CDKN2A germline mutations are not associated with poor survival in an Italian cohort of melanoma patients

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Background: Cyclin dependent kinase inhibitor 2A gene (*CDKN2A*) germline mutations have recently been associated with poor survival in patients with melanoma. Despite the high mutation rate in our cohort (up to 10% in patients with apparently sporadic melanoma), information on the impact of *CDKN2A* on survival in this cohort is lacking.

Objective: To investigate whether poor survival associated with *CDKN2A* germline mutations was confirmed in a high mutation–prevalence cohort of Italian patients with melanoma undergoing a mutation-based follow-up.

Methods: A total of 1239 patients with cutaneous melanoma were tested for *CDKN2A* mutational status and then assigned to a follow-up scheme according not only to family history but also to *CDKN2A* mutational status, as follow-up intervals were more frequent for *CDKN2A* germline mutation–positive (MUT^+) patients. From this cohort, we selected 106 MUT^+ patients (with familial melanoma or apparently sporadic melanoma) and 199 *CDKN2A* germline mutation–negative (MUT^-) patients with sporadic melanoma who were matched by age and sex and had a similar tumor stage distribution.

Results: We found no difference in overall survival (hazard ratio, 0.85; 95% confidence interval, 0.48-1.52; $P = .592$,) or melanoma-specific survival (hazard ratio, 0.86; 95% confidence interval, 0.38-1.95; $P = .718$,) between MUT^+ and MUT^- patients. MUT^+ patients were more likely to develop multiple melanomas and to undergo surgical excision of dysplastic nevi than were MUT^- patients.

Limitations: Retrospective study.

Conclusion: *CDKN2A* mutations were not associated with survival in our cohort. (J Am Acad Dermatol 2019;80:1263-71.)

Key words: cancer genetics; CDKN2A; follow-up; genetic testing; germline mutation; melanoma; predisposition; surveillance; survival; susceptibility.

The incidence of malignant melanoma in Italy is rapidly increasing.[1,2] Although most melanoma cases are sporadic and linked to interactions between phenotype and environmental risk factors, 6% to 12% of all patients with melanoma are clustered within melanoma-prone families, up to 40% of which harbor inherited germline mutations in the cyclin dependent kinase inhibitor

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2A (*CDKN2A*)/p16Ink4 tumor suppressor gene.[3-5] Individuals harboring *CDKN2A* mutations have a lifelong increased risk of development of multiple primary melanomas (MPMs) and other cancers, and at a younger age than their counterparts with sporadic melanoma.[6-8] In fact, the rate of occurrence of pancreatic cancer in those individuals is estimated to be up to 17%.[9-14]

The prevalence of *CDKN2A* mutations is 20% to 40% in melanoma-prone families depending on the country, being inversely associated with local incidence of melanoma.[6,15,16] Moreover, penetrance of *CDKN2A* mutations can be modified by several environmental factors such as tobacco[17,18] and molecular factors. Among the latter, melanocortin 1 receptor gene (*MC1R*) variants seem to increase the risk of melanoma, although studies performed on our population have not confirmed this finding as yet.[7,19,20]

Melanoma prognosis is influenced by several factors, such as tumor thickness at diagnosis, nodal status, ulceration, and mitotic rate.[21] Moreover, several studies are investigating gene expression signatures and other molecular tools to help estimate melanoma prognosis.[22]

Recently, a study conducted on a Swedish cohort showed that *CDKN2A* germline mutation–positive (MUT^+) patients with familial melanoma had worse prognosis in terms of survival than did *CDKN2A* germline mutation–negative (MUT^-) and untested patients with sporadic melanoma.[23] In this Swedish study, MUT^+ and MUT^- patients from melanoma-prone families underwent similar follow-up programs. Similarly, *CDKN2A* mutations were associated with worse survival in another Swedish study involving individuals affected by MPMs[24]

Our population is among those with the highest incidence of *CDKN2A* germline mutations, mainly because of the founder effect of the G101W mutation.[4,25-27] The multidisciplinary melanoma group in our hospital provides an intensive follow-up regimen for all affected individuals harboring a *CDKN2A* mutation, regardless of family history. Despite the inherited risks of multiple melanomas and other malignancies, no information regarding the *CDKN2A* effect on the prognosis of our patients with melanoma in terms of survival has been available thus far. On the basis of the aforementioned findings and considering that mutations in the same genes can lead to nonidentical effects in different populations (because of other interfering genetic/environmental factors), we decided to investigate the relationship between *CDKN2A* and survival in our cohort of patients with melanoma.

CAPSULE SUMMARY

- Cyclin dependent kinase inhibitor 2A gene (*CDKN2A*) germline mutations have recently been associated with poor prognosis in Swedish patients with melanoma, but these data have not yet been confirmed in other populations.
- We found no association between *CDKN2A* germline mutations and survival in an Italian cohort of patients with cutaneous melanoma.
- Follow-up differences may be implicated in regional differences concerning the impact of *CDKN2A* on the survival of patients with melanoma.

PATIENTS AND METHODS

Patient characteristics

Between 2000 and 2015 we enrolled, from among all patients with a diagnosis of melanoma in our hospital, a consecutive series of 1239 patients for whom we had results of genetic testing for *CDKN2A* mutations and collected and stored clinical and pathologic information.

Part of this cohort consisted of probands of melanoma-prone families and patients with apparently sporadic melanoma who had MPMs and had been tested for either diagnostic or research purposes. Additionally, a series of patients with apparently sporadic single melanoma on whom genetic testing had been performed for research purposes were included. For 448 patients, molecular and clinical information has previously been described.[20]

Follow-up was carried out according to the standard practice of our hospital. Briefly, follow-up of MUT^+ patients is carried out by our multidisciplinary team every 4 months starting from diagnosis, regardless of familial status, or more frequently if justified by tumor stage according to the guidelines of the Italian Association of Medical Oncology.[1] Skin examination by a dermatologist is performed every 4 months. MUT^- patients with familial melanoma are followed up at least every 6 months, or more frequently if justified by phenotype or tumor stage. Follow-up of MUT^- patients with sporadic melanoma is carried out at least every 6 months for 5 years, and then once a year, according to phenotype and tumor stage. Skin examination by a dermatologist is performed every 6 months for 5 years, then once a year (or every 6 months even after 5 years for patient with high-risk phenotype).

Collection of clinical and pathologic data

Clinical information was obtained through a questionnaire administered by a trained interviewer;

Abbreviations used:

CI: confidence interval
HR: hazard ratio
MPM: multiple primary melanoma
MSS: melanoma-specific survival
MUT^-: *CDKN2A* germline mutation—negative
MUT^+: *CDKN2A* germline mutation—positive
OR: odds ratio
OS: overall survival

the questionnaire collected personal information, phenotype, and personal/family history of other melanomas and other tumors as previously described.[4,20] Clinical records and/or local cancer registry data were used to collect follow-up information and confirm causes of death. Pathologic information included tumor histology and staging according to the American Joint Committee on Cancer tumor, node, and metastasis staging system.[28]

Molecular analysis

All patients provided a blood sample from which we extracted genomic DNA. Sanger sequencing to assess the mutational status of *CDKN2A*, cyclin-dependent kinase 4 gene (*CDK4*), and *MC1R* were performed as previously described.[20,29]

Selection of patients for survival analysis

From our cohort of 1239 patients, we filtered out all patients with incomplete data concerning follow-up, mutational status, and stage and those with noncutaneous melanoma. Subsequently, we selected all MUT^+ patients and grouped them together regardless of familial status. Moreover, we selected a second group of MUT^- patients matched by age and sex and having a similar tumor stage distribution.

Because our follow-up scheme is the same for MUT^+ patients regardless of whether they have familial or sporadic melanoma whereas follow-up of MUT^- patients differs according to familial status, we decided to exclude MUT^- patients with familial melanoma from the survival analysis so as to have a higher homogeneity of follow-up within groups. The resulting data set consisted of 305 patients (106 MUT^+ and 199 MUT^-). The patient selection workflow is outlined in Fig 1.

To make sure that our results were not affected by events that occurred within the time elapsed between the diagnosis of melanoma and the start of the mutation-based follow-up, we also verified whether survival analysis results remained consistent when only incident patients were included; this was done by using the cutoff of 24 months that had previously been used to assess survival in patients with melanoma.[30] To obtain this incident patients—only subset, the same selection process was again applied to patients from our melanoma cohort. Only patients enrolled within 24 months from diagnosis of their melanoma were selected, resulting in a total of 199 incident patients matched for age and sex and having a similar of tumor stage distribution (62 and 137 of whom were MUT^+ and MUT^-, respectively).

Informed consent was signed by all patients before enrollment according to local ethics committee approved protocol.

End points and statistical analyses

Our objective was to investigate whether *CDKN2A* mutational status is linked to patients' prognosis in terms of overall survival (OS) and melanoma-specific survival (MSS) in our melanoma cohort undergoing a mutation-based follow-up.

When evaluating the difference of a numeric variable between two groups, we performed the Mann-Whitney U test. To assess the association between 2 categoric variables, we used the Fisher exact test. Associations between 1 ordinal and 1 categorical variable were determined by using the Kruskal-Wallis test. OS and MSS were calculated with Cox proportional hazard regression models and Kaplan-Meier curves.

To analyze OS, events were defined as deaths from any cause. For MSS, only deaths due to melanoma were considered events, whereas deaths from other causes were censored. Considering that mutation-based follow-up started after patients' enrollment and *CDKN2A* genetic testing, we calculated follow-up as months from inclusion to censoring or death.

All analyses were 2 sided, and the threshold for statistical significance was set at $P = .05$. Statistical analyses were performed within the R computational environment[31] by using the packages stats, survival,[32] and the R/Bioconductor package survcomp.[33]

RESULTS

Patients characteristics

Whole cohort. Our cohort, after filtering out 30 patients with either missing information on *CDKN2A* mutational status or variants of uncertain significance, consisted of 1187 patients (129 MUT^+ and 1058 MUT^-). Patient and tumor characteristics and the corresponding statistics are shown in Table I.

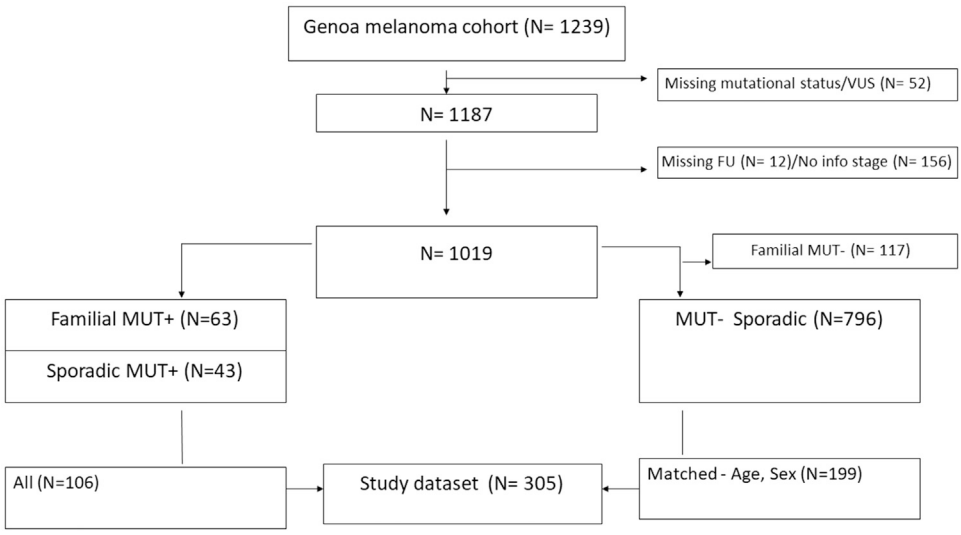

Fig 1. Cutaneous melanoma: patient selection workflow. The flowchart shows the selection strategy adopted to obtain a data set of patients matched for age and sex and eligible for survival analysis. *FU*, Follow-up; *MUT*$^-$, germline mutation−negative; *MUT*$^+$, germline mutation−positive; *VUS*, variant of uncertain significance.

Overall, 59 of 977 patients with apparently sporadic melanoma (6%) and 70 of 210 patients with familial melanoma (33%) were MUT$^+$. The median age was lower in MUT$^+$ patients than in MUT$^-$ patients (42 and 50 years, respectively, $P < .01$). Conversely, sex, tumor stage, and median Breslow thickness did not differ depending on *CDKN2A* mutational status. As expected, MPMs were more frequent among MUT$^+$ patients ($P < .01$). Moreover, 31 of 130 patients with apparently sporadic melanoma (24%) and a diagnosis of MPMs were MUT$^+$ compared with only 28 of 847 patients with apparently sporadic melanoma who had a single melanoma (3%), as shown in Table II.

Among MUT$^+$ patients there was a higher rate of individuals who had 1 or more dysplastic nevi and other skin lesions surgically removed. At least 1 nonmelanoma cancer had been diagnosed in 19% of MUT$^+$ patients versus in 12% of MUT$^-$ patients (odds ratio [OR], 1.7%; $P = .042$).

The most frequent *CDKN2A* mutation was G101W (in 97 patients), followed by E27X (in 13 patients); A127P, P48T, and R24P (in 3 patients each); and A36T, A68L, D74Y, and F90S (in 1 patient each).

The distribution of *MC1R* variants was similar in MUT$^+$ and MUT$^-$ patients regardless of whether the 5-point score described by Davies et al.[30] or a dichotomous approach was used ($P > .7$ in both cases [Table I]).

Study data set. After patient filtering and matching for age and sex, the median age was 43 years in MUT$^+$ and 44 years in MUT$^-$ patients ($P = .719$). Moreover, 48 patients in the MUT$^+$ group (45%) and 95 in the MUT$^-$ group (48%) were male, and 58 (55%) and 104 (52%) in the respective groups were female ($P = .81$). Tumor stage distribution and median Breslow thickness remained similar in MUT$^+$ and MUT$^-$ patients (both $P > .8$), with the majority of patients having stage Ia to IIc tumors. Similarly, the distribution of *MC1R* variants did not differ significantly between groups ($P > .7$). The median follow-up length was 123 months (95% confidence interval [CI], 43-182) in MUT$^+$ patients and 105 months (95% CI, 42-154) in MUT$^-$ patients.

As in the main cohort, patients in whom MPM had been diagnosed were more frequently MUT$^+$ (42% vs 11% of MUT$^-$ patients [OR, 5.97; $P < .01$]). *CDKN2A* mutations were also associated with removal of 1 or more dysplastic nevi (OR, 2.25; $P = .026$), especially when only dysplastic nevi removed after genetic testing for *CDKN2A* were considered (OR, 3.06; $P = .023$).

In line with previous reports, the MUT$^+$ group had a higher rate of individuals with a diagnosis of nonmelanoma cancers than did the MUT$^-$ group (17% vs 9%), although this difference was not statistically significant (OR, 2.08, $P = .054$). The results of descriptive statistics analysis performed on the study data set are shown in Table III.

Survival analysis

The overall rate of events was 17% in both MUT$^+$ patients and matched MUT$^-$ patients, whereas the rates of death from melanoma were 10.8% and 7.8% among MUT$^+$ and MUT$^-$ patients, respectively.

Table I. Whole cohort: clinical, pathologic, and molecular characteristics

Characteristic	n	MUT	WT	OR	Lower CI	Upper CI	T	H	*P* value
Sex									
M	1187	56 (0.43)	485 (0.46)	1.1	0.75	1.63			.64
F		73 (0.57)	573 (0.54)						
Age									
Median (IQR)	1187	42 (32-53)	50 (39-63)				87372		**1.938E-07**
Stage									
IS	1027	5 (0.02)	121 (0.06)					2.06	.151
I		71 (0.27)	537 (0.26)						
II		20 (0.08)	171 (0.08)						
III		7 (0.03)	56 (0.03)						
IV		5 (0.02)	34 (0.02)						
Familial									
fam	1187	70 (0.54)	140 (0.13)						
spo		59 (0.46)	918 (7.12)						
No. of melanomas									
cum	1185						93989		**2.548E-30**
1	1185	68 (0.53)	942 (0.89)	7.39	4.88	11.21			**1.687E-21**
2+		61 (0.47)	114 (0.11)						
Breslow thickness									
Median (IQR)	1133	0.9 (0.4-1.9)	0.84 (0.4-1.9)				63592.5		.573
No. of dysplastic nevi									
cum	1169						72134.5		**.007**
0	1169	108 (0.84)	944 (0.91)	1.91	1.09	3.24			**.019**
1+		21 (0.16)	96 (0.09)						
No. of dysplastic nevi after inclusion									
cum	1167						69823		**.032**
0	1167	118 (0.91)	993 (0.96)	2.06	0.93	4.18			**.047**
1+		11 (0.09)	45 (0.04)						
Other skin lesions									
cum	1183						83172.5		**8.836E-06**
0	1183	30 (0.23)	432 (0.41)	2.26	1.46	3.6			**1.109E-04**
1+		98 (0.77)	623 (0.59)						
Other tumors									
0	1124	96 (0.81)	882 (0.88)	1.72	1	2.85			**.042**
1+		23 (0.19)	123 (0.12)						
MC1R									
score 0-4	754							0.008	.9308
WT	754	22 (0.26)	192 (0.29)	1.15	0.68	2.03			.702
any r/R		63 (0.74)	477 (0.71)						

Boldface indicates statistical significance.

CI, 95% Confidence interval; *cum*, cumullative; *F*, female; *fam*, familial; *H*, Kruskal-Wallis test statistic; *IQR*, interquartile range; *IS*, melanoma in situ; *M*, male; *MC1R*, melanocortin 1 receptor; *MUT*, mutation; *OR*, odds ratio; *r/R*, nonred hair color/red hair color variants; *spo*, sporadic; *T*, Wilcoxon test statistic; *WT*, wild type.

Table II. Relative frequencies of *CDKN2A* mutations among patients with single and multiple melanomas

Frequency	No. of melanomas	MUT^+		MUT^-		Row total
Sporadic	1	28 (0.22)	(0.03)	819 (0.78)	(0.97)	847 (0.715)
	2+	31 (0.24)	(0.24)	99 (0.09)	(0.76)	130 (0.110)
Familial	1	40 (0.31)	(0.25)	123 (0.12)	(0.75)	163 (0.138)
	2+	30 (0.23)	(0.67)	15 (0.01)	(0.33)	45 (0.038)
Column total		129 (0.109)		1056 (0.891)		1185*

Absolute number of patients is shown outside brackets. Row frequencies are reported on the right, and column frequencies are reported at the bottom of each cell. Boldface indicates statistical significance.

MUT^-, Cyclin dependent kinase inhibitor 2A gene (*CDKN2A*) germline mutation—negative; MUT^+, cyclin dependent kinase inhibitor 2A gene (*CDKN2A*) germline mutation—positive.

*Two patients were removed because of missing information on multiple melanomas.

Table III. Clinical and molecular characteristics of patients selected for survival analysis

Characteristic	n	MUT	WT	OR	Lower CI	Upper CI	T	H	*P* value
Sex									
M	305	48 (0.45)	95 (0.48)	1.1	0.67	1.82			.719
F		58 (0.55)	104 (0.52)						
Age									
Median (IQR)	305	43 (32.25-55.5)	44 (33-56)				11084		.464
Stage									
IS	305	5 (0.02)	22 (0.05)					1.27	.26
Ia-Ib		70 (0.27)	122 (0.27)						
IIa-IIb-IIc		19 (0.07)	37 (0.08)						
IIIa-IIIb-IIIc		7 (0.03)	15 (0.03)						
IV		5 (0.02)	3 (0.01)						
Familial status									
fam	305	63 (0.5)	0 (0)						
spo		43 (0.34)	199 (1)						
No. of melanomas									
cum	305						13914.5		**1.341E-10**
2+		44 (0.42)	21 (0.11)						
Breslow thickness									
Median (IQR)	305	0.9 (0.36-1.7)	0.9 (0.44-1.7)				10489.5		.955
No. of dysplastic nevi									
cum	299						11233		**.013**
0	305	87 (0.82)	176 (0.91)	2.25	1.05	4.87			**.026**
1+		19 (0.18)	17 (0.09)						
No. of dysplastic nevi after inclusion									
cum	299						10929		**.018**
0	299	95 (0.9)	186 (0.96)	3.06	1.05	9.64			**.023**
1+		11 (0.1)	7 (0.04)						
Other skin lesions									
cum	303						11379.5		.19
1+		83 (0.78)	142 (0.72)						
Other tumors									
0	287	82 (0.83)	171 (0.91)	2.08	0.94	4.58			.054
1+		17 (0.17)	17 (0.09)						
MC1R									
Score 0-4	221							0.1309	.718
WT	221	19 (0.25)	38 (0.26)	1.04	0.53	2.09			1
Any r/R		56 (0.75)	108 (0.74)						

CI, 95% Confidence interval; *cum*, cumulative; *F*, female; *fam*, familial; *H*, Kruskal-Wallis test statistic; *IQR*, interquartile range; *IS*, melanoma in situ; *M*, male; *MC1R*, melanocortin 1 receptor; *MUT*, mutation; *OR*, odds ratio; *r/R*, nonred hair color/red hair color variants; *spo*, sporadic; *T*, Wilcoxon test statistic; *WT*, wild type.

As shown in Fig 2, *A*, we did not detect differences in OS between MUT^+ and MUT^- patients, as confirmed by a Cox proportional hazard regression model: hazard ratio (HR), 0.85; $P = .592$; 95% CI, 0.48-1.52. Similarly, MSS did not differ depending on *CDKN2A* mutational status, as shown in Fig 2, *B* (HR, 0.86; 95% CI, 0.38-1.95; $P = .718$).

To verify survival in an even more follow-up–homogeneous setting, we then performed an analyses in the incident patients–only subset, obtaining overlapping results both for OS (HR, 0.64; 95% CI, 0.28-1.45; $P = .282$,) and MSS (HR, 1.87; 95% CI, 0.39-2.95; $P = .9$). Kaplan-Meier curves along with log-rank–computed *P* values of the incident patients–only subset are shown in Fig 3.

DISCUSSION

Our study shows that *CDKN2A* mutational status did not negatively affect survival in our melanoma cohort. Neither OS nor MSS varied according to *CDKN2A* mutational status when known confounding variables such age, sex, and tumor stage were similar in MUT^+ and MUT^- patients.

Interestingly, our results are not in line with those of the previously described Swedish study, in which *CDKN2A* MUT^+ patients with familial melanoma had

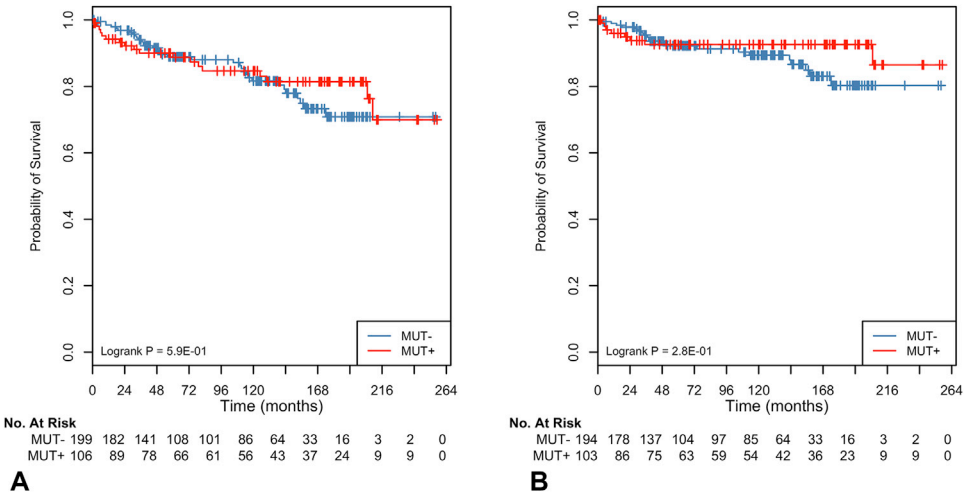

Fig 2. Cutaneous melanoma: overall survival and melanoma-specific survival in cyclin dependent kinase inhibitor 2A gene (*CDKN2A*) mutation–positive (MUT^+) and *CDKN2A* mutation–negative (MUT^-) patients with melanoma. The Kaplan-Meier curves show similar overall survival (**A**) and melanoma-specific survival (**B**) in MUT^+ and MUT^- patients. Censored patients are shown as vertical lines.

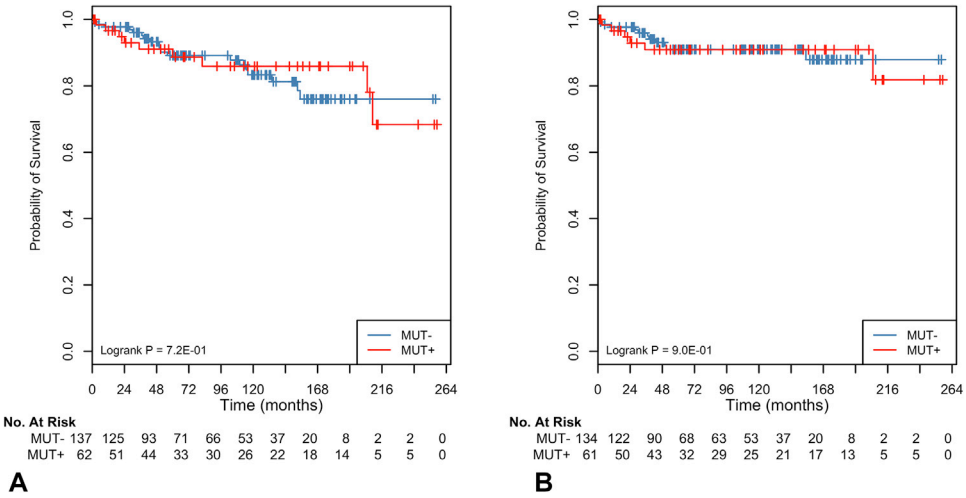

Fig 3. Cutaneous melanoma: overall survival and melanoma-specific survival in the cyclin dependent kinase inhibitor 2A gene (*CDKN2A*) mutation–positive (MUT^+) and *CDKN2A* mutation–negative (MUT^-) incident-only subsets of patients with melanoma. *CDKN2A* mutational status did not modify overall survival (**A**) or melanoma-specific survival (**B**) in patients with incident cutaneous melanoma, as shown by the overlapping Kaplan-Meier curves. Censored patients are shown as vertical lines.

worse survival than did MUT^- patients with either familial or sporadic melanoma.[23]

It is possible that intrinsic population differences may modulate the impact of *CDKN2A*. Indeed, although MUT^+ and MUT^- had a comparable distribution of *MC1R* variants that have been suggested to affect survival,[30] we cannot rule out the possibility that somatic mutations/germline variants in other genes may have had a protective effect on survival in our study cohort.

Moreover, survival according to the *CDKN2A* mutations in different regions might be modulated by an asymmetric distribution of nongenetic risk factors. For instance, it is not known yet whether different environmental exposures can influence prognosis in MUT^+ individuals.

A third hypothesis is that intensive clinical surveillance may modulate survival in this high-risk population, possibly by counteracting negative effects on survival owing to the mutation itself. In

fact, the impact of follow-up intensity on survival according to *CDKN2A* mutations is currently unknown, and it must be kept in mind that the Swedish study was performed on patients who underwent a familial melanoma–specific follow-up whereas our hospital has adopted a different strategy. Considering the high *CDKN2A* mutation rate of our population, we have a considerable number of MUT^+ patients with apparently sporadic melanoma whose risk deriving from their first melanoma and risk of developing MPMs may not be inferior to those of their counterparts with familial melanoma.[4,25-27] Indeed, we observed a 24% *CDKN2A* mutation rate in apparently sporadic patients who had MPMs, compared with a rate of 3% in those who only had 1 melanoma diagnosis. Considering that close surveillance in high-risk groups such as MUT^+ patients is encouraged by multiple pieces of evidence to improve early diagnosis,[5,34,35] our hospital offers an intensive follow-up to MUT^+ individuals.

The proportion of individuals who had 1 or more dysplastic nevi removed was higher among MUT^+ patients, especially when only dysplastic nevi removed after DNA testing were considered. This difference was even higher when we restricted the analysis to incident patients. Hence, it is possible that intensive follow-up resulting in detection and removal of dysplastic lesions reduced the occurrence of metachronous melanomas in MUT^+ patients.

Unfortunately, because of the retrospective nature of our cohort, our data on individual patients' follow-up is incomplete, and thus we cannot compare median follow-up intervals between MUT^+ and MUT^- patients, even though the higher rate of removal of dysplastic nevi after DNA testing may be an indirect indicator of a more intensive follow-up in the MUT^+ group. Therefore, although follow-up may be involved in the noninferior survival of MUT^+ patients, this hypothesis needs to be verified prospectively.

Another limitation is that only probands of patients with familial melanoma were included in our cohort; although this provided the advantage of having independent observations, it lowered the size of our familial subset. Likely for this reason, we did not have enough data to analyze both the association of *CDKN2A* mutations with the occurrence of specific cancers (such as pancreatic cancer) and survival according to nonmelanoma cancers. The downsizing of our cohort needed to obtain an accurate data set for survival analysis also prevented us from carrying out further analyses, such as direct comparison between MUT^+ and MUT^- status among familial melanoma–only patients. In addition, the majority of patients in both groups were still alive at censoring time. Because of the aforementioned exclusion of affected family members of the probands and also because the majority of our cohort's patients had stage I and II melanomas, it is possible that the number of deaths that we observed was insufficient to detect an effect of *CDKN2A* on survival.

In conclusion, despite recent findings, *CDKN2A* mutational status is not associated with survival in our cohort. Whereas several potential modifiers could be implicated in region-specific differences concerning *CDKN2A*-related melanoma survival, further studies are needed to verify these hypotheses.

This study is part of an ongoing project aimed at unraveling the relationship between *CDKN2A*, disease characteristics, and survival. Upon the enrollment of a higher number of patients, we plan to compare MUT^+ and MUT^- patients with familial melanoma and to analyze mortality by melanoma and other cancers in different subgroups, also extending the analysis to affected family members of the already included probands.

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