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Familial melanoma by histology and age: Joint data from five Nordic countries

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Abstract ***Background:*** We aimed to estimate lifetime cumulative risk of melanoma (CRM) in relatives of patients with melanoma by histology and age at diagnosis in patients and relatives. ***Methods:*** A population-based cohort of 238 724 first-degree relatives of 46 091 melanoma patients diagnosed in 1955–2010 in Nordic countries was followed for cancer incidence. ***Findings:*** The CRM (0–79 years) in first-degree relatives of a patient with superficial spreading (SSM), nodular (NM), or lentigo maligna melanoma was quite similar, ranging from 2.5% to about 3%, which represents about 2-fold increase over the general population risk. When one melanoma patient in the family was diagnosed before age 30, the CRM was about 3%. When there were $\geqslant 2$ melanoma patients diagnosed before age 30 in a family, CRM for relatives was about 14%, 6% for diagnoses at age 30–59, and 5% for diagnoses at age 60 or older. Depending on age at diagnosis of same-sex twins (not known whether monozygotic/dizygotic), their CRM was about 7–21%. Although no familial case of concordant histological types of acral lentiginous/desmoplastic/compound nevus/spindle cell melanomas or malignant blue nevus was found, familial risks of discordant histological types of melanoma were interchangeably high for most of the types, e.g. higher risk of SSM when a first-degree relative had NM [standardized incidence ratios (SIR) = 2.6, 95% confidence interval (CI) = 2.1–3.3, $n = 72$] or acral lentiginous (4.0, 95%CI = 1.5–8.8, $n = 6$) and vice versa. There was a tendency toward concordant age at diagnosis of melanoma among relatives of melanoma patients.

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Interpretation: Findings of this study may help clinicians to find subjects at high melanoma risk for the genetic counseling. The risk was highest when melanoma occurred in a same-sex twin, one first-degree relative diagnosed at young age (<30), or ⩾2 first-degree relatives. Histological type of melanoma does not seem to play an important role in familial melanoma.
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Introduction

Incidence of melanoma continues to increase with about 200 000 new melanoma patients diagnosed in the world per year (about 170 000 new patients in the more developed regions) and it is expected to rise significantly to about 260 000 new cases in 2020 (about 190 000 in more developed regions) [1]. A retrospective analysis on data from 29 European cancer registries study showed a worrying continuously rapid rise in the burden of melanoma across all Europe, especially in the eastern part [2]. In a large study on about 54 000 United States (US) melanoma patients with specified histology, the most common melanoma was superficial spreading melanoma (SSM 71%), followed by nodular (NM 15%), lentigo maligna (LMM 12%) and acral lentiginous (ALM 1.5%) melanoma [3]. Other very rare variants of melanoma are desmoplastic, spindle cell and melanoma in compound nevus. Malignant blue nevus (MBN) is a rare melanocytic lesion and controversy exists whether it is a melanoma or a unique entity. A large US study demonstrated similar clinical behaviour and survival between patients with MBN and those with melanoma and concluded that MBN can be a variant of melanoma and suggest using a similar treatment algorithm as that of melanoma [4].

Familial risk of melanoma is known to be around 2-fold [5–7]. Advice and management of known melanoma risk factors and family history, which is an available risk factor for melanoma, may bring both medical and psychosocial benefits. Current familial risk management guidelines for the cancers, such as melanoma, need more evidence-based advice about when to refer relatives of cancer patients to genetic counselling clinics. The counsellors and the caregivers along the entire medical referral system need to be aware of the true familial risks based on valid studies.

A limited number of population-based cohort studies were able to quantify the familial relative risk of histological types of melanoma, but none had a large sample size to analyse rare histological types, or familial associations of histological types with each other. One melanoma study reported only the risk of SSM and NM when parents had any melanoma (combined histological types) [5]. Moreover, all previous studies only provide estimates of relative risk (standardized incidence ratio (SIR), hazard ratio, or odds ratio), which needs to be translated to an easy to understand estimate, such as cumulative risk, to be used in clinical practice. Therefore, a merged dataset was created by pooling the nation-wide family-cancer data from five Nordic countries (including melanoma patients from Denmark, Finland, Iceland, Norway, and Sweden with their unbiased genealogical and high quality cancer data) to be able to systematically and comprehensively quantify the familial risks of all concordant histological types of melanoma and to elucidate the familial associations between different (discordant) histological types. Our goal was to present the familial risks also in terms of cumulative risk, which is tangible for clinicians, patients and their relatives.

2. Materials and methods

Our large dataset consisted of pooled family-cancer data from five Nordic countries. Information on all melanoma index patients in the large dataset ($n = 46\,091$) and their relatives ($n = 238\,724$) was used for this study. The Nordic countries have population-based registers, through which any melanoma patient can be identified with the cancer status (and histological type) in their parents, siblings or children. With the exception of Iceland, sibships could be ascertained only in the offspring generation (those with identified parents). The data characteristics of each country are shown in Supplementary Table 2 and some additional information is presented elsewhere [8]. The lifetime cumulative risk of melanoma (CRM) was assumed to be 0–79 years based on the average life expectancy in Nordic countries, 78.5 years in 2010 [9]. Statistical analyses are explained in the Online Supplementary materials.

2.1. Role of the funding source

None of the funding sources had any role in any part of the study.

3. Results

3.1. Histology-specific estimates

As shown in Table 1, not only familial risk of concordant (similar) histological types of melanoma increased, but also did the familial risks of discordant histological