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INVESTIGATIVE REPORT

Role of Age and Sex in the Diagnosis of Early-stage Malignant Melanoma: A Cross-sectional Study

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Age and sex have been identified as predictors of outcome in malignant melanoma (MM). The aim of this multicentre, cross-sectional study was to analyse the role of age and sex as explanatory variables for the diagnosis of thin MM. A total of 2,430 patients with MM were recruited. Cases of *in situ* (Tis) and T1 MM were more frequent than T2–T4 MM (56.26% vs. 43.74%). Breslow thickness increased throughout decades of life (analysis of variance (ANOVA) $p<0.001$), with a weak correlation between Breslow thickness and patient's age ($r=0.202$, $p<0.001$). Breslow thickness was significantly less in women (1.79 vs. 2.38 mm, $p=0.0001$). Binary logistic regression showed a significant ($p<0.001$) odds ratio for age 0–29 years (1.18), and 30–59 years (1.16), and for women (1.09). Age and sex explained 3.64% of the variation observed in Tis–T1 frequency ($R^2=0.0364$). Age and sex appear to explain a low percentage of the variation in the early detection of MM.

Key words: malignant melanoma; prognostic predictors; thin melanoma; early-stage malignant melanoma; age; sex.

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Malignant melanoma (MM) diagnosed at early stage (Tis and T1) has been observed with increased frequency in recent decades (1, 2). This is partially explained by improvements in access to specialized care, and by the potential "overdiagnosis" of pigmented lesions (3); however, other studies reporting increasing incidences of MM among all Breslow thickness categories conclude that this increasing incidence is not solely due to overdiagnosis (4).

The influence of age and sex on the variation in early detection and diagnosis of thin MM has been analysed repeatedly over recent decades (5, 6). The current study involved subanalysis of the Trends in the Diagnosis of Malignant Melanoma (TEDIMEL) project, a 10-year, multicentre study analysing the role of healthcare provision and demographic determinants in the early detection of MM, the global results of which have been published recently (1). The aim of this analysis was to assess the potential role of demographic determinants, age and sex, and their weight in explaining variations in the diagnosis of patients with early-stage MM.

METHODS

A multicentre, cross-sectional study was conducted at 14 hospitals in the Public Health System of Andalusia (PHSA), a region in southern Spain. Cases of primary *in situ* MM (Tis) or invasive cutaneous MM diagnosed between 1 January 2000 and 31 December 2009 were included in the study after verifying that the MMs failed to meet the following exclusion criteria: second primary MM, lack of Breslow thickness in the pathology report, primary MM pathologically diagnosed but not excised at the participating centres (biopsy specimens referred for specialized diagnosis were excluded), and lack of valid demographic information. A complete methodology of the TEDIMEL project has been published elsewhere (1).

Demographic, and pathological study variables recorded included: age, sex, year of diagnosis, Breslow thickness, and T-stage as defined by the American Joint Committee on Cancer Tumor-Node-Metastasis (TNM) Melanoma Staging System, 7th edition (7). Tumours diagnosed as Tis and MMs with a Breslow thickness < 1 mm (T1) were grouped together (Tis–T1). Likewise, tumours with a Breslow thickness ≥ 1 mm (i.e. T2, T3 and T4) were also grouped and jointly analysed (T2–T4). This information, together with the demographic data (age, sex), were gathered from the pathology reports stored in the information systems of the participating pathology units.

In a first descriptive phase, the primary outcomes assessed were the mean Breslow thickness, and the frequency of Tis–T1 and T2–T4 MM in the 10-year series as a whole.

In a second analytical phase, the role of demographic variables (age and sex) in explaining variations in Breslow thickness, and in the proportion of Tis–T1 MMs was tested through bivariate and multivariate analyses with the calculation of odds ratios (ORs).

For statistical analysis, XLSTAT® 2014 for Mac® software (v. 4.05 Addinsoft SARL) was used. For quantitative data, statistically significant differences were shown using Student's *t* and ANOVA tests. For qualitative data, the χ^2 test, and the χ^2 test for linear trend were used to show significant differences. The direction and strength of the linear relationship between 2 quantitative variables were measured by the linear correlation coefficient "r". For the multivariate analysis, logistic binary regression with the Hosmer-Lemeshow test for goodness of fit was applied. The R^2 Nagelkerke coefficient of determination was used to express the proportion of the total variance of the response variable explained by the independent variables. The age was coded as a dummy dichotomous variable (0–29, 30–59 and ≥ 60 years). The results of the bivariate and multivariate analyses were expressed as ORs and correspon-

ding 95% confidence intervals (95% CIs). All significance tests were 2-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

A total of 2,430 patients with MM, for whom valid data was available, were recruited. A significant predominance of female patients was observed (54.65% female vs. 45.35% males), with a non-significant lower mean age for women (54.27 vs. 56.35 years; $p = 0.005$). As a whole, Tis–T1 MM cases were more frequent than T2–T4 MM (56.26% vs. 43.74%).

Breslow thickness increased progressively throughout the decades of life, with a significantly higher mean Breslow thickness in patients aged ≥70 years (ANOVA $p < 0.001$) (Fig. 1). Correlation and simple regression analysis showed a very weak association between Breslow thickness and patient age (r = 0.202 95% CI 0.163–0.241, $p < 0.001$), with age explaining 4.05% of the Breslow thickness variation (R^2 coefficient = 0.0405) (Fig. S1[1]). Tis–T1 MM was more frequent in patients aged 0–29 years (70.73%), followed by patients aged 30–59 years (60.92%) and patients aged ≥60 years (48.19%) ($p < 0.001$). The ORs for identifying Tis–T1 stage were 1.12 (95% CI 1.07–1.18, $p < 0.001$) in patients aged 0–29 years, 1.12 (95% CI 1.06–1.18, $p < 0.005$) in the 30–59 group, and 0.84 (95% CI 0.80–0.88, $p < 0.01$) in patients aged ≥60 years.

The mean Breslow thickness of the series was significantly lower in women than in men (1.79 mm vs. 2.38 mm, $p = 0.0001$) (Fig. 2) with a difference in the median Breslow thickness between sex groups of 0.21 mm (median Breslow thickness in women 0.79 mm vs. 1.00 in men). Tis–T1 tumours were more frequent in women than in men (54.65% vs. 45.35%, $p = 0.001$) with an OR of identifying a Tis–T1 in women of 1.10 (95% CI 1.05–1.16, $p = 0.001$).

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2115

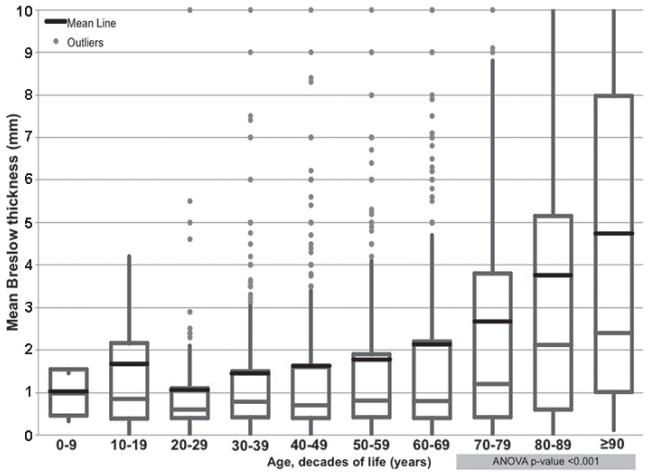

Fig. 1. Mean and median Breslow thickness distribution by decades of life.

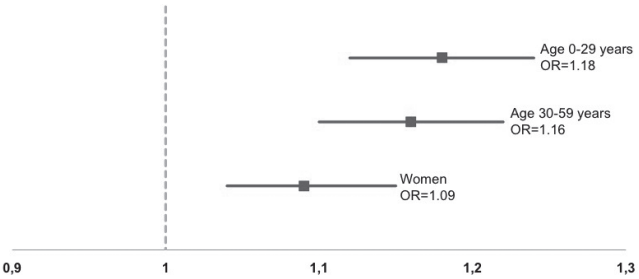

Fig. 2. Forest plot representation of the resulting binary logistic regression odds ratios of detecting a Tis-T1 malignant melanoma for the explanatory variables "age group" (as dummy variable) and "sex".

Binary logistic regression including age and sex for Tis–T1 as the reference category showed significant ORs for age 0–29 years (OR 1.18, 95% CI 1.12–1.24, $p < 0.001$), and 30–59 years (OR 1.16, 95% CI 1.10–1.22, $p < 0.001$), and for women (OR 1.09, 95% CI 1.04–1.15, $p < 0.001$) (Fig. 2). After adjustment by age group, a higher likelihood of having Tis–T1 MM was observed in women aged 30–59 years (OR 1.62, 95% CI 1.28–2.05, $p < 0.001$). No differences were observed as for the likelihood of having thin MM in the other age groups (0–29 years: OR 0.88, 95% CI 0.48–1.62, $p = 0.68$; 60–90 years: OR 1.16, 95% CI 0.91–1.48, $p = 0.22$). Based on the R^2 coefficient, age, as a categorical variable (0–29, 30–59 and ≥60 years), explained 3.00% of the variability observed in the frequency of Tis–T1 MM (R^2 coefficient = 0.030), and sex explained 0.80% of this variation (R^2 coefficient = 0.008). These variables, age and sex together, explained 3.64% of the variability observed in Tis–T1 frequency ($R^2 = 0.0364$).

DISCUSSION

This 10-year cross-sectional study including 2,430 patients with MM has revealed a 9.3% increased frequency of Tis–T1 MM in women (54.65% vs. 45.35%), and a difference of 0.58 mm in the mean Breslow thickness between women and men. This advantage in the detection of early MM was also observed in middle-aged patients. The differences found in these endpoints were all statistically significant in both the descriptive and analytical phases. Likewise, the ORs and correlation coefficient calculated also supported the advantage in early diagnosis observed for women and middle-aged patients. These results are in line with previous reports in which the detection of thin MM is partially determined by the age and sex of the patients (8, 9). Swetter et al. (8) found a higher frequency of thinner tumours (≤1 mm) in patients younger than 60 years and in women, an advantage that is explained by improved self-detection behaviours and habits. Mervic et al. (5) also described a higher median tumour thickness in middle-aged male patients compared with female patients in the same age group (0.83 vs. 0.75

mm, $p < 0.001$), a difference that was not significant in the older patient group (1.04 vs. 1.00 mm, $p = 0.47$).

However, a more careful assessment of statistics that provide information on the strength of the associations observed and to what extent the independent variables explain variations in the primary outcomes (Breslow thickness and T-stage) is warranted. In this study, even though both the "r" coefficient, and the R2 coefficient of determination support a significant and direct association between variables, the strength of the associations, as shown by the magnitude of these statistics, is weak. Both age and sex, analysed separately, served to explain 3% and less than 1% of the variation in the response variables, respectively. Taken together, both predictor variables explained just 3.64% of the variation in the proportion of Tis–T1 MM. In other words, sex and age failed to explain 96% of the variation observed in the response variables. Thus, despite the statistically significant ORs and correlation coefficient observed, the weakness of the associations should prevent us from referring to age and sex as independent predictors of the response variable, but instead as partial reasons for its variation. Moreover, the inclusion of these statistics in studies aimed at identifying predictor or determinant factors would help to diminish the possibility of overestimations of the real effects of explanatory variables, which might also influence prevention strategies. In this regard, Goldberg et al. (10) analysed the screening data of patients with MM to identify factors associated with MM detection, and thereby derive a model of increased likelihood for MM detection through visual skin examinations at screenings. Among the factors that independently increased the likelihood of suspected MM, age over 50 years (OR 1.2; 95% CI 1.1–1.3) and male sex (OR 1.4; 95% CI 1.3–1.5) were identified (10). This result led the authors to conclude that refocusing efforts on providing a complete skin examination to those individuals with multiple risk factors (i.e. men and patients older than 50 years) has the potential to increase yields for suspected MM and, consequently, to enhance early detection of MM (10). In this case, the ORs obtained reached the threshold for statistical significance, but no data was provided about the extent to which age and sex explain the likelihood of suspected MM.

The primary methodological limitation of this study is its retrospective nature. A second potential limitation relates to the study endpoints assessed and the lack of a survival analysis. However, the TEDIMEL project was not focused on recurrence or mortality outcomes, but on Breslow thickness and T-stage, both considered proxy markers of initial prognosis. In this regard, Breslow thickness and T-stage are still considered the strongest predictors of survival in patients with primary MM with no metastatic disease (1).

In conclusion, early diagnosis of MM is the multifactorial result of demographic, socioeconomic and healthcare provision determinants. Although age and sex demonstrate an association with the early detection of MM, the burden of thin MM (Tis–T1) explained by demographic factors is too low to accept them as major determinants of this outcome.

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