

RESEARCH LETTER

Lack of association between *CDKN2A* germline mutations and survival in patients with melanoma: A retrospective cohort study

To the Editor: 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.¹ Mutation carriers have a lifetime risk of melanoma of approximately 70%, and many patients develop melanoma at a younger age.² For other cancer types, there is evidence that patients with hereditary tumors have different prognoses than patients with sporadic tumors. However, it is uncertain whether *CDKN2A* mutation carriership (*CDKN2A*-mut) affects melanoma prognosis.³⁻⁵ The aim of this study was to compare the survival of *CDKN2A*-mut patients with that of patients with sporadic melanoma.

All adults newly diagnosed with invasive, clinically localized, primary cutaneous melanoma between January 1, 2000, and December 31, 2014, were included. Data of 89 *CDKN2A*-mut patients were extracted from the database of the Netherlands Foundation for Detection of Hereditary Tumors. A population-based cohort of 56,929 patients with sporadic melanoma was extracted from PALGA (the Dutch Nationwide Network and Registry of Histopathology and Cytopathology) and the Netherlands Cancer Registry. Ethical approval was granted by the ethical review boards of PALGA and Leiden University Medical Center. Cox proportional hazards regression analyses were performed. See the Supplementary Text (available via Mendeley at <https://doi.org/10.17632/h4m4zwdysx.1>) for all statistical analyses.

CDKN2A-mut patients more often developed multiple primary melanomas (MPMs) than patients with sporadic melanoma (42.7% vs 4.0%; $P < .0001$). 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; $P < .0001$). *CDKN2A*-mut patients had thinner melanomas (median Breslow thickness, 0.6 mm vs 0.9 mm; $P < .0001$) (Table I). After correcting for gender, Breslow thickness, age at diagnosis of first melanoma, primary site, ulceration, sentinel node

status, melanoma subtype, and year of diagnosis, overall survival (OS) and recurrence-free survival (RFS) were not significantly different for patients with and without germline *CDKN2A* mutations (OS hazard ratio [HR], 1.44; 95% CI, 0.85-2.43; RFS HR, 0.91; 95% CI, 0.45-1.83) (Table II).

Our finding that *CDKN2A* mutation status is not associated with worse OS or RFS is in line with that of an Italian cohort study.⁵ In contrast, 2 Swedish studies showed worse survival for *CDKN2A*-mut patients.^{3,4} The aims and design of the studies differed. We used a nationwide control group of almost 60,000 patients, which made it possible to control for multiple confounders. Previous studies did not control for primary site, ulceration, melanoma subtype, or sentinel node status.^{3,5} In 1 study, only MPM patients were included.⁴ OS was assessed in all 4 studies, while in our study, RFS was studied instead of melanoma-specific survival.³⁻⁵ In accordance with earlier studies, *CDKN2A*-mut patients were younger at diagnosis and more prone to developing MPM.^{2,3,5} Close surveillance of *CDKN2A*-mut patients is probably one of the reasons why melanomas of *CDKN2A*-mut patients were diagnosed at less advanced stages. The retrospective design, a relatively small number of *CDKN2A*-mut patients, missing melanoma-specific survival, ascertainment bias, and longevity bias are limitations of this study.

In conclusion, the presence of germline *CDKN2A* mutation was not associated with melanoma survival in the present study.

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Table I. Baseline characteristics of *CDKN2A* germline mutation–positive and sporadic melanoma patients

Characteristics	<i>CDKN2A</i> -mut (N = 89)	Sporadic (N = 56,929)	P value
Gender, n (%)			.13
Female	57 (64.0)	31,916 (56.1)	
Male	32 (36.0)	25,013 (43.9)	
Median age at diagnosis of first melanoma, y (IQR)	42 (31-50)	57 (44-68)	<.0001
Year of diagnosis			<.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)	15,759 (27.7)	
Primary site, n (%)			.04
Head and neck	5 (5.6)	7127 (12.5)	
Trunk	35 (39.3)	23,892 (42.0)	
Upper limb	18 (20.2)	8327 (14.6)	
Lower limb	31 (34.8)	15,725 (27.6)	
Not known	0 (0.0)	1858 (3.3)	
Median Breslow thickness, mm (IQR)	0.6 (0.4-0.9)	0.9 (0.5-1.8)	<.0001
Breslow thickness, mm, n (%)			<.0001
<0.8	53 (60.9)	23,270 (40.9)	
≤0.8-1.0	16 (18.4)	9311 (16.4)	
1.1-2.0	15 (17.2)	12,614 (22.2)	
2.1-4.0	3 (3.4)	7668 (13.5)	
>4.0	0 (0.0)	4066 (7.1)	
Subtype, n (%)			.03
Nonnodular	84 (94.4)	49,248 (86.5)	
Nodular	5 (5.6)	7679 (13.5)	
Ulceration, n (%)			<.0001
No	53 (59.6)	39,030 (68.6)	
Yes	1 (1.1)	7587 (13.3)	
Unknown	35 (39.3)	10,312 (18.1)	
Mitoses, n (%)			.05
No	14 (15.7)	9914 (17.4)	
Yes	29 (32.6)	12,522 (22.0)	
Unknown	46 (51.7)	34,493 (60.6)	
Multiple melanoma			<.0001
No (SPM)	51 (57.3)	54,645 (96.0)	
Yes (MPM)	38 (42.7)	2284 (4.0)	
SN status, n (%)			.50
Negative	7 (87.5)	9162 (77.5)	
Positive	1 (12.5)	2666 (22.5)	
Not performed	81	45,099	
Median follow-up, y (IQR)	11.5 (9.4-15.7)	6.3 (3.6-10.3)	<.0001

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

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Table II. Uni- and multivariable Cox regression for overall survival and recurrence-free survival for all patients (N = 51,921)

Variable	Class	Overall survival (10,457 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
CDKN2A	Not mutated	1		1		1		1	
	Mutated	0.52 (0.31-0.88)	.01	1.44 (0.85-2.43)	.18	0.48 (0.24-0.98)	.04	0.91 (0.45-1.83)	.78
Gender	Male	1		1		1		1	
	Female	0.58 (0.55-0.60)	<.0001	0.69 (0.66-0.72)	<.0001	0.59 (0.57-0.63)	<.0001	0.72 (0.68-0.75)	<.0001
Breslow thickness	Per mm	1.11 (1.10-1.11)	<.0001	1.06 (1.06-1.07)	<.0001	1.11 (1.11-1.11)	<.0001	1.08 (1.08-1.09)	<.0001
Age at diagnosis of first melanoma	18-27	1		1		1		1	
	28-37	0.16 (0.94-1.45)	.17	1.14 (0.91-1.41)	.26	0.98 (0.82-1.16)	.80	1.00 (0.84-1.19)	.99
	38-47	1.67 (1.36-2.05)	<.0001	1.61 (1.31-1.97)	<.0001	1.19 (1.01-1.40)	.04	1.24 (1.05-1.46)	.01
	48-57	2.54 (2.08-3.09)	<.0001	2.30 (1.89-2.82)	<.0001	1.54 (1.31-1.81)	<.0001	1.43 (1.21-1.68)	<.0001
	58-67	4.32 (3.55-5.26)	<.0001	3.66 (3.01-4.47)	<.0001	1.90 (1.62-2.22)	<.0001	1.66 (1.42-1.95)	<.0001
	68-77	8.49 (6.98-10.33)	<.0001	7.00 (5.75-8.53)	<.0001	2.30 (1.96-2.69)	<.0001	1.83 (1.56-2.15)	<.0001
	78-87	19.55 (16.07-23.79)	<.0001	14.94 (12.25-18.22)	<.0001	2.86 (2.42-3.38)	<.0001	2.02 (1.71-2.40)	<.0001
	88+	45.53 (37.03-55.97)	<.0001	29.22 (23.65-36.10)	<.0001	3.44 (2.74-4.31)	<.0001	1.49 (1.17-1.91)	.001
Primary site	Head and neck	1		1		1		1	
	Trunk	0.53 (0.50-0.55)	<.0001	0.95 (0.90-1.01)	.09	0.77 (0.71-0.82)	<.0001	0.88 (0.82-0.95)	.001
	Upper limb	0.52 (0.48-0.55)	<.0001	0.78 (0.73-0.83)	<.0001	0.52 (0.48-.58)	<.0001	0.61 (0.55-0.67)	<.0001
	Lower limb	0.46 (0.43-0.48)	<.0001	0.83 (0.78-0.88)	<.0001	0.81 (0.76-0.88)	<.0001	1.01 (0.93-1.09)	.83
Ulceration	No	1		1		1		1	
	Yes	4.25 (4.08-4.42)	<.0001	2.18 (2.08-2.28)	<.0001	5.42 (5.16-5.69)	<.0001	2.97 (2.81-3.14)	<.0001
SN status	Negative	1		1		1		1	
	Positive	2.87 (2.64-3.11)	<.0001	2.42 (2.23-2.63)	<.0001	3.20 (2.95-3.47)	<.0001	2.39 (2.20-2.60)	<.0001
	Not performed	1.21 (1.15-1.28)	<.0001	1.15 (1.09-1.22)	<.0001	0.71 (0.66-0.75)	<.0001	0.96 (0.90-1.02)	.17
Subtype	Nonnodular	1		1		1		1	
	Nodular	2.83 (2.71-2.95)	<.0001	1.41 (1.34-1.48)	<.0001	3.61 (3.43-3.80)	<.0001	1.80 (1.70-1.91)	<.0001
Year of diagnosis	2000/2001	1		1		1		1	
	2002/2003	0.94 (0.88-1.01)	.12	0.87 (0.81-0.94)	<.0001	0.92 (0.84-1.01)	.09	0.84 (0.76-0.93)	<.0001
	2004/2005	0.93 (0.86-0.99)	.03	0.87 (0.81-0.94)	<.0001	0.93 (0.85-1.02)	.11	0.89 (0.81-0.98)	.02
	2006/2007	0.99 (0.92-1.06)	.68	0.93 (0.87-1.01)	.07	0.98 (0.89-1.07)	.61	0.98 (0.89-1.07)	.64
	2008/2009	0.93 (0.87-1.01)	.07	0.82 (0.76-0.88)	<.0001	0.85 (0.78-0.94)	.001	0.85 (0.77-0.93)	.001
	2010/2011	0.94 (0.87-1.02)	.12	0.79 (0.73-0.86)	<.0001	0.89 (0.81-0.98)	.01	0.88 (0.80-0.97)	.007
	2012/2013/2014	0.91 (0.84-0.98)	.01	0.71 (0.65-0.76)	<.0001	0.94 (0.86-1.02)	.15	0.91 (0.83-0.99)	.04

HR, Hazard ratio; SN, sentinel node.

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Conflicts of interest

None disclosed.

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