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Multiple primary (even in situ) melanomas in a patient pose significant risk to family members

Tianhui Chen [a,*], Kari Hemminki [a,b], Elham Kharazmi [a], Jianguang Ji [b], Kristina Sundquist [b,c], Mahdi Fallah [a]

[a] *Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany*
[b] *Center for Primary Health Care Research, Lund University, Malmö, Sweden*
[c] *Stanford Prevention Research Center, Stanford University School of Medicine, CA, USA*

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Abstract ***Background:*** We aimed at assessing familial risk of melanoma by considering a detailed family history of multiple primary (invasive/in situ) melanomas (MPM), stratified by histology and location.

Methods: Among 65,429 melanoma patients diagnosed in 1958–2010 in the Swedish Family-Cancer Database, there were 4248 patients with familial melanoma. A detailed family history of MPM was investigated by number of melanomas in one first-degree relative (FDR) and in $\geqslant 2$ FDRs. Familial melanoma risk was assessed by standardised incidence ratios (SIRs) comparing those with family history of melanoma to those without. Combining invasive/in situ melanoma was due to essentially identical familial risks.

Results: For one affected FDR, familial risk increased from SIR = 2.2 (95% confidence interval (CI) = 2.2–2.3) for single melanoma to 16.3 (9.5–26.1) for $\geqslant 5$ melanomas, while for $\geqslant 2$ affected FDRs, the risk increased from 5.5 (4.8–6.2) for single melanoma to 23.9 (13.6–38.8) for $\geqslant 2$ melanomas. Significantly higher familial risks for superficial spreading melanoma (SSM) [2.5 (2.3–2.6)] than lentigo maligna melanoma (LMM) [1.8 (1.6–2.1)], and for multiple parts [5.3 (3.1–8.4)] and trunk [2.6 (2.5–2.8)] than head/neck [2.0 (1.8–2.2)] were observed. Only at head/neck, significantly higher risk for SSM [2.4 (1.9–3.0)] than LMM [1.6 (1.4–1.8)] was noted.

Conclusion: We found, for the first time, that familial risks were similar for two/three melanomas in one FDR or for a single melanoma in $\geqslant 2$ FDRs and, higher familial risks for SSM

* *Corresponding author:* Address: Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, 69120 Heidelberg, Germany. Tel.: +49 6221 421805; fax: +49 6221 421810.
E-mail address: t.chen@dkfz.de (T. Chen).

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than LMM occurred only at head/neck. This study provides new evidence for genetic counselling in melanoma, suggesting the need for considering not only the number of affected family members but also the diagnosis of MPM (even in situ) in relatives.

1. Introduction

Although the vast increases in the incidence of cutaneous melanoma over the past half century have been largely unexplained [1], genetic, phenotypical and environmental factors may contribute [2]. In addition to ultraviolet radiation and phenotypic factors (e.g. types of hair, eye colour, freckles) [2,3], family history of melanoma, accounting for approximately 5–12% of melanoma patients [4,5], is an independent risk factor [3]. Familial melanoma, known as the clustering of melanoma patients among at least two first-degree relatives (FDRs), has an earlier age at diagnosis of first melanoma, thinner lesions, different distributions of histological subtypes and a higher frequency of multiple primary melanomas (MPM) than non-familial melanoma [6–8]. However, a recent study shows that familial melanoma occurs even in advanced age; around 35% of familial cases occurs in patients whose parents were diagnosed with melanoma at an old age (>69 years) [9]. About 5% of melanoma patients have one or more additional primary melanomas and 8–24% of patients with MPM have a family history of melanoma [10].

Overall a family history of melanoma was associated with a significant 2-fold elevated risk of melanoma, according to a recent meta-analysis including studies with registry-verified family history data [11]. A study based on the previous version of nationwide Swedish Family-Cancer Database (FCD) has reported a 2.4-fold elevated risk in patients whose one parent had melanoma, about 3-fold elevated risk in patients whose one sibling had melanoma, and about 9-fold elevated risk in patients whose one parent and one sibling had melanoma [12]. Another study using registry-verified family history data shows 3-fold elevated risk in patients whose one FDR had one melanoma and 8.5-fold elevated risk in patients whose one FDR had two or more melanomas [13]. Another Nordic study on familial melanoma also did not address the familial melanoma risk by number of melanomas in affected family members [14]. However, to our knowledge, no population-based studies have considered a detailed family history of melanoma with regard to MPM in a single individual and in multiple family members.

Using the world's largest family-cancer database, the nationwide Swedish Family-Cancer Database (FCD), we aimed to test whether the familial risk of melanoma increases by increasing number of melanomas occurring in a single relative or multiple relatives. Furthermore, little is known about familial risks stratified by histology and anatomical subsite. We thus also aimed to provide, a comprehensive analysis on familial risk, stratified by sex, and age at diagnosis, histology and subsite of the first melanoma.

2. Materials and methods

Details on the latest version of the FCD (FCD2010, updated in 2013) were described elsewhere by the same group [15]. Briefly, information on cancer cases were retrieved from the Swedish Cancer Registry, relying on separate compulsory notifications from clinicians, pathologists and cytologists and, close to 100% registered neoplasms were histologically verified and the Swedish Cancer Registry only records primary invasive and primary in situ tumours [16]. Tumours were recorded according to the International Classification of Diseases, 7th version (ICD-7), with separately recorded information on up to five primary invasive cancers and/or five primary in situ carcinomas, e.g. for melanoma, with ICD-7 code 190. Four-digital ICD-7 codes were used for anatomical subsite (trunk, limb, head/neck, multiple parts, and unspecified subsites). Multiple parts of subsite were coded for cancer registration purposes, meaning tumour occurs in more than one subsite. ICD-O-2/3 morphology codes were used for classification of histological subtypes, i.e. superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), acral lentiginous melanoma (ALM), others and unspecified melanoma, while histology-specific data with ICD-O-2/3 morphology were available from 1993 onwards. Data on family relationships, comprising all first-degree relatives (including parents, siblings and children), were obtained from the Multigeneration Register with high quality and practically complete coverage [16]. A detailed family history of (invasive/in situ) MPM diagnosed during the years 1958–2010 was investigated in general ($\geqslant$1 melanoma in $\geqslant$1 FDR), and by number of melanomas (1, 2, 3, 4 and $\geqslant$5 melanomas) in one FDR and number of melanomas (a single melanoma and $\geqslant$2 melanomas) in $\geqslant$2 FDRs. For $\geqslant$2 FDRs, the number of melanomas refers to each of the FDRs. Combing invasive/in situ