Germline CDKN2A Mutation Status and Survival in Familial Melanoma Cases

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Abstract

Background: Germline mutations in CDKN2A have been associated with increased risk of melanoma and tobacco-related cancers in respiratory and upper digestive tissues. In CDKN2A wild-type (wt) melanoma families, other known high-risk, melanoma-predisposing mutations are rare, and no increased risk has been observed for nonskin cancers in this group. This study is the first to compare survival in germline CDKN2A mutated (mut) and nonmutated melanoma cases.

Methods: Melanoma-prone families participating in this study were identified through a nationwide predictive program starting in 1987. Information on cancer diagnoses (types, stages, and dates) and deaths (causes and dates) were obtained through the Swedish Cancer Registry and Cause of Death Registry. Kaplan Meier and Cox proportional hazards regression models were used to assess survival in CDKN2A mut (n = 96) and CDKN2A wt (n = 377) familial melanoma cases and in matched sporadic melanoma cases (n = 1042). All statistical tests were two-sided.

Results: When comparing CDKN2A mut and CDKN2A wt melanoma cases, after adjusting for age, sex, and T classification, CDKN2A mut had worse survival than melanoma (hazard ratio [HR] = 2.50, 95% confidence interval [CI] = 1.49 to 4.21) and than nonmelanoma cancers (HR = 7.77, 95% CI = 3.65 to 16.51). Compared with matched sporadic cases, CDKN2A mut cases had statistically significantly worse survival from both melanoma and nonmelanoma cancers while no differences in survival were seen in CDKN2A wt compared with sporadic cases.

Conclusions: CDKN2A mut cases had statistically significantly worse survival from nonmelanoma cancers and, intriguingly, also from melanoma, compared with melanoma cases with no CDKN2A mutations. Further studies are required to elucidate possible mechanisms behind increased carcinogen susceptibility and the more aggressive melanoma phenotype in CDKN2A mutation carriers.

Germline mutations in the tumor suppressor gene CDKN2A are among the strongest known inherited genetic risk factors for cutaneous melanoma. Carriers have a risk of melanoma that is greater than 65-fold increased, compared with the normal population, and a lifetime penetrance for melanoma of 60% to 90% (1–3). CDKN2A mutation penetrance is associated with population incidence rates of melanoma, and the same factors that affect population incidence of melanoma, such as UV exposure, pigmentation traits, and risk-modifying genes, appear to mediate CDKN2A penetrance (2,4). In carriers of some CDKN2A mutations, increased risks have also been reported for nonmelanocytic cancers, in particular pancreatic, lung, and head and neck cancers (1,3,5–9), which occur more prominently in carriers who smoke tobacco (1,9). Collectively, these findings indicate that the development of tumors in CDKN2A mutation carriers is also dependent on interactions between environmental and host factors other than the germline mutation. High-risk melanoma-associated germline mutations in other genes than CDKN2A have yet only been identified in very few melanoma families. We have previously reported that in a cohort of 1168 members of melanoma-prone families with CDKN2A wild-type (wt) status,
there was a statistically significantly increased risk of melanomas and squamous cell skin cancers but no increased risk of nonskin cancers (10). Furthermore, the allele frequencies of red hair color variants of the pigmentation gene MC1R were observed to be highest in CDKN2A wt melanoma cases, intermediate in sporadic melanoma cases, and lowest in healthy control subjects, indicating a gene dosage effect (10,11). In the Swedish CDKN2A wt melanoma families, it is likely that many members harbor skin cancer–associated gene variants and pigmentation traits that, in combination with UV exposure, cause a familial sensitivity to developing both melanoma and nonmelanoma skin cancers, and probably only relatively few families have high-risk cancer-associated mutations in tumor suppressor genes or oncogenes (10).

Several studies have compared patient- and tumor-specific factors among germline CDKN2A mutation carriers and noncarriers. In summary, the only consistent finding has been that CDKN2A mutation carriers are younger at melanoma diagnosis whereas findings on differences in tumor-specific features such as body site of the primary tumor, invasiveness, thickness, and histological type have been statistically nonsignificant or divergent (12–16). There have been indications that primary melanomas from CDKN2A mutation carriers are less advanced at diagnosis; however, in most of the studies, control subjects have consisted of sporadic melanoma cases (12–14). This is of importance because members of melanoma families are normally enrolled in dermatologic follow-up programs aimed at diagnosing melanomas at earlier or premalignant stages while sporadic melanoma cases have usually not participated in any such programs. Also, it is not specified in the reviewed studies whether the first melanoma diagnosed or subsequent melanomas were used for comparative analysis. This is also important because multiple melanomas are common among familial melanoma cases and the first melanoma is usually the thickest (17–20). After the first melanoma diagnosis, awareness increases, resulting in subsequent melanomas being thinner and less invasive. The presumption that melanoma tumors of CDKN2A mutation carriers have more favorable prognostic features has led to speculations that mutation carriers might have similar or even more beneficial outcomes from their melanomas, but research addressing this specific question has until now been entirely lacking. The aim of this study was to evaluate survival from all causes, from melanoma alone, and from nonmelanoma cancers in familial melanoma cases with mutations in the CDKN2A gene, compared with familial and sporadic cases without such mutations.

**Methods**

**Participants and Register Linkages**

In 1987, the Swedish Melanoma Study Group initiated a national program to identify kindreds with familial cutaneous malignant melanoma and to provide members of these families the possibility to participate in a preventive program (17). Melanoma families were defined as kindreds with at least two blood relatives (first-, second-, or third-degree relatives) with verified melanomas (in situ or invasive). Melanoma families were identified through questioning of newly diagnosed melanoma patients regarding relatives with melanoma. Melanoma tumors in relatives were verified by pathology and/or clinical records. In this survival study, families where at least one familial melanoma case had been screened for germline mutations in the CDKN2A gene were included. In the flowchart in Figure 1, an overview of study
participants and register linkages is shown. The national 10-digit personal identity number of each CDKN2A-tested familial melanoma index case was linked with the Swedish Multi-Generation Registry, which contains connections between all individuals born after 1931 and their biological parents, who were registered in Sweden after 1960 (21). This allowed identification of familial melanoma cases’ first-degree relatives (parents, siblings, and children) and second-degree relatives (grandparents, uncles/aunts, nieces/nephews, half-siblings, and grandchildren). The personal identity numbers of all identified family members were linked with the Swedish Cancer Registry to obtain data on all registered cancers (types, stages, and dates) and with the Cause of Death Registry to obtain data on all deaths (causes and dates).

The Swedish Cancer Registry was established in 1958, and reporting to this registry is compulsory for both clinicians and pathologists/cytologists diagnosing a cancer; completeness of the register has been estimated to 97% (22). To identify registered cancer types, ICD7 codes and histology codes (WHO/HS/CANC/24.1) were used; for the T classifications of primary melanoma tumors, the 2009 American Joint Committee on Cancer melanoma staging and classification system was used (23). In the Cause of Death registry, information on all deaths of individuals...
living in Sweden has been registered since 1961 (24). Only family members who had a registered melanoma diagnosis were included in this survival study. Sporadic melanoma cases, matched for age, sex, T classification, and year of diagnosis, were obtained from the Regional Melanoma Registry of the Stockholm-Gotland health care region. In a previous study on sporadic melanoma cases from this region, a CDKN2A mutation was found in only one of 526 cases (0.2%) (11).

### CDKN2A Mutation Analyses

Melanoma family members were invited to undergo germline CDKN2A mutation analysis for the purpose of study. Procedures used for DNA isolation from peripheral blood mononuclear cells, polymerase chain reaction (PCR) of CDKN2A exons, and direct sequencing of PCR products have been described previously (1). Informed consent was obtained before family members underwent mutation analysis, and the study was approved by Research Ethical Review Boards in Lund and Stockholm. Of the 270 identified families, protein-altering mutations have been identified in 31 families, of which 29 carry the Swedish founder mutation in CDKN2A (p.Arg112dup), one has an in-frame deletion of 24 bases (p.delA60_Gly67), and one has an amino acid substitution (p.Pro48Leu). It has previously been reported that these mutations disrupt function of the p16 protein and segregate with melanoma (8,25,26).

### Follow-up

Follow-up started at the date when the first invasive melanoma was diagnosed in each case. The CDKN2A mutation test has, until now, solely been a research test in Sweden, and all identified melanoma families have been enrolled in the same clinical follow-up program, with regular skin exams and education on skin cancer prevention, irrespective of CDKN2A mutation status. Follow-up ended at the date of death, emigration, or census date of December 31, 2011.

### Statistical Analysis

Survival from all causes, from melanoma, and from nonmelanoma cancers (all cancer types except melanoma) was studied. For overall survival, all deaths were considered events. For melanoma-specific survival, only deaths from melanoma were counted as events; deaths from other causes were labeled as censored, and follow-up ended on the date of death. In the same way, for nonmelanoma cancer-specific survival, only deaths from nonmelanoma cancers were counted as events, deaths from other causes were labeled as censored, and follow-up ended on the date of death. For survival plots, Kaplan-Meier analyses with log-rank P values were computed. Cox proportional hazards regression models, unadjusted and adjusted for age, sex, and T classification of the primary tumor were used to assess survival in CDKN2A$^\text{mut}$ compared with CDKN2A$^\text{wt}$ familial melanoma cases. Proportional hazards hypothesis was verified by investigating Schoenfeld residuals. All statistical tests were two-sided. P values under .05 were considered statistically significant. Statistical analyses were performed with StatSoft Statistica software, version 10.

### Results

#### Patient and Tumor Characteristics of Familial Melanoma Cases

The CDKN2A$^\text{mut}$ (n = 104) and CDKN2A$^\text{wt}$ (n = 444) melanoma cases (in situ and invasive) were identified from 31 CDKN2A$^\text{mut}$ and 238 CDKN2A$^\text{wt}$ melanoma families, respectively (Table 1). In the CDKN2A$^\text{mut}$ and CDKN2A$^\text{wt}$ familial melanoma cases, 76.9% and 71.8% had a confirmed mutation status, respectively.

### Table 2. Causes of death in CDKN2A$^\text{mut}$ and CDKN2A$^\text{wt}$ and sporadic melanoma cases

<table>
<thead>
<tr>
<th>Deaths</th>
<th>CDKN2A$^\text{mut}$ (n = 104) No. (%)</th>
<th>CDKN2A$^\text{wt}$ (n = 444) No. (%)</th>
<th>Sporadic melanoma (n = 312)† No. (%)</th>
<th>P†,‡</th>
<th>P†,§</th>
<th>P†,¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deceased</td>
<td>47 (45.2)</td>
<td>135 (30.4)</td>
<td>105 (33.7)</td>
<td>.004</td>
<td>.03</td>
<td>.28</td>
</tr>
<tr>
<td>Non–cancer related</td>
<td>6 (5.8)</td>
<td>56 (12.6)</td>
<td>41 (13.1)</td>
<td>.024</td>
<td>.04</td>
<td>.77</td>
</tr>
<tr>
<td>Melanoma</td>
<td>23 (22.1)</td>
<td>56 (12.6)</td>
<td>44 (14.1)</td>
<td>.01</td>
<td>.05</td>
<td>.71</td>
</tr>
<tr>
<td>Nonmelanoma cancer</td>
<td>18 (17.3)</td>
<td>23 (5.2)</td>
<td>20 (6.4)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.73</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8 (7.7)</td>
<td>2 (0.5)</td>
<td>1 (0.3)</td>
<td>.76</td>
<td>.74</td>
<td>.72</td>
</tr>
<tr>
<td>Lung</td>
<td>5 (4.8)</td>
<td>3 (0.7)</td>
<td>1 (0.3)</td>
<td>.01</td>
<td>&lt;.001</td>
<td>.38</td>
</tr>
<tr>
<td>Breast</td>
<td>2 (1.9)</td>
<td>2 (0.5)</td>
<td>4 (1.3)</td>
<td>.11</td>
<td>.26</td>
<td>.50</td>
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<tr>
<td>Gastrointestinal</td>
<td>1 (1.0)</td>
<td>6 (1.4)</td>
<td>2 (0.6)</td>
<td>.75</td>
<td>.74</td>
<td>.58</td>
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<tr>
<td>Urinary</td>
<td>1 (1.0)</td>
<td>6 (1.1)</td>
<td>2 (0.6)</td>
<td>.95</td>
<td>.41</td>
<td>.84</td>
</tr>
<tr>
<td>Head and neck</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>—#</td>
<td>—#</td>
<td>—#</td>
</tr>
<tr>
<td>Gynecological</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (0.9)</td>
<td>—#</td>
<td>—#</td>
<td>—#</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.0)</td>
<td>4 (0.9)</td>
<td>7 (2.2)</td>
<td>.95</td>
<td>.41</td>
<td>.84</td>
</tr>
</tbody>
</table>

* Sporadic melanoma cases, matched for age, sex, year of diagnosis, and tumor thickness of CDKN2A$^\text{mut}$ cases. CDKN2A$^\text{mut}$ – familial melanoma case with germline CDKN2A gene mutation; CDKN2A$^\text{wt}$ – familial melanoma case with no CDKN2A mutations (wild-type).
† Sporadic melanoma cases, matched for age, sex, year of diagnosis, and tumor thickness of CDKN2A$^\text{wt}$ cases.
‡ P value comparing CDKN2A$^\text{mut}$ and CDKN2A$^\text{wt}$ cases.
§ P value comparing CDKN2A$^\text{mut}$ and matched sporadic melanoma cases.
¶ P value comparing CDKN2A$^\text{wt}$ and matched sporadic melanoma cases.
# Noncalculable because of 0 cases.
Sporadic Melanoma Cases

CDKN2A

primary melanoma cases, a minority were confirmed to have mutations.

17.3% had three or more melanomas, compared with 14.6% and 5.2% in the CDKN2Awt and CDKN2Awt families, respectively. In the CDKN2Amut cases, 52 (22%) had deaths from melanoma, with one to two melanoma deaths per family, and 25 (11%) families had deaths from nonmelanoma cancers, all with one nonmelanoma cancer death per family. In conclusion, there were no individual families that accounted for any substantial portion of the mortalities. The family with the p.Pro48Leu mutation in CDKN2A had deaths from both melanoma and nonmelanoma cancer while the family with the p.delAla60 Gly67 mutation (n = 2) had no deaths from any cause among the melanoma cases. Causes of death subdivided depending on whether cases had been diagnosed with multiple primary melanomas or belonged to families with few (≤3) or many (>4) members affected with melanoma are shown in Supplementary Table 3 and Supplementary Table 4, respectively (available online). In all subgroups, there were higher frequencies of death from melanoma and nonmelanoma cancer in CDKN2Amut cases compared with CDKN2Awt cases.

Causes of Death Among CDKN2A<sup>mut</sup>, CDKN2A<sup>wt</sup>, and Sporadic Melanoma Cases

Of the CDKN2A<sup>mut</sup> familial melanoma cases (in situ and invasive), 45.2% were deceased at the censor date, compared with 30.4% of the CDKN2A<sup>wt</sup> cases (Table 2). This statistically significant difference in deaths (P = .004) from any cause was seen even though non-cancer-related deaths were more frequent in the CDKN2A<sup>wt</sup> cases (5.8% vs 12.6%). The increased frequency of deaths in the CDKN2A<sup>mut</sup> cases was explained by a statistically significantly higher mortality in CDKN2A<sup>mut</sup> cases from both melanoma (22.1% vs 12.6%, P = .01) and nonmelanoma cancers (17.3% vs 5.2%, P < .001) compared with the CDKN2A<sup>wt</sup> cases. Among the matched sporadic melanoma cases, the numbers and causes of deaths were comparable with those in the CDKN2A<sup>wt</sup> group. In particular, CDKN2A<sup>mut</sup> cases had many deaths from pancreatic and lung cancers; of the 18 nonmelanoma cancer deaths among CDKN2A<sup>mut</sup> cases, 13 (72%) were from pancreatic or lung cancer, compared with 23% of the CDKN2A<sup>wt</sup> cases and 35% of the sporadic cases. Causes of deaths among the melanoma cases of each identified CDKN2A<sup>mut</sup> and CDKN2A<sup>wt</sup> family are shown in Supplementary Table 1 and Supplementary Table 2 (available online). Of the 31 CDKN2A<sup>mut</sup> families, 18 (58%) had deaths from melanoma, with one to three melanoma deaths per family and 12 (39%) families had deaths from nonmelanoma cancers, with one to three nonmelanoma cancer deaths per family. Of the 238 CDKN2A<sup>wt</sup> families, 52 (22%) had deaths from melanoma, with one to two melanoma deaths per family, and 25 (11%) families had deaths from nonmelanoma cancers, all with one nonmelanoma cancer death per family. In conclusion, there were no individual families that accounted for any substantial portion of the mortalities. The family with the p.Pro48Leu mutation in CDKN2A had deaths from both melanoma and nonmelanoma cancer while the family with the p.delAla60 Gly67 mutation (n = 2) had no deaths from any cause among the melanoma cases. Causes of death subdivided depending on whether cases had been diagnosed with multiple primary melanomas or belonged to families with few (≤3) or many (>4) members affected with melanoma are shown in Supplementary Table 3 and Supplementary Table 4, respectively (available online). In all subgroups, there were higher frequencies of death from melanoma and nonmelanoma cancer in CDKN2A<sup>mut</sup> cases compared with CDKN2A<sup>wt</sup> cases.

Survival Among CDKN2A<sup>mut</sup>, CDKN2A<sup>wt</sup>, and Sporadic Melanoma Cases

In the survival analyses, only cases with a diagnosis of invasive melanoma (for CDKN2A<sup>mut</sup>, CDKN2A<sup>wt</sup>, and sporadic melanoma cases: n = 96, n = 377, and n = 1.042, respectively) were included. In Figure 2, Kaplan-Meier plots are shown, demonstrating that in CDKN2A<sup>mut</sup> familial cases compared with CDKN2A<sup>wt</sup> cases statistically significantly worse survival was seen from all causes (P = .03), from melanoma (P = .03) and from nonmelanoma cancers (P < .001). In an unadjusted Cox proportional hazards model, age of 50 years or older was found to be statistically significantly associated with increased death rates from all causes, from melanoma and from nonmelanoma cancers (Table 3). Male sex was statistically significantly associated with higher death rates from all causes and from melanoma but not from nonmelanoma cancers. Higher T classification of the primary melanoma was associated with increased death rates from all causes and from melanoma and, interestingly, also with increased death rates from nonmelanoma cancer. In an unadjusted hazards model, CDKN2A<sup>mut</sup> familial melanoma cases had, compared with CDKN2A<sup>wt</sup> cases, worse survival from all causes (hazard ratio [HR] = 1.44, 95% confidence interval [CI] = 1.02 to 2.04), from melanoma (HR = 1.69, 95% CI = 1.04 to 2.75),
and from nonmelanoma cancers (HR = 3.50, 95% CI = 1.76 to 6.94) (Table 4). After adjusting for age (age ≥ 50 vs age < 50 years), sex (male vs female), and T classification (T2-T4 vs T1), CDKN2A\(^{\text{mut}}\) familial melanoma cases had, compared with CDKN2A\(^{\text{wt}}\) cases, worse survival from all causes (HR = 2.59, 95% CI = 1.76 to 3.78), from melanoma (HR = 2.50, 95% CI = 1.49 to 4.21), and from nonmelanoma cancers (HR = 7.77, 95% CI = 3.65 to 16.51). The increase in hazard ratios after adjustments was mainly a result of the cohort of CDKN2A\(^{\text{wt}}\) cases being older and having more men, both factors related to a worse prognosis. Also, CDKN2A\(^{\text{mut}}\) cases had statistically significantly worse survival outcomes when compared with the matched sporadic cases (HR = 1.46, 95% CI = 1.01 to 2.09) while no statistically significant differences were found between CDKN2A\(^{\text{wt}}\) and sporadic cases (HR = 0.82, 95% CI = 0.66 to 1.01).

To assess whether death rates from melanoma were affected by multiple primary melanomas, an analysis was performed wherein all cases with multiple invasive primary melanomas were excluded. Also in this subgroup analysis, the CDKN2A\(^{\text{mut}}\) single melanoma cases had statistically significantly worse survival from all causes (HR = 3.92, 95% CI = 2.51 to 6.10), from nonmelanoma cancers (HR = 15.93, 95% CI = 6.50 to 39.04), and from melanoma (HR = 3.46, 95% CI = 1.92 to 6.24) compared with CDKN2A\(^{\text{wt}}\) single melanoma cases, both in the adjusted and in the unadjusted hazard models (Table 4). Similarly, to assess if melanoma-specific death rates were affected by diagnoses of other cancers (eg, deaths from other cancers misclassified as deaths from melanomas), an analysis was done where all cases with a diagnosis of nonskin cancers were excluded. Also in this subgroup, in the adjusted model, there was statistically significantly worse overall (HR = 2.23, 95% CI = 1.30 to 3.87) and melanoma-specific survival (HR = 2.33, 95% CI = 1.25 to 4.33). Furthermore, an analysis was performed wherein all cases diagnosed with either lung or pancreatic cancer were excluded. Interestingly, also with the pancreatic and lung cancer cases excluded, survival from nonmelanoma cancers was statistically significantly worse among the CDKN2A\(^{\text{mut}}\) cases (HR = 4.51, 95% CI = 1.11 to 18.30), indicating that other cancer types also contribute to the worse survival rates seen among the mutated cases.

**Discussion**

In this study, we show that familial melanoma cases with germline mutations in CDKN2A have younger age at onset, have increased numbers of melanoma cases per family, and are more prone to developing multiple melanomas and other cancers, compared with familial cases lacking CDKN2A mutations. No differences were seen between melanomas in CDKN2A mutation carriers compared with noncarriers with respect to melanoma-specific tumor features such as body site, invasiveness, or T classification of the primary tumor. However, CDKN2A mutation carriers had statistically significantly worse survival from all causes, from melanoma, and from nonmelanoma cancers, independent of sex, age, and T classification. Because Swedish CDKN2A mutation carriers previously have been shown to have an increased risk of developing nonmelanoma tumors (18), worse survival from other cancers was not an unexpected finding. Also, pancreatic and lung cancers, which are particularly common in carriers, are cancers with a poor prognosis. The finding of a statistically significantly worse melanoma-specific survival in mutation carriers was a novel and somewhat unexpected finding, albeit this result was unambiguous and independent of the covariates analyzed. We considered the possibility that the increased predisposition for multiple primary melanomas and other cancers in CDKN2A mutation carriers affected the melanoma-specific survival. Therefore, we performed analyses in which cases with multiple primary melanomas and nonskin cancers were excluded; however, also in these subgroups, melanoma-specific prognosis was statistically significantly worse in the CDKN2A\(^{\text{mut}}\) familial melanoma cases.

Our results indicate that the presence of a CDKN2A germline mutation is associated with a more aggressive phenotype of cutaneous melanoma, but the mechanism behind this is unclear. In a recent study, it was demonstrated that primary melanomas from CDKN2A mutation carriers do not exhibit a distinct gene expression signature compared with sporadic melanomas and, although BRAF mutations and PTEN losses were more frequent in melanomas from CDKN2A mutation carriers, these differences were not statistically significant after adjustments for tumor thickness and age (14). Still, somatic losses of CDKN2A have been associated with worse outcomes in melanoma (27–29) and also in various other cancers (gliomas, sarcomas, certain leukemias and lymphomas, lung, oral, gastroesophageal, renal cell, pancreatic, breast, bladder, hepatocellular cancers) (30–42).

Melanoma penetrance in CDKN2A mutation carriers has been shown to be associated with sun exposure patterns (2). Additionally, we have previously shown that CDKN2A mutation carriers have an increased incidence of tobacco-associated cancers (1). Hence, CDKN2A mutation carriers appear to be more
### Table 4. Cox proportional hazards regression models for effect of CDKN2A mutation status on survival in familial and sporadic cases with invasive melanoma

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Unadjusted survival from:</th>
<th>Adjusted* survival from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>CDKN2A**mut (n = 377)</td>
<td>CDKN2A*wt (n = 377)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.26 (0.77 to 2.07)</td>
<td>0.82 (0.66 to 1.01)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Normal melanoma cancer</td>
<td>CDKN2A**mut (n = 377)</td>
<td>CDKN2A*wt (n = 377)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.26 (0.77 to 2.07)</td>
<td>0.82 (0.66 to 1.01)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Nonmelanoma cancer</td>
<td>CDKN2A**mut (n = 377)</td>
<td>CDKN2A*wt (n = 377)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.26 (0.77 to 2.07)</td>
<td>0.82 (0.66 to 1.01)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Familial melanoma cases (n = 754)</td>
<td>CDKN2A**mut (n = 108)</td>
<td>CDKN2A*wt (n = 97)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.26 (0.77 to 2.07)</td>
<td>0.82 (0.66 to 1.01)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Sporadic melanoma cases (n = 288)</td>
<td>CDKN2A**mut (n = 377)</td>
<td>CDKN2A*wt (n = 377)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.26 (0.77 to 2.07)</td>
<td>0.82 (0.66 to 1.01)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and T classification of the primary melanoma tumor. CI = confidence interval, HR = hazard ratio.

**Adjusted for age, sex, and T classification of the primary melanoma tumor in familial melanoma cases with germline CDKN2A gene mutations, CDKN2A**mut = familial melanoma case with no germline mutations.

Sensitivity in melanoma patients to CDK4/6 inhibitors that are emerging as promising novel kind of therapeutic agents in various cancers (45,46).

The main limitation of this study is the size of the CDKN2A**mut melanoma cohort. This has to be considered in light of the fact that germline mutations in the CDKN2A gene are very rare in the normal population (<0.1%) (11). In this study, we included all CDKN2A-mutated melanoma families that have been identified in a national program in Sweden (current population = 10 million) aimed at detecting melanoma families, started in 1987. In spite of the relatively low number of mutation-carrying melanoma cases, the differences in survival rates between mutation carriers and noncarriers were so distinctive that statistically significant results were obtained. Also, this study reflects the situation of Swedish melanoma families where the main CDKN2A mutation found is the p.Arg112dup founder mutation and generalizability is uncertain until survival studies have been performed in other groups of CDKN2A mutation carriers. The strengths of this study are that all families have, independent of mutation status, been included in the same follow-up program and all data on family members (sex, dates of birth, death, and emigration), cancer diagnoses (dates, types, stages, body sites) were obtained from national registers with nearly full coverage that go back more than 50 years in time. Also, matched sporadic melanoma cases were included in the study, and this group had survival outcomes similar to the CDKN2A**wt familial cases, further corroborating the finding of poor outcomes in the CDKN2A**mut cases.

To summarize, we present the first study that estimates survival in familial melanoma cases depending on CDKN2A mutation status. The finding of statistically significantly worse survival in Swedish CDKN2A mutation carriers needs to be confirmed in other familial melanoma cohorts but nonetheless raises important questions regarding the possible underlying biological processes. Also, this finding indicates that CDKN2A...
mutation carriers not only need thorough surveillance aimed at prevention and earlier detection of primary tumors but also may benefit from more intense follow-up for melanoma recurrences.

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Notes
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