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Is surveillance effective, and who should be under surveillance? Results of a national surveillance program for familial melanoma

Submitted

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Abstract

Objective:
To investigate the efficacy of a program launched in 1989 by the foundation for the Detection of Hereditary Tumours (NFDHT) aimed at the surveillance of members of melanoma families and to compare the melanoma detection rate in families with different clinical and genetic characteristics.

Patients and Methods:
From the NFDHT 72 families were selected. A total of 450 individuals were followed for 15 years between 1992 and 2008 at 85 hospitals throughout the Netherlands..

Results:
During follow-up 52 invasive melanomas were diagnosed in 37 individuals. Ten year cumulative melanoma incidence was 10.2% (95% CI: 6.9 – 13.5). Family members with a history of melanoma had a higher probability of being diagnosed with melanoma than their first degree relatives without a history of melanoma (HR: 3.9, 95% CI 2.0 – 7.7).
Median Breslow thickness of surveillance-detected invasive melanomas was 0.50 mm compared to 0.94 mm in pre-surveillance index melanomas. None of the patients with surveillance-detected melanomas died of melanoma during follow-up (median: 4.2 yrs).
Melanoma detection rate was higher in families with a germline CDKN2A mutation compared to CDKN2A wildtype families (HR: 3.6, 95% CI: 1.4 – 9.0) and borderline non-significantly higher for families with ≥ 3 affected family members compared to 2-case families (HR: 2.2, 95% CI: 0.9 – 5.0).

Conclusion:
Our findings are in support of a beneficial effect of surveillance on tumour thickness at diagnosis and survival. Members of CDKN2A mutated families may need more stringent surveillance than members of CDKN2A wildtype families.

Introduction

Being a member of a family with a hereditary predisposition for cutaneous malignant melanoma (CMM) is one of the main risk factors for melanoma. Up to 10% of all melanoma cases have been reported to occur in families.[1]

The prognosis of melanoma patients is highly dependent on the stage at diagnosis.[2] Early melanomas can be cured by a local excision with adequate margins, but for metastatic melanoma the outcome is generally poor. Early detection is considered the most effective way to prevent melanoma mortality. In 1989 a national registry for familial melanoma was established at the Netherlands Foundation for the Detection of Hereditary Tumours (NFDHT) in order to promote the detection and surveillance of members of melanoma families throughout the Netherlands. Regular surveillance, consisting of a minimum of annual total skin examinations complemented by skin self-examinations, has been recommended for all family members with a history of melanoma and their first degree relatives (parent, siblings and children).

So far, two high-penetrance melanoma susceptibility genes associated with an autosomal dominant inheritance have been identified. Pathogenic germline mutations in the tumour suppressor gene CDKN2A (MIM# 600160) are detected in approximately 39% of families with ≥3 melanoma cases, and have an estimated penetrance of 67% by the age of 80 years.[3,4] Mutations in the oncogene CDK4 (MIM# 123829) have been detected only in few families (estimated 2%). For the majority of families the genetic background has not been fully clarified, but appears to be mostly the result of a combination of low (e.g. MC1R) and intermediate (e.g. MITF) risk modifier genes, and (possibly) some rare high penetrance genes.[5,6] In families without a pathogenic germline mutation, melanoma susceptibility is suggested by familial clustering of patients with melanoma, but cannot be confirmed by genetic testing and therefore remains a clinical diagnosis.

Besides genetic differences, clinical experience learns that melanoma pedigrees might also be characterized by clinical differences concerning the number of melanoma patients and the age of melanoma diagnosis of the affected relatives. It is probable that genetic and clinical family characteristics are related to the magnitude of melanoma risk of family members. To the best of our knowledge no prospective studies on these issues have been published.

The goal of this study was to investigate the efficacy of surveillance and to compare the detection rate of melanomas in families with different clinical and genetic characteristics. Analyses were based on prospective NFDHT data of 450 individuals from 72 melanoma families that were followed for 15 years between 1992 and 2008 at 85 hospitals throughout the Netherlands.

Patients and methods

Data collection

The organization and methods of the NFDHT have been published elsewhere.[7,8] In brief, physicians from all parts of the Netherlands refer families suspected for familial melanoma to the registry. Genealogical studies are performed and all reported malignancies are verified by medical records. A genetic predisposition to melanoma is suspected if a family consists of a patient with invasive CMM with at least one first degree relative with invasive CMM or two additional relatives with invasive CMM. If these criteria are met, the registry monitors the continuity of the surveillance program for all family members with a history of melanoma and their unaffected first degree relatives by annually sending letters to the responsible clinician (mostly dermatologists). In return these clinicians report the results of surveillance and histo-pathologic examination.

From the NFDHT 72 families were selected based on the studied clinical and genetic familial characteristics (see below). Families were eligible if they contained a minimum of 2 first degree relatives with confirmed invasive CMM. All family members with: 1. age 12 years or older, 2. either having a personal history of melanoma (affected relative), or being an unaffected first degree relative of a melanoma patient. 3. registration at the NFDHT, and 4. having been subjected to at least one skin examination prior to the end date of the study (1-1-2008), were included in the study. Family-, patient-, tumour- and follow-up data were ascertained from the NFDHT database. For all individuals that were lost to follow-up, letters were sent to their clinician, and in case of no reply, to their general practitioner to obtain additional follow-up data.

Analyses

Cumulative melanoma incidence was calculated using the Kaplan Meier method. Survival times were calculated from the date of registration at the NFDHT until the date of melanoma diagnosis or last date of follow-up (censored). For patients with multiple melanomas only the first surveillance detected melanoma was included in the analyses.
Breslow tumour thicknesses of surveillance detected CMM were compared to pre-surveillance index CMM, which consisted of the first melanoma of the first two CMM patients from each family. For this purpose multivariate linear regression and binary logistic regression analyses were used. In the linear regression analyses a log-transformed Breslow thickness was used. Since differences in the log-transformed variable translate to multiplication factors on the original scale, results are reported as multiplication factors on the original scale. We adjusted for gender, age at diagnosis, order (first or subsequent melanoma) and year of diagnosis. Generalized estimating equations (GEE) were used to correct for within-patient correlations.[9]

We compared the melanoma incidence in families with different genetic and clinical characteristics by investigating: 1. Familial CDKN2A mutation status; coded as positive,

negative (CDKN2A wildtype) or unknown (in case no genetic testing had been performed). All members from a single family were coded equally for this covariate, independent of personal test results. 2. The number of affected relatives (melanoma patients); families were categorized as 2-case families in case of 2 first degree relatives with melanoma, without additional first or second degree relatives with melanoma. In case of one or more additional first or second degree relatives with melanoma, families were categorized as ≥3-case families. 3. The age at melanoma diagnosis of the youngest melanoma patient in the family; families were divided in two categories: youngest melanoma diagnosis at age younger or older than 30 years.

Correlation of these three family characteristics with cumulative melanoma incidence were analysed using multivariate Cox regression analyses with covariates: gender, age, history of melanoma, family CDKN2A mutation status, number of affected relatives, and age of youngest melanoma patient < or ≥30 yrs. To adjust for changes in familial characteristics during follow-up, the follow-up of patients was split up into disjoint (hence independent) follow-up intervals with the moment of change in familial characteristics as stopping time, and analyzed using "delayed entry". Two time dependent covariates were used, one for the number of affected relatives and one for age of the youngest melanoma patient. Generalized estimating equations (GEE) were used to correct for within-family correlations.[9] Based on these analyses adjusted cumulative melanoma incidences were calculated for different risk categories.

All analyses were performed with SPSS 17.0 and R 2.13.0. The package geepack was used for the calculation of adjusted standard errors in R.[10] Statistical significance was determined at $\alpha = .05$, and all tests were two-sided**.** For analyses in which more than two groups were compared a Bonferroni correction for multiple testing was performed.

Results

Data characteristics

In total 450 family members (197 males, 253 females) were included in the study. They consisted of 124 patients with a history of melanoma and 326 unaffected first degree relatives of patients with a history of melanoma. Mean age at registration was 39.7 years (range 12.0 – 80.4 yrs, SD: 15.7 yrs). Median follow-up was 6.3 years (range 0.1 – 15.1 yrs). Follow-up was complete for 336 patients (75%). Eleven patients died during follow-up (details below). For 6 members of CDKN2A mutated families participation in the surveillance program was discontinued after they were tested negative for the mutation.

Data on CDKN2A mutation status was available for thirty-four families (47%). In 15 families (92 patients) the p16-Leiden mutation (c.225-243del19) in the CDKN2A gene was detected.[11] In 19 families (138 patients) melanoma patients were tested negative for a mutation in

CDKN2A. For the remaining 38 families (220 patients) no data on the CDKN2A gene mutation status was available. There were no families with pathogenic CDKN2A mutations other than the p16-Leiden mutation, unclassified variants or CDK4 mutations included in the study. At the time of registration, 49 families (68%) classified as 2-case families, and 23 families (32%) as ≥3-case families. During follow-up eight 2-case families (16%) became ≥3-case families as additional family members were diagnosed with melanoma. In 32 (44%) of the 72 families the youngest melanoma patient was diagnosed with melanoma before the age of 30 years.

Mean age at diagnosis of (first) melanomas was 38.1 years (SD: 12.9, range: 16.5 – 69.3 yrs) in CDKN2A mutated families, 43.2 years (SD: 14.3 yrs, range: 16.4 – 78.2 yrs) in gene-tested CDKN2A wildtype families, and 42.8 years (SD: 13.0, range: 19.7 – 75.6 yrs) in untested families (n = 203, including all first melanomas of included family members and index melanomas). The differences in mean age at diagnosis according to CDKN2A mutation status was not statistically significant (p = 0.11, using a one-way ANOVA test). Of the 203 first melanomas, 2.5% (n = 5) were diagnosed before age 20 years and 3.4% (n = 7) after age 70 years.

Results of surveillance

During follow-up 37 patients (8%) were diagnosed with a total of 52 invasive melanomas (table 1). Twenty-nine patients were diagnosed with a single melanoma, four patients with two melanomas, one patient with three melanomas, and three patients with four melanomas. In addition five in situ melanomas were diagnosed, which were not included in the analyses.

Twenty-three (62%) of the 37 patients that were diagnosed with invasive melanoma during follow-up, had a history of melanoma prior to registration at the NFDHT. Ten year cumulative melanoma incidence during surveillance was 10.2% (95% CI: 6.9 – 13.5).

The median Breslow thickness of surveillance-detected melanomas (n = 51, 1 missing value) was 0.50 mm (range 0.25 – 2.60 mm), compared to 0.94 mm (range 0.18 – 6.00 mm) for index melanomas (n = 124). The Breslow thickness of surveillance-detected melanomas was significantly thinner than that of index melanomas (multiplication factor 0.65, 95% CI 0.44 – 0.96, p = 0.033).

Of the surveillance-detected melanomas 22% (n = 11) had a Breslow-thickness > 1.00 mm, compared with 49% (n = 61) of index melanomas. The higher proportion of melanomas > 1.00 mm among index cases was not statistically significant (odds ratio 2.50, 95% CI 0.61 – 10.29, p = 0.204).

Eleven patients (2.4%) died during follow-up. For seven patients cause of death was metastasized melanoma. These patients all had their melanoma before registration and

Table 1 Characteristics of patients with surveillance detected melanomas

Patient number	Gender	CDKN2A mutation[a]	Number of melanomas[b]	Age at registration	Age at diagnosis	Breslow thickness[c]
60005	Male	Unknown	1	49,3	59,6	Unknown[e]
60008	Female	Unknown	1	49,0	53,7	0,40
60020	Male	Unknown	1	15,9	21,1	1,00
60021	Female	Unknown	2	17,7	26,0[1] / 27,9[2]	0,62[1] / 1,05[2]
80007	Male	Unknown	1	42,0	43,7	0,49
130033	Male	No	1	63,0	76,5	0,27
240003	Male	Unknown	1	48,0	55,4	0,40
390014	Female	Yes	1	43,3	49,2	0,40
410007	Female	No	1	60,0	62,3	1,40
420001	Male	No	2	40,4	43,4[1] / 46,6[2]	0,50[1] / 0,70[2]
480019	Male	Unknown	1	40,9	44,3	0,50
530099	Female	No	1	37,0	37,7	0,40
630025	Female	Unknown	1	29,0	30,4	0,50
770004	Female	Yes	1	27,9	35,9	0,50
880006	Male	Unknown	1	47,8	54,7	0,32
900005	Female	Yes	4	33,3	38,4[1] / 38,4[1] / 40,0[2] / 40,4[3]	0,83[1] / 0,72[1] / 1,00[2] / 0,40[3]
900006	Male	Yes	4	33,1	35,3[1] / 39,2[2] / 39,2[2] / 42,1[3]	0,85[1] / 2,60[2] / 2,00[2] / 0,50[3]
1030001	Male	Yes	1	38,5	43,3	0,45
1050001	Male	No	1	61,6	70,6	0,35
1330003	Female	Unknown	1	52,6	56,0	0,35
1660002	Female	Unknown	1	47,0	56,0	0,45
1890002	Female	Unknown	1	49,1	54,0	0,50
1890028	Female	Unknown	2	51,4	53,8[1] / 54,2[2]	0,79[1] / 0,67[2]
1910006	Male	Unknown	1	44,6	49,8	0,40
1920018	Female	Unknown	1	35,1	37,3	1,10
2110001	Male	Yes	4	43,1	43,1[1,d] / 43,7[2] / 46,5[3] / 47,1[4]	0,50[1] / 0,70[2] / 0,60[3] / 0,75[4]
2190002	Female	Yes	1	52,8	55,0	0,42
2190016	Male	Yes	2	57,6	60,1[1] / 62,8[2]	0,50[1] / 1,20[2]
2580005	Female	Unknown	1	28,5	30,8	0,60
2630102	Male	Yes	1	43,7	46,9	0,30
2650019	Female	Unknown	1	33,0	33,4	0,25
2770101	Female	Yes	1	52,7	56,7	0,25
2840003	Male	Yes	1	33,9	35,2	0,26

Table 1 Continued

Patient number	Gender	CDKN2A mutation[a]	Number of melanomas[b]	Age at registration	Age at diagnosis	Breslow thickness[c]
2840103	Female	Yes	3	26,2	27,9[1] / 28,7[2] / 29,3[3]	0,32[1] / 1,40[2] / 0,92[3]
3030101	Male	No	1	47,6	48,6	1,94
3080065	Male	Yes	1	62,9	63,2	1,60
3160009	Female	Yes	1	19,4	20,2	0,55

[a] ; Familial CDKN2A mutation status, [b] ; Number of melanomas during follow-up, [c] ; Breslow thickness in millimetres, [d] ; The first melanoma of patient 2110001 was diagnosed one month after registration, [e] ; Because of low clinical suspicion this lesions was removed by curettage, and the pathologist was unable to determine the Breslow thickness, [1] ; 1st melanoma, [2] ; 2nd melanoma, [3] ; 3rd melanoma, [4] ; 4th melanoma

none of them was diagnosed with a subsequent primary melanoma during follow-up. Two patients died from oesophagus carcinoma. For two patients cause of death was unknown, but neither of them was diagnosed with melanoma during follow-up. None of the 37 patients that were diagnosed with melanoma during follow-up died of melanoma (median follow-up after diagnosis: 4.2 yrs, range 0.0 – 11.4 yrs, follow-up complete for 33 patients, 4 patients lost to follow-up).

Risk factors

In table 2 the results of the multivariate Cox proportional hazard analyses for family members with a history of melanoma and first degree relatives are presented separately. The analyses showed a significantly increased melanoma detection rate for family members with a history of melanoma who were member of a family in which a relative had been diagnosed with melanoma before age 30 (hazard ratio (HR) 3.6, table 2). An increased melanoma detection rate was also seen for family members with a history of melanoma from CDKN2A-mutated families compared to families without a CDKN2A mutation (HR 5.9), though this finding was not statistically significant after correction for multiple testing. For first degree relatives, no significant personal or familial risk factors could be identified.

An additional Cox proportional hazard analysis combining the data of affected relatives and first degree relatives (table 3) identified a personal history of melanoma (HR 3.93) as the main predictor of melanoma detection. Ten year cumulative melanoma incidence was 23.3% (95% CI: 13.9 – 32.7) for family members with a history of melanoma and 6.0% (95% CI: 2.7 – 9.3) for first degree relatives. In addition, melanoma detection rate was significantly higher in family members from families with the p16-Leiden mutation compared with family members from families without a CDKN2A mutation (HR 3.6). Adjusted ten year cumulative melanoma incidence was 16.2% for CDKN2A mutated families, 7.6% for untested families, and 4.8% for CDKN2A wildtype families (figure 1).

Table 2 Multivariate analyses of personal and familial risk factors for melanoma of affected relatives and first degree relatives.

	Affected relatives[#]			First degree relatives		
Covariate	**HR**	**(95% CI)***	**P**	**HR**	**(95% CI)***	**P**
Family size ≥ 3 cases	0.7	(0.3 – 1.7)	0.44	1.5	(0.5 – 4.4)	0.47
Age youngest relative < 30 yrs	3.6	(1.4 – 9.4)	0.01[$]	0.6	(0.2 – 1.5)	0.29
No CDKN2A mutation in family	1.0					
CDKN2A mutation in family	5.9	(1.2 – 30.2)	0.039[%]	2.4	(0.7 – 8.3)	0.17
Familial CDKN2A status unknown	2.7	(0.5 – 13.9)	0.23	1.0	(0.3 – 4.0)	0.99
Male gender	2.0	(0.8 – 5.0)	0.10	0.4	(0.2 – 1.2)	0.12
Age (years)	1.0	(1.0 – 1.1)	0.97	1.0	(1.0 – 1.1)	0.58

[#] Affected relatives = relatives with a history of melanoma; * HR (95% CI); Hazard Ratio (95% Confidence Interval), [$] statistically significant, [%] not statistically significant after adjustment for multiple testing (significance level at 0.017

Table 3 Multivariate analyses of personal and familial risk factors for melanoma: affected and first degree relatives combined.

Covariate	**HR**	**(95% CI)***	**P**
Personal history of melanoma	3.9	(2.0 – 7.7)	< 0.001[$]
Family size ≥ 3 cases	1.0	(0.5 – 2.1)	0.99
Age youngest relative < 30 yrs	1.8	(0.9 – 3.5)	0.090
No CDKN2A mutation in family		1.0	
CDKN2A mutation in family	3.6	(1.4 – 9.0)	0.006[$]
Familial CDKN2A status unknown	1.6	(0.6 – 4.3)	0.33
Male gender	1.2	(0.7 – 2.2)	0.56
Age (years)	1.0	(1.0 – 1.0)	0.81

* HR (95% CI); Hazard Ratio (95% Confidence Interval), [$] statistically significant

A sub-analysis was performed in which members from CDKN2A mutated families were excluded (table 4). In this analysis a personal history of melanoma again came up as the main predictor of melanoma detection. There were borderline non-significant differences in melanoma detection rate between patients from ≥3-case families and 2-case families (p = 0.074), with an adjusted ten year cumulative melanoma incidence of 9.7% in ≥3-case families and 4.6% in 2-case families.

Table 4 Multivariate analyses of personal and familial risk factors for melanoma in families without a CDKN2A mutation and untested families (families with a CDKN2A mutation excluded).

Covariate	HR	(95% CI)*	P
Personal history of melanoma	4.2	(1.8 – 9.7)	< 0.001[$]
Family size ≥ 3 cases	2.2	(0.9 – 5.0)	0.074
Age youngest relative < 30 yrs	0.8	(0.4 – 1.5)	0.42
No CDKN2A mutation in family	1.0		
CDKN2A mutation in family	excluded		
Familial CDKN2A status unknown	1.9	(0.8 – 4.7)	0.15
Male gender	1.3	(0.6 – 3.0)	0.49
Age (years)	1.0	(1.0 – 1.0)	0.82

* HR (95% CI); Hazard Ratio (95% Confidence Interval), [$] statistically significant

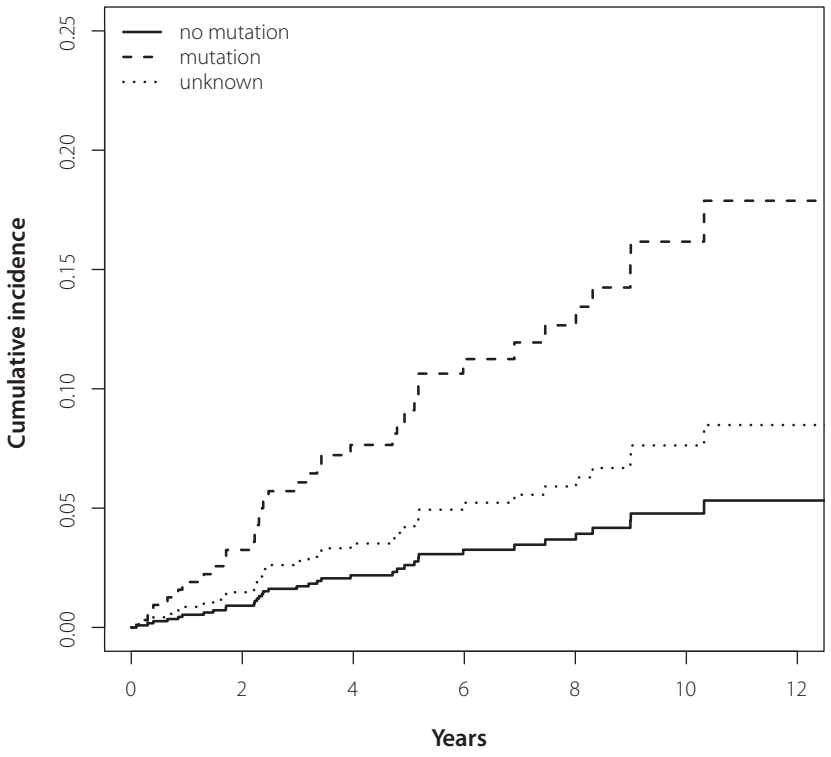
Discussion

In this study we report the results of surveillance of 72 families selected from the NFDHT Dutch national registry for familial melanoma. Overall 450 individuals were followed for 15 years between 1992 and 2008 at 85 hospitals throughout the Netherlands. Only few prospective studies have investigated the effectiveness and safety of surveillance of melanoma families and to the best of our knowledge this is the first prospective study to compare melanoma detection rates in families with different clinical and genetic characteristics.

The 10 year cumulative melanoma incidence during surveillance was 10.2%, which affirms the high melanoma risk and necessity of adequate surveillance of these families. Family members with a history of melanoma at the moment of entering surveillance were more likely to be diagnosed with melanoma during surveillance than their unaffected first degree relatives (HR: 3.9, 95% CI 2.0 – 7.7).

Patient survival is strongly correlated with Breslow tumour thickness, which is illustrated by the fact that 10-year survival is 92% in case of melanomas ≤ 1.00 mm, and 50% if > 4.00 mm.[2] In our study, surveillance-detected invasive CMM's had a statistically significant, almost 40%, thinner Breslow thickness (median 0.50 mm) than melanomas of pre-surveillance index patients (median 0.94 mm). Moreover, the proportion of melanomas with a Breslow thickness > 1.00 mm was 22% in surveillance-detected cases, compared to 49% in index cases, though the difference was not statistically significant after correction

Figure 1 Cumulative melanoma incidence during surveillance according to familial CDKN2A mutation status



No mutation; CDKN2A wildtype, Mutation: p16-Leiden mutation (c.225-243del19) in CDKN2A, Unknown; family has not been genetically tested.

for possible confounders. The median thickness of surveillance-detected melanomas in our study was comparable to other studies (0.50 mm – 0.56 mm) with equally or more stringent surveillance regiments.[12,13,14,15,7] None of the patients with surveillance-detected melanomas died of melanoma during follow-up. This finding needs to be viewed with some reserve as the duration of follow-up was limited (median 4.2 years), 12% of melanoma patients were lost to follow-up and lead time bias may have affected our results. The overall picture of our findings suggests that surveillance results in the detection of a considerable number of CMM, mostly diagnosed at an early stage and with a generally good prognosis.

Less than 40% of melanoma families are characterized by mutations in the high penetrance melanoma susceptibility genes CDKN2A and CDK4, and clinical characteristics like the number of affected relatives and age of melanoma diagnoses, differ considerably between pedigrees. As the clinical significance of these genetic and clinical differences have not been fully clarified, it is uncertain if and how they should affect surveillance guidelines. We compared melanoma detection rates during surveillance in clinically and genetically different families in order to support the development of a tailored surveillance program. The melanoma detection rate was significantly higher in families with a germline mutation in CDKN2A compared to CDKN2A wildtype families. Adjusted ten year cumulative melanoma incidence was 16.2% in CDKN2A mutated families compared to 4.8% in CDKN2A wildtype families. This finding is in accordance with a relatively higher melanoma risk in families with a high-penetrance melanoma susceptibility gene mutation compared to families lacking such mutation and in which melanoma risk is most likely the result of low and intermediate risk modifier genes. The relatively high melanoma detection rate in CDKN2A mutated families may also, to some extent, be attributable to the selection of high risk individuals for surveillance as a result of genetic testing. In our dataset 6 patients (6.5%) from CDKN2A mutated families were released from surveillance during follow-up when they were tested negative for the mutation.

In a subanalysis of CDKN2A wildtype and untested families a borderline non-significant two-fold increased melanoma detection rate (HR: 2.2, 95% CI: 0.9 – 5.0) in ≥3-case compared to 2-case families was found. It seems plausible that the familial melanoma risk is reflected in the number of affected relatives. Statistical non-significance of this finding may be due to lack of power, but more studies are needed to confirm these results.

Our study had several limitations. Only 47% (34/72) of families were genetically tested. Our data suggest that families with more affected relatives were more likely to be tested (the proportion of ≥3-case families in p16-Leiden mutation families, CDKN2A wildtype families and untested families were 40% (6/15), 42% (8/19) and 24% (9/38) respectively). This selection bias most likely resulted in an underestimation of the difference in melanoma detection rate between CDKN2A mutated and wildtype families. We performed sub-analyses (data not shown) in which only gene-tested families were included, but this had little effect on the results.

Prevention of melanomas due to excision of changing and suspicious nevi as happens regularly in daily practice, could not be accounted for in this study design, and may have resulted in an underestimation of the efficacy of surveillance. To limit the effect of overdiagnosis, melanomas in situ were excluded from the analyses.

Concluding, our findings are in support of a beneficial effect of surveillance on tumour Breslow thickness at diagnosis and survival of members of melanoma families. Our results suggest that surveillance should start during puberty and may need to be continued

beyond seventy. Surveillance may need to be more frequent in melanoma patients compared to their first degree relatives without a history of melanoma and CDKN2A mutated families may need more stringent surveillance than CDKN2A wild-type families. Compared to other melanoma families, CDKN2A wild-type two-case families appear to be at a relatively low risk. More studies are needed to facilitate the development of a tailored, cost-effective surveillance program for familial melanoma.

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