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Dermato-oncology · Epidemiology · Melanoma · Risk factors

Abstract

Background: No studies are available in the literature on the distribution of different melanoma features nd risk factors in the Italian geographical areas. Objective: To identify the differences in clinical-pathological features of melanoma, the distribution of risk factors and sun exposure in various Italian macro-areas. Methods: Multicentric-observational study involving 1,472 melanoma cases (713 north, 345 centre, 414 south) from 26 referral centres belonging to the Italian Multidisciplinary Group for Melanoma. Results: Melanoma patients in northern regions are younger, with thinner melanoma, multiple primaries, lower-intermediate phototype and higher counts of naevi with respect to southern patients; detection of a primary was mostly connected with a physician examination, while relatives were more involved in the south. Northern patients reported a more frequent use of sunbeds and occurrence of sunburns before melanoma despite sunscreen use and a lower sun exposure during the central hours of the day. Conclusions: The understanding of differences in risk factors distribution could represent the basis for tailored prevention programmes.

The incidence of melanoma in Italy, according to the Italian network of cancer registries (Airtum) database, varies between 6 and 15 new cases per 100,000 yearly, following a gradient from north to south [1]. Indeed, higher rates are registered in the north (particularly Piedmont, Trentino, Friuli, Romagna) and, to a lesser extent, the centre (Tuscany) with respect to the south, where the lowest values are reported in Campania, Sicily and Sardinia. In a paper based on Airtum data, the effect of latitude was statistically significantly present also when adjusting for other variables (incidence rate ratio = 1.08) [2]. Similarly, in a cross-sectional study the risk increased with latitude, from the province of Brindisi to Rome and Forlì up to Genova (odds ratio 1.16) [3]. According to 2013 Airtum data, standardized melanoma incidence rates decrease from north (14.7 in 100,000 inhabitants/year in males and 14.2 in females) to centre (11.6 in males and 11.9 in females) and to south (7 in males and 6.3 in females) [1].

The differences in the incidence of melanoma reflect a different distribution of climatic conditions. According to the Köppen classification, in fact, Italy can be subdivided into different climatic areas, ranging from Mediterranean to the humid subtropical up to the oceanic/mountain climate [4,5] (fig. 1). It is therefore evident that solar radiation intensity as well as sun exposure behaviour and outdoor/indoor activities are different among the north, centre and south of Italy. The intermittent sun exposure which could represent a more frequent behaviour for people living in the northern regions could well explain the relationship between higher latitudes and increased risk of sunburns [6].

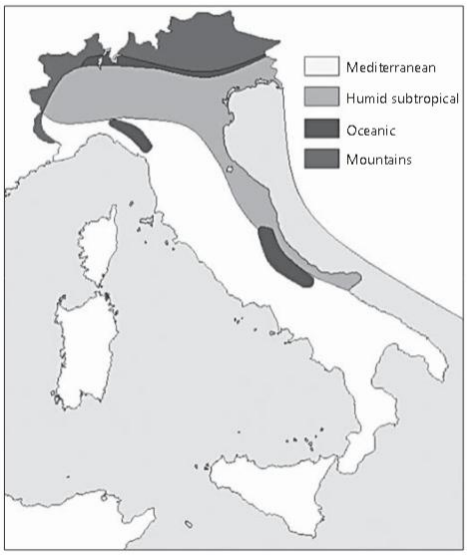

Fig. 1. Italian climatic areas according to the Köppen-Geiger classification

In spite of this evidence, no studies are available in the literature focusing on the differences of clinical-pathological features of melanoma as well as of the distribution of known risk factors in the geographical Italian areas.
This prompted us to perform this multicentric study between the centres belonging to the GIPMe (Italian Multidisciplinary Group for Melanoma), with the aim to identify the differences in the clinical-pathological features of melanoma, distribution of risk factors and sun exposure behaviour between 3 main geographical Italian macro-areas (north, centre and south).

Patients and Methods

Patient Selection

In this multicentric observational study, melanoma patients seen during an 18-month period from June 2012 to December 2013, at 26 dermatological melanoma referral centres in Italy, were enrolled after signing written informed consent. Enrolled patients included both cases with a new melanoma diagnosis and cases seen for periodical follow-up examinations.
The Italian territory has been divided into 3 main geographical areas (north, centre and south) based on the ISTAT (Istituto nazionale di Statistica) criteria [7]. The north area includes the regions of Valle d'Aosta, Piedmont, Lombardia, Liguria, Trentino, Veneto, Friuli Venezia Giulia and Emilia-Romagna. The centre area includes the regions of Tuscany, Marche, Lazio and Umbria. The south area includes Abruzzi, Molise, Puglia, Campania, Basilicata, Calabria and the islands of Sicily and Sardinia. The populations of these 3 areas are distributed as follows: north 27,653,188 inhabitants, centre 12,070,842 and south 13,973,865 according to the 2013 ISTAT database [7]. The distribution of GIPMe centres on the Italian territory was as follows: 10 in the north, 10 in the centre and 6 in the south. All centres are referral Institutions for the diagnosis and treatment of melanoma in Italy and therefore share similar equipments, guidelines and experience in the management of this kind of patients. On the basis of this criterion, no significant differences in any of the parameters analysed were found according to the size of the centres.
A total of 1,789 cases were analysed in the participating centres during the analysed period. The data file included the demographic characteristics of the patients, their clinical history and the clinical-pathological features of the melanoma. Constitutional risk factors for melanoma including phototype, phenotype, family history of melanoma and previous melanoma excision were identified in each patient. Phototype was determined according to the Fitzpatrick classification [8] during the clinical examination and on the basis of the personal history reported by the patient. Moreover, each patient was given a survey to be filled in on his personal sun exposure behaviour, indoor or outdoor working as well as hobbies, previous sunburns and use of sunscreens. Each patient was given a thorough clinical examination by a dermatologist, expert in pigmented lesions, and data on the number and type of naevi distributed by anatomical site were recorded. The characteristics of ‘total naevi' and ‘atypical naevi' to be included were preliminarily discussed among centres and identified according to previously published criteria: naevi ≥5 mm (and meeting at least 2 of the following criteria: irregular border, sharp margins, dishomogeneous pigmentation) were classified as atypical naevi; naevi ≥2, but <5 mm in diameter were classified as ‘total naevi' as well as naevi ≥5 mm without the 2 morphological criteria mentioned [9]. Pigmented non-melanocytic skin lesions such as seborrhoeic keratoses were identified on the basis of clinical and dermoscopic features and not included. Melanoma patients with unknown anatomical site, or with missing and/or equivocal data, were not enrolled in the study.
Surveys were administered at the first dermatological visit after melanoma diagnosis or during scheduled follow-up visits.

Statistical Analyses

From the original series of 1,789 cases, the following were excluded: (1) 273 patients with melanoma diagnosis before 2005; (2) 43 patients born outside Italy; (3) 3 patients who had lived for more than 10 years outside Italy. Data analysis and results were therefore drawn from a restricted cohort of 1,472 patients.
Differences in the distribution of the analysis variables between the 3 Italian geographical areas were evaluated with the $\chi 2$ test for proportions, with ANOVA for the comparison of means (e.g. age at diagnosis),

and the non-parametric test for equality of medians for variables which have a skewed distribution (e.g. Breslow thickness, number of naevi).
A variable summing all the naevi for each subject was created, and the median of such variables was compared across areas.

Results
A total of 1,472 cases were analysed, 713 from the north, 345 from the centre and 414 from the south of Italy.
Demographic Features
Gender (736 men and 736 women) was equally distributed (p = 0.82). The age at diagnosis was different (p = 0.04), with the youngest patients in the south (mean age = 52.0 years), intermediate values in the north (53.4 years) and the oldest, on average, in the centre (54.9 years) (table 1). The instruction level of patients decreased from the north (70.7% of patients had a high level of education, at least high school) to the south (61.4%) (p = 0.003).

	North (n = 713)	Centre (n = 345)	South (n = 414)	p
Mean age at diagnosis, years	53.4	54.9	52.0	0.04
Median Breslow thickness, mm	0.5	0.7	0.8	<0.001
Nodular histotype, %	6.2	7.3	9.7	<0.001

Table 1. Distribution of demographic and clinicopathological features of melanoma between north, centre and south regions

Diagnosis
The suspected lesion was found more frequently by the patient himself (37.2, 38.8 and 38.9%, from north to south, respectively) and by the dermatologist (39.0, 36.2 and 35.3%, from north to south, respectively) without differences between the 3 geographical areas (p = 0.04). The spouse, other relatives or friends identified more frequently the suspected lesion in the centre (20.8%) and south (18.4%) with respect to the north (14.2%); on the other hand, in the north, the general practitioner or other specialists were most frequently responsible for the excision of the lesion (9.7 vs. 4.6% in the centre and 7.5% in the south) (fig. 2). No significant differences in the percentage of patient-referring periodical self-examinations for the findings of new or suspected naevi were found between the 3 different areas (values ranging from 65.1 to 66.2%, p = 0.93).

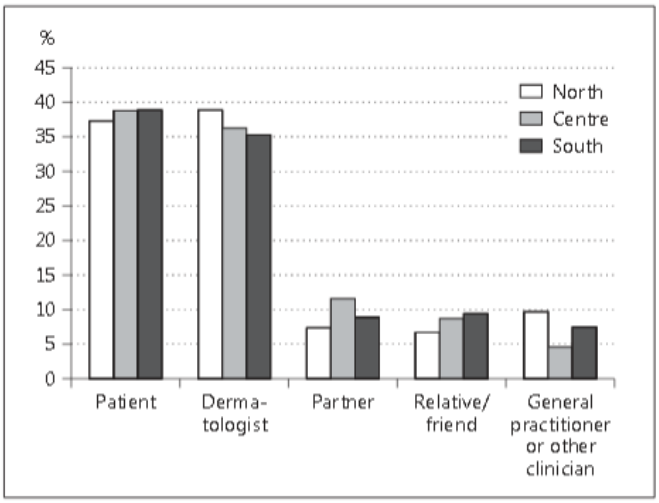

Fig. 2. Differences between the detection of primaries between the geographical areas.

Clinicopathological Features of Melanoma

The posterior trunk and the lower limbs were the most common sites for melanoma, without differences between the 3 areas. Thin melanomas accounted for the majority of cases; Breslow thickness was higher in southern regions (median: 0.85 mm; no statistically significant differences were found in Breslow thickness according to the phototype in the 3 main geographical areas) in comparison with the centre (median: 0.7 mm) and especially the north (median: 0.5 mm) ($p < 0.001$).

The types of melanoma were not homogeneously distributed ($p < 0.001$), and superficial spreading melanoma was the most common histological type in all 3 areas (85.4% north, 76.2% centre and 78.5 south); nodular melanomas were rarely found but were shown to be more frequent in the south (9.7%) with respect to the north (6.2%) and centre (7.3%) (table 1). Histological ulceration of the primary accounted for about 10% of cases in all 3 areas ($p = 0.28$).

Melanoma Risk Factor Distribution

The distribution of constitutional risk factors as well as sun exposure behaviour, sunburns and sunscreen use is summarized in table 2.

	North (n = 713)	Centre (n = 345)	South (n = 414)	p
Previous melanoma, %	11.4	11.4	7	0.045
Family history of melanoma, %				0.86
1st grade	7.7	7.0	6.0	
2nd grade	3.2	2.9	2.9	
Phototype, %				0.03
I	4.5	6.1	4.3	
II	48.9	46.4	42.3	
III	43.1	42.9	45.7	
IV	3.5	4.6	7.7	
Skin phenotype, %				<0.001
Fair	55.9	58.6	57.6	
Intermediate	39.8	38.2	32.5	
Dark	4.2	3.2	9.8	
Number of naevi				0.001
Median	36	28	33	
Range	0–210	0–165	0–256	
Number of atypical naevi				<0.001
Median	0	0	0	
Mean	1.67	1.99	1.34	
Range	0–100	0–58	0–50	
History of previous sunburns, %	80.7	83.8	68.8	<0.001
Outdoor work sun exposure, %	15.4	19.2	16.4	0.30
Sun exposure during central hours, %	18.5	27.7	28.2	<0.001
Sunscreen use (SPF >20), %	58.2	50.45	43.0	<0.001
Sunbed use, %	23.6	23.5	10.1	<0.001

Table 2. Distribution of melanoma risk factors between north, centre and south region

A history of a previous melanoma was significantly more frequent in melanoma patients living in the north and centre (11.4% both) with respect to the south (p = 0.045), whilst there were no differences for a positive melanoma family history.

Phototypes II/III were the most common in all geographical areas. Phototype II showed a significant prevalence in the north (49.0%) with respect to the centre (46.4%) and particularly the south (42.3%); phototype IV was on the other hand more frequently represented in the southern patients (7.7%) with respect to those of the centre (4.6%) and north (3.5%) (p = 0.03). A fair phenotype was the most frequently found (more than half of the cases); a dark phenotype was exceedingly more frequent in the south (9.8% of patients) which figures 2-3 times higher than in the other areas (p < 0.001).

As to the naevus counts, melanoma patients living in the south showed statistically significant lower counts of both total naevi and atypical naevi (median 33 and mean 1.34, respectively) in comparison to the northern patients (p < 0.001).

The large majority of patients reported at least 1 severe sunburn before melanoma diagnosis (78%). Sunburns were more frequent in northern/central regions, even if the exposure during the central hours of the day was more common in the south and centre (28.2 and 27.7%, respectively) (p < 0.001) and the habit of sun protection decreased inversely from the north to south, with a less frequent constant use of sunscreen >20 sun-protective factor in the south (43%) (p < 0.001). Sunbed use was significantly prevalent in northern and central regions (23.6 and 23.5%, respectively) than in the south (only 10.1%) (p < 0.001).

Discussion

Our study takes a picture of the clinical characteristics of melanoma patients and the associated distribution of risk factors throughout Italy, focusing on the identification of differences on the basis of the geographical areas of Italy, characterized by markedly different climate conditions. Even if a lot of papers reported the clinical-pathological characteristics of Italian patients with large cutaneous melanoma, no data are reported as to the distribution of these features as well as the risk factors differentiating between the north, centre and south of Italy. For example, the recent paper by Gandini et al. [10], showing that sunny

holidays were associated with thinner melanomas in women and reduced rates of relapse in both sexes, included 449 patients living in northern Italy and 242 in the central and southern regions; the authors showed that more than half the patients had phototype I-II (53.7%) without however distinguishing between the areas where the patients lived.

The new finding which comes to light from our study is that there exist significant differences in both clinical-pathological features as well as risk factor distribution according to the geographical area. Melanoma patients living in the northern regions are younger, with thinner melanoma and multiple primaries; the detection of their primary, apart from themselves, was mostly connected with a physician's examination, mainly dermatologists but also general practitioners or other specialists (fig. 1). They show an intermediate skin phenotype, with high counts of total as well as atypical naevi. They reported a frequent use of sunbeds and occurrence of sunburns before melanoma in spite of the reported use of sunscreens and a low sun exposure during the central hours of the day. On the other hand, people with melanoma living in the southern regions are elderly, with thicker melanomas; the spouse or other relatives are frequently engaged in the detection of the primary. With respect to the northern patients, they show a higher prevalence of dark phototypes and phenotypes, reduced counts particularly of atypical naevi, higher exposure during the central hours of the day but less frequent sunburns and use of sunbeds. Melanoma patients living in the centre showed features resembling predominantly those of the north (for example multiple primaries, low prevalence of dark phenotypes, high atypical naevus counts, previous sunburns and use of sunbeds), even if some of their features are more similar to the south (lesion frequently seen by the spouse or relatives, sun exposure during central hours).

The reasons why these differences take place were not focused in the present study, even if it can be argued that they lay on the reciprocal interactions between different factors including the socio-economic background, the migration of specific ethnic populations from abroad to Italy during the recent past, genetic factors and climate conditions. The darker phenotypes in the south imply a smaller risk of sunburns and a reduced need to use sunscreens, whilst the 'Mediterranean climate' could favour a persistent sun exposure also during the central hours of the day as well as determine a reduced use of sunbeds. Again, a less frequent request for a physician consultation and thus a potential delay in melanoma diagnosis may have induced a slight increase in melanoma thickness in southern regions.

A first consequence from these findings is that they can play a role as surrogate markers for the evaluation of the efficacy of prevention programmes and campaigns. As to this topic, the arguments which favour a positive impact of prevention programmes in Italy are represented by the evidence that in the majority of patients an early diagnosis of the melanoma was made (median Breslow thickness less than 1 mm) and that more than half of the patients report periodical self-examinations for the finding of suspected lesions. On the other hand however, the percentage of patients complaining of at least 1 severe sunburn before melanoma diagnosis is exceedingly high (up to 83%), and the fact that the majority of patients report constant use of sunscreens implies that they do not apply these topical treatments in the right way. Moreover, the understanding of the differences in risk factor distribution could represent the basis upon which tailored prevention programmes and campaigns could be developed. Patients living in the north need more accurate examinations of their atypical naevi (also for the higher frequency of multiple primaries), should be encouraged to reduce the use of sunbeds and taught how to correctly use sunscreens. Carli et al. [11] found that high counts of common naevi correlate with prevalence of atypical naevi independently of phototype, phenotype or sunburns. Stanganelli et al. [12] conducted a survey of 4,703 people in the region Emilia-Romagna (northern Italy), showing that the use of sunbeds was higher in people already at a higher risk for melanoma, i.e. those with freckles, fair skin and eyes. On the other hand, patients living in the southern regions should be encouraged to consult their general practitioner more frequently and to reduce sun exposure during the central hours of the day; moreover, dermatologists should be aware of the increased percentage of nodular melanoma, which could present difficult clinical and dermoscopic features [11].

A second issue of our study is the potential meaning of our data in terms of different prevalent risk factors associated with melanoma development in the geographical areas of Italy. Overall, independently from the geographical area, our population harbours the typical characteristics of high-risk melanoma patients, i.e. prevalent light phenotype, high naevus counts, high frequency of previous sunburns. As far as we are concerned, there are no studies specifically aimed to ascertain the prevalence and distribution of different

phototypes and phenotypes within the Italian population; some indications can be drawn by data retrieved during screening prevention events, even if in some way they are controversial. For instance, in the population screened during the Italian Euromelanoma day 2010, 6.1% had phototype I, 18.6% II whilst a higher prevalence of dark phototypes (44.9% III and 30.4% phototype IV) was reported with respect to our population; moreover, a sunburn was reported to have taken place before 18 years of age in 35.2% [12]. In the previous similar events from 2005 to 2007, different figures were reported, more similar to those found in our study, with only 7.9% phototype IV and 39.9% phototype II [13]. There are also some studies which reported phenotype and/or phototype distribution in specific regions of Italy in patients without melanoma, who could constitute a valid comparison. In a case-control study conducted in Emilia-Romagna, phototype I was found in 15.2% of controls, phototype II in 33.1%, phototype III in 43.4% and phototype IV in 8.3%, thus a prevalence of either phototype I but also IV with respect to our figures in northern Italy [14]. In another case-control study in Lazio (central Italy) on 304 incident melanomas and 305 controls, phototype IV was found in 13.2% of controls and 4.4% of melanoma cases, previous sunburns in 57.5% of controls and 79.3% of patients. Carli et al. [11] found that in a population of 90 patients with more than 100 common naevi living in Florence (centre of Italy), 53 had phototypes I and II (61%) whilst 34 patients had phototypes III and IV (39%). In another study including 557 patients living in Tuscany (centre of Italy), the majority had phototype III (58.7%) and 10.7% phototype IV [15]. Other studies from the centre and south of Italy reported higher figures of dark phototypes. In a survey on 5,837 young men aged 18-19 years from Marche (centre) and Abruzzo (south of Italy), 44.5% had phototype IV and only 10.3% phototype I or II [16,17]. It seems therefore conceivable that an increase in dark photo/phenotypes can be detected from the north to south of Italy. The different distribution of specific factors between the geographical areas (for example, a larger percentage of patients in the south show phototype IV) could therefore reflect a different distribution of this variable, and it does not mean necessarily that in the southern region melanoma arises more frequently in this group of patients. To address this issue, a control group should be analysed including patients without melanoma coming from the different geographical areas of Italy. Even if the lack of this control group limits the significance of our data, some speculations could be drawn from our results in terms of melanoma pathogenesis. Indeed, according to the so-called divergent hypothesis formulated for the first time by Whiteman et al. [18] in 2003 and confirmed by other papers [19,20], melanoma may arise through 2 different pathways: one in young people, associated with melanocyte proliferation and thus high naevus counts frequently localized to the trunk, the other with chronic sun exposure with a more frequent localization on the head and neck in elderly people [17,18,19]. Some of the characteristics reported in our study fit quite well with the prevalence of the first pathway in the northern people (namely being younger, with very frequent sunburns and higher naevus counts) and in contrast to the second one in the southern regions (elderly people, lower naevus counts and less frequently sunburned, with potentially chronic sun exposure due to the climate) in spite of the fact that we failed to identify related differences in body site localization. Future studies could be directed to evaluate whether different mutations and thus a specific molecular signature characterize melanomas which arose in different Italian regions.

Disclosure Statement

The authors declare no conflicts of interest between themselves and others.

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