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Original Research

Risk factors for keratinocyte skin cancer in patients diagnosed with melanoma, a large retrospective study

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Abstract ***Background:*** Melanoma survivors are at an increased risk of developing other malignancies, including keratinocyte skin cancer (KSC). While it is known that many risk factors for melanoma also impact risk of KSC in the general population, no previous study has investigated risk factors for KSC development in melanoma patients.

Objective: We assessed associations of personal and clinical characteristics, including skin phenotype and variations in the melanocortin 1 receptor (*MC1R*) gene, with KSC risk in melanoma patients.

Patients and methods: We used prospective follow-up information on 1200 patients treated for melanoma at the Instituto Valenciano de Oncología, Spain, between 2000 and 2011. We computed hazard ratios and 95% confidence intervals (CIs) for the association of clinical, personal and genetic characteristics with risk of KSC, squamous cell carcinoma (SCC), or basal cell carcinoma (BCC) from Cox proportional hazard models. Five-year cumulative incidence based on competing risk models of SCC, BCC or KSC overall was computed using multivariate subdistribution hazard models. To assess predictive performance of the models, we computed areas under the receiver-operating characteristic curves (AUCs, discriminatory power) using cross-validation.

Results: Median follow-up was 57.2 months; a KSC was detected in 163 patients (13.6%). In multivariable Cox models, age, sex, sunburns, chronic sun exposure, past personal history of

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non-melanoma skin cancer or other non-cutaneous neoplasia, and the *MC1R* variants p.D294H and p.R163Q were significantly associated with KSC risk. A cumulative incidence model including age, sex, personal history of KSC, and of other non-cutaneous neoplasia had an AUC of 0.76 (95% CI: 0.71–0.80). When p.D294H and p.R163Q variants were added to the model, the AUC increased to 0.81 (95% CI: 0.77–0.84) (p-value for difference <0.0001). ***Conclusions:*** In addition to age, sex, skin characteristics, and sun exposure, p.R163Q and p.D294H *MC1R* variants significantly increased KSC risk among melanoma patients. Our findings may help identify patients who could benefit most from preventive measures.

Research in context

Evidence before this study

According to the current knowledge, patients who survive melanoma are at increased risk of developing keratinocyte skin cancer (KSC). Population- and hospital-based studies have demonstrated this fact. Although many environmental and clinical factors increase the risk for developing both melanoma and KSC, no prospective study to date has assessed in detail if these risk factors also increase KSC risk in melanoma survivors.

Added value of this study

In this study, we have shown cumulative incidence figures of non-melanoma skin cancer and related risk factors in a large cohort of melanoma patients. The estimated cumulative incidence exceeds by far that of the general population. Besides the obvious effect of advanced age, male sex, severe sunburns, previous diagnosis of keratinocyte skin cancer (KSC), chronic sun exposures and the presence of two polymorphisms in melanocortin 1 receptor (*MC1R*) (p.D294H and p.R163Q) were the most relevant risk factors for developing subsequent KSC.

Implications of all the available evidence

Our results indicate that some characteristics, including some melanocortin 1 receptor (*MC1R*) variants, are helpful to define melanoma patients at higher risk of developing keratinocyte skin cancer and therefore might benefit of implemented preventive measures.

1. Introduction

Although malignant melanoma remains the major cause of death associated with skin cancers, public awareness, early detection and improved treatment strategies have markedly prolonged patient survival. Increased incidence and improved survival have led to an ever increasing number of melanoma survivors. However, like survivors of other cancers, patients who survive melanoma are also at an increased risk of developing second primary malignancies, which include second melanomas and keratinocyte skin cancers (KSCs) [1–4].

Considering the morbidity caused by KSC in melanoma survivors and the added burden to healthcare systems, it is important to identify factors associated with increased risk for such malignancies for targeted prevention efforts. We hypothesised that risk factors associated with both primary melanoma and KSC also increase KSC risk in melanoma survivors. Factors associated with both risk of melanoma and risk of KSC include susceptible skin phototype with propensity to sunburn and sun exposure. Genetic variations in low-penetrant pigmentation genes that are major determinants of predisposing phenotypes like skin and hair colour are also known risk factors for both melanoma and KSC [5,6]. Variants in the melanocortin 1 receptor (*MC1R*) gene are among the most important genetic determinants of high-risk phenotypes like fair skin and red hair and consequently increased risk of skin cancers in general [7–15].

Despite known risk of KSC in patients who survived melanoma, no prospective study to date has assessed risk factors in detail. Thus, we investigated the association of personal, clinical and genetic factors with risk of developing of KSC in melanoma patients in a cohort of 1200 melanoma patients followed for over 10 years. We also estimated cumulative incidence of KSC risk to stratify patients for increased surveillance and preventative measures.

2. Patients and methods

Patients with cutaneous melanoma in this study include individuals who had been treated at the Instituto Valenciano de Oncología between 1st January 2000 and 31th December 2011. At the end of this period, the database contained information for 1792 incident and prevalent patients. A wide range of clinical, epidemiological and histological variables evaluated by dermatologists with specialised training in melanoma management were collected, as described in detail previously [16].