ACTA ONCOLOGICA
2023, VOL. 62, NO. 12, 1967–1972
https://doi.org/10.1080/0284186X.2023.2265052

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LETTER TO THE EDITOR

Familial features affecting the melanoma risk in *CDKN2A*-negative melanoma families: a study based on the Swedish Cancer Registry

Hildur Helgadottir[a,b], Karina Schultz[a,b], Jan Lapins[c,d] and Veronica Höiom[a,b]

[a]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; [b]Theme Cancer, Karolinska University Hospital, Stockholm, Sweden; [c]Department of Dermatology, Karolinska University Hospital, Stockholm; [d]Dermatology and Venereology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

ARTICLE HISTORY Received 25 August 2023; Accepted 26 September 2023

Background

While population-based dermatologic screening for cutaneous melanoma is generally not recommended, screening of high-risk individuals is considered as an effective measure for primary and secondary prevention [1–9]. Individuals at a high risk for melanoma are, e.g., patients affected by multiple primary melanomas, members of melanoma-prone families, and individuals that carry germline mutations in known high-penetrance genes, such as *CDKN2A*, that are found in 10–25% of melanoma prone families [10–14]. In families where high-penetrance germline pathogenic variants (PVs) are identified, surveillance is primarily directed towards the carriers, although non-carrier members ought to be made aware that their risk of skin cancers is somewhat higher than in the normal population [15]. In families where no melanoma associated PVs are identified, it is less established how to target surveillance activities. In such wild type (WT) families, surveillance is primarily offered to the melanoma affected members, while recommendations for unaffected members may vary. Considering the high incidence of melanoma in many countries, and familial melanoma commonly reported in 5–10% of cases, it is clearly a substantial number of unaffected relatives that the health care providers need to take measures about

While high-risk PVs are identified in a minority of families, carrier families often gain more research interest and are more closely explored compared to WT families. Families without PVs still make up the bulk of identified melanoma families and it is hence of importance to assess the characteristics and risk spectrums in this group. The authors of this study are involved in the care of melanoma-prone families at the Karolinska University Hospital in Stockholm, including identification of the families, germline genetic testing, and dermatologic surveillance of members. According to the current recommendations in Sweden, familial melanoma is defined as at least three melanomas (invasive or *in situ*) in family or two melanomas in first-degree relatives, if one case was under the age of 55 [16]. According to the Swedish guidelines, *CDKN2A* is still the only gene that is recommended for routine germline genetic testing in defined families, while testing for other genes, including *BAP1* is recommended only in the presence of other specific tumor diagnoses. In WT families, melanoma cases are recommended dermatologic surveillance with at least yearly skin exams with total-body photography and digital dermoscopy of selected lesions. In unaffected first-degree relatives, dermatologic surveillance is recommended if they have other risk factors, related to the skin phenotype (including nevus, pigmentation and sun damage), non-melanoma skin cancers or immunosuppression.

The research question addressed in this study arose from our clinical practice, where we wanted to identify if certain features of the melanoma-prone WT families could help to direct surveillance towards those that have the highest risks. Our hypothesis was that a young age of onset, more melanomas, deaths from melanoma and diagnoses of other malignancies could potentially increase the melanoma propensity of family members. The aim of this study was to address if such different features of WT families, would predict the melanoma risk in affected and unaffected members. Specifically, Swedish health care registries, including the Swedish Cancer Registry, Cause of Death Registry, Multigeneration Registry and Population registry were used to assess if different factors related to the tumors in each family affected the prospective melanoma risk of the family members.

Materials and methods

Surveillance program and register linkages

Familial melanoma cases were identified in the years 1994–2010 at the Karolinska University Hospital in Stockholm and invited to participate in a preventive surveillance program. The program that included dermatologic surveillance and *CDKN2A* mutation testing has been described in previous studies, as well as the register linkages to the Swedish

CONTACT Hildur Helgadottir hildur.helgadottir@sll.se Department of Oncology and Pathology, Karolinska Institutet, Theme Cancer, Karolinska University Hospital, Solna, 171 76 Stockholm, Sweden

Supplemental data for this article can be accessed online at https://doi.org/10.1080/0284186X.2023.2265052.

Multigeneration Registry, Cancer Registry and Cause of Death Registry and Population Registry [7,11,17,18]. A summary of the surveillance program, genetic testing, registry linkages, and population controls is provided in the Supplementary Material. Follow-up started at the date when the family was identified and commenced surveillance as part of a study, where affected members also underwent germline genetic testing. This study included families where no *CDKN2A or CDK4* mutation had been identified. Subgroups of the included families were also tested for *TP53, PTEN, TERT, POT1*, and *BAP1*, with no identified carriers [17,19,20]. In Sweden *BAP1* mutations have not been detected in any families with exclusively cutaneous melanoma, only in families with multiple cases of *BAP1* associated tumors, that besides cutaneous melanoma includes uveal melanoma, mesothelioma, renal cell carcinoma and BAP1 inactivated melanocytoma tumors (BIMT) [21]. The majority of families were also tested for medium risk *MITF* E318K variant, with two affected families identified that were not included in this analysis [17]. The study was approved by the Swedish ethical authorities (Dnr 98–154 and Dnr 2012/422).

Features of the families

Each family was assessed for different features based on the registry data. These factors included age of the youngest melanoma case in the family (<40 or ≥ 40), sex of the affected cases (women only, men only or both), numbers of melanomas in the family (2 or >2), numbers of individuals with melanoma (2 or >2), numbers of invasive melanomas (<2 or ≥ 2), multiple primary melanomas in any of the members (yes or no), deaths from melanoma in the family (yes or no), cases of cutaneous squamous cell carcinoma (cSCC) (yes or no) or other non-cutaneous malignancies (yes or no) in the family. Basal cell carcinomas are not included in the Swedish Cancer Registry (since 2004 they are registered in a separate register held by the Swedish National Board of Health and Welfare) and were therefore not included in the study. Those already affected by melanoma and their unaffected first-degree relatives were followed where it was assessed if any of the defined family feature affected the melanoma risk.

Statistical analysis

Relative risks for new primary melanoma (invasive or *in situ*) occurring during the surveillance were evaluated together with, 95% confidence intervals (CIs) and *p* values that were calculated from incidence rates (number with a new melanoma/person years). Relative risk of melanoma was assessed to compare members belonging to families with the defined features. Relative risk was also used to compare the risk of the family members to the risk of an age- and sex-matched reference population obtained from the Swedish Population Registry, where diagnosed tumors also had been retrieved from the Cancer Registry, as has been described in a previous publication [17,22]. Statistical tests were two-sided and *p* values under 0.05 were considered statistically significant. Statistical analyses were performed with StatSoft Statistica software, version 10 (Tulsa, OK).

Results

Characteristics of the families and members

In total, 151 families consisting of 1192 family members were included in the study. The included families fulfilled the criteria of having at least two first-degree relatives with cutaneous melanoma and no *CDKN2A* mutation. Collectively there were 349 melanomas that had been diagnosed among 319 family members. The numbers of melanomas that had been diagnosed per family and were 2 ($N = 116$), 3 ($N = 30$), 4 ($N = 3$), 6 ($N = 1$), and 7 ($N = 1$). Of the 151 families, 85 (56.3%) had at least one member diagnosed with melanoma before the age of 40 years (Table 1). In 41 families, only men (27.2%) had been affected and in 43 (28.5%), only women and in the remaining families both men and women were affected by melanoma (43.7%). In a majority of families only two melanomas had been diagnosed (76.8%) or only two individuals with melanoma (88.7%) in the family. Multiple primaries had been diagnosed in 23 (15.2%) families. Majority of families (70.9%) had two or more invasive melanomas. In 29 families (19.2%) there were members that had been diagnosed with cSCC. In 30 (19.9%) families there were cases that had died from melanoma. In 38 families (25.2%) there were members affected by non-cutaneous malignancies before the age of 60 years. The diagnosed malignancies were, breast cancer ($n = 14$), endometrial cancer ($n = 6$), colorectal cancer ($n = 4$), lymphoma ($n = 3$), renal cell cancer ($n = 2$), prostate cancer ($n = 2$), ovarian cancer ($n = 2$), brain tumors ($n = 2$), bladder cancer ($n = 2$), testicular cancer ($n = 2$), and hepatocellular carcinoma ($n = 1$). In one family a breast and a bladder cancer had been diagnosed in members before the age of 60, in the remaining families only one non-skin tumor had been diagnosed (<60 years) in each family. Hence, none of the included families arose a suspicion of any other hereditary tumor predisposition syndrome.

Follow-up

At the timepoint when the families were identified they consisted of 319 melanoma-affected individuals, whereof 41 were not alive and hence 278 melanoma-affected cases were available for follow-up. There were 873 unaffected first-degree relatives, where only relatives contributing person years after the age of 12 years were included. The median number of included family members (affected and non-affected) per family were 7 (range 2–23), where comprehensive data on any malignant diagnoses were available for all from the Cancer Registry. The median time of follow-up was 14 years. During the follow-up, 81 new melanomas were diagnosed, 50 (33 invasive and 17 *in situ*) among the affected members and 31 (27 invasive and 5 *in situ*) among previously non-affected first-degree relatives.

Table 1. Characteristics of melanoma families and members followed-up after the identification of the family.

	Numbers of families ($N = 151$)	%	Members with melanoma ($n = 278$)*	%	Non-affected first-degree relatives ($n = 758$)**	%
Age of youngest melanoma case						
<40	85	56.3	164	59.0	462	60.9
≥40	66	43.7	114	41.0	296	39.0
Sex of melanoma cases in family						
Only women affected	43	28.5	84	30.2	215	28.3
Only men affected	41	27.2	78	28.1	228	30.0
Both sexes affected	66	43.7	116	41.7	315	41.5
Numbers of melanomas diagnoses in family						
2	116	76.8	202	72.7	527	69.4
>2	35	23.2	76	27.3	231	30.4
Numbers of individuals with melanoma in family						
2	134	88.7	233	83.8	602	79.3
>2	17	11.3	45	16.2	156	20.6
Numbers of invasive melanomas in family						
<2	44	29.1	82	29.5	198	26.1
≥2	107	70.9	196	70.5	560	73.8
Multiple primary melanoma (MPM) in family						
No MPM in family	128	84.8	236	84.9	652	85.9
MPM in family	23	15.2	42	15.1	106	14.0
Cases deceased from melanoma in family						
None deceased from melanoma in family	121	80.1	233	83.8	615	81.0
At least one deceased from melanoma in family	30	19.9	45	16.2	143	18.8
Non-skin cancer before age of 60 years in family						
None in family with non-skin cancer	113	74.8	203	73.0	517	68.1
At least one in family with non-skin cancer	38	25.2	75	27.0	241	31.8
Cutaneous squamous cell skin carcinoma (cSCC) in family						
None in family with cSCC	122	80.8	244	87.8	653	86.0
At least one in family with cSCC	29	19.2	34	12.2	105	13.8

*Alive at the timepoint when family was identified.
**Contributed years after the age of 12 years to the follow-up.

Relative melanoma risk in members of families with different features

Having a young age of onset of melanoma in family did not significantly increase the risk of melanoma, not in the already affected melanoma cases nor in the non-affected first-degree relatives (Table 2). The sex of the melanoma cases in the family was not either associated with the risk of melanoma. Melanoma cases in families where a higher number of melanomas had been diagnoses tended to have higher risk of additional melanomas but did not confer any increased risk to the unaffected first-degree relatives. Members of families that had cases that had died from melanoma did not have significantly increased melanoma risk nor did members of families that had cases of non-cutaneous malignancies diagnosed before the age of 60 years. Members of families where cSCCs had been diagnosed had a higher risk of melanoma, particularly in those already diagnosed with melanoma (HR 2.2, 95% CI 1.1–4.2, $p = 0.020$).

Relative melanoma risk in family members compared to population controls

Compared to the population controls the familial melanoma cases had a RR for new melanomas of 35.0 (95% CI 18.8–63.4, $p < 0.001$). As for the first-degree relatives that were unaffected from start of follow-up, their RR of being diagnosed with melanoma during the surveillance was 9.1 (95% CI 5.7–14.1, $p < 0.001$), compared to the controls from the general population. Figure 1. It also depicts the relative melanoma risk, compared to the general population, in members of families having or not having the defined features. As an example, while the melanoma affected cases collectively had a RR of 35.0 for new melanoma, those that belonged to families with cSCC had a RR for melanoma of 68.3 compared to the normal population, while those that had no cSCC in family had a RR of 30.8 compared to the normal population. It hence demonstrates that among the melanoma affected, the risk of additional melanomas diverged dependent on if they belonged to families with with/without cSCC and also if there were >2 or 2 individuals with melanoma or in families with/without multiple primaries or families. It also demonstrates that these features to a lesser extent diverged the melanoma risk of the unaffected first-degree relatives.

Discussion

To summarize, in WT melanoma families, both affected and non-affected had, a significantly increased melanoma risk, approximately 35-fold and 9-fold, respectively, compared to the reference population. Of note, the majority of the families were 2-case families (77%), as such families were previously routinely tested for *CDKN2A* PVs. After a study evaluating the genetic testing in Sweden, demonstrating a very low frequency of *CDKN2A* PVs in 2-case families, the guidelines were altered to include only families with ≥3 melanomas for genetic testing [10]. The present study shows

Table 2. Relative risk of new melanoma dependent on different factors in the family at the timepoint when the family was identified.

	Risk of additional melanomas in members affected by melanoma			Risk of melanomas in previously non-affected first-degree relatives		
	RR	95% CI	*p* Value	RR	95% CI	*p* Value
Age of youngest melanoma case in family						
<40 vs. ≥40	1.0	0.6–1.9	0.883	0.6	0.3–1.3	0.193
Sex of melanoma cases in family						
Men affected *vs.* women affected	1.1	0.6–2.2	0.708	1.0	0.9–4.0	0.948
Numbers of melanomas diagnoses in family						
>2 vs. 2	1.7	0.9–2.9	0.073	1.0	0.5–2.1	0.979
Numbers of individuals with melanoma in family						
>2 vs. 2	1.6	0.9–3.1	0.119	1.3	0.6–2.8	0.511
Numbers of invasive melanomas in family						
≥2 *vs.* <2	2.0	1.0–4.3	0.045	0.7	0.3–1.5	0.406
Multiple primary melanoma (MPM) in family						
MPM *vs.* no MPM	1.7	0.9–3.4	0.104	1.1	0.4–2.9	0.879
Cases deceased from melanoma in family						
≥1 *vs.* 0 deceased from melanoma	0.8	0.4–12.0	0.680	1.9	0.9–4.0	0.071
Non-skin cancer before age of 60 years in family						
≥1 *vs.* 0 cancer in family	0.8	0.4–1.6	0.551	1.3	0.7–2.7	0.410
Cutaneous squamous cell skin carcinoma (cSCC) in family						
≥1 *vs.* 0 cSCC in family	2.2	1.1–4.2	0.020	2.1	1.0–4.7	0.063

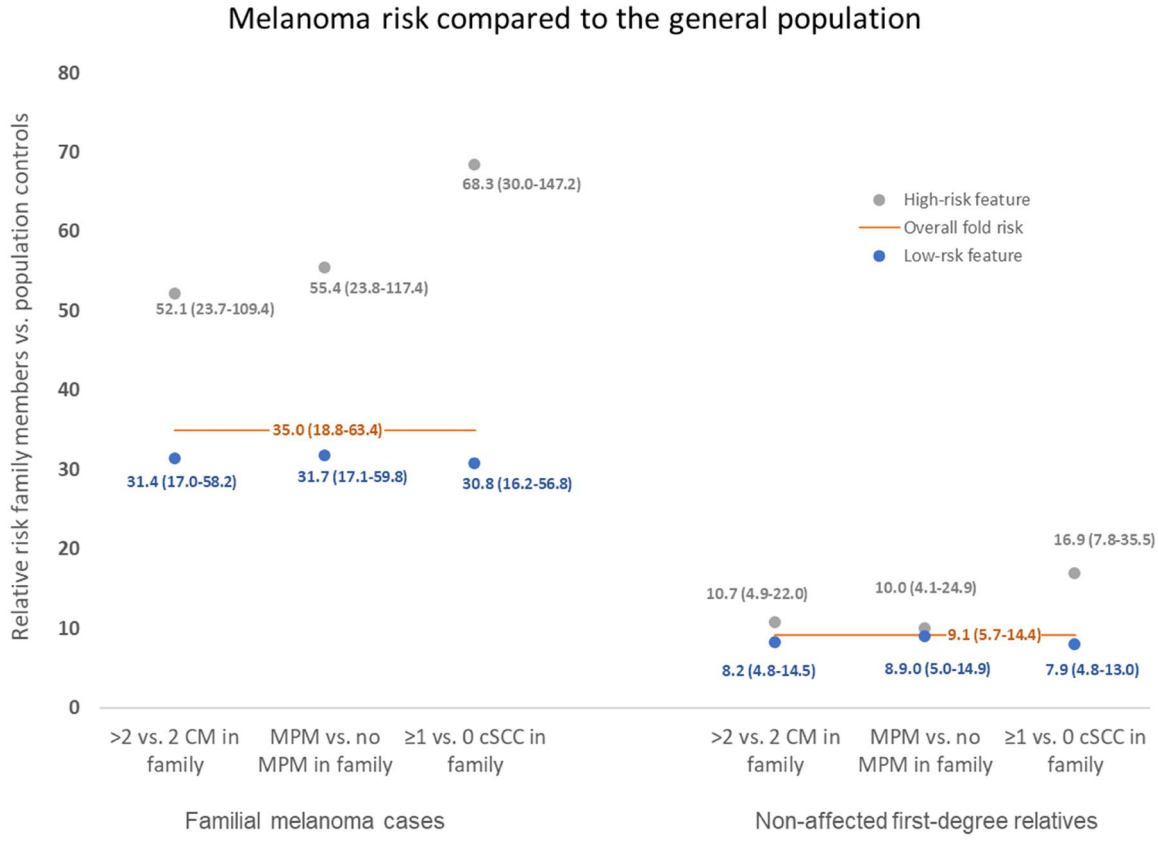

Figure 1. Relative risk for melanoma in members of melanoma-prone families, compared to population controls. The left part illustrates the prospective risk of additional melanomas in melanoma affected members and the right side the melanoma risk in previously non-affected first-degree relatives. Family members are groped depending on if they had "high-risk features" or "low-risk features", i.e., belonging to families with >2 or 2 individuals with melanoma, families with or without cases of multiple primary melanoma (MPMs) or families with or without cases of cutaneous squamous cell skin carcinoma (cSCC). Relative risks and 95% confidence intervals are shown.

that, the melanoma risk is however considerably elevated, also in 2-case families, and although not eligible for genetic testing, members should be offered dermatologic surveillance [16]. We found that more melanomas diagnosed in a family, particularly invasive melanomas, were related to an increased risk of additional melanomas, but only in those already affected, not in the unaffected first-degree relatives. Furthermore, age of onset, sex of the cases, deaths from melanoma or diagnoses of non-cutaneous malignancies were not associated with increased melanoma risk, neither in previously affected nor in the unaffected. Interestingly, the factor with the most evident association to new melanomas, was a previous diagnosis of cSCC in the family. cSCC is the skin tumor that has been described as having the strongest

association with UV exposure, as it predominantly occurs in sun-exposed areas, often on UV-damaged skin [23]. Hence, it is plausible that the UV exposure pattern of the family members is a prominent risk factor in WT familial melanoma. In a study including the whole Swedish population using the Multigeneration Registry to identify blood relatives and spouses in three generations it was found that the melanoma risk was closely related to both the childhood and adult environment [24]. Anecdotally, we have noted that a remarkably high portion of the WT members in our hereditary melanoma clinic have recreational boats where the family gathers to spend holidays in the Swedish archipelago during the summer. The co-occurring genetic predisposition is in most families considered as complex, involving many different low-penetrance genes [17,25,26]. Polygenetic risk score panels with pigmentation-associated genes such as *MC1R*, *ASIP*, *TYR, SLC45A2*, and *OCA2,* but also genes in other pathways have been studied in sporadic and familial melanoma. Highest such polygenetic risk scores have been observed in familial melanoma cases, followed by sporadic cases that were similar as in non-affected family members, and lowest in healthy controls [27]. However, the polygenic risk alleles have broad overlaps in the affected and unaffected, and hence the implication of a certain polygenic risk score on an individual level have largely not been defined [27,28]. Previous studies with next-generation sequencing (NGS, whole exome or whole genome) have identified rare families (approximately 1%) with PVs in genes included in telomere regulating pathways (*TERT, POT1, ACD, TERF2IP, TERF1, TERF2*, and *TINF2* [29–31]. While a few of the Swedish families have undergone NGS as part of these international collaborative studies (non with identified novel PVs), the majority of the families here included, have not undergone NGS or been tested for these genes.

In a study where familial cases were identified through the Nordic cancer registries, it was found that a young age of melanoma onset and >2 melanoma cases was associated with significantly increased risks of melanoma in the relatives [32]. This could to a substantial extent be affected by the presence of carrier families with *CDKN2A* and to a lesser extent *BAP1* or other high-risk PVs. In families with high-risk PVs, significantly earlier age of onset and higher numbers of melanomas has consistently been observed together with a considerably higher risk of new melanomas [10,18,22,33,34]. Hence, the families with the youngest cases and the largest numbers of melanomas are probably enriched with families with melanoma-associated PVs, that give an increased melanoma risk. In this study, the melanoma cases were genotyped to exclude such high-risk families, which in part could explain this discrepancy. In families lacking PVs where melanoma propensity is rather attributed to the skin phenotype and UV-exposure, the association with age and numbers of melanomas seems not as clearly related to an increased risk in the relatives. Of note is that in our study we did not specifically address the effect of, UV exposure, skin and nevus phenotype or polygenetic risk scores.

A strength in this study is the population-based approach where the familial melanoma clinic at the Karolinska University Hospital is the only such practice in the Stockholm region (current population, 2.4 million inhabitants). Also, a majority of the invasive melanomas diagnosed in the Stockholm Region are followed-up at Karolinska where investigation and surveillance for familial melanoma has routinely been offered. In addition, the linkage to high-quality national registries has offered accurate data on family members, tumor diagnoses and deaths. In this study, features of WT families regarding the diagnoses of melanoma and other cutaneous and non-cutaneous malignancies were related to the melanoma risk, and to our knowledge this has not been done previously. Notably, we did not find any such feature that was significantly associated with an increased risk in the unaffected relatives.

Conclusion

Based on the results from this study, we think that it is still largely the skin phenotype as for phototype, nevus traits, UV-damage together with previous non-melanoma skin tumors and UV-exposure habits that should guide in determining the need of surveillance in unaffected close relatives of familial melanoma cases. Counselling regarding UV protection is also of essence in the setting of WT familial melanoma since the increased propensity is invariably a combination of complex genetic traits and the UV exposure.

Disclosure statement

The authors have no disclosures to make.

Funding

This work was supported by grants from the Swedish Cancer Society (20 0156 F and 21 1486 Pj), ALF grant from Region Stockholm (grant number FoUI-954830 and FoUI-975235) and the Cancer Research Funds of Radiumhemmet (grants numbers 194092 and 2240233)

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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