poorly defined lateral margins, grouped on the face, upper back, and upper arms. Their presence at the time of examination was evaluated by comparison with drawings showing schematic patterns and classified on a seven-category scale (from none to widespread). Solar lentigines were defined as medium to dark brown macular lesions with sharply defined indented margins and a diameter larger than 3 mm. The concordance of the judgement on pigmentary characteristics, freckles and solar lentigines was evaluated in preliminary exercises and judged to be satisfactory with both intra and interobserver intraclass correlation values ranging from 0.58 to 0.95 (unpublished data).

Data Analysis

For each variable, we computed the odds ratios of malignant melanoma as estimates of relative risks and the corresponding 95% confidence intervals. Initially estimates were obtained from data stratified by age and gender according to the Mantel–Haenszel procedure. Subsequently, logistic regression analysis was used to adjust for additional potentially confounding variables.[25] The Mantel test was applied to test for trend.[26]

RESULTS

Hair, eye, and skin color, degree of freckling, propensity to sunburn, history of sunburns in infancy, number of solar lentigines, and number of melanocytic nevi all were associated with malignant melanoma when adjustment was limited to age and gender. Most of the mentioned variables appeared to be interrelated to some degree. Of the pigmentary traits, only eye and skin color maintained a significant association with malignant melanoma but with odds ratios closer to one, when data were adjusted simultaneously for all the other variables (Table 2). Similarly, the association of malignant melanoma with propensity to sunburn, history of sunburns before age 15 years, and solar lentigines was confirmed after adjustment for pigmentary traits, but odds ratios estimates were decreased in magnitude to some extent (Table 3).

With regard to melanocytic nevi, the control for pigmentary traits in the multivariate analysis did not involve any important changes in odds ratios (Table 4). The risk for malignant melanoma increased steadly with increased total counts of nevi $>$ 2 mm. Large nevi ($>$ 6 mm) had effects on risk that appeared to be independent from the effect of smaller nevi (2–6 mm) even if the mutual adjustment of small and larger nevus counts involved a decrease in the magnitude of the estimated risks as compared with age- and gender-adjusted estimates. The analysis of the combined effect of the number of nevi 2 –6 mm in diameter and of those $>$ 6 mm did not provide any clear evidence for interaction (data not shown).

Because persons with a higher number of melanocytic nevi may be more prone to seek medical advice for their nevi and more likely to have had moles removed and, in the end, a diagnosis of malignant

TABLE 2
Distribution of Cases and Controls According to Pigmentary Characteristics

Characteristic	No. of cases (%)	No. of controls (%)	Odds ratio (95% confidence interval) M-H[a]	Odds ratio (95% confidence interval) MLR[b]
Hair color[c]				
Black/dark brown	275 (50.7)	324 (60.3)	1[d]	1[d]
Light brown	183 (33.8)	161 (30.0)	1.3 (1.0–1.7)	1.0 (0.7–1.3)
Blonde, red	84 (15.5)	52 (9.7)	1.9 (1.3–2.9)	1.3 (0.8–2.1)
Chi-square test for trend (*P* value)			13.12 (0.0003)	0.65 (0.42)
Eye color				
Brown	141 (26.0)	212 (39.4)	1[d]	1[d]
Green, hazel	194 (35.8)	167 (31.0)	1.8 (1.3–2.4)	1.7 (1.2–2.3)
Blue, gray	207 (38.2)	159 (29.6)	2.0 (1.5–2.7)	1.6 (1.0–2.2)
Chi-square test for trend (*P* value)			19.97 (0.0001)	6.19 (0.01)
Skin color[c]				
Dark, olive	37 (6.8)	63 (11.8)	1[d]	1[d]
Medium	246 (45.5)	275 (51.6)	1.5 (1.0–2.4)	1.3 (0.8–2.0)
Fair/pale	258 (47.7)	195 (36.6)	2.3 (1.5–3.7)	1.6 (1.0–2.7)
Chi-square test for trend (*P* value)			17.80 (0.0001)	4.67 (0.03)
Freckles[c]				
None	347 (64.0)	393 (73.2)	1[d]	1[d]
Few	164 (30.3)	125 (23.3)	1.5 (1.1–2.0)	1.2 (0.9–1.7)
Many	31 (5.7)	19 (3.5)	1.9 (1.0–3.4)	1.4 (0.7–2.6)
Chi-square test for trend (*P* value)			10.79 (0.0010)	2.67 (0.10)

M-H: Mantel–Haeszel; MLR: multiple logistic regression.

[a] Estimates adjusted for age and gender.

[b] Estimates including terms for age, gender, education, marital status, history of sunburns, number of nevi (≥ 2 mm), and, in turn, other pigmentary characteristics.

[c] The sum does not add up to the total because of some missing values.

[d] Reference category.

melanoma, data also were analyzed in strata of tumor thickness and according to the past history of skin surgery and dermatologic examinations. No difference in risks were observed when the analyses were restricted to the thicker lesions or after adjustment for the history of previous dermatologic consultations. Analyses also were performed according to the hospital center and the geographic origin of the cases. No important variations in risk estimates were found (data not shown).

DISCUSSION

Our study provides further quantitative evidence of the importance of selected pigmentary traits and the number of melanocytic nevi in the risk of cutaneous malignant melanoma. In addition, the study confirms the role of sun exposure, expecially during early life, in the development of the tumor. These results are of interest in that they have been obtained in a mixed population from southern Europe and are largely similar to data obtained in northern European countries, the U.S., and Australia.[1–11]

Conflicting results have been reported in three previous case–control studies of malignant melanoma conducted in Italy.[16–18] In one study, from a mountainous region bordering Austria.[16] no association was documented between malignant melanoma and the number of common and so-called dysplastic melanocytic nevi, and a significant excess risk was documented with fair skin but not with hair and eye color or sunburns in adolescence. In another study from the Piedmont region in northern Italy,[17] the number of nevi was not assessed; hair color was associated with malignant melanoma as were sunburns in infancy. In a study from the Florence area in central Italy,[18] the number of common melanocytic nevi appeared to be the strongest risk factor for cutaneous malignant melanoma whereas no significant association was documented with pigmentary traits. Given the different methodologies used, it is hard to assess whether these data, if not due to chance, reflect a true heterogeneity of risk factors for cutaneous malignant melanoma in different parts of the country.

Our study involved hospital centers in the North and South of the country where all the consecutive cases were identified and asked to participate. Approximately 3000 new cases of maligant melanoma per year were expected in Italy in 1990,[27] and it can be

TABLE 3
Distribution of Cases and Controls According to Modality of Reaction to Sun Exposure, History of Sunburns and Presence of Solar Lentigines

			Odds ratio (95% confidence interval)	
Characteristic	**No. of cases (%)**	**No. of controls (%)**	**M-H[a]**	**MLR[b]**
Skin reaction to first sun exposure				
Never burn	172 (31.7)	205 (38.1)	1[c]	1[c]
Burn occasionally	129 (23.8)	174 (32.3)	0.9 (0.6–1.2)	0.8 (0.5–1.1)
Burn frequently/always	241 (44.5)	159 (29.6)	1.8 (1.3–2.4)	1.5 (1.1–2.0)
Chi-square test for trend (*P* value)			15.51 (0.0001)	4.50 (0.04)
Sunburns[d]				
Never	322 (59.7)	363 (67.6)	1[c]	1[c]
First episode at or after age 15 yrs	138 (25.6)	125 (23.3)	1.2 (0.9–1.7)	1.1 (0.8–1.5)
First episode before age 15 yrs	79 (14.7)	49 (9.1)	1.9 (1.3–2.9)	1.6 (1.0–2.4)
Solar lentigines[d]				
None	239 (44.2)	283 (53.0)	1[c]	1[c]
One or more	302 (55.8)	251 (47.0)	1.4 (1.1–1.9)	1.3 (1.0–1.7)

M-H: Mantel–Haenszel; MLR: multiple logistic regression.

[a] Estimates adjusted for age and gender.

[b] Estimates including terms for age, gender, education, and pigmentary characteristics.

[c] Reference category.

[d] The sum does not add up to the total because of some missing values.

TABLE 4
Distribution of Cases and Controls According to Count of Melanocytic Nevi

			Odds ratio (95% confidence interval)	
Characteristic	**No. of cases (%)**	**No. of controls (%)**	**M-H[a]**	**MLR[b]**
Total nevus count (≥ 2 mm)				
0–5	167 (30.8)	262 (48.7)	1[c]	1[c]
6–15	150 (27.7)	150 (27.9)	1.7 (1.2–2.2)	1.7 (1.3–2.4)
16–30	94 (17.3)	77 (14.3)	2.2 (1.5–3.2)	2.2 (1.5–3.2)
31–45	46 (8.5)	31 (5.8)	2.8 (1.7–4.8)	2.8 (1.7–4.8)
≥ 46	85 (15.7)	18 (3.3)	9.5 (5.4–16.8)	9.7 (5.4–17.4)
Chi-square test for trend (*P* value)			70.75 (0.0000)	64.82 (0.0000)
No. of small nevi (2–6 mm)				
0–5	183 (33.8)	276 (51.3)	1[c]	1[c]
6–15	152 (28.0)	142 (26.4)	1.7 (1.3–2.3)	1.4 (1.0–2.0)
16–30	99 (18.3)	74 (13.8)	2.3 (1.6–3.4)	1.6 (1.1–2.5)
31–45	36 (6.6)	30 (5.6)	2.1 (1.2–3.6)	2.0 (1.1–3.5)
≥ 46	72 (13.3)	16 (3.0)	8.6 (4.7–15.6)	5.7 (3.1–10.8)
Chi-square test for trend (*P* value)			57.99 (0.0000)	28.35 (0.0000)
No. of large nevi (> 6 mm)				
0	284 (52.4)	410 (76.2)	1[c]	1[c]
1–4	174 (32.1)	109 (20.3)	2.4 (1.8–3.1)	1.9 (1.4–2.5)
≥ 5	84 (15.5)	19 (3.5)	6.9 (4.1–11.8)	3.1 (1.7–5.6)
Chi-square test for trend (*P* value)			75.00 (0.0000)	23.87 (0.0000)

M-H: Mantel–Haenszel; MLR: multiple regression estimate.

[a] Estimates adjusted for age and gender.

[b] Estimates including terms for age, gender, height, weight, education, marital status, pigmentary characteristics, and history of sunburns. In addition, the estimates for the number of small and large nevi are mutually adjusted.

[c] Reference category.

calculated that, during the study period, we recruited approximately 10% of all the Italian incident cases. The distribution of our cases according to age, gender, and location, clinicopathologic variants, and thickness of the primary tumor was very similar to the pattern reported in a few population-based studies from Italy[28,29] These considerations, together with the lack of heterogeneity in risk estimates according to the hospital center and the geographic origin of cases, provide indirect support to a generalization of our findings to the whole Italian situation.

Our results concerning melanocytic nevi are in agreement with the results of a smaller case–control study conducted in central Italy.[18] Moreover, our risk estimates are in the order of magnitude of those obtained in a number of studies from other countries.[5–9,12] Note that large variations in the total count of nevi from different studies can be observed. These may be explained by different methods in counting nevi or by real variations among different populations. Patient interview, direct examination by trained interviewer or nurse, and a whole body examination by a dermatologist have been used to count nevi in different studies. Better interobserver correlations have been reported for nevus counts conducted by medical observers who were applying, as in our case, a 2-mm or 3-mm size cutoff.[12]

The number of nevi is related to pigmentary traits.[12,30] The finding that there is a rather larger proportion of individuals in our study with lower total number of nevi as compared with similar studies from northern Europe or Australia and, for converse, a lower proportion with higher nevus counts may be, at least partly, explained by a darker prevalent phenotype in our populaton.

In view of the classification difficulties, we decided not to collect information on atypical or dysplastic nevi and concentrated our efforts on collecting sound information on the diameter of nevi. Of note, we can confirm that large nevi ($>$ 6 mm in diameter) add to the risk of melanoma independently of the count of smaller melanocytic nevi.[5–9,31,32]

Although the number of nevi proved to be the strongest risk factor, eye and skin color, modalities of sun reaction, history of sunburns before age 15, and solar lentigines also appeared to be independent risk factors for malignant melanoma. After mutual adjustment, a significant association with hair color (blond and red), a borderline association with eye color (blue), and a significant association with light skin color have been documented in a recent systematic review of 10 case–control studies of malignant melanoma.[10] The different distribution of pigmentary characteristics among different populations may affect risk estimates. The stronger association with eye color compared with hair color that we documented after mutual adjustment might be explained with the remarkably low prevalence of blonde and red hair in our study population in comparison with the studies considered in the systematic review. It has been postulated that hair and eye color may represent risk factors by virtue of their correlation with skin color and that a residual association after mutual adjustment may persist because hair and eye color are easy to measure and have a wide color range whereas skin color is difficult to measure and has a much narrower color range.[10]

We were not able to confirm an association between freckles and malignant melanoma but documented such an association with solar lentigines. The distinction between freckles and solar lentigines is not always straightforward in case–control studies of melanoma. Freckles (or ephelides) are more common in children and in individuals of all ages who are red haired and fair skinned. They tend to fade during winter months. Solar lentigines are darker in color and usually larger in size as compared with freckles and have sharp angulated margins. They frequently follow a history of sunburn and tend to persist indefinitely being more prevalent in older patients.[33] The low prevalence of red-haired individuals in our population may explain our negative findings concerning freckles. Data similar to ours concerning solar lentigines have been obtained in a case–control study from Germany attempting to separate them from freckles.[5]

The associations with solar lentigines, tendency to sunburns, and history of sunburns before age 15 lend support to the role of skin sensitivity and acute intense sun exposure, expecially in childhood, as risk factors for malignant melanoma. An overview of 29 published studies has documented an association of malignant melanoma with sunburns in adult life as well as in childhood and adolescence.[11] It also has been suggested that the combined risk for intense sun exposure during childhood and adult life is greater than the simple addition of the two independent risks.[34] In geographic areas of relatively high solar irradiation like Italy, intense exposure early in life may play a more crucial role on the melanoma risk than sun exposure later in life. The importance of sun-related events during the first few decades of life is reinforced by considering that an association between intense sun exposure early in life and the density of melanocytic nevi has been documented in several epidemiologic studies.[30,35,36] The number of melanocytic nevi per se may reflect the interaction between constitutional factors, e.g., pigmentary traits and environmental stimuli such as sunlight that are crucial to the

development of malignant melanoma. The stronger association of malignant melanoma with melanocytic nevi and the weaker association with sun exposure also may partly reflect the different validity and precision with which the two risk factors are measured in retrospective studies (physical examination vs. case history data).

In conclusion, according to our data, in Italy, risk factors for melanoma do not remarkably differ from those observed in other countries and include: number of nevi $\geq$ 2 mm in diameter on the whole body surface, number of nevi $>$ 6 mm, eye and skin color, modality of sun reaction, history of sunburn in childhood, and solar lentigines. These data should be taken into consideration when planning campaigns for the prevention of malignant melanoma in Italy, and they reinforce the value of similar data already obtained in other countries.

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