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## **Prognostic factors in distinct melanoma types**

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# CHAPTER 5

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## The influence of *CDKN2A* germline mutations on survival of melanoma patients: a retrospective cohort study

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## ABSTRACT

**Background.** Approximately 10% of patients with cutaneous melanomas have a positive melanoma family history. Germline mutation of the *CDKN2A* gene is the most common cause of familial melanoma. It is uncertain whether carriership affects prognosis.

**Objective.** To compare survival of *CDKN2A* germline mutation-positive melanoma (*CDKN2A*-mut) patients with sporadic melanoma patients.

**Methods.** A population-based cohort of sporadic melanoma patients diagnosed between 2000 and 2014 (n=56,929) and a cohort of *CDKN2A*-mut patients (n=89) were analyzed. Recurrence-free survival (RFS) and overall survival (OS) were calculated. Multivariable Cox proportional hazards analyses were performed.

**Results.** *CDKN2A*-mut patients were significantly younger than sporadic melanoma patients at melanoma diagnosis (median 42 vs. 57 years;  $p<0.0001$ ). Their melanomas were thinner (median Breslow thickness 0.6mm vs. 0.9mm;  $p<0.0001$ ) and less often ulcerated (1% vs. 13%;  $p<0.0001$ ) than sporadic melanoma patients. After correcting for potential confounders, OS and RFS were not significantly different for *CDKN2A*-mut and sporadic patients (OS hazard ratio 1.44; 95% confidence interval 0.9-2.4 and RFS hazard ratio 0.91; 95% confidence interval 0.5-1.8).

**Limitations.** Retrospective study, cause of death was not available

**Conclusion.** Presence of a germline *CDKN2A* mutation was not associated with survival in our cohort of melanoma patients.

## INTRODUCTION

Approximately 10% of patients with cutaneous melanomas have a positive melanoma family history.<sup>1,2</sup> Pathogenic germline mutation of the *CDKN2A* gene, encoding the p16 and p14 tumor suppressor proteins, is the most common cause of familial melanoma.<sup>1,3</sup> In the Netherlands, the most prevalent inactivating *CDKN2A* mutation is a 19 bp deletion in exon 2 (c.225-243del19), a founder mutation termed the p16-Leiden mutation.<sup>4</sup> Mutation carriers have a life-time risk of melanoma of approximately 70%, and many patients develop melanoma at a younger age.<sup>5</sup> In addition, they are at increased risk of developing solid tumors such as pancreatic cancer and head and neck cancer.<sup>2,4,6-10</sup> Since a subset of patients presents with atypical melanocytic nevi, the condition has been referred to by some as familial atypical multiple mole melanoma (FAMMM) syndrome. For other cancer types, there is evidence that patients with hereditary tumors have different prognoses than patients with sporadic tumors. As an example a number of studies have reported worse survival outcomes for *BRCA1* germline mutation-positive breast cancer patients.<sup>11</sup> Recent studies on survival of *CDKN2A* germline mutation-positive melanoma patients (*CDKN2A*-mut) showed conflicting results.<sup>12-14</sup> Swedish *CDKN2A*-mut patients (n=96) had worse survival than *CDKN2A* germline mutation-negative melanoma patients. In a second study among Swedish *CDKN2A* mutation carriers, 43 *CDKN2A*-mut multiple melanoma patients (MPM) had a worse survival than melanoma patients without this germline mutation.<sup>12,13</sup> However, 106 Italian *CDKN2A*-mut patients had similar survival as a matched cohort of *CDKN2A* germline mutation-negative melanoma patients.<sup>14</sup> Since there is ongoing debate regarding the prognostic impact of germline *CDKN2A* mutation status on survival of melanoma patients, the aim of the current study was to compare the survival of *CDKN2A*-mut with that of patients with sporadic melanoma.

## METHODS

This nation-wide retrospective study obtained *CDKN2A*-mut patients from the melanoma database of the Netherlands Foundation for Detection of Hereditary Tumors (NFDHT). The organization and methods of the NFDHT have been described previously.<sup>7,15</sup> Since 1985, Dutch physicians admit patients suspected of familial melanoma to the registry. All reported malignancies are verified by medical records and genealogic studies are performed. The registry collects follow-up data on proven *CDKN2A* mutation carriers and their relatives. In this study, *CDKN2A*-mut patients were carriers of the p16-Leiden variant of *CDKN2A*

(c.225\_243del, p.Ala-76Cysfs\*64; RefSeq NM\_000077.4) or first-degree relatives of proven carriers of this mutation. Sporadic melanoma patients were extracted from PALGA, the Dutch Nationwide Network and Registry of Histopathology and Cytopathology.<sup>16</sup> Since 1991, PALGA has been collecting data prospectively from all pathology laboratories in the Netherlands. Follow-up data of sporadic melanoma patients were obtained from the Netherlands Cancer Registry, which gathers information about every patient with cancer in the Netherlands. All data were encoded and used anonymously. Ethical approval was granted by the ethical review board of PALGA, Houten, the Netherlands, and Leiden University Medical Center (Protocol number P00.117).

### *Study population*

All adults newly diagnosed with invasive, clinically localized, primary cutaneous melanoma diagnosed between January 1, 2000 and December 31, 2014 were included. Patients were included based on their first primary melanoma diagnosis. Noncutaneous melanoma, melanoma of unknown primary and melanomas occurring among children (<18 years of age) were excluded. Furthermore, patients presenting with clinically detected lymph nodes, in-transit metastases or micro-satellites (stage III) or distant disease (stage IV) at time of diagnosis were excluded. Sentinel node (SN)-positive melanomas were included.

### *Data collection*

Data on patient demographics (gender, age at diagnosis, *CDKN2A* status), primary tumor characteristics (date of diagnosis, primary site, Breslow thickness, melanoma subtype, ulceration status, tumor mitotic rate, sentinel node (SN) status), subsequent melanomas, recurrence (date, site and type), and vital status were recorded. Patients with multiple primary melanomas (MPM) were defined as those with a new primary melanoma on or after the date of first melanoma diagnosis, irrespective of topography.

The outcomes of interest were recurrence-free survival (RFS) and overall survival (OS). In patients with first recurrences at multiple sites, the site with the most unfavorable prognosis was scored as the first site (hierarchical order: local, regional, distant). RFS and OS were calculated from the date of initial melanoma diagnosis to the date of diagnosis of recurrence, or death, respectively. Patients without recurrence were censored at their date of death, the last date known to be alive or January 1st, 2018 (the database cut-off date), whichever occurred first.

### *Statistical analysis*

Categorical variables were summarized as numbers and percentages. Continuous variables were summarized as medians with interquartile range (IQRs). Differences in proportions and medians were analysed using chi-square tests or Mann-Whitney *U* test, respectively. Univariable and multivariable Cox proportional hazards regression analysis were performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for RFS and OS. No statistical variable selection procedure was performed, because all clinicopathological factors that were included are basic, readily available in pathological reports. Variables included were *CDKN2A* status, age, gender, year of diagnosis, Breslow thickness, ulceration status, primary site, melanoma subtype and SN status. Because of a relatively large number of missing values for ulceration, a “not known” category was created for this variable.<sup>17</sup> Since it has been suggested that a missing-indicator variable might lead to bias, a sensitivity analysis was performed, categorizing patients with a “not known” status for ulceration as “not present” to assess the impact on HRs of *CDKN2A* status in the multivariable model.<sup>18</sup> Multiple imputation was not considered, given the pathologist involved in this study believes these histopathological variables are not missing at random, but rather because they were not seen during pathological assessment. The missing at random assumption, a condition for multiple imputation, would therefore be too strong.<sup>19</sup> The proportional hazards assumption was examined by plotting a log-minus-log graph for categorical variables. If the lines were parallel, it was assumed that the proportional hazards assumption was not violated. For continuous variables (Breslow thickness and age), Schoenfeld residuals were plotted as a function of time, and a loess curve was fitted. If the curve was horizontal, it was assumed that the proportional hazards assumption was not violated. To assess linearity of continuous variables, Martingale residuals were plotted against time. In case of non-linearity, continuous variables were categorized. All statistical analyses were performed using R version 3.6.1 (R Core Team, Vienna, Austria). Two-sided P-values <0.05 were considered significant.

## **RESULTS**

### *Patient and tumor characteristics of CDKN2A-mut patients*

A total of 89 *CDKN2A*-mut and 56,929 sporadic melanoma patients were eligible for inclusion in this study. The baseline characteristics are shown in Table 1. The majority of *CDKN2A*-mut patients were female (64%) with a median age of 42 years (IQR 31-50 years). Their melanomas were most frequently located on the trunk (39.3%). Melanomas were most often

<0.8mm thick (60.9%). Ulceration was present in 1.1% of the *CDKN2A*-mut patients and mitoses in 32.6%. Eight *CDKN2A*-mut patients underwent SN biopsy of which one had a positive SN (12.5%).

Table 1. Baseline characteristics of *CDKN2A* germline mutation-positive and sporadic melanoma patients

<b>Characteristics</b>	<b><i>CDKN2A</i>-mut (n=89)</b>	<b>Sporadic (n=56929)</b>	<b>P-value</b>
<b>Gender</b>			0.13
Female	57 (64.0)	31916 (56.1)	
Male	32 (36.0)	25013 (43.9)	
<b>Median age at diagnosis in years (IQR)</b>	42 (31-50)	57 (44-68)	<0.0001
<b>Year of diagnosis</b>			<0.0001
2000/2001	15 (16.9)	4928 (8.7)	
2002/2003	17 (19.1)	5459 (9.6)	
2004/2005	13 (14.6)	6396 (11.2)	
2006/2007	15 (16.9)	6979 (12.3)	
2008/2009	10 (11.2)	810 (14.2)	
2010/2011	11 (12.4)	9308 (16.4)	
2012/2013/2014	8 (9.0)	15759 (27.7)	
<b>Primary site</b>			0.04
Head & Neck	5 (5.6)	7127 (12.5)	
Trunk	35 (39.3)	23892 (42.0)	
Upper limb	18 (20.2)	8327 (14.6)	
Lower limb	31 (34.8)	15725 (27.6)	
Not known	0 (0.0)	1858 (3.3)	
<b>Median Breslow thickness in mm (IQR)</b>	0.6 (0.4-0.9)	0.9 (0.5-1.8)	<0.0001
<b>Breslow thickness in mm</b>			<0.0001
<0.8	53 (60.9)	23270 (40.9)	
≤0.8-1.0	16 (18.4)	9311 (16.4)	
1.1-2.0	15 (17.2)	12614 (22.2)	
2.1-4.0	3 (3.4)	7668 (13.5)	
>4.0	0 (0.0)	4066 (7.1)	
<b>Subtype</b>			0.03
Non-nodular	84 (94.4)	49248 (86.5)	
Nodular	5 (5.6)	7679 (13.5)	
<b>Ulceration</b>			<0.0001
No	53 (59.6)	39030 (68.6)	
Yes	1 (1.1)	7587 (13.3)	
Unknown	35 (39.3)	10312 (18.1)	

Characteristics	<i>CDKN2A</i> -mut (n=89)	Sporadic (n=56929)	P-value
<b>Mitoses</b>			0.05
No	14 (15.7)	9914 (17.4)	
Yes	29 (32.6)	12522 (22.0)	
Unknown	46 (51.7)	34493 (60.6)	
<b>Multiple melanoma</b>			<0.0001
No (SPM)	51 (57.3)	54645 (96.0)	
Yes (MPM)	38 (42.7)	2284 (4.0)	
<b>SN status</b>			0.50
Negative	7 (87.5)	9162 (77.5)	
Positive	1 (12.5)	2666 (22.5)	
Not performed	81	45099	
<b>Median follow-up in years (IQR)</b>	11.5 (9.4-15.7)	6.3 (3.6-10.3)	<0.0001

Data are expressed as n (%) unless otherwise specified

*CDKN2A*-mut = *CDKN2A* germline mutation-positive melanoma patients; IQR = interquartile range; SPM = single primary melanoma; MPM = multiple primary melanoma; SN = sentinel node

### *Differences between CDKN2A-mut and sporadic melanoma patients*

*CDKN2A*-mut patients more often developed MPM than patients with sporadic melanoma (42.7% vs. 4.0%;  $P < 0.0001$ ). The median age at diagnosis of the first melanoma was 15 years lower for *CDKN2A*-mut patients than for patients with sporadic melanoma (42 vs. 57 years;  $P < 0.0001$ ). *CDKN2A*-mut patients had thinner melanomas (median Breslow thickness 0.6mm vs 0.9mm;  $P < 0.0001$ ) and none of the *CDKN2A*-mut patients had a Breslow thickness of more than 4.0 mm (0% vs. 7.1%). Melanomas of sporadic melanoma patients were more often nodular (13.5% vs. 5.6%;  $P = 0.03$ ) and ulcerated (22.0% vs. 1.1%;  $P < 0.0001$ ). Gender and SN status did not differ significantly between the two groups. The median follow-up was 11.5 years for *CDKN2A*-mut patients and 6.3 years for sporadic melanoma patients.

### *Overall survival according to CDKN2A mutation status*

Due to missing data, a total of 51,921 cases were analyzed: 89 (14 deaths) *CDKN2A*-mut patients and 53,589 (10,800 deaths) sporadic melanoma patients. On univariable analysis, the presence of a germline *CDKN2A* mutation was significantly associated with better OS (HR=0.52; 95% CI 0.31-0.88). In multivariable analysis, Breslow thickness per mm, ulceration, SN positivity, and nodular subtype all independently increased the HR with 1.06 (95% CI 1.06-1.07), 2.18 (95% CI 2.08-2.28), 2.42 (95% CI 2.23-2.63), and 1.41 (95% CI



1.34-1.48), respectively. The proportional hazards assumption was not violated for any of the included variables. Due to non-linearity, age and year of diagnosis were categorized. Corrected for all determinants (i.e. gender, Breslow thickness, age, primary site, ulceration, SN status, melanoma subtype, and year of diagnosis), a non-significant HR for *CDKN2A*-mut versus sporadic melanoma patients of 1.44 (95% CI 0.85-2.43) was found (Table 2). Addition of an unknown category as a separate category to ulceration (i.e. “yes” vs. “no” vs. “unknown”), did not change the HR of *CDKN2A*-mut patients (HR 1.43; 95% CI 0.85-2.42).

### *Recurrence-free survival according to CDKN2A mutation status*

On univariable analysis, the presence of a germline *CDKN2A* mutation was associated with a better RFS (HR 0.48; 95% CI 0.24-0.98). After correcting for all aforementioned confounders, RFS was not significantly different for patients with or without a germline *CDKN2A* mutation (HR 0.91; 95% CI 0.45-1.83). Addition of an unknown category to ulceration (i.e. “yes” vs. “no” vs. “unknown”) did not change the HR of *CDKN2A*-mut patients (HR 0.91; 95% CI 0.45-1.84).

**Table 2.** Univariable and multivariable Cox regression for overall survival and recurrence-free survival for all patients (n = 51,921)

Variable	Class	Overall survival (10457 events)				Recurrence free survival (6865 events)			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>CDKN2A</b>	Not mutated	1		1		1		1	
	Mutated	0.52 (0.31-0.88)	0.01	1.44 (0.85-2.43)	0.18	0.48 (0.24-0.98)	0.04	0.91 (0.45-1.83)	0.78
<b>Gender</b>	Male	1		1		1		1	
	Female	0.58 (0.55-0.60)	<0.0001	0.69 (0.66-0.72)	<0.0001	0.59 (0.57-0.63)	<0.0001	0.72 (0.68-0.75)	<0.0001
<b>Breslow thickness</b>	Per mm	1.11 (1.10-1.11)	<0.0001	1.06 (1.06-1.07)	<0.0001	1.11 (1.11-1.11)	<0.0001	1.08 (1.08-1.09)	<0.0001
<b>Age at diagnosis</b>	18-27	1		1		1		1	
	28-37	0.16 (0.94-1.45)	0.17	1.14 (0.91-1.41)	0.26	0.98 (0.82-1.16)	0.80	1.00 (0.84-1.19)	0.99
	38-47	1.67 (1.36-2.05)	<0.0001	1.61 (1.31-1.97)	<0.0001	1.19 (1.01-1.40)	0.04	1.24 (1.05-1.46)	0.01
	48-57	2.54 (2.08-3.09)	<0.0001	2.30 (1.89-2.82)	<0.0001	1.54 (1.31-1.81)	<0.0001	1.43 (1.21-1.68)	<0.0001
	58-67	4.32 (3.55-5.26)	<0.0001	3.66 (3.01-4.47)	<0.0001	1.90 (1.62-2.22)	<0.0001	1.66 (1.42-1.95)	<0.0001
	68-77	8.49 (6.98-10.33)	<0.0001	7.00 (5.75-8.53)	<0.0001	2.30 (1.96-2.69)	<0.0001	1.83 (1.56-2.15)	<0.0001
	78-87	19.55 (16.07-23.79)	<0.0001	14.94 (12.25-18.22)	<0.0001	2.86 (2.42-3.38)	<0.0001	2.02 (1.71-2.40)	<0.0001
	88+	45.53 (37.03-55.97)	<0.0001	29.22 (23.65-36.10)	<0.0001	3.44 (2.74-4.31)	<0.0001	1.49 (1.17-1.91)	0.001
<b>Primary site</b>	Head and neck	1		1		1		1	
	Trunk	0.53 (0.50-0.55)	<0.0001	0.95 (0.90-1.01)	0.09	0.77 (0.71-0.82)	<0.0001	0.88 (0.82-0.95)	0.001
	Upper limb	0.52 (0.48-0.55)	<0.0001	0.78 (0.73-0.83)	<0.0001	0.52 (0.48-0.58)	<0.0001	0.61 (0.55-0.67)	<0.0001
	Lower limb	0.46 (0.43-0.48)	<0.0001	0.83 (0.78-0.88)	<0.0001	0.81 (0.76-0.88)	<0.0001	1.01 (0.93-1.09)	0.83

Variable	Class	Overall survival (10457 events)				Recurrence free survival (6865 events)			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Ulceration</b>	No	1		1		1		1	
	Yes	4.25 (4.08-4.42)	<0.0001	2.18 (2.08-2.28)	<0.0001	5.42 (5.16-5.69)	<0.0001	2.97 (2.81-3.14)	<0.0001
<b>SN status</b>	Negative	1		1		1		1	
	Positive	2.87 (2.64-3.11)	<0.0001	2.42 (2.23-2.63)	<0.0001	3.20 (2.95-3.47)	<0.0001	2.39 (2.20-2.60)	<0.0001
	Not performed	1.21 (1.15-1.28)	<0.0001	1.15 (1.09-1.22)	<0.0001	0.71 (0.66-0.75)	<0.0001	0.96 (0.90-1.02)	0.17
<b>Subtype</b>	Non-nodular	1		1		1		1	
	Nodular	2.83 (2.71-2.95)	<0.0001	1.41 (1.34-1.48)	<0.0001	3.61 (3.43-3.80)	<0.0001	1.80 (1.70-1.91)	<0.0001
<b>Year of diagnosis</b>	2000 / 2001	1		1		1		1	
	2002 / 2003	0.94 (0.88-1.01)	0.12	0.87 (0.81-0.94)	<0.0001	0.92 (0.84-1.01)	0.09	0.84 (0.76-0.93)	<0.0001
	2004 / 2005	0.93 (0.86-0.99)	0.03	0.87 (0.81-0.94)	<0.0001	0.93 (0.85-1.02)	0.11	0.89 (0.81-0.98)	0.02
	2006 / 2007	0.99 (0.92-1.06)	0.68	0.93 (0.87-1.01)	0.07	0.98 (0.89-1.07)	0.61	0.98 (0.89-1.07)	0.64
	2008 / 2009	0.93 (0.87-1.01)	0.07	0.82 (0.76-0.88)	<0.0001	0.85 (0.78-0.94)	0.001	0.85 (0.77-0.93)	0.001
	2010 / 2011	0.94 (0.87-1.02)	0.12	0.79 (0.73-0.86)	<0.0001	0.89 (0.81-0.98)	0.01	0.88 (0.80-0.97)	0.007
	2012 / 2013 / 2014	0.91 (0.84-0.98)	0.01	0.71 (0.65-0.76)	<0.0001	0.94 (0.86-1.02)	0.15	0.91 (0.83-0.99)	0.04

HR = hazard ratio; CI = confidence interval; SN = sentinel node

## DISCUSSION

In this study, we found no evidence for a survival difference between *CDKN2A* mutation carriers and sporadic melanoma patients. No significant difference in OS and RFS was found between *CDKN2A*-mut and sporadic melanoma patients when controlling for known confounders such as age, gender, Breslow thickness, primary site, year of diagnosis, ulceration, melanoma subtype, and SN status.

The results of the current study are in line with those of Dalmaso et al., who also did not find a significant difference in survival between *CDKN2A*-mut and *CDKN2A* germline mutation-negative melanoma patients.<sup>14</sup> In contrast, a Swedish cohort of *CDKN2A*-mut patients with familial melanoma had worse survival than *CDKN2A* germline mutation-negative patients with familial or sporadic melanoma.<sup>12</sup> Another study from the same Swedish group demonstrated that *CDKN2A*-mut MPM patients had worse survival than *CDKN2A* germline mutation-negative MPM patients.<sup>13</sup> The type and location of the *CDKN2A* germline mutation might be of influence on the effect that this mutation has on survival. In the current study, patients had the p16-Leiden mutation, a *CDKN2A* germline mutation which mainly inactivates p16, while the function of p14ARF is only slightly impaired. In the study by Dalmaso et al. most patients harbored the G101W mutation, a *CDKN2A* missense mutation, while in the study by Helgadottir et al. the Swedish founder mutation, p.Arg112dup, was most often found.<sup>12-14,20</sup>

The aims and design of these studies and our study differ on several points. In one of the Swedish studies, only MPM patients were included, while in the other two studies and in this study also single primary melanoma (SPM) patients were included.<sup>12-14</sup> MPM patients have worse survival than SPM patients, complicating comparison of these studies.<sup>21</sup> The selection and size of the control group, i.e. sporadic melanoma patients, is also different. We used a nationwide control group of almost 60,000 patients, which made it possible to control for a large number of confounders. Previous studies did not control for primary site, ulceration, melanoma subtype, and SN status.<sup>12,14</sup> A drawback of our approach is the fact that *CDKN2A* mutation status was unknown for patients in the control group. Since all newly diagnosed clinically localized cutaneous melanoma patients in the Netherlands were included in this study, the 89 *CDKN2A*-mut patients will most likely also be present in the control group. However, since this concerns less than 0.2% of the control patients, we do not expect this to reduce the validity of the results.<sup>22</sup> The outcome measures also differ between the above studies. OS was assessed in all four studies, while in the current study RFS was studied instead of melanoma-specific survival.<sup>12-14</sup>

The patient and tumor characteristics of *CDKN2A*-mut and sporadic melanoma patients differed considerably in our study. In accordance with earlier studies, *CDKN2A*-mut patients were much younger when their first melanoma was diagnosed and were more prone to develop MPMs.<sup>5,12,14,23,24</sup> In the current study, melanomas of sporadic melanoma patients were thicker and more often nodular and ulcerated. Prior studies comparing histological features of *CDKN2A*-mut and *CDKN2A* germline mutation-negative melanomas have found conflicting results. In some studies, melanomas of *CDKN2A*-mut were less advanced at diagnosis, while in others no difference between the groups was found.<sup>5,12,14,23-26</sup>

To detect melanomas at earlier stages, Dutch *CDKN2A* mutation carriers are subjected to thorough surveillance. Biannual total skin examination with the use of dermoscopy and total body photography is recommended to *CDKN2A*-mut patients from the age of 12. Furthermore, patients are instructed to perform skin self-examination. From the age of 40, annual pancreatic screening by MRI and/or endoscopic ultrasound is performed in proven mutation carriers who are enrolled in several prospective studies.<sup>27-29</sup> Close surveillance of *CDKN2A*-mut patients is probably one of the reasons why melanomas of *CDKN2A*-mut patients were diagnosed at less advanced stages. As previously demonstrated, *CDKN2A*-mut patients are at increased risk of misdiagnosis of their benign melanocytic lesion as melanoma.<sup>30</sup> Melanoma overdiagnosis of *CDKN2A*-mut patients might falsely skew their prognosis.<sup>30,31</sup>

There are several limitations affecting this study. Due to the fact that cause of death for sporadic melanoma patients is not registered in the Dutch Cancer Registry, melanoma-specific survival could not be calculated. However, we were able to calculate RFS, which was not assessed in prior studies comparing survival of *CDKN2A*-mut and sporadic melanoma patients.<sup>12-14</sup> Ascertainment bias and longevity bias might also limit the results of this study. Ascertainment bias is difficult to prevent in mutation-based studies. Pedigrees with many affected relatives and MPM patients are more likely to be identified, registered and genetically tested. In addition, patients who survive longer are more likely to be offered genetic testing, thus causing an overestimation of survival (longevity bias).<sup>32</sup> The *CDKN2A*-mut patients are at increased risk of developing MPM and pancreatic cancer. These competing risks might have influenced the outcomes of interest. Other limitations were the retrospective design, the relatively small number of *CDKN2A*-mut patients, and some missing values.

## **CONCLUSION**

The presence of germline *CDKN2A* mutation was not associated with melanoma survival in the present study. Melanomas of *CDKN2A*-mut patients were diagnosed at an earlier stage. This emphasizes the importance of early dermatological surveillance of *CDKN2A*-mut patients.

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