See related commentary on page 1932

Number of Nevi at a Specific Anatomical Site and Its Relation to Cutaneous Malignant Melanoma

Giorgia Randi[1], Luigi Naldi[2], Silvano Gallus[1], Anna Di Landro[2] and Carlo La Vecchia[1,3] on behalf of the Oncology Study Group of the Italian Group for Epidemiologic Research in Dermatology (GISED)[4]

The risk of cutaneous malignant melanoma (CMM) is strongly associated with total number of nevi. Scanty information is available on the association between CMM at a specific anatomical site and number of nevi at the same site. We analyzed data from a case–control study conducted in Italy between 1992 and 1994, on 542 cases of CMM and 538 hospital controls. Cases and controls were examined by trained dermatologists who counted the number of melanocytic nevi. We derived multivariate odds ratios (ORs) and 95% confidence intervals (95% CIs) of site-specific risk of CMM for high *versus* low number of nevi at the corresponding site. The ORs of CMM for the highest *versus* the lowest tertile of number of nevi at the corresponding site was 1.4 (95% CIs: 0.7–2.8) at face and neck, 2.3 (95% CIs: 1.1–4.9) at anterior trunk, 4.9 (95% CIs: 2.9–8.4) at posterior trunk, 2.9 (95% CIs: 1.2–6.6) at upper limbs and 5.0 (95% CIs: 2.9–8.5) at lower limbs. In a case–case analysis, comparing CMM cases at a specific site and CMM cases at all other sites, the only excess risk was found for the posterior trunk, the ORs being 2.1 (95% CIs: 1.2–3.6) for the highest *versus* the lowest tertile of number of nevi. Our data do not support the hypothesis of a specific effect of nevi at each single anatomical site.

Journal of Investigative Dermatology (2006) **126,** 2106–2110. doi:10.1038/sj.jid.5700334; published online 27 April 2006

INTRODUCTION

Cutaneous malignant melanoma (CMM) is strongly associated with total number of nevi. A meta-analysis including data on 46 studies published until 2002 reported that both total number of common nevi and atypical nevi were important and independent risk factors for melanoma, the pooled relative risks of melanoma being 6.89 for high (101–120) *versus* low (<15) number of common melanocytic nevi, and 6.36 for 5 *vs* 0 atypical nevi (Gandini *et al.*, 2005).

However, scanty information is available on the relation between CMM at a specific site and number of nevi at the corresponding site (Holman and Armstrong, 1984; Green *et al.*, 1985; Swerdlow *et al.*, 1986; Bain *et al.*, 1988; Weinstock *et al.*, 1989; Bataille *et al.*, 1998; Whiteman *et al.*, 2003).

In a multicentric hospital-based case–control study conducted in Germany, Switzerland, and Austria based on 278 patients with melanoma and 278 controls, matched for age and sex, the risk of melanoma on the trunk and on the legs was best predicted by number of nevi on the corresponding sites, but the study did not unequivocally support a site-specific risk (Rieger *et al.*, 1995).

A population-based case–control study including 548 newly diagnosed CMM cases and 494 controls (Caucasian Connecticut residents) collected information on risk factors by anatomical site in the arms and the back (Chen *et al.*, 1996). No relation was found between naevus count and risk of melanoma on these sites. The study also reported that gender was the only risk factor that affected the risk of melanoma across anatomical sites (Chen *et al.*, 1996), men having higher risk for melanoma on the trunk and women on the limbs.

Another hospital-based case–control study from southern Spain (Rodenas *et al.*, 1997), including 116 CMM cases and 116 controls, analyzed the risk of CMM at several sites (face and neck, chest and abdomen, back, arms, and palms and hands) and reported that the site-specific risk of CMM was strongly associated with the number of melanocytic nevi on the corresponding sites, especially among patients with superficial spreading melanoma subtype. The study did not report which were the most strongly associated sites.

In order to assess and quantify the site-specific association between risk of CMM and number of nevi, we analyzed data

[1]*Istituto di Ricerche Farmacologiche ''Mario Negri'', Milan, Italy;* [2]*Centro studi GISED, Ospedali Riuniti di Bergamo, Bergamo, Italy and* [3]*Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy*

[4]*Participants: F. Arcangeli, D. Calista, G. Landi (Cesena), P. Puiatti (Torino), C. Catricalà, L. Eibenschutz (Roma), G. Lo Scocco, V. Di Lernia (Reggio Emilia), A. Tosti, C. Misciali (Bologna), F. Scardigli, M. Cristofolini (Trento), M. Simonacci, M. Sigona (Macerata), G. Pasolini, A. Manganoni, A. Lonati (Brescia), R. Betti (Milano), A. Barba, F. De Agostini, C. Chieregato (Verona), G. Fabbrocini, N. Balato, P. Santoianni (Napoli), M.G. Bertazzoni, P. Danese (Mantova), I. Stanganelli (Ravenna), S. Moretti, P. Carli (Firenze), M. Iannantuono (S. Giovanni Rotondo), P. Taddeucci (Siena), A. Virgili (Ferrara), G. Fenizi (Foggia), E. Rossi, M. Pini, G. Galbiati (Monza), A. Locatelli (Como).*

Correspondence: Dr Giorgia Randi, Istituto di Ricerche Farmacologiche ''Mario Negri,'' Via Eritrea 62, Milan 20157, Italy.
E-mail: randi@marionegri.it

Abbreviations: CMM, cutaneous malignant melanoma; OR, odds ratio; 95% CI, 95% confidence interval

Received 11 January 2006; revised 17 March 2006; accepted 20 March 2006; published online 27 April 2006

from a multicentric case–control study conducted in Italy (Naldi *et al.*, 2000, 2005).

RESULTS

Whereas CMM on the limbs was more frequent in women (upper 72.8% and lower limbs 82.5%), CMM on the trunk was more frequent in men (anterior 64.6% and posterior trunk 63.0%). CMM at face and neck was more frequent at older ages for both sexes, while CMM at anterior and posterior trunk was more frequent in younger women (<40 years) (Table 1).

In both genders, mean number of nevi among cases was higher than among controls for each site considered (Table 2).

In order to quantify the association between number of nevi at a specific site and risk of CMM at each anatomical site, we derived the multivariate odds ratios (ORs) of site-specific risk of CMM for approximate tertiles of number of nevi on each anatomical site. For CMM on face and neck, the highest association was observed with number of nevi on lower limbs, but direct associations were found with number of nevi at other sites too. The risk of CMM on the anterior trunk was associated with number of nevi on all anatomical sites, and the strongest associations were found for number of nevi on the limbs: the ORs for CMM on the anterior trunk were 2.89 for ⩾6 nevi on lower limbs and 2.84 for ⩾5 nevi on the upper limbs. Likewise, the number of nevi on the posterior trunk was the best predictor of the risk of CMM on the posterior trunk, the ORs being 4.92 for ⩾6 nevi. Risk of CMM at upper limbs was strongly associated with number of nevi on lower limbs (ORs = 5.01) and, less strongly on posterior trunk and upper limbs. Number of nevi at lower limbs was the best predictor for risk of CMM at lower limbs and the ORs for ⩾6 nevi was 4.99. Number of nevi at lower limbs was also the best predictor of the risk of CMM at all sites, and the ORs for ⩾6 nevi compared to 0 was 3.80 (Table 3).

The previous analyses on the risk of CMM at different sites were repeated in a case–case analysis comparing cases of CMM at a specific site with cases of CMM at different sites according to number of nevi at the specific site considered. Only CMM at posterior trunk was significantly associated

Table 1. Distribution[1] of 542 cases of CMM and 538 controls by gender, age group, and anatomical site of CMM, Italy 1992–1994

	Men						Women					
	Age group (years)						Age group (years)					
Anatomical site	<40	40–49	50–59	60–69	⩾70	Total	<40	40–49	50–59	60–69	⩾70	Total
Face/neck	6	3	5	12	10	36	4	4	12	9	16	45
Anterior trunk	10	10	10	8	4	42	10	3	4	4	2	23
Posterior trunk	16	23	26	13	19	97	20	9	14	9	5	57
Upper limbs	3	2	1	6	2	14	5	12	9	4	4	34
Lower limbs	7	3	3	11	8	32	26	29	34	33	29	151
Controls	49	36	45	56	44	230	70	57	64	61	56	308

[1]Information on site was missing for 11 cases.

Table 2. Mean number of melanocytic nevi and SE by anatomical site and gender for cases of CMM and controls, Italy 1992–1994

	Men				Women			
	Cases		Controls		Cases		Controls	
Anatomical site	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Whole surface	25.8	2.2	12.6	1.1	20.4	1.5	11.3	1.0
Face/neck	2.0	0.3	1.1	0.1	2.3	0.3	1.5	0.2
Anterior trunk	5.5	0.5	2.9	0.3	2.9	0.2	1.8	0.2
Posterior trunk	7.4	0.6	3.7	0.4	4.2	0.3	2.7	0.3
Upper limbs	5.3	0.6	2.5	0.3	5.3	0.5	3.0	0.3
Lower limbs	5.6	0.9	2.4	0.3	5.8	0.6	2.3	0.3

Table 3. Odds ratios[1] and 95% CIs for CMM at different anatomical locations by number of nevi: comparison with controls

Approximate tertiles of number of nevi by site	CMM site					
	Face/neck	Anterior trunk	Posterior trunk	Upper limbs	Lower limbs	All sites
Face/neck						
0[2]	1	1	1	1	1	1
1–2	1.01 (0.56–1.84)	0.81 (0.41–1.61)	1.02 (0.64–1.65)	0.80 (0.38–1.66)	1.08 (0.71–1.65)	0.99 (0.74–1.33)
⩾3	1.38 (0.68–2.80)	1.70 (0.84–3.43)	**2.15 (1.30–3.55)**	1.04 (0.43–2.50)	**1.55 (0.95–2.52)**	**1.65 (1.17–2.31)**
Anterior trunk						
0[2]	1	1	1	1	1	1
1–3	1.27 (0.70–2.32)	1.50 (0.72–3.13)	1.47 (0.86–2.51)	1.00 (0.47–2.13)	1.09 (0.71–1.67)	1.21 (0.89–1.64)
⩾4	1.95 (0.90–4.20)	**2.32 (1.09–4.90)**	**4.36 (2.49–7.62)**	1.56 (0.64–3.78)	**2.02 (1.19–3.44)**	**2.54 (1.77–3.65)**
Posterior trunk						
0–1[2]	1	1	1	1	1	1
2–5	**1.98 (1.07–3.65)**	1.04 (0.51–2.09)	**1.70 (1.02–2.84)**	1.07 (0.47–2.43)	0.92 (0.60–1.40)	1.19 (0.88–1.60)
⩾6	**3.26 (1.50–7.09)**	**2.28 (1.11–4.68)**	**4.92 (2.87–8.42)**	**3.27 (1.42–7.53)**	**2.16 (1.28–3.67)**	**3.00 (2.09–4.31)**
Upper limbs						
0[2]	1			1	1	1
1–4	**1.64 (0.90–3.01)**	1.84 (0.90–3.78)	**1.77 (1.09–2.90)**	1.56 (0.71–3.39)	**1.67 (1.08–2.59)**	**1.63 (1.21–2.21)**
⩾5	**2.80 (1.37–5.74)**	**2.84 (1.37–5.91)**	**2.97 (1.75–5.04)**	**2.85 (1.24–6.56)**	**2.78 (1.68–4.61)**	**2.69 (1.90–3.80)**
Lower limbs						
0[2]	1	1	1	1	1	1
1–5	**2.06 (1.12–3.80)**	1.46 (0.75–2.85)	1.28 (0.81–2.02)	1.41 (0.65–3.06)	1.42 (0.92–2.19)	**1.44 (1.08–1.93)**
⩾6	**5.32 (2.40–11.80)**	**2.89 (1.36–6.12)**	**3.60 (2.05–6.33)**	**5.01 (2.11–11.86)**	**4.99 (2.92–8.53)**	**3.80 (2.61–5.54)**
Total						
0–6[2]	1	1	1	1	1	1
7–21	**2.06 (1.10–3.87)**	1.47 (0.73–2.97)	**1.78 (1.07–2.98)**	1.67 (0.78–3.59)	**1.82 (1.18–2.80)**	**1.69 (1.25–2.30)**
⩾22	**3.97 (1.88–8.41)**	**2.54 (1.23–5.22)**	**5.15 (3.01–8.79)**	**3.36 (1.42–7.94)**	**3.21 (1.90–5.42)**	**3.50 (2.45–5.00)**

[1]Adjusted for sex, age, education, body mass index, eye, hair and skin color, solar lentigines, propensity to sunburn, sunburn episodes, and tobacco smoking.
[2]Reference category.
Significant ORs are given in bold.

Table 4. Odds ratios[1] and 95% CIs for CMM at specific anatomical locations by number of nevi: comparison with cases of CMM at other sites

Approximate tertiles of number of nevi[2]	CMM site				
	Face/neck	Anterior trunk	Posterior trunk	Upper limbs	Lower limbs
I[3]	1	1	1	1	1
II	1.15 (0.61–.15)	1.31 (0.60–2.87)	1.50 (0.88–2.55)	0.87 (0.40–1.90)	1.12 (0.68–1.84)
III	1.06 (0.52–2.17)	0.95 (0.43–2.09)	**2.07 (1.21–3.56)**	0.91 (0.40–2.10)	1.17 (0.68–2.01)

[1]Adjusted for sex, age, education, body mass index, eye, hair and skin color, solar lentigines, propensity to sunburn, sunburn episodes, and tobacco smoking.
[2]Number of nevi counted on the same site of CMM.
[3]Reference category.
Significant ORs are given in bold.

with number of nevi on the corresponding site, the ORs for CMM being 2.07 for $\geqslant 6$ nevi compared to $\leqslant 1$ (Table 4).

DISCUSSION

Our study confirmed the effect of total number of nevi on the risk of CMM, but did not show a site-specific association for all sites considered, except for posterior trunk, where the risk of CMM can be associated not only with common nevi (>2 mm), but particularly with atypical nevi which are more likely present in the trunk than in other anatomical sites (Rieger *et al.*, 1995). In our study, atypical nevi (>6 mm) were more prevalent on the trunk than in other sites both in men and in women. Thus, the mean percentage of site-specific number of atypical nevi among male controls was 29.1% (SE = 5.3%) on the anterior trunk and 49.5% (SE = 6.0%) on the posterior trunk. Corresponding values for female controls were 28.3% (SE = 4.4%) and 23.6% (SE = 4.0%), respectively. In contrast with Rieger *et al.* (1995), we found a relatively higher mean percentage of atypical nevi on the face and neck in women (22.4%) than in men (10.8%).

A previous study suggested that the site-specific association between CMM risk and number of nevi was stronger for superficial spreading melanoma subtype (Rodenas *et al.*, 1997): we therefore repeated the analysis in the subset of superficial spreading melanoma cases, but we did not find any site-specific association.

Whiteman *et al.* (2003), in a study from Queensland, Australia, based on 231 cases of invasive superficial spreading melanoma on the trunk, and face and neck and 75 lentigo malignant melanoma, proposed different etiological patterns for cutaneous melanoma occurring on different body sites according to sun exposure and individual tendency to develop nevi. Among subjects with low number of nevi and frequent exposure to sunlight, melanomas were more likely to arise on the head and neck, while among people with high susceptibility to nevi, little sun exposure was required to develop melanoma, and melanomas were more likely to arise in sites with high density of nevi, like the trunk (Whiteman *et al.*, 2003). Accordingly, in our study, we found a strong correlation between total number of nevi and risk of CMM on the trunk. However, we also found a strong correlation with CMM on the face and neck. Moreover, the proportion of cases with CMM on face and neck did not vary across strata of total number of nevi, both for men and women. The apparent discrepancies between the two studies could be in part due to the different locations where the studies were conducted (Australia and Italy), whose populations differ in terms of risk factors for CMM, including in particular sun exposure.

The main strength of this study is that cases and controls were examined by trained dermatologists to assess pigmentary traits and to count melanocytic nevi. Moreover, participation rate was almost complete, and the catchment areas for cases and controls were comparable. Cases were not selected according to the anatomical site of CMM, but were consecutive patients of each center, likely reflecting the real body distribution of CMM in the Italian population. Thus, number of cases in our dataset varied considerably across various body sites (from 48 for upper limbs to 183 for lower limbs), which implies that the statistical power differed by body sites. With reference to potential information bias, the interviews were conducted in the same setting for cases and controls, and the hospital setting should improve the comparability of recall between the two groups. Further, careful adjustment was made for the strongest risk determinants, including pigmentary traits, history of sunburns, and a number of other potentially relevant lifestyle covariates. Thus, it is unlikely that the present results are substantially influenced by selection and information bias, or confounding.

In conclusion, our data did not support the hypothesis of a specific effect of nevi at each single anatomical site, with the exception of posterior trunk. Total count of melanocytic nevi may be a general risk indicator and melanocytic nevi by themselves may not be an important precursor to CMM.

MATERIALS AND METHODS

A case–control study on CMM was conducted within the framework of the Italian Group for Epidemiologic Research in Dermatology (GISED) between 1992 and 1994 in 27 centers, 16 in the North and 11 in the South of Italy (Naldi *et al.*, 2000, 2005). Cases were 542 consecutive patients (226 males and 316 females; median age 54 years, range 15–87) with incident, histologically confirmed invasive CMM information on anatomical site was missing for 11 cases. Approximately 1% of cases had been excluded because of a previous diagnosis of a primary malignant melanoma. Controls were 538 patients (230 males and 308 females; median age 54 years, range 15–92) of similar age and gender distributions as cases, admitted to the same hospitals of cases for non-dermatological and non-neoplastic diseases. Of controls, 30% were admitted for acute surgical and gynecologic conditions, 23% had acute medical disorders, 12% had traumatic or other orthopedic conditions, and 35% had other illnesses, such as disorders of the ear, nose, throat, or teeth. Of cases and controls, $<1\%$ refused to participate. Data collection was approved by the medical directors of the institutions and the consultants of the wards involved, and informed consent was obtained by subjects interviewed.

Trained interviewers administered a structured questionnaire to cases and controls, including information on socio-demographic characteristics, anthropometric measures, personal pigmentary phenotype, lifetime history of sun exposure, and smoking habit. Cases and controls were also examined by trained dermatologists who counted the number of melanocytic nevi and made judgments on pigmentary traits according to standardized criteria. Nevi >2 and >6 mm in diameter were counted over the whole body surface excluding the genitalia and scalp area. A simple instrument, called a ''nevometer,'' was used to rapidly assess the diameter (2 and 6 mm). A photographic atlas of nevi was used to facilitate judgments. 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. Common nevi had a diameter of up to 6 mm. Atypical nevi had a diameter >6 mm, lacking features of congenital nevi.

For the present analysis, CMM cases were grouped according to the anatomical site of the neoplasm in five different locations (face/neck, anterior and posterior trunk, upper and lower limbs).

ORs for CMM at different sites by number of common nevi (>2 mm) were estimated by unconditional multiple logistic regression models (Breslow and Day, 1980), after allowance for age, sex, education, body mass index, history of sunburns, propensity to sunburn, number of solar lentigines, skin, hair and eye color, and tobacco smoking.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

The study was supported by the Italian Association for Cancer Research (AIRC), the Italian League against Tumours, and the Italian Ministry of Education (COFIN 2003).

REFERENCES

Bain C, Colditz GA, Willett WC, Stampfer MJ, Green A, Bronstein BR *et al.* (1988) Self-reports of mole counts and cutaneous malignant melanoma in women: methodological issues and risk of disease. *Am J Epidemiol* 127:703–12

Bataille V, Sasieni P, Grulich A, Swerdlow A, McCarthy W, Hersey P *et al.* (1998) Solar keratoses: a risk factor for melanoma but negative association with melanocytic nevi. *Int J Cancer* 78:8–12

Breslow NE, Day NE (1980) *Statistical Methods in Cancer Research, Vol. 1. The Analysis of Case-Control Studies*. Lyon, France: IARC Scientific Publication 32. IARC

Chen YT, Dubrow R, Holford TR, Zheng T, Barnhill RL, Fine J *et al.* (1996) Malignant melanoma risk factors by anatomic site: a case–control study and polychotomous logistic regression analysis. *Int J Cancer* 67:636–43

Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P *et al.* (2005) Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical nevi. *Eur J Cancer* 41:28–44

Green A, MacLennan R, Siskind V (1985) Common acquired nevi and the risk of malignant melanoma. *Int J Cancer* 35:297–300

Holman CD, Armstrong BK (1984) Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. *J Natl Cancer Inst* 72:257–66

Naldi L, Imberti GL, Parazzini F, Gallus S, La Vecchia C (2000) 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. *Cancer* 88:2703–10

Naldi L, Altieri A, Imberti GL, Gallus S, Bosetti C, La Vecchia C (2005) Sun exposure, phenotypic characteristics, and cutaneous malignant melanoma. An analysis according to different clinico-pathological variants and anatomic locations (Italy). *Cancer Causes Control* 16:893–9

Rieger E, Soyer HP, Garbe C, Buttner P, Kofler R, Weiss J *et al.* (1995) Overall and site-specific risk of malignant melanoma associated with nevus counts at different body sites: a multicenter case–control study of the German Central Malignant-Melanoma Registry. *Int J Cancer* 62: 393–7

Rodenas JM, Delgado-Rodriguez M, Farinas-Alvarez C, Herranz MT, Serrano S (1997) Melanocytic nevi and risk of cutaneous malignant melanoma in southern Spain. *Am J Epidemiol* 145:1020–9

Swerdlow AJ, English J, MacKie RM, O'Doherty CJ, Hunter JA, Clark J *et al.* (1986) Benign melanocytic nevi as a risk factor for malignant melanoma. *Br Med J (Clin Res Ed)* 292:1555–9

Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Bronstein BR, Mihm MC Jr *et al.* (1989) Moles and site-specific risk of nonfamilial cutaneous malignant melanoma in women. *J Natl Cancer Inst* 81:948–52

Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC (2003) Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* 95:806–12