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Melanoma risk assessment based on relatives' age at diagnosis

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Abstract

Purpose—The aim of this study was to determine risk for melanoma among individuals who have a first- or second-degree relative with a history of melanoma, based on the unaffected individual's age and age at diagnosis of the relative.

Methods—The study employed a case–control design using a statewide database linked with a Surveillance Epidemiology and End Results cancer registry. A population-based sample of individuals who received at least one diagnosis of first primary, malignant melanoma ($n = 14,281$), as well as their first- and second-degree relatives, was included. Control individuals with no history of melanoma ($n = 70,889$) were matched to cases on birth year, gender, race/ethnicity, and county at birth.

Results—Risk for melanoma among relatives of melanoma patients declined with relative's age and age at diagnosis. Individuals between ages 40 and 49 who are first-degree relatives of melanoma patients diagnosed between ages 40 and 49 had the greatest risk for melanoma compared with individuals without a first-degree relative with a melanoma history (HR 4.89; 95% CI 3.11–7.68). Increased melanoma risk among second-degree relatives of patients was typically lower than that for first-degree relatives.

Conclusions—Risk for melanoma, at earlier ages than expected, is increased among relatives of individuals with a history of melanoma, particularly if the melanoma case was diagnosed at a

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young age. Further research on the relationship between age at diagnosis and relative's melanoma risk could inform melanoma screening recommendations for individuals with a family history of the disease.

Keywords

Melanoma; Familial risk; Early detection; Age at diagnosis

Introduction

Total body skin examinations (TBSEs) conducted by a healthcare provider are thought to assist with early detection of skin cancers, including melanoma, the most deadly form of skin cancer that is responsible for the majority of skin cancer deaths [1–4]. Currently, there is limited literature documenting clear benefits to mortality rates associated with TBSE in the general population; however, there are calls to examine potential benefits of TBSEs for individuals who carry an elevated risk for skin cancer [5, 6].

One at-risk population that could potentially benefit from TBSEs is individuals who have a family history of skin cancer. Meta-analytic results indicate that individuals who have any family history of melanoma have a twofold risk for the disease [7–9]. In particular, melanoma risk may be elevated among relatives of cases diagnosed at younger ages [10, 11]. However, most existing studies using case–control or population-based designs have examined onset of melanoma using broad age ranges, and concluded that a greater proportion of individuals with a high familial risk for melanoma were diagnosed with invasive melanomas before age 30 and that risk for melanoma among individuals with a family history of melanoma compared with those without was similar for individuals below and over the age of 50 years [12, 13]. Prior studies were not able to examine risk for melanoma based on both age at family member's diagnosis and family member's age [10, 13]. Only one study has examined potential differences in risk for melanoma based on family member's age and also the age at which relatives were diagnosed with melanoma [11]. Fallah and colleagues [11] reported that among first-degree relatives of melanoma patients, cumulative risk of melanoma was increased, including at younger ages, if patients were diagnosed before age 30. In addition, prior studies documenting risk for melanoma among relatives of cases have primarily relied on relatives' reports of melanoma diagnosis in the family and who in the family had melanoma (with a notable exception [11]), which could have limited accuracy. For example, individuals may hold misunderstandings about the difference between melanoma and non-melanoma skin cancers and/or atypical nevi.

Earlier age of onset is a hallmark of inherited cancer predisposition. However, unlike other common cancers that predominately occur in late adulthood, melanoma can occur throughout the lifespan. There is significant debate regarding whether melanoma occurring in childhood is a biologically distinct entity from adult melanoma, and whether childhood melanoma may be related to different genetic and environmental risk factors [14, 15]. It is currently unknown how age of melanoma diagnosis should be incorporated into risk assessment for relatives.

To more accurately counsel individuals with a family history of melanoma about the optimal ages to consider regular TBSEs, increased understanding of one's risk for melanoma based on age and relative's age at diagnosis is needed. The goal of the current analysis was to explore risk for melanoma among individuals who have a family history of melanoma, specifically, individual who are first- or second-degree relatives (FDR, SDR) of individuals with a diagnosis of melanoma. We document melanoma risk for relatives, stratified by relative's age and age at diagnosis of the affected family member.

Materials and methods

Database

The Utah Population Database (UPDB) housed at the University of Utah contains computerized data records for over 8 million individuals including an extensive set of genealogical information. It is the only database of its kind in the U.S., and one of only a few in the world [16]; most families living in Utah are represented in pedigrees that often span 3–11 or more generations to a common founder. The database is linked to annually updated Utah vital records and statewide cancer records from the Utah Cancer Registry (UCR), a Surveillance Epidemiology and End Results (SEER) registry. Probabilistic linking methods are used to link records [17]. By providing an accurate assessment of cancer family history in close and more distant relatives that does not depend on self- or family-report, the UPDB provides a valuable resource for a thorough analysis of the familial nature of melanoma risk in a large population.

Participants

Cases were defined as all individuals born in Utah who received at least one diagnosis of invasive, first-primary cutaneous melanoma in UCR records for the period of 1966–2012. Individuals ($n = 53$) with a known melanoma-predisposing genetic mutation (*CDKN2A/p16*) were excluded, as were individuals with no pedigree information in UPDB ($n = 2,886$). The resulting study participants included 14,281 melanoma patients and their relatives (FDR, $n = 95,245$; SDR, $n = 244,098$). Approvals were received from the University of Utah's Institutional Review Board and Resource for Genetic Epidemiologic Research (the governing body that reviews use of UPDB data) to conduct this study. As this retrospective study posed minimal risk to participants, a waiver of informed consent was obtained.

Controls, born in Utah and with no personal history of melanoma, were randomly selected from the population and matched to cases on birth year, gender, race (Caucasian, American Indian/Alaska Native, Asian, African American, and Native Hawaiian/Other Pacific Islander) and ethnicity (Hispanic or non-Hispanic), and county at birth (as a proxy for early life ultraviolet radiation (UVR) exposure). Matching occurred using a 5:1 ratio of controls to cases. This ratio was selected to maximize the potential for all case subjects to have control matches and to increase statistical power particularly for age groupings with smaller numbers of cases [18, 19]. For some cases ($n = 308$), fewer than five controls were identified. In addition, controls had to have follow-up for at least as long as the year of diagnosis for their respective case, and had to have family relationships documented in UPDB, resulting in 70,889 controls and their FDR ($n = 691,242$) and SDR ($n = 1,859,946$).

Statistical analysis

Using software developed specifically for the UPDB kinship analysis and in conjunction with the software package R [20], risk of melanoma in relatives of cases was compared to the risk in relatives of controls. The risk in relatives of cases compared with relatives of controls was determined independently for each relationship category: FDR, including parents, children, siblings; and, SDR including grandparents, grandchildren, aunts/nieces, uncles/nephews. Individuals were stratified by their diagnosis age into eight age groups for analysis (0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+). The FDR and SDR of each case and control were included in the analysis within each of the same eight age groups until they reach their respective ‘end-of-analysis’ age as described. For each individual FDR or SDR relative corresponding to each case and control, an end-of-analysis age was determined as either age at diagnosis, if a relative is diagnosed with a subsequent melanoma; age at death; or age at end of follow-up (whichever occurred earliest). Time at risk was measured from 1 year prior to the year corresponding to the earliest age of each analysis group’s age range, to the year corresponding to their end-of-analysis age. Relatives were included in all analysis age groups up to and including the group containing their end-of-analysis age and were not included in any subsequent age group analyses.

Familial recurrence risk (a hazard ratio of melanoma recurrence) in FDR and SDR of patients compared to FDR and SDR of individually matched controls was estimated using a clustered Cox regression model. To account for case–control matching, separate hazard functions (i.e., stratified Cox regressions) were specified for each matched group consisting of a melanoma patient and five associated controls. The model also included covariate adjustment to control for sex and birth year of the relative. Risk is represented as a hazard ratio (HR) of recurrence in an FDR or SDR family member. The Cox model is often used to estimate recurrence risk in families, including among population-based, case–control family studies. Because observations within families are non-independent, the Huber–White sandwich estimator of variance for clustered data was used because it accounts for departures from standard statistical assumptions. The analysis corrects for families being analyzed multiple times when multiple melanoma cases occur within the same family [21–25].

Results

Cases and controls were born in Utah during the period of 1877–2006. Demographic characteristics for participants are contained in Table 1. The average age of melanoma diagnosis for participants with a single diagnosis was 56.9 (SD = 18.0 years), and for participants with multiple melanoma diagnoses, the first diagnosis was at 60.0 (SD = 15.9). On average, across cases and controls, each case had 6.7 FDR. The sample sizes for all analyses are contained in Online Resource 1.

Overall, FDR of cases had a 92% increased risk of melanoma compared to FDR of their respective controls (HR 1.92, CI 1.79–2.07). Sex-stratified risk of melanoma in female FDR and male FDR of patients compared to controls did not substantively differ (female FDR, HR 1.89; CI 1.70–2.10; male FDR, HR 1.95; CI 1.78–2.13). A multiplicative interaction between sex and affected status of the relative, when included in the overall model, was not

significant ($p = 0.67$). Therefore, the results presented below are for women and men combined.

Figure 1 displays the melanoma familial recurrence risk among FDR of cases who had one or more lifetime diagnosis of melanoma compared to controls, stratified by the case's age at diagnosis and the relative's end-of-analysis age (see Methods). HRs are contained in Online Resource 2. Sensitivity analyses conducted to explore potential differences between familial risk of melanoma in relatives of individuals with a single diagnosis of melanoma and relatives of individuals who had more than one diagnosis of melanoma were not significant.

The highest familial recurrence risk for melanoma (four to fivefold) was FDR between the ages 40 and 49 who were related to cases diagnosed at ages 40–49 (HR 4.89, CI 3.11–7.68). Individuals with a threefold risk for melanoma included FDR between the ages of 0 and 29 who were related to cases diagnosed between ages 30 and 39 (HR 2.97, CI 1.56–5.66), and FDR between ages 40 and 49 or ages 60–69 of cases diagnosed between ages 60 and 69 (HR 3.36, CI 2.39–4.72; HR 2.98, CI 2.15–4.14, respectively) (Online Resource 2). Risk generally declined with increasing age, with the highest risk at the same age group as the index case or in earlier years. Other familial risk estimates generally ranged from a twofold to threefold risk (Online Resource 2). Familial risk of melanoma among SDR was typically lower (most HRs between 1.4 and 2.1) than that for FDR (Online Resource 3). Among SDR, higher risk for melanoma was observed for SDR ages 29 or younger and SDR between ages 30 and 39 related to cases diagnosed between ages 30 and 39 (HR 2.46, CI 1.18–5.14; HR 3.18, CI 1.77–5.74, respectively).

Discussion

We observed increased risk for melanoma among FDR of individuals with a history of melanoma, including potentially elevated risk among younger FDR of individuals who had earlier age of melanoma diagnosis. Importantly, we obtained these results using a population-based resource that allowed us to include all eligible individuals statewide and use an objective measure of melanoma family history that does not rely on self-report. Our results are consistent with those in prior studies documenting elevated risk for melanoma among individuals with a family history of melanoma, particularly among relatives of individuals who were diagnosed at early ages (i.e., before age 30) [7–11, 26]. Based on this prior literature, we expected that risk for melanoma would be higher among individuals who had relatives diagnosed early in life. Indeed, our findings pointed to several age groups for FDR and SDR with significantly increased risk for melanoma at young ages (before age 50). We also identified that for FDR, risk for melanoma was notably elevated (i.e., threefold risk) among relatives between ages 60 and 69 of cases diagnosed between ages 60 and 69. We did not control for multiple comparisons in the current analysis as the study was restricted to a limited number of planned comparisons by age group and within first- or second-degree relationships and nominal p values were reported [27]. Thus, we cannot rule out a chance observation. However, many of the significance values associated with risk estimates in our analysis would meet a conservative Bonferroni correction ($p = 0.001$).

The current findings extend those in the existing literature by examining how risk varies by age at diagnosis of both the index case and their relatives. If our findings are confirmed in future studies, individuals with a family history of melanoma could be given more precise information about their risk for melanoma based on their age and the age at diagnosis of their family member with melanoma. Such risk information could be integrated with other risk models that focus on phenotypic features and amount of sun exposure [28]. Our analysis was based on family history, and particularly the impact of age of onset of relatives' cancers, on risk. Family history often represents shared phenotypic and environmental exposures, but these factors were not specifically addressed in our analysis. Our work indicates that family history is a significant risk factor for melanoma, and should be considered in risk assessment and future comprehensive models that takes into all relevant melanoma risk factors.

Future work that examines the relationship between age at diagnosis and relative's melanoma risk could lead to more tailored melanoma screening recommendations for individuals who have a family history of the disease. For example, for other cancer screenings such as mammograms for breast cancer and colonoscopies for colorectal cancer, clinical consensus recommendations indicate that screening among relatives should begin earlier than recommended for the general population. However, such screening recommendations do not yet exist for melanoma and remain unclear given that early or pediatric onset melanoma could confer different risks from adult-onset melanoma [14, 15]. The most recent United States Preventive Services Task Force (USPSTF) guidelines on skin cancer screening focus on individuals who carry a population risk for skin cancer, and does not address potential differences in screening needs among higher-risk populations [29, 30]. Ideally, future preventive efforts targeting individuals who have a family history of melanoma should address not only screening, but also implementation of other skin cancer prevention behaviors, such as sun protection [31, 32].

This study demonstrated the importance of understanding the heterogeneity of familial risk using a population-based resource, the UPDB, in which family relationships can be objectively determined from genealogy and other records that do not rely on self-report. Future studies, for instance with smaller but well-characterized samples, should investigate other factors (e.g., atypical nevus patterns, lethality of the familial melanoma) that may explain some of the variation in risk profiles. For instance, relatives of individuals with more lethal forms of the disease may be at even higher risk of melanoma. Other factors, such as geographic location or socioeconomic status may also moderate the familial effect. For example, if there is an interaction between familial risk and the environment, individuals residing in areas with high UVR exposure may have an even stronger familial risk of melanoma. Further refining the definitions of family history of melanoma has the potential to lead to the creation of more personalized risk profiles. In addition, future studies could seek to understand the extent to which family history of melanoma is due to shared genetics versus lifestyle or behavioral choices shared within families (e.g., use of sun protection, engagement in outdoor activities).

The current findings should be interpreted within the context of study limitations. Although this is the largest study to date examining the potential role that age at diagnosis has on melanoma risk for relatives, there were limited cell sizes for certain age ranges (e.g., cases

diagnosed with melanoma at ages 29 or younger); thus, these estimates should be interpreted with caution. In addition, data on race or ethnicity were unavailable for approximately 20% of relatives of case or control subjects. As the vast majority of our subjects were Caucasian and non-Hispanic (which reflects the Utah population), our ability was limited to examine potential differences between racial or ethnic groups. Given the composition of Utah's population, unreported race or ethnicity is likely primarily White and non-Hispanic. Our study was also limited to individuals residing in Utah for whom genealogical information was available. We used birth county as a proxy for early life sun exposure; however, it would be ideal in future work to assess UVR exposure in childhood through prospective and longitudinal measurements, in addition to other important factors such as skin type and sun protection behavior implementation. Our reliance on existing data also precluded our ability to detect the potentially unique and interactive influences of shared genetics and environmental exposures (e.g., UVR exposure) on melanoma risk and occurrence. In regard to our analytic approach, we tested a large number of models to obtain risk estimates for each age range among patients and relatives. We also reported unadjusted p values for these a priori comparisons given that FDR share more genetic and environmental contributors than SDR, and differences in melanoma risk between age groups have been previously reported in other populations [33]. Future studies could consider developing statistical methods to test a grand Cox model linking diagnosis age with relative's risk for melanoma. We recognize that the associations we observed may be due to chance as a number of comparisons were made; thus, our findings should be interpreted with caution and replication in other studies is warranted. However, it is notable that we generally observed nominal p values below the 0.001 level, particularly for FDR.

In summary, individuals who have a FDR or SDR with a history of melanoma are at increased risk for the disease, particularly if their relative was diagnosed with melanoma at younger ages. Future work is needed to understand the potentially unique prevention and screening needs of individuals who have a family history of melanoma, and could inform targeted prevention and screening efforts for these at-risk individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Risk of melanoma among first- and second-degree relatives

Table 1

Characteristics of melanoma cases and 5:1 controls in Utah, and in their respective first-degree relatives

	Cases		Controls		FDR of cases		FDR of controls	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Total	14,281	(100.0)	70,889	(100.0)	94,867	(100.0)	691,242	(100.0)
Sex								
Male	8,058	(56.4)	39,984	(56.4)	47,538	(50.1)	346,940	(50.2)
Female	6,223	(43.6)	30,905	(43.6)	47,329	(49.9)	344,302	(49.8)
Race								
Caucasian	14,214	(99.5)	70,640	(99.6)	94,473	(99.6)	687,751	(99.5)
Non-Caucasian	67	(0.5)	249	(0.4)	394	(0.4)	3,491	(0.5)
Ethnicity								
Non-hispanic	13,947	(97.7)	69,334	(97.8)	93,606	(98.7)	680,704	(98.5)
Hispanic	334	(2.3)	1,555	(2.2)	1,261	(1.3)	10,538	(1.5)
Vital status								
Alive at last follow-up	9,137	(64.0)	49,044	(69.2)	65,254	(68.8)	468,564	(67.8)
Deceased	5,144	(36.0)	21,845	(30.8)	29,613	(31.2)	222,678	(32.2)

FDR first-degree relative