A follow-up study of cutaneous melanoma cases and controls in Rosario, Argentina

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Summary

In recent years, cutaneous melanoma (CMM) incidence rates have increased in fair-skinned populations generating a growing demand for healthcare service. The aim of this study was to analyze the clinical characteristics of patients with CMM in our area – with a high proportion of European immigrant descendants – and to follow them up for assessing the development of new skin lesions, and primary noncutaneous cancers. Age at diagnosis, gender, sociodemographic and phenotypic characteristics, family history, anatomical location, thickness and histopathological characteristics of CMM and subsequent lesions occurring during a follow-up for at least 5 years were recorded. Clinical and pathological data were recorded at the time of diagnosis, with follow-up information being gathered in 65 cases and 65 controls. Subsequent non-cutaneous primary malignancies were seen in 10 cases (15.4%) and 3 controls (4.6%, p=0.041). A comprehensive follow-up together with a close dermatological monitoring through clinical and dermoscopically skin observation in patients with CMM are recommended not only to early detect new melanomas, but also to identify other skin neoplasm and internal malignancies.

KEY WORDS: cutaneous melanoma, follow-up, histological subtype, tumours.

Introduction

Skin cancer incidence has been increasing in recent years in most countries of the Western world, leading to a growing demand for healthcare service (1-4). Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the commonest skin cancers. Cutaneous malignant melanoma (CMM) is less frequent, but is more aggressive and presents a worse prognosis. Incidence rates, age distribution, anatomic site, and histological subtype vary among different populations and geographical areas. CMM is predominantly a neoplasm from Caucasian populations. Even though our country has no official epidemiological data, the unofficial figures and data extrapolated from other countries, point out to a yearly increase in the incidence of these tumours between 3 and 5% in the last decade. In recent years CMM has increased in fair-skinned populations resulting in a significantly increased morbidity and mortality (5).

Sunburn and intermittent sun exposure are the dominant environmental determinants of CMM risk, instead of large cumulative exposures of temperate climes (6, 7). In addition to its increasing occurrence (3, 8-10) CMM patients seems to be at a greater risk of developing a second primary melanoma, non-melanoma skin cancers (NMSC), and primary noncutaneous malignancies compared with the general population (11-19).

The aim of this study was to analyze the clinical features of patients with CMM in our area, characterized by a high proportion of European immigrant descendants. Patients were also followed-up for at least 5 years to assess the development of new skin lesions, second primary melanoma, non-melanoma skin tumours, and primary noncutaneous malignancies.

Methods

A case-control study was carried out in patients attending for dermatological consultation at medical institutions in Rosario, Argentina. Rosario is the most important city in the province of Santa Fe, and is the third major urban concentration in the country. The city has about one million inhabitants and is surrounded by smaller cities. Both cases and controls were city residents.

We studied 159 patients, 130 of whom were clinically followed-up for at least 5 years. Clinical and pathological data were recorded at the time of diagnosis,
whereas follow-up information was recorded in 65 cases and 65 controls. Exclusion criteria for both cases and controls were: SCC, BCC, Merkel tumor, lymphomas, past history of arsenic intake, radiotherapy or chemotherapy, treatment with photosensitizing agents (including psoralens), immunosuppressed patients, and the occurrence of Dysplastic Nevoid Syndrome (DNS).

Age at diagnosis, gender, sociodemographic and phenotypic characteristics, family history, anatomical location, thickness and histopathological characteristics of the primary tumour and subsequent lesions were recorded in all cases. The main diagnoses of control patients were skin infections (30%: fungal, viral and bacterial), benign tumours (16%: mainly nevi and seborrhoeic warts), and skin allergies (14%).

Statistical analysis
Quantitative variables were expressed as mean ± standard deviation. The t-test was used to compare mean differences. The Chi-square test was used for case/control comparisons of categorical variables. For descriptive purposes, valid percentages (percentages based on sample size excluding missing values) were calculated. A two-sided p value of 0.05 or less was considered to be statistically significant. All data analyses were performed using STATA statistical software (20).

Ethical considerations
The study was approved by the Bioethic Committee of Rosario School of Medicine and all patients provided informed consent.

Results
The distribution of selected demographic and potential confounding factors by disease status is summarized in Table 1. Patients’ mean age was 54.2±13.3 years, and mean follow-up was 8.9±4.2 years (range 5-24). Most patients had skin phototypes II and III, according to the classification of Fitzpatrick (21). The ethnic origin of patients was mainly Italian and Spanish. There were no between-group differences in age, years under follow-up, gender, and skin phototype distribution. The mean age of CMM development was 52.4±16.2 years for women and 57.5±12.6 in men; but the trend remained statistically insignificant (p=0.202).

Table 2 shows the CMM site distribution by gender. The most common site of the first melanoma in men was the trunk (56.5%), whereas in women mostly affected the lower limbs (40.5%). The most frequent histological subtype of the first primary melanoma was superficial spreading melanoma (SSM), followed by nodular melanoma (NM) and lentigo maligna melanoma (LMM) (Table 3). As shown, there was a gender significant difference (p=0.013) All lesions were clinically pigmented. Nine melanoma cases were associated with a dysplastic nevus. Twenty-three CMM (39.1%) were in situ being more often diagnosed in women than in men (23.8% versus 8.0%, p=0.04). Among invasive CMM (n=42; 60.9%), Breslow thickness was <1.01 mm in 19 cases (45.2%); 1.01-2.00 mm in 17 cases (40.5%); 2.01-4.00 mm in 5 cases (11.9%); and >4 mm in one patient (2.4%). All patients were surgically treated, and none of them received chemotherapy. During the follow-up, 5 subsequent CMM were diagnosed. One patient developed two CMM, and another three cases presented a new CMM. Remaining skin tumours are shown in Table 4.

Further non-cutaneous primary malignancies occurred in 10 CMM cases (15.4%) and 3 controls (4.6%, p=0.041). They included breast cancer (n=4), prostate (n=3), thyroid, colon and cervical cancer (one case each) in the CMM group, whereas in the control group there were 3 cancer patients (2 breast cancers and 1 parotide cancer). CMM was invasive in all patients who were subsequently diagnosed as having a primary noncutaneous malignancy.

Two out of four patients developing a second CMM also developed BCC and actinic keratoses (AK). Among CMM cases free from a second CMM, 4.9% were diagnosed with BCC (p = 0.001) and 14.8% with AK (p = 0.069).

Eight cases (12.3%) died during follow-up, 5 of CMM and the 3 remaining ones from another causes. One patient in the control group died during the study.

Table 1 - Basic demographic data and characteristics of cases and controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CMM cases</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.2±15.1</td>
<td>53.7±11.3</td>
<td>0.812</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>9.4±5.1</td>
<td>8.4±3.1</td>
<td>0.184</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 23 (35.4%)</td>
<td>27 (41.5%)</td>
<td>0.471</td>
</tr>
<tr>
<td></td>
<td>Female 42 (64.6%)</td>
<td>38 (58.5%)</td>
<td></td>
</tr>
<tr>
<td>Skin phototype</td>
<td>I 5 (7.7%)</td>
<td>3 (4.6%)</td>
<td>0.102</td>
</tr>
<tr>
<td></td>
<td>II 39 (60.0%)</td>
<td>27 (41.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III 19 (29.2%)</td>
<td>32 (49.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV 2 (3.1%)</td>
<td>3 (4.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Quantitative data are given as means ± SD.

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Discussion

Melanoma development is a complex process influenced by environmental factors (mainly UV radiation), constitutional and somatic genotype, as well as phenotypic characteristics, like patient age and skin type (22). Although the overall mortality rate of CMM has increased over the last 40 years, long-term survival rates are improving, mainly due to earlier tumour detection and treatment. In our study the distribution of gender and age of patients with CMM is consistent with European data (3, 8, 9, 23, 24). In line with other reports, we found anatomical distribution of melanoma to be sex-dependent. In our patients the most frequently affected sites were the trunk in men and the arms and legs in women (3, 9, 23-25). Such dissimilarity may be explained by differences in sun-exposure patterns, which matches differences in usual clothing patterns and hair cover (26).

Studies indicate that approximately 10% of CMM patients have a positive family history for melanoma (27). A positive family history of CMM is regarded as being a strong risk factor for melanoma occurrence. The risk for developing CMM is roughly 2-fold increased in persons with a history of melanoma in a first-degree relative, compared with the risk of those without such antecedent (28-30). Unfortunately, information about this issue was incomplete in our research.

NMSC was diagnosed in approximately 12% of our patients. We found a higher incidence of BCC than SCC. BCC and SCC were found in 8.2% and 4.6% of our CMM patients that did not differ from the 5.6% and 3.1% respectively seen in controls. Although other studies conducted in cohorts of patients with CMM found that the ratio BCC:SCC is between 7:1 and 9:1 (18, 31) the present ratio was 1.8:1. The correlation between NMSC and CMM risk may be the effect of some common risk factors, such as phenotype and UVR exposure (31). Furthermore, a genetic susceptibility for skin cancers may explain the development of different types of skin cancers in the same patient. It has also been reported that when compared to the overall population, melanoma patients have at least a 30-fold increased risk for the development of a subsequent melanoma (14).

Table 2 - CMM site distribution by gender.

<table>
<thead>
<tr>
<th>Site</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Head/Neck</td>
<td>7 (16.7)</td>
<td>5 (21.7)</td>
<td>12 (18.5)</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>17 (40.5)</td>
<td>4 (17.4)</td>
<td>21 (32.3)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>9 (21.4)</td>
<td>1 (4.3)</td>
<td>10 (15.4)</td>
</tr>
<tr>
<td>Trunk</td>
<td>9 (21.4)</td>
<td>13 (56.5)</td>
<td>22 (33.8)</td>
</tr>
<tr>
<td>Total</td>
<td>42 (100.0)</td>
<td>23 (100.0)</td>
<td>65 (100.0)</td>
</tr>
</tbody>
</table>

p=0.012

Table 3 - CMM histological subtype by gender.

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>SSM</td>
<td>40 (95.2)</td>
<td>16 (69.6)</td>
<td>56 (86.1)</td>
</tr>
<tr>
<td>NM</td>
<td>2 (4.8)</td>
<td>5 (21.7)</td>
<td>7 (10.8)</td>
</tr>
<tr>
<td>LMM</td>
<td>0 (0.0)</td>
<td>2 (8.7)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Total</td>
<td>42 (100.0)</td>
<td>23 (100.0)</td>
<td>65 (100.0)</td>
</tr>
</tbody>
</table>

SSM: superficial spreading melanoma; NM: nodular melanoma; LMM: lentigo maligna melanoma. 
p=0.013

Table 4 - Other (additional) tumours in cases and controls.

<table>
<thead>
<tr>
<th>Other tumours</th>
<th>CMM cases (%)</th>
<th>Controls (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign tumours</td>
<td>27.7</td>
<td>20.0</td>
<td>0.303</td>
</tr>
<tr>
<td>Actinic keratoses</td>
<td>16.9</td>
<td>7.7</td>
<td>0.109</td>
</tr>
<tr>
<td>Isolated atypical nevi</td>
<td>13.8</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>8.2</td>
<td>5.6</td>
<td>0.381</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4.6</td>
<td>3.1</td>
<td>0.648</td>
</tr>
</tbody>
</table>

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Follow-up study of cutaneous melanoma

Reportedly, there is an increased risk of developing a subsequent primary cancer in patients with a history of primary melanoma (32, 33). Several studies have reported coexistent or subsequent primary tumors among patients with CMM, with the rate of incidence ranging from 1.5 to 20%, depending on sample size and follow-up duration (11). A prospective study performed in Germany to evaluate the occurrence of second primary malignancies in patients with invasive CMM showed that 6.4% of patients developed one or more neoplasms at the time of, or subsequent to, the diagnosis of the first cutaneous melanoma (15). In the present study, subsequent primary tumors reached to 15.4%.

The increased risk for developing breast cancer, malignant lymphoma and neoplasms of the kidney as second primary cancers in patients with CMM was discussed in some studies. Bradford et al. recently showed that the most common cancers with increased incidence after an initial CMM were prostate cancer, female breast cancer, and non-Hodgkin lymphoma. The risk was also significantly increased for cancers of the salivary gland, small intestine, kidney, ocular melanoma, and thyroid, as well as soft tissue sarcomas and chronic lymphatic leukaemia (32). Our study reveals several interesting findings. Ten patients (15.4%) with a first primary melanoma developed a subsequent primary cancer. In line with data from the literature the most frequent ones were breast cancer, followed by prostate, thyroid, bowel, and cervix cancers (15).

This study was a registry-based investigation; for which it may be a bit biased because of an increased attention of the patient and the physician after the first diagnosis of cancer may exist, leading to early detection of subsequent neoplasm. Although an exhaustive medical supervision may lead to a higher rate of diagnosis, melanoma survivors are at a higher risk for subsequent primary cancer development, probably due to genetic susceptibility and to certain behavioral risk factors. A comprehensive follow-up and a close dermatological monitoring through clinical and dermoscopically skin observation in CMM patients are recommended not only to early detect new melanomas, but also to identify other skin neoplasms and internal malignancies.

References

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