

## Epidemiology of malignant melanoma in the province of Palermo (2003-2005)

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### Abstract

**Background:** The incidence of melanoma has steadily increased worldwide and shows geographical variability according to latitude. The aim of this study was to describe the incidence of cutaneous malignant melanoma (CMM) cases in the Province of Palermo during the period 2003-2005.

**Methods:** 231 incident cases of CMM, registered by the Cancer Registry of Palermo, were analysed. Anatomic localization, histological type, thickness, ulceration, margins, any lymph node involvement and metastases were evaluated. A statistical analysis of survival rates was performed.

**Results:** Distribution by sex and stage of diagnosis showed a slight, but not significant, difference between females and males diagnosed both in early and late stage CMM. Age incidence rates were higher in women before the age of 40 and in men over the age of 50. No statistically significant difference in stage was observed between residents in Palermo and of its Province.

148 cases (64%) were found in people living in Palermo, with an incidence rate (EU) of 7.2 over 100,000 in males and 6.1 in females, while in the province the incidence rate was lower (4.7 vs 3.9). Univariate analysis by gender showed better survival in females than in males and a better survival for age <49 and for stage I-II at diagnosis ( $p < 0.05$ ). Multivariate analysis including gender, age and cancer stage showed that survival is significantly positively related to earlier stage ( $p < 0.05$ ) and younger age ( $p = 0.01$ ) but not to sex ( $p = 0.19$ ).

**Conclusions:** Diagnosis of CMM is mainly performed in the early stages, in both sexes and regardless of residence, suggesting no difference in early diagnosis and access to care between city and province. The incidence of CMM appears to be higher in the city compared to the province. Survival following diagnosis was strongly, and independently, related to age and stage of CMM, while gender did not significantly predict survival.

*Key words: malignant melanoma, incidence, survival*

### Introduction

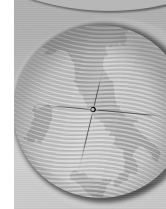
The incidence of cutaneous malignant melanoma (CMM) has increased worldwide, affecting predominantly the Caucasian skin type. It does not have a gender predominance and is rare before puberty, occurring more frequently between 30 and 60 years of age.

In the United States, CMM represents 5% of all tumours in males and 4% in females [1]. It is the sixth most common cancer in males and the seventh in females in the 44-55 year age group. In the European Union, the incidence rate of CMM is 9 cases per 100,000 per year. The incidence increases with latitude, i.e. with increasing prevalence of less-pigmented skin types, from 3-5 cases/100,000 per year in Mediterranean countries to 12-17/100,000 per year in Nordic countries.

The mortality is 2.3 cases/100,000 per year with a lesser variation related to geography [2].

In Italy, the incidence of CMM has increased more than 4% per year in both sexes in the last 20 years. The recent trend continues to show a rise of CMM in males (APC +3.8) and a smaller increase in females (APC +1.9). An annual average of 14.3 cases per 100,000 males/years and 13.6 cases per 100,000 females/years was registered between 2003 and 2005 by Associazione Italiana Registri Tumori (AIRTUM). Moreover, according to 2006 national Italian vital statistics data, CMM accounted for 943 deaths every year in the male population and 635 in the female population [3].

There is also a geographical variability: in fact, in the South both incidence and mortality are lower than in the centre and in the North of Italy [4].



The aim of this study is to analyze the cases of CMM recorded by the Cancer Registry of Palermo, during the period 2003-2005, and to compare the observed results regarding incidence, clinical types, stage distribution, localization, and survival, to those published in the literature.

### Methods

The province of Palermo, placed in the north-west of Sicily, extends for about 5000 km<sup>2</sup>, with a population of 1,243,385 inhabitants. The city of Palermo counts 663,173 people, (314,928 males and 348,245 females), while the remaining 580,212 live in Palermo province outside the city.

In a three year period (2003-2005), the Cancer Registry of Palermo registered about 18,000 cases of cancer, of which 231 (1.3%) were cases of CMM. These were compared to data obtained from the AIRTUM's database (CMM represents 1.9% of all cancers registered in Italy and 1.38% referred to the pool of southern Italian registries) [5]. Incidence rates are expressed as annual cases per 100,000 population.

The AIRTUM guidelines and the International Classification of Diseases Oncology Section were used (2005) [6] to describe the localization and histological type, while the TNM AJCC was used to classify the stage of the tumours [7] with particular attention to the body site of the tumour, the histological type, thickness, ulceration, margins, lymph node involvement and metastases.

Data sources from the demographic service of the municipalities of Palermo were used to follow up patients for vital status. Medical records were consulted for cases with missing vital status data. The last date on which the vital status were confirmed for all patients was January 31<sup>st</sup>, 2009. Authorization for the study was not required according to our institutional policy as described in the legislative Decree 24 giugno 2003, n. 211, item. 1 "Application field". This decree is derived from the Directive 2001/20/CE. More recent regulation regarding the ethics committee in Italy does not require an approval by these organisms, when the investigation is not an intervention study.

Life-table survival analysis was performed according to the Kaplan Meier method. The statistical significance of the comparisons was assessed by the log-rank test. Multivariate analysis was performed with Cox regression models on 187 patients (41 patients with missing data on stage were excluded). All variables that showed a p value below 0.10 in the univariate analysis were entered into a multivariate Cox regression to adjust for confounding. Covariates in the Cox regression model included age (>49 years vs ≤49 years as referent group), gender (males vs females

as referent group) and stage (late [III/IV] vs early [I/II] as referent groups).

Statistical analysis was performed with SPSS 13.0 software [8,9].

### Results

Two hundred thirty one cases of CMM were diagnosed in the Province of Palermo over a three year period (2003-2005), nearly half (48.9%) of which were female (Table 1).

Almost all cases (211, 91.4%) were microscopically verified, and included 193 primary lesions and 18 metastatic lesions. Seventeen cases (7.3 %) were diagnosed clinically and three cases (1.3%) were identified from death certificate only (DCO).

The most common morphologies were epithelioid cells melanoma (25.1%), malignant melanoma NOS (24.7%), superficial spreading melanoma (22.5%) and nodular melanoma (15.6%). The Localization of the tumour was different in men and women. Specifically, melanoma of the leg was much more common in women (34.5%) than in men (12.7%, p=0.0001).

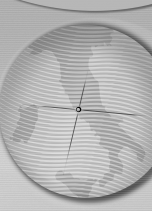
Distribution by sex and stage of condition at diagnosis showed a slight, but non significant difference, between females and males diagnosed in Stage I-II (66.4% versus 64.4%) and in stage III and IV (14.2% versus 16.9%) respectively. In total, sixty five percent of CMM were diagnosed at a localized stage (stage I 48.5%, stage II 16.9%) in both sexes, 11% of cases showed nodal involvement (stage III), 4.6% were metastatic, while in the remaining 19% of the sample an accurate staging was not possible. No statistically significant difference in stage was observed between residents in Palermo city with respect to other 81 municipalities of Palermo Province.

One hundred and forty eight cases (64%) were found in people living in Palermo, with an incidence rate (European standard population) of 7.2 over 100,000 in males and 6.1 in females, while in the province the incidence rate was lower (4.7 in males and 3.9 in females).

In total, the crude incidence rate of our cases was 6.22/100,000 (men 6.59 vs women 5.87). If we consider standardized values of the Italian population (1981), our incidence rate was 5.6 (men 5.8 vs women 5.3), and standardized to the world population it was 4.3 (men 4.5 vs women 4.2).

Table 2 shows the CMM incidence rates, which differed by sex and age. We observed an increased incidence up to 45-49 years old, with higher values in women than in men. At older ages, incidence was substantially higher, particularly in men compared to women.

Figure 1 shows overall and relative survival rates of cases at 1, 3 and 5 years after first diagnosis and



**Table 1. 231 cases of cutaneous melanoma in the province of Palermo during the period 2003-2005.**

<i>Distribution by sex</i>					
Males			Females		
(n=118) 51.1%			(n=113) 48.9%		
<i>Basis of diagnosis</i>					
Histology		Clinical		DCO	
(n=211) 91.4%		(n=17) 7.3%		(n=3) 1.3%	
<i>Morphologies</i>					
Superficial spreading melanoma	Epithelioid cell melanoma	Nodular melanoma	Malignant melanoma, NOS	Others *	
(n=52) 22.5%	(n=58) 25.1%	(n=36) 15.6%	(n=57) 24.7%	(n=28) 12.1%	
<i>Body sites</i>					
	Trunk	Arm	Leg	Skin. NOS	Head and neck
Males	(n=47) 39.8%	(n=19) 16.1%	(n=15) 12.7%	(n=19) 16.1%	(n=18) 15.3%
Females	(n=33) 29.2%	(n=21) 18.6%	(n=39) 34.5%	(n=11) 9.7%	(n=9) 8%
<i>Distribution by sex and stage</i>					
	I-II	III-IV		ND	
Males	(n=76) 64.4%	(n=20) 16.9%		(n=22) 18.6%	
Females	(n=75) 66.4%	(n=16) 14.2%		(n=22) 19.5%	
<i>Distribution by sex and stage between Palermo and province</i>					
	I-II	III-IV		ND	
Palermo	(n=98) 66.2%	(n=22) 14.9%		(n=28) 18.9%	
Province	(n=53) 63.9%	(n=14) 16.9%		(n=16) 19.3%	
<i>Incidence rates (Standardized EU)</i>					
	Palermo	Province		p-value	
All	6.6	4.3		0.0049	
Males	7.2	4.7		0.068	
Females	6.1	3.9		0.0301	
* Includes: epithelioid and spindle cell melanoma, desmoplastic melanoma, amelanotic melanoma, lentigo maligna melanoma					

**Table 2. Age-specific incidence rates of cutaneous malignant melanoma (cases per 100,000 subjects/years) by sex, 2003-2005.**

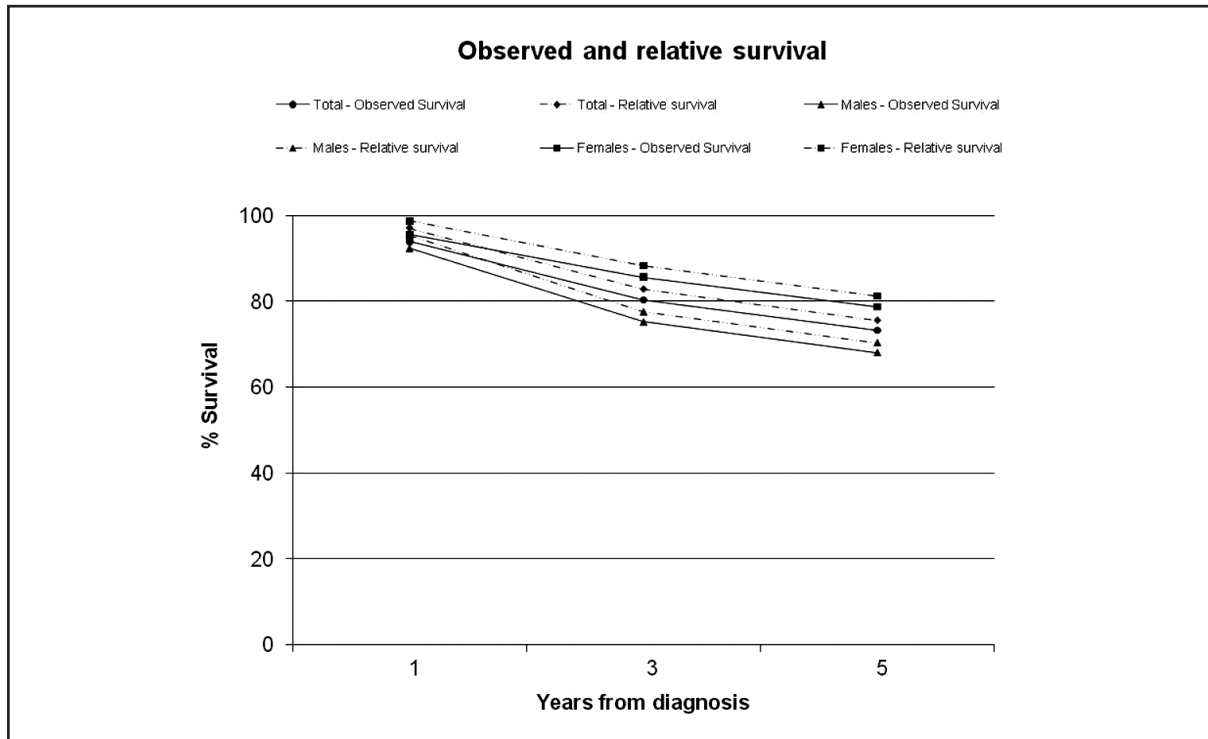
231 Cases of Malignant cutaneous Melanoma (118 males - 113 females)																			
Age classes	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Totale
Males	0.0	0.0	0.0	0.0	0.0	0.7	2.9	3.7	8.5	6.8	13.5	14.8	16.2	18.8	13.8	16.4	28.6	9.6	6.6
Females	0.0	0.0	0.0	0.9	2.4	4.5	6.4	6.9	5.7	9.5	5.8	5.4	12.3	16.7	7.7	10.5	7.6	10.0	5.9

observation. The survival was higher in women than in men along all the points of observation. At 5 years, overall survival was 78% in women and 67% in men. The estimates of five-year overall and relative survival for both sexes (Figure 1) was slightly lower than that reported by the pool of Italian Cancer Registries (77% vs 83% respectively), while no difference in survival

was observed when comparing Palermo to the pool of southern Italian Registries (5-year crude survival 68% vs 74% respectively) [10].

Figure 2 shows the survival of cases divided into two groups, according to age. The cases aged below 49 years old had a better survival time than those aged above 49 years old. Figure 3 shows the

Figure 1. Observed and relative survival curves at 1, 3 and 5 years by sex.



survival of cases analyzed according to their stage of illness at diagnosis: cases (151) classified at stages I and II had a better survival time than those (36) classified at stages III and IV. Intermediate survival was noted for cases (41) which lacked data regarding stage of illness.

Univariate analysis by gender, computed according to the Kaplan-Meier method, showed a better survival in females than in males (Figure 1) and a better survival for age <49 and for stage I-II at diagnosis compared to stage III-IV (Figures 2 and 3). However, no statistically significant difference by gender was observed using the log rank test (chi-square 2.65,  $p=0.10$ ). Instead, statistically significant better survival was observed for those of younger age and at an earlier stage at diagnosis ( $p<0.05$ ).

Multivariate analysis performed by the Cox regression model with these three variables showed that better survival was significantly related to earlier stage at diagnosis ( $p<0.05$ ) and to younger age ( $p=0.01$ ), but not to sex ( $p=0.19$ ), as shown in Table 3.

## Discussion

We present the first population based results from the Cancer Registry of the province of Palermo, which show that some characteristics of CMM in the province of Palermo are comparable with those obtained in other Italian Cancer Registries. Notably, the incidence rate was lower than that reported in other Northern Italian Registries, confirming the geographical variability in the incidence of CMM in the Italian national

territory, with a decreasing incidence from north to south. Also, the survival trend observed through 5 years of observation, both in Palermo and in all the other areas of the province, was slight lower than that registered in the northern Italian registry. Our CMM cases were diagnosed mainly in the early stages of the condition, regardless of gender and place of residence, suggesting that the lower survival rate is not correlated, either in Palermo or the province, to the lack of early diagnosis or to access to care facilities. Nearly all the cases were well characterized, except some cases that lacked stage classification, indicating that data were sufficiently complete for conclusions regarding incidence rates and survival outcomes.

We observed a quantitatively different pattern of clinical representation in Palermo compared to other parts of Sicily (data not shown). In Trapani (a western Sicilian province), the most common clinical subtype detected was superficial spreading melanoma (about 40%) while in Siracusa (an eastern Sicilian province) epithelioid melanoma cell type was noted (31.6%), similar to Palermo (25.1%). This result could be attributed to a variation in the recording of different morphologies among Sicilian cancer registries. However, most epidemiological studies suggest that superficial spreading melanoma is the most common histological subtype of malignant melanoma, but a recent study challenged this notion, at least in patients with extensive sun exposure [11]. Changing patterns of sun exposure

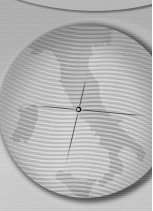


Figure 2. Observed survival curves by early and late age at diagnosis (49 years old).

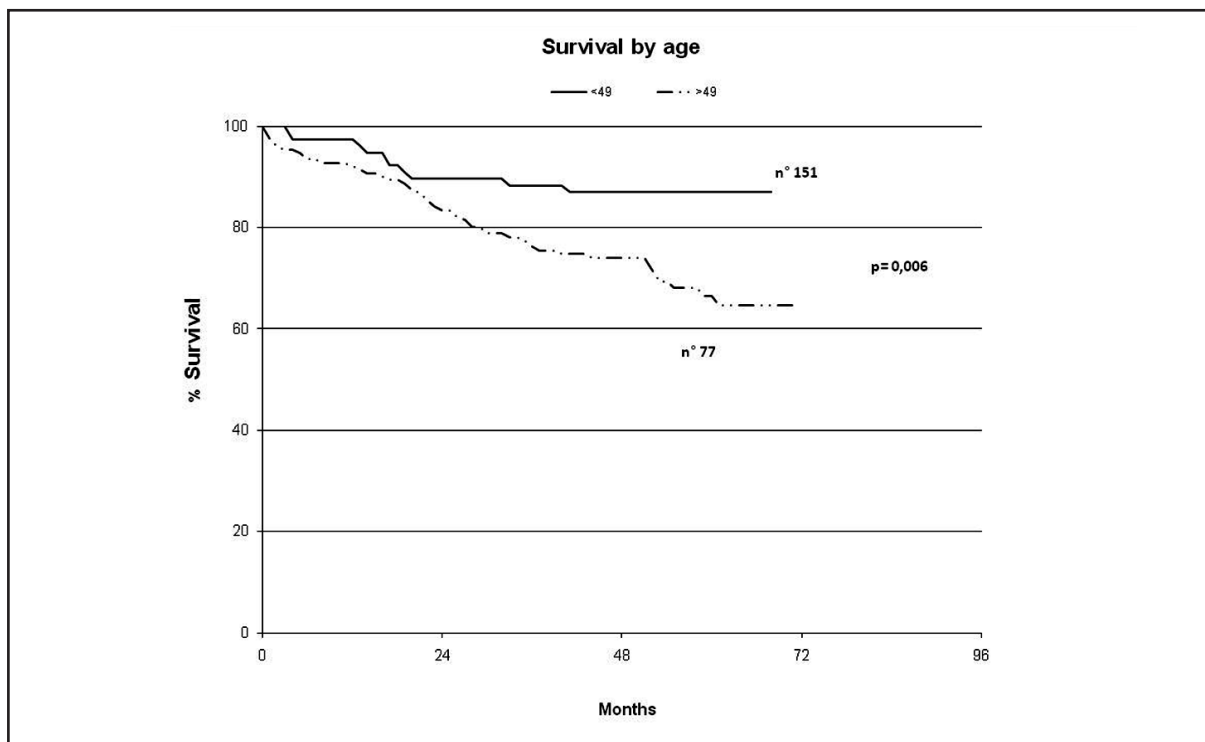
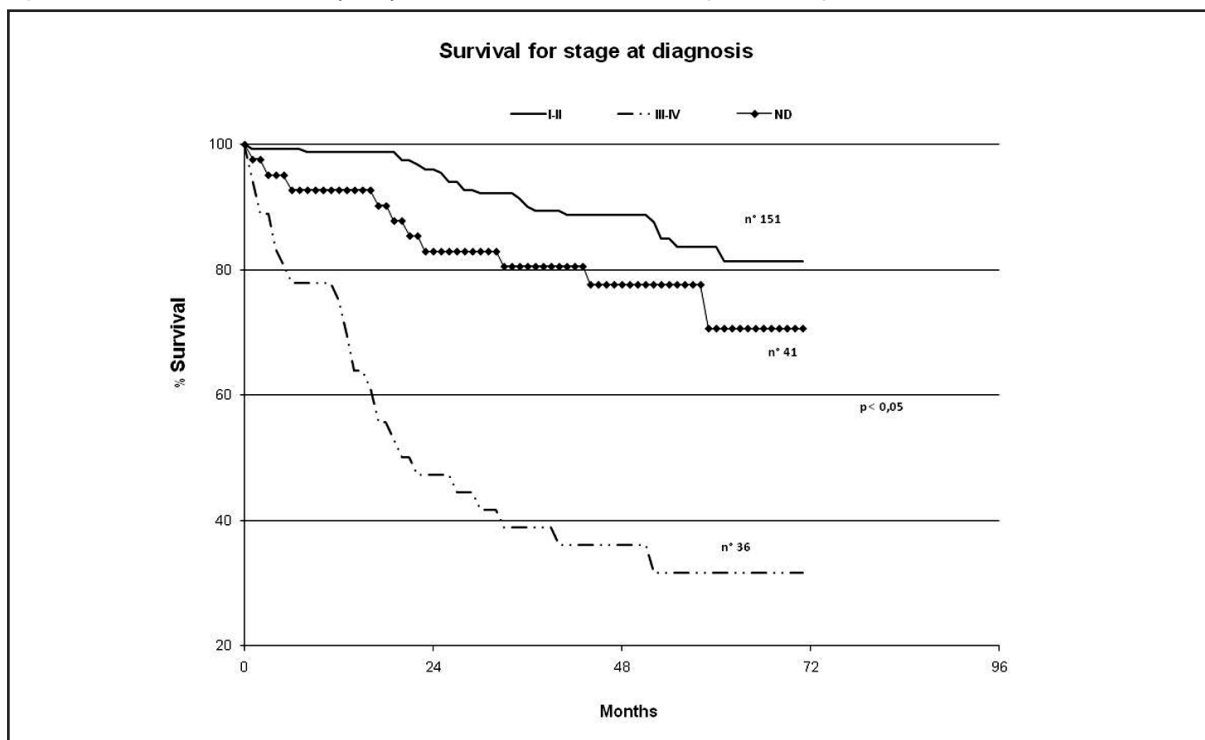


Figure 3. Observed survival curves by early (I and II) and late (III and IV) stage at the diagnosis.



or environmental factors may contribute to the changing epidemiology of malignant melanoma. Therefore, the current prevalence of subtypes of melanoma should be studied in other populations with particular attention to the patterns of sun exposure and other risk factors.

It is interesting to note the increasing incidence in women, up to 45-49 years of age. In the United States, recently published data showed an increase in melanoma in young women (age 15-39) over the past several years. In addition, investigators have found that the incidence of cutaneous



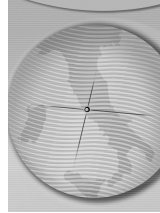


Table 3. Cox-regression model of survival of 187 patients with melanoma.

		<i>Crude Hazard Ratio (95% CI)</i>	<i>Adjusted Hazard Ratio (95% CI)</i>
<b>Age in years</b>			
	≤ 49	Referent	Referent
	> 49	2.19 (1.05-4.53) <sup>b</sup>	2.6 (1.25-5.55) <sup>b</sup>
<b>Gender</b>			
	Female	Referent	Referent
	Male	1.7 (0.93-3.1) <sup>a</sup>	1.38 (0.75-2.54)
<b>Stage</b>			
	Early (I/II)	Referent	Referent
	Late (III/IV)	7.92 (4.4-14.2) <sup>b</sup>	8.8 (4.88-15.9) <sup>b</sup>
<b>Residence</b>			
	Palermo	Referent	-
	Province	1.03 (0.57-1.88)	-
<sup>a</sup> P-value <0.10 <sup>b</sup> P-value <0.05			

melanoma in young men in the United States has increased from 4.7 to 8.7 cases per 100,000 persons from 1973 to 2004. In young women over the same period of time, the incidence has increased much more rapidly, from 5.5 to 13.9 cases per 100,000. When they compared the data by birth cohorts, the investigators found that melanoma increased for women born after 1965. The authors postulated that the increase in incidence among women born after 1965 reflected a change in exposure to risk factors for CMM across cohorts of people born in different years. Why the significant increase in melanoma in women? It is not likely due to improved detection of melanoma because we would expect that melanoma rates would have increased in both men and women equally. It is more likely due to increased exposure to ultraviolet radiation, a well established risk factor for CMM. In the United Kingdom, it was noted that females before age 50, and especially among those in the 20s, were over-represented in CMM case incidences. Based on recent studies, [12] the different pattern of disease between sexes (higher in women than in men before age 40, equivalent between 40 and 50 years and higher in men over the age of 50) might be attributed to the action of oestrogen, mediated by a genetic variant in the MDM2 gene [13]. However, further and more extensive studies should be carried out to confirm this genetic hypothesis, and exclude other possible explanations. It has been shown that the incidence

in other endocrine-related cancers, particularly breast and ovary, differ markedly by age [14].

Besides a hormonal hypothesis, other confounding factors should be considered, which should be adjusted for in multiple regression models. For example, young women are style conscious and traditionally more accustomed to show off their body (which could lead them to visit dermatologists more often, perhaps) [15]. It also is possible that, compared to men, women have more intermittent exposure to ultraviolet radiation at different ages. We note that the proportion of CMM on the leg areas was much higher among women than men, presumably because women's legs are more exposed to ultraviolet radiation compared to men.

Despite the limitations resulting from our small sample, the incidence of CMM appears to be higher in the city compared to the province. This suggests that there could be different risk factors between the two populations, and other contributing factors perhaps such as occupational stress, or environmental pollution, might be involved. In the city, most jobs are related to the tertiary and public sector [3], activities that rarely entail intensive sun exposure, while in the province many of the prevalent occupations, such as farming and fishing, are normally conducted in open air. Perhaps the higher incidence of melanoma in the city is related to acute and intermittent sun exposure [16], compared to those working outdoors [17-19].



Survival following diagnosis was strongly and independently related to age and stage of the CMM. Although late diagnosis (stage III-IV) was less frequent in women (14.2%) than men (16.9%), sex did not significantly predict survival. Finally, an interesting finding was that CMM was diagnosed mainly in the early stages regardless of gender and place of residence, in agreement with published data from the Surveillance, Epidemiology and End Results (SEER) [20] of the National Cancer Institute. This suggests that there is no difference between the city and the periphery regarding early diagnosis and access to care.

Our study has provided an initial insight to the incidence of melanoma in the Province of Palermo. It represents a preliminary effort to improve the knowledge of the distribution of this cancer in this province. Therefore, the limits of this study refer to the small sample analyzed and

the short time-span of incidence considered. Thus, it was not possible to examine trends in incidence and survival over time. The future goal will be to correlate our epidemiological data with possible genetic mutations to identify the population's risk of developing cutaneous melanoma and, at the same time, to identify patients more likely to benefit from new "targeted therapy".

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