

## Article

# Altitude effect on cutaneous melanoma epidemiology in the Veneto Region (Northern Italy): a pilot study.

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**Abstract:** The incidence of cutaneous melanoma has been increasing in the last decades among fair-skinned population. Despite etiology is complex and multifactorial, the exposure to ultraviolet

radiation (UVR) is the most consistent modifiable risk factor associated with melanoma. Several factors influence the amount of UVR reaching Earth's surface. The aim of our study is to explore the association between melanoma and altitude in an area characterized by a mixed geographic morphology, such as in the Veneto region. For this purpose, 2752 melanoma patients, who referred to our attention between 1998 and 2014, were included in this study. For each patient we extracted demographic, histological and clinical-survival data. Head/neck and acral melanoma were more common in patients from the hills and the mountains, while the prevalence of limb and trunk melanoma was higher in patients living in plain and coastal areas. With increase of altitude, the Breslow thickness, ulceration and mitotic rate get worse but no significant difference was observed in overall and disease free-survival. Geographical area of origin of melanoma patients and the "coast-plain-hill gradient" could help to estimate the influence of different sun exposure and to explain the importance of vitamin D level in skin-cancer control.

**Keywords:** cutaneous melanoma; altitude; coast-plain-hill gradient.

## 1. Introduction

Over the last decades, the incidence of melanoma has been continuously increasing around the world [1-2]. In Italy, melanoma incidence and mortality vary greatly across the country, and the geographic variability is associated with a decreasing incidence from Northern (22 cases / 100,000 people) to Southern Italy (about 10 cases / 100,000 people) [3-4]. In the Veneto region (North-eastern Italy), melanoma cases have more than tripled in the last 30 years, with a heterogeneous incidence within the regional territory [5].

The epidemiology of melanoma is complex and individual risk depends on host, genetic, and environmental risk factors, as well as their interactions [6]. The most important and potentially modifiable environmental risk factor for developing melanoma is excessive exposure to ultraviolet radiation (UVR) due to the genotoxic effect. Several factors influence the amount of UVR reaching Earth's surface, including latitude, altitude, ozone depletion, UV light elevation and weather conditions [7].

Among factors associated with UVR exposure, altitude has been estimated to contribute to a 10–12% emission increment for every 1000 m elevation [7-8].

Veneto region is characterized by a mixed morphology including hills (15%), mountains (29%), and plains or coastal areas (56%), with altitudes ranging from sea level up to 3,383 meters above sea level, but negligible differences in latitude [9]. Therefore, this seems a suitable area for exploring the association between melanoma and altitude within a population of similar pigmentation characteristics.

This study aimed to investigate the clinicopathological characteristics and outcome in a cohort of melanoma patients living in the Veneto region (Italy) according to the different geographical areas of residency.

## 2. Materials and Methods

### 2.1.1 Study design

This is a retrospective cohort study on melanoma patients who were diagnosed and/or treated at Veneto Institute of Oncology (IOV) and at the University Hospital of Padua (UHP) during a period of 16 years. The study was conducted in accordance with the Declaration of Helsinki principles and all patients gave their consent for data collection and analysis for scientific purpose. The study was approved by the local ethical committee (CESC IOV Not.2 on 20 January 2020).

### 2.1.2 Patients

All patients who were diagnosed and/or treated for melanoma in 1998-2014 at IOV and at UHP (Italy) were considered for inclusion in the study. The inclusion period was chosen to potentially achieve a minimum follow-up period of 5 years at the time of data analysis. Most patients are referred to Veneto Institute of Oncology for diagnosis and/or first-line treatment, while some patients are referred for disease progression after being treated in peripheral centers.

### 2.1.3 Diagnosis

All the diagnoses of melanoma were histologically confirmed according to the fourth edition of the World Health Organization classification of skin tumors and the staging was updated to the 8th edition of the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours [10-11].

### 2.1.4 Data collection

All data were extracted from a prospectively maintained local database. Data collection included demographics, tumor characteristics, and follow-up information. Geographical residential area was classified in four categories (hill, mountain, plain, coast) based on patient address and according to the Italian Central Statistics Institute (ISTAT) [12].

Follow-up information was extracted from scheduled visits. Follow-up duration was calculated from date of diagnosis to December 31, 2019. Disease-specific survival was calculated from the date of diagnosis to the date of disease-related death (uncensored case) or last visit (or disease-unrelated death) (censored case). Disease-free survival was calculated in patients with primary melanoma from the date of diagnosis to the date of disease recurrence or the date of last visit (or death). Recurrence included local recurrence, regional skin/in-transit metastases, regional lymph node metastases, and/or distant metastases.

### 2.1.5 Statistical Analysis

Continuous data were summarized as median and interquartile range (IQR). Categorical data were compared between groups using the Chi Square test or Fisher's exact test, while continuous data used Mann-Whitney test and Kruskal-Wallis test. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariable analyses of survival (disease-specific survival and recurrence-free survival) were performed using Cox regression models, and effect sizes were expressed as hazard ratio (HR) with 95% confidence interval (CI).

Since the participating centers are the hubs for most patients living in the plain area, a sensitivity analysis including only referred patients was performed to strengthen the findings of the main analysis. All tests were two-sided and a *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using R 4.0 (R Foundation for Statistical Computing, Vienna, Austria) [13].

### 3. Results

#### 3.1.1 Patients

2,752 melanoma patients (1,310 males and 1,442 females; median age: 51 years, IQR: 39-64) were included in the study. Most patients lived in plain area (2400 patients, 87.3%), followed by 262 patients living near the coast (9.5%), 56 in the hills (2.0%) and 34 in the mountains (1.2%). Demographics and tumor characteristics according to the geographical area of residency are reported in Table 1. Primary site, Breslow, ulceration, number of mitoses/mm<sup>2</sup>, and pTNM stage were different among patients living in different geographical areas (Table 1). Melanoma of the head/neck region and acral melanoma were more frequent in patients from the hills and the mountains, while melanoma of the trunk and limbs were more common in patients from the plain and the coast. Breslow thickness was higher in patients from the mountains and the hills compared to patients living in the plain area and near the coast. The presence of ulceration and the number of mitoses/mm<sup>2</sup> were higher in patients coming from the hills. Altogether, patients living in the plain region and the coast presented with an early pTNM stage than those from the hills and the mountains.

The sensitivity analysis on 1,118 referred patients (766 living in the plain area, 262 near the coast, 56 in the hills and 34 in the mountains) confirmed the differences in terms of primary site, Breslow, ulceration, number of mitoses/mm<sup>2</sup>, and pTNM stage among patients living in different geographical areas (Table 2).

#### 3.1.2 Disease-specific survival

At a median follow-up of 96 months (IQR 60-132), 523 patients died (312 for the disease and 211 due to other causes) and 2,211 were alive, while the information was not available in 18 patients who were lost to follow-up. 5-year disease-specific survival was 83% in patients living in the hills, 92% in those living near the coast, 91% in those living in the mountains, and 91% in those living in plain area ( $p=0.10$ ) (Figure 1A). In the sensitivity analysis, 5-year disease-specific survival was 83% in patients living in the hills, 92% in those living near the coast, 91% in those living in the mountains, and 88% in those living in plain area ( $p=0.20$ ) (Figure 1B).

Adjusting for imbalanced characteristics at baseline, geographical area and primary site were not associated with disease-specific survival, while higher Breslow (HR 1.07, 95% CI 1.05 to 1.09;  $p<0.0001$ ), presence of ulceration (HR 2.96, 95% CI 2.25 to 3.89;  $p<0.0001$ ), higher number of mitoses/mm<sup>2</sup> (HR 1.07, 95% CI 1.06 to 1.09;  $p<0.0001$ ), and pTNM III-IV (HR 2.68, 95% CI 2.06 to 3.48;  $p<0.0001$ ) were identified as risk factors for disease-specific survival (Table 2).

The sensitivity analysis on referred patients confirmed such findings (Table 2).

#### 3.1.2 Disease-free survival

At the time of the analysis, 393 out of 2,732 patients had experienced a disease recurrence, while the information was not available in 20 patients. 5-year disease-free survival was 78% in patients living in the hills, 87% in those living near the coast, 88% in those living in the mountains, and 88% in those living in plain area ( $p=0.05$ ) (Figure 2A). In the sensitivity analysis, 5-year disease-free survival was 78% in patients living in the hills, 87% in those living near the coast, 88% in those living in the mountains, and 82% in those living in plain area ( $p=0.05$ ) (Figure 2B).

Adjusting for imbalanced characteristics at baseline, geographical area was not associated with disease-free survival, while melanoma in head/neck vs. trunk (HR 2.03, 95% CI 1.42 to 2.90;  $p<0.0001$ ), higher Breslow (HR 1.06, 95% CI 1.04 to 1.08;  $p<0.0001$ ), presence of ulceration (HR 2.28, 95% CI 1.78 to 2.91;  $p<0.0001$ ), higher number of mitoses/mm<sup>2</sup> (HR 1.07, 95% CI 1.05 to 1.08;  $p<0.0001$ ) and pTNM III-IV (HR 3.50, 95% CI 2.75 to 4.45;

p<0.0001) were identified as risk factors for disease-free survival (Table 3). These findings were broadly confirmed by the sensitivity analysis on referred patients (Table 3).

3.2. Figures and Tables

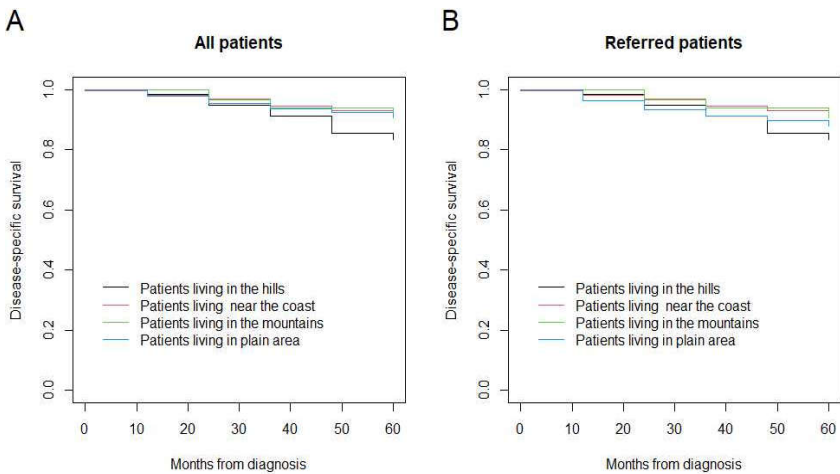


Figure 1. Disease-specific survival in all patients (A) and referred patients (B).

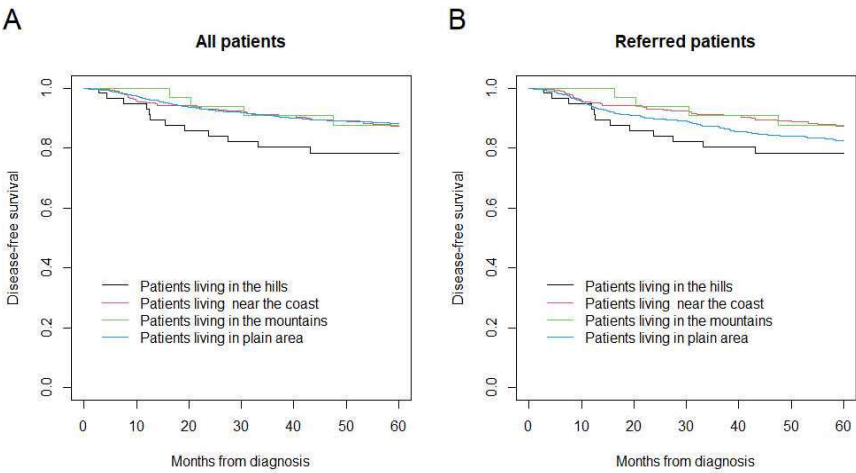


Figure 2. Disease-free survival in all patients (A) and referred patients (B).

**Table 1.** Demographics and tumor characteristics according to the geographical area of residency of referred patients.

|   | Hills (n=56)  | Coast (n=262) | Mountains (n=34) | Plain area (n=766) | p-value           |
|---|---------------|---------------|------------------|--------------------|-------------------|
| Age, years <sup>a</sup>                   | 46 (39-63)    | 53 (39-63)    | 46 (38-64)       | 49 (38-62)         | 0.43              |
| Males                                     | 29 (51.8)     | 127 (48.5)    | 21 (61.8)        | 357 (46.6)         | 0.32              |
| Primary site:                             |               |               |                  |                    | <b>0.005</b>      |
| Hand and foot                             | 5 (8.9)       | 13 (5.0)      | 3 (8.8)          | 58 (7.6)           |                   |
| Head/neck                                 | 17 (30.4)     | 23 (8.8)      | 4 (11.8)         | 76 (9.9)           |                   |
| Upper limb                                | 6 (10.7)      | 35 (13.4)     | 4 (11.8)         | 187 (24.4)         |                   |
| Trunk                                     | 17 (30.4)     | 120 (45.8)    | 14 (41.2)        | 336 (43.9)         |                   |
| Lower limb                                | 11 (19.6)     | 71 (27.0)     | 9 (26.4)         | 109 (14.2)         |                   |
| Breslow, mm <sup>ab</sup>                 | 2.0 (1.1-4.4) | 0.7 (0.5-1.8) | 1.6 (0.5-2.3)    | 1.0 (0.5-2.5)      | <b>&lt;0.0001</b> |
| Ulceration: <sup>c</sup>                  |               |               |                  |                    | <b>0.009</b>      |
| Absent                                    | 33 (63.5)     | 206 (81.7)    | 27 (79.4)        | 539 (73.0)         |                   |
| Present                                   | 19 (36.5)     | 46 (18.2)     | 7 (20.6)         | 199 (27.0)         |                   |
| Mitoses per mm <sup>2</sup> <sup>ad</sup> | 4 (2-8)       | 1 (0-3)       | 2 (0-3)          | 2 (0-4)            | <b>&lt;0.0001</b> |
| pTNM:                                     |               |               |                  |                    | <b>&lt;0.0001</b> |
| I   | 23 (41.1)     | 175 (66.8)    | 18 (52.9)        | 435 (56.8)         |                   |
| II  | 21 (37.5)     | 48 (18.3)     | 8 (23.6)         | 153 (20.0)         |                   |
| III                                       | 12 (21.4)     | 39 (14.9)     | 7 (20.6)         | 177 (23.1)         |                   |
| IV  | 0 (0.0)       | 0 (0.0)       | 1 (2.9)          | 1 (0.1)            |                   |
| Subtype: <sup>e</sup>                     |               |               |                  |                    | 0.25              |
| ALM                                       | 2 (3.7)       | 3 (1.2)       | 0 (0.0)          | 26 (3.5)           |                   |
| LMM                                       | 2 (3.7)       | 5 (2.0)       | 0 (0.0)          | 14 (1.8)           |                   |
| NM  | 13 (24.1)     | 44 (17.2)     | 6 (17.6)         | 165 (22.6)         |                   |
| SSM                                       | 32 (59.3)     | 192 (75.3)    | 26 (76.5)        | 495 (67.7)         |                   |
| Other                                     | 5 (9.2)       | 11 (4.3)      | 2 (5.9)          | 32 (4.4)           |                   |

Data expressed as n (%) or <sup>a</sup> median (IQR). Data not available in <sup>b</sup>54, <sup>c</sup>42, <sup>d</sup>11 and <sup>e</sup>56 patients. ALM = acral lentiginous melanoma; LMM = lentigo maligna melanoma; NM = nodular melanoma; SSM = superficial spreading melanoma.

**Table 2.** Multivariable analysis of predictors of disease-specific survival

|                             | All patients<br>p-value                   |                   | Referred patients                         |                   |
|-----------------------------|---|-------------------|---|-------------------|
|                             | Hazard ratio (95%<br>confidence interval) | p-value           | Hazard ratio (95%<br>confidence interval) | p-value           |
| Geographical area:          |   |                   |   |                   |
| Hills                       | 0.95 (0.52 to 1.72)                       | 0.86              | 1.23 (0.66 to 2.29)                       | 0.51              |
| Coast                       | 1.09 (0.73 to 1.62)                       | 0.68              | 1.09 (0.73 to 1.62)                       | 0.89              |
| Mountains                   | 0.65 (0.21 to 2.04)                       | 0.46              | 0.65 (0.21 to 2.04)                       | 0.54              |
| Plain area                  | Reference                                 |                   | Reference                                 |                   |
| Primary site:               |   |                   |   |                   |
| Head/neck                   | 1.46 (0.98 to 2.17)                       | 0.06              | 1.68 (0.38 to 1.19)                       | 0.18              |
|                             | Reference                                 |                   | Reference                                 |                   |
| TrunkLimbs                  | 0.95 (0.74 to 1.22)                       | 0.71              | 0.75 (0.52 to 1.07)                       | 0.11              |
| Breslow, mm                 | 1.07 (1.05 to 1.09)                       | <b>&lt;0.0001</b> | 1.13 (1.10 to 1.16)                       | <b>&lt;0.0001</b> |
| Ulceration:                 |   |                   |   | <b>0.0006</b>     |
| Absent                      | Reference                                 |                   | Reference                                 |                   |
| Present                     | 2.96 (2.25 to 3.89)                       | <b>&lt;0.0001</b> | 1.95 (1.33 to 2.85)                       |                   |
| Mitoses per mm <sup>2</sup> | 1.08 (1.06 to 1.09)                       | <b>&lt;0.0001</b> | 1.06 (1.02 to 1.09)                       | <b>0.0006</b>     |
| pTNM:                       |   |                   |   |                   |
| I-II                        | Reference                                 |                   | Reference                                 |                   |
|                             | 2.68 (2.06 to 3.48)                       | <b>&lt;0.0001</b> | 2.39 (1.65 to 3.46)                       | <b>&lt;0.0001</b> |
| III-IV                      |   |                   |   |                   |

**Table 3.** Multivariable analysis of predictors of disease-free survival

|                             | All patients<br>p-value                   |                   | Referred patients                         |                   |
|-----------------------------|---|-------------------|---|-------------------|
|                             | Hazard ratio (95%<br>confidence interval) | p-value           | Hazard ratio (95%<br>confidence interval) | p-value           |
| Geographical area:          |   |                   |   |                   |
| Hills                       | 0.97 (0.56 to 1.68)                       | 0.91              | 0.98 (0.55 to 1.73)                       | 0.94              |
| Coast                       | 1.12 (0.78 to 1.60)                       | 0.54              | 0.95 (0.65 to 1.39)                       | 0.80              |
| Mountains                   | 0.68 (0.25 to 1.84)                       | 0.45              | 0.62 (0.23 to 1.68)                       | 0.35              |
| Plain area                  | Reference                                 |                   | Reference                                 |                   |
| Primary site:               |   |                   |   |                   |
| Head/neck                   | 2.03 (1.42 to 2.90)                       | <b>&lt;0.0001</b> | 1.56 (0.99 to 2.47)                       | 0.05              |
| Trunk                       | Reference                                 |                   | Reference                                 |                   |
| Limbs                       | 1.22 (0.97 to 1.53)                       | 0.09              | 1.23 (0.89 to 1.70)                       | 0.21              |
| Breslow, mm                 | 1.06 (1.04 to 1.08)                       | <b>&lt;0.0001</b> | 1.10 (1.07 to 1.13)                       | <b>&lt;0.0001</b> |
| Ulceration:                 |   |                   |   | <b>0.004</b>      |
| Absent                      | Reference                                 |                   | Reference                                 |                   |
| Present                     | 2.28 (1.78 to 2.91)                       | <b>&lt;0.0001</b> | 1.63 (1.17 to 2.26)                       |                   |
| Mitoses per mm <sup>2</sup> | 1.07 (1.05 to 1.08)                       | <b>&lt;0.0001</b> | 1.06 (1.03 to 1.09)                       | <b>&lt;0.0001</b> |
| pTNM:                       |   |                   |   |                   |
| I-II                        | Reference                                 |                   | Reference                                 |                   |
| III-IV                      | 3.50 (2.75 to 4.45)                       | <b>&lt;0.0001</b> | 3.20 (2.32 to 4.1)                        | <b>&lt;0.0001</b> |

#### 4. Discussion

The most important environmental risk factor for developing melanoma is excessive exposure to UVR. However, the relationship between sun exposure and melanoma is very complex depending on the level and the pattern of UVR exposure. The measurement of sun exposure represents a particular challenge as methods of recording and coding vary considerably between studies. No objective approach has been found for the evaluation of different patterns of exposure and for the categorization of levels of exposure. Geographical area of origin of melanoma patients could represent an interesting factor which may help to estimate pattern and level of sun exposure of melanoma patients. Previous studies evaluated how incidence and mortality of melanoma vary according to the latitude [14-15]. Several investigators reported an inverse relationship between latitude of residence and melanoma incidence within populations of similar pigmentation characteristics [16-19]. An inverse relationship between melanoma mortality and latitude has also been reported [20-22]. Among factors associated with UVR exposure, altitude has been estimated to contribute to a 10–12% emission increment for every 1000 m elevation [7]. Veneto region is characterized by a mixed morphology including plain, coastal areas, hills,



and mountains with altitudes ranging from sea level up to 3,383 meters above sea level, but negligible differences in latitude. Therefore, Veneto region may be a suitable area for analyzing the relationship between melanoma and altitude. The Veneto Population Registry reports that incidence rates of melanoma in the mountain and hilly areas are higher than the regional average [5]. In this study we have investigated clinicopathological characteristics and outcomes of a cohort of melanoma patients living in different geographical areas of the Veneto region. A significative difference concerning primary site of melanoma has been highlighted. The prevalence of head/neck melanoma was higher in patients from the hills and the mountains than in those from the coastal and plain areas. This is probably due to the high and intermittent UV exposure of this anatomical district in people living at higher altitude. The prevalence of melanoma of the trunk and limbs was higher in patients from the coastal and plain areas than in patients from hilly and mountain areas. This may be explained by the more frequent exposure of these anatomical sites by people living in the plain and coastal areas and suggest a different behavior of people from different geographical areas. The population of the hills and mountains could be less prone to develop melanoma of the trunk and limbs because these body areas are less frequently exposed to the sun, while people living in the plains and near the coast have more chance to have intense and irregular sun exposure of these sites during the summer. Results from our study show a “coast-plain-hill” gradient, characterized by a progressive increasing number of melanomas involving the head/neck site and progressive reducing number of melanomas involving the trunk and the limbs. At the same time, there is an increase in the incidence of melanoma of the trunk and limbs as the altitude decreases. Our data don't reveal a significant difference in the distribution of malignant melanoma subtypes in the different geographical areas. It was possible to expect a higher prevalence of lentigo-maligna melanoma in the mountains and hills (where the prevalence of head/neck melanoma is higher) and a higher prevalence of superficial-spreading melanoma in the plain and coastal areas. To date, there are few studies [7-8] that investigate the relationship between the melanoma subtype and the geographical area of residence. We believe that further studies are needed to investigate the relationship between residence altitude and melanoma subtype. Breslow thickness was higher in patients from the mountains and the hills compared to patients living in the plain area and near the coast. Furthermore, the presence of ulceration and the number of mitoses/mm<sup>2</sup> were higher in patients coming from the hills. Altogether, patients living in the plain region and the coast presented with an early pTNM stage than those from the hills and the mountains. These data may be explained by the higher level of UV exposure and by the intermittent pattern of UV exposure observed in people living in the hilly and mountains areas. It could also be related to a lower vitamin D level of people living at higher altitude due to reduced chronic sun exposure and a different diet. Low vitamin D seems to be associated to a more aggressive biology of cancer and in particular to a high number of mitoses [23-24]. We also have evaluated the impact that altitude has on the prognosis. No significant survival differences emerge from the multivariate analysis when considering the different geographical areas. In fact, adjusting for imbalanced characteristics at diagnosis, geographical area and primary site were not associated with disease-specific survival, while, as expected, higher Breslow, presence of ulceration, higher number of mitoses per mm<sup>2</sup> and pTNM III-IV were risk factors for disease-specific survival. Geographical area of residency was not associated with disease-free survival, while melanoma in head/neck vs. trunk, higher Breslow, presence of ulceration, higher number of mitoses per mm<sup>2</sup> and pTNM III-IV were associated with disease-free survival. We globally found a worse outcome in patients living in hills and mountains, this difference in terms of survival has been traced to a different molecular profile that would characterize melanomas in patients living in hilly and mountainous districts. A recent study found some differences in the expression profiles of certain mRNAs and miRNAs with respect to the altitude of residence in patients who had been living in different geographic areas and at different altitudes [25]. Since miRNAs are highly regulated by reactive oxygen species, it is possible that different regulatory

mechanisms characterize melanoma at different altitudes due to the different environment and UVR intensity.

Moreover, the lower mortality found in the plains and coastal areas could be related also to more effective prevention systems and better treatment of melanoma. A greater efficacy in screening is described in the geographic areas with the highest concentration of densely populated urban centers which are less numerous in the hilly and mountainous areas than in the plain and coastal areas. In conclusion, we believe that the worse survival of patients from hilly and mountainous areas should be attributed to a less effective screening program suggesting that early diagnosis is essential to reduce poor outcomes. The major limitation of this study is the uneven distribution of patients inside provinces and geographical areas. More than 60% of patients come from the province of Padua. Thus, statistical analysis was performed both in the complete sample and in the sub-sample consisting only of patients referred from other provinces (excluding Padua).

## 5. Conclusions

Results from our study show a “coast-plain-hill” gradient, characterized by a progressive increasing number of melanomas involving the head/neck site and progressive reducing number of melanomas involving the trunk and the lower limbs. These data suggest that geographical area of origin of melanoma patients represents an interesting factor which may help to estimate pattern and level of sun exposure of melanoma patients. Further studies including data regarding host risk factors as Fitzpatrick phototype, number of melanocytic nevi, familiar history and genetic susceptibility are needed to better evaluate the role of altitude in melanoma epidemiology.

**Author Contributions:** Conceptualization, PDF, IR and BF.; methodology, ADM and FC; validation, FC, LN and ST; formal analysis, ADM and FC; data curation, PDF, ADM and JT; writing—original draft preparation, IR and BF; writing—review and editing, PDF, IR, RC and MDM; supervision SM, MA, APDT, AB, VCS, CM and AV

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Ethics Committee (CESC-IOV number 2/2020) and all patients gave their consent to have their anonymized data used for scientific purpose.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study

**Data Availability Statement:** The raw data supporting the conclusions of this article will be made available by the authors,

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**Conflicts of Interest:** The authors declare no conflict of interest

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