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Effectiveness and causes for failure of surveillance of CDKN2A-mutated melanoma families

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Abstract

Background:
For more than 25 years families with an increased susceptibility to melanoma have been under surveillance at our institution.

Objective:
We sought to investigate the effectiveness of surveillance for CDKN2A-mutated families and causes for failure of the program in patients with more advanced tumors.

Methods:
In a retrospective case-control study, Breslow thickness of melanomas diagnosed in relatives enrolled in the surveillance program were compared with melanomas of unscreened index patients. We investigated the influence of mode of detection and length of surveillance interval on outcome.

Results:
Surveillance melanomas (n = 226, median thickness: 0.50 mm) had a significantly lower Breslow thickness (multiplication factor: 0.61 [95% confidence interval 0.47-0.80], P \ .001) than index melanomas (n = 40, median thickness: 0.98 mm). Index melanomas were more likely diagnosed with a Breslow thickness greater than 1.0 mm (odds ratio: 3.1 [95% confidence interval 1.2-8.1], P = .022). In all, 53% of surveillance melanomas were diagnosed during regular screens, 7% during patients' first screen, 20% between regular screens, and 20% in patients who were noncompliant with the surveillance schedule. The majority of surveillance melanomas (58%) were detected within 6 months after the last screen. There was no correlation between tumor thickness and the length of the screening interval for tumors diagnosed within 24 months since the last screen.

Limitations:
The study is retrospective.

Conclusions:
Surveillance was associated with earlier detection of melanomas. Noncompliance was an important cause for failing surveillance. Shortening surveillance intervals may advance detection of tumors, but may paradoxically have little impact on prognosis.

Introduction

About 10% of primary cutaneous malignant melanomas have been reported to occur in families.[1] In 1994, germline mutations in the CDKN2A gene (MIM# 600160) were demonstrated in kindreds with hereditary melanoma.[2,3] CDKN2A encodes two distinct proteins: p16INK4 and p14ARF, both of which function as tumor suppressors. CDKN2A is the most prevalent high-penetrance melanoma susceptibility gene, mutations being detected in the germline in 20% to 40% of melanoma families.[4-6] Mutations in CDKN2A have an estimated penetrance of 67% by the age of 80 years.[4]

In 1981 the familial melanoma study group of the Leiden University Medical Center (LUMC) initiated a surveillance program for familial melanoma kindreds. Many of the first families that were screened at the LUMC were later shown to have a founder mutation in CDKN2A, consisting of a 19 base pair deletion in exon 2 (the p16-Leiden mutation).[7]

In 1989 we evaluated the surveillance program for these families, and reported that screen-detected melanomas (n = 31) had more favorable prognostic characteristics than those detected before the start of the surveillance program (n = 19).[8] We have noticed, however, that in spite of the surveillance program, some melanomas are detected relatively late. Possible explanations include: noncompliance with follow-up instructions; intervals between screens being too long to warrant early detection in all instances, because some melanomas grow rapidly[9]; failure to recognize melanomas because of an atypical clinical presentation[10]; or inadequate screening.

In the current study we compared the Breslow thickness of 226 melanomas of patients from p16-Leiden mutation positive families who were enrolled in the surveillance program with 40 melanomas of index patients from the same families, diagnosed before recognition of heredity for melanoma in these families. In addition we looked at the length of the surveillance intervals and the mode of detection of the melanomas.

Methods

The majority of families under surveillance at the LUMC were ascertained through the pigmented lesions clinic of the department of dermatology from 1980 onward. Family trees have been constructed for each kindred, initially at the clinic and later at The Netherlands Foundation for the Detection of Hereditary Tumors. Ascertainment of family data at the clinic[11] and The Netherlands Foundation for the Detection of Hereditary Tumors[8,12] has been described in detail elsewhere. Family members of clinically proven melanoma pedigrees were invited to the surveillance program, which consisted of an annual total skin examination. If a melanoma was diagnosed, surveillance was intensified

during the first 5 years after diagnosis (every 3 months during the first year, every 4 months during the second year, and every 6 months during the third to fifth year).

Before and after the identification of the p16-Leiden mutation in 1994, blood samples for research purposes have been collected from relatives who signed an informed consent form. Pedigree information was updated on a regular basis. We consider cancer data for all included families to be complete from 1970 onward. All melanomas diagnosed in family members who had been enrolled in the LUMC surveillance program were selected. These included tumors detected at the pigmented lesions clinic of the LUMC, and melanomas incidentally detected at other departments and by general practitioners. Melanomas detected before the start of the surveillance program in relatives who were under surveillance because of previous melanomas were also included. They were all termed "surveillance melanomas." Melanomas diagnosed in patients who had continued their surveillance at another institution were excluded. The first melanoma of the first two patients with melanoma from each family served as controls. They were detected before recognition of heredity for melanoma in these families, and termed "index melanomas." In total, 344 melanomas diagnosed in relatives from 37 families were eligible to the study.

For each patient, data were collected concerning date of birth and gender. For all melanomas, data on Breslow thickness, histologic type, and date of diagnosis were gathered and patient age at time of diagnosis was calculated. Screening intervals were calculated as the time between the last screen and melanoma detection. All tumors with missing data on Breslow thickness or histologic type, all in situ melanomas, and melanomas other than the superficial spreading histologic type (n = 132) were reviewed by one of us (W. J. M.). In all, 28 lesions were excluded from the study, because they were reclassified as benign (n = 22), unclassifiable (n = 5), or recurrent melanoma (n = 1). In situ melanomas and invasive melanomas with missing data on Breslow thickness that were unavailable for revision were excluded from the study.

We distinguished 4 modes of detection after enrollment in the surveillance program and surveillance melanomas were classified accordingly. Melanomas diagnosed at the first screen were termed "first-screen melanomas." If melanomas were detected at a subsequent screen, they were termed "regular-screen melanomas." Tumors that were detected between scheduled screens were termed "interval melanomas." The final category, "noncompliance melanomas," consisted of melanomas that were detected more than 2 months after the recommended screening interval. The margin of 2 months was taken because there have been waiting lists for the pigmented lesions clinic in the past (Fig 1).

Figure 1 Screening categories according to mode of ascertainment

Bold vertical lines = scheduled screening appointment; *dashed vertical line* = skipped screening appointment. *Arrows* indicate moment of diagnosis, and accompanying numbers refer to screening category: *1* = first-screen melanoma; *2* = regular-screen melanoma; *3* = interval melanoma; *4* = noncompliance melanoma.

Statistical analysis

Multivariate linear regression and binary logistic regression analyses were performed to calculate the effect of surveillance on Breslow thickness. Comparisons were made between surveillance melanomas and index melanomas, and among the 4 surveillance melanoma categories and index melanomas. In the linear regression analyses a log-transformed Breslow thickness was used. Because differences in the log-transformed variable translate to multiplication factors on the original scale, results are reported as multiplication factors on the original scale. In the logistic regression analyses Breslow thickness was analyzed as a categorical variable, coded 1 for Breslow thickness less than or equal to 1.00 mm, and 2 for greater than 1.00 mm. All analyses were adjusted for gender, age at diagnosis (in years), and year of diagnosis.

Many patients had multiple primary melanomas. We anticipated that these patients had their subsequent melanomas diagnosed at a more favorable prognostic stage than their first melanoma, not just because of surveillance, but also because of a change of the patients' and physicians' attitudes and behavior because of the previous (first) melanoma. For this reason we adjusted for melanoma rank, using a covariate coded 1 for first melanoma and 2 for all subsequent melanomas. In addition we used generalized estimating equations[13] to correct for within-patient correlations; this method uses sandwich estimators to calculate robust SEs. Correlation between the length of the screening interval and tumor thickness was calculated with linear regression analyses, with log-transformed Breslow thickness as dependent and the screening interval (in years) as covariate.

All analyses were performed with software (SPSS 14.0, SPSS Inc, Chicago, IL, and R 2.5.1, R Development Core Team, Vienna, Austria). The package geepack[14] was used for the calculation of adjusted SEs. Statistical significance was determined at a = .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

In total, 266 melanomas from 114 patients were included (Table 1). These melanomas consisted of 40 index melanomas and 226 surveillance melanomas. Median Breslow thickness was 0.98 mm for index melanomas and 0.50 mm for surveillance melanomas (Table II). The mean thickness of surveillance melanomas was 0.61 times that of index melanomas (95% confidence interval [CI] 0.47-0.80, P < .001). The probability of being diagnosed with a Breslow thickness greater than 1.00 mm was significantly larger for index melanomas (odds ratio [OR] 3.1, CI 1.2-8.1, P = .022).

Table 1 Patient characteristics

	Patients (n = 114)	
Gender		
Male	50	(44%)
Female	64	(56%)
No. of melanomas / patient		
1	61	(54%)
2	22	(19%)
3-5	19	(17%)
6-10	8	(7%)
> 10	4	(4%)

Mode of detection of surveillance melanomas

Classification according to mode of detection was possible for 191 surveillance melanomas (85%) (Table 2). Tumors were classified as follows: 13 first-screen (7%), 102 regular-screen (53%), 38 interval (20%), and 38 noncompliance (20%) melanomas. Compliance was related to the number of melanomas for which patients had previously been given a diagnosis. The proportion of noncompliance melanomas was 46% among first melanomas, and 26% of first melanomas were regular-screen melanomas. For subsequent melanomas, patient compliance steadily increased (Table 2).

Screening interval

Most regular-screen (72%) and interval (68%) melanomas were diagnosed in patients who were under intensified surveillance because of a previous melanoma. The median interval between the last screen and moment of detection was 5 months for regular-screen melanomas, 3.5 months for interval melanomas, and 24 months for noncompliance

Table 2 Tumor characteristics according to screening category

	Index	Surveillance					
		First	Regular	Interval	Noncompliant	Unclassified	Total
Patients (n)	35	12	49	20	36	20	92*
Melanomas (n)	40	13	102	38	38	35	226
Age at diagnosis**							
1st melanoma (years)	42 (17 – 62)	32 (22 – 72)	34 (15 – 66)	33 (27 – 44)	39 (23 – 67)	27 (15 – 43)	36 (15 – 72)
all melanomas (years)	42 (17 – 62)	39 (22 – 72)	46 (22 – 72)	35 (25 – 76)	42 (23 – 67)	43 (15 – 64)	41 (15 – 76)
Year of diagnosis**	'84 ('68 – '00)	'85 ('81 – '04)	'97 ('73 – '06)	'98 ('72 – '06)	'98 ('84 – '06)	'92 ('77 – '06)	'97 ('72 – '06)
Screening interval (months)**	NA	NA	5.0 (1 – 14)	3.5 (0 – 11)	24 (12 – 159)	NA	NA
Diagnosis < 5 yrs after previous melanoma	NA	NA	73 (71.6%)	26 (68.4%)	4 (10.5%)	NA	118 (52.2%)
Melanoma rank							
1st melanoma	40	11 (18%)	16 (26%)	6 (10%)	28 (46%)	10	71
2nd melanoma	0	2 (6%)	19 (58%)	8 (24%)	4 (12%)	10	43
3rd melanoma	0	0	15 (63%)	6 (25%)	3 (13%)	5	29
> 3rd melanoma	0	0	52 (71%)	18 (25%)	3 (4%)	10	83
Breslow thickness							
Median	0.98 mm	0.69 mm	0.50 mm	0.49 mm	0.52 mm	0.50 mm	0.50 mm
Range	(0.30 – 12.00)	(0.30 – 1.80)	(Mis – 2.10)	(Mis – 3.90)	(Mis – 2.60)	(Mis – 3.10)	(Mis – 3.90)
Mean***	1.48 mm	0.75 mm	0.58 mm	0.76 mm	0.84 mm	0.70 mm	0.68 mm

*Numbers in row do not total 92 as some patients with multiple melanomas had melanomas belonging to different screening categories; **, Numbers in table represent median and range; NA, not applicable; Mis, melanoma in situ; ***, based on invasive melanomas only

melanomas (Table2). The Breslow thickness of surveillance melanomas was not correlated with the length of the screening interval for intervals less than 24 months (Table 3) (linear regression analysis, multiplication factor: 1.01/y, 95% CI 0.83-1.23, P = .917). If melanomas detected after an interval of more than 24 months were included in the analysis a significant correlation between screening interval and Breslow thickness was found (multiplication factor: 1.09/y, 95% CI 1.03-1.15, P = .003).

Table 3 Tumor thickness according to the time interval between the last screening and the moment of melanoma diagnosis

Time Interval	n	Median* (range)	n	Mean** (SD)
0 – 4 months	69	0.48 (Mis – 2.10)	57	0.62 (0.39)
5 – 8 months	43	0.55 (Mis – 3.90)	36	0.70 (0.64)
9 – 12 months	27	0.50 (Mis – 1.40)	23	0.53 (0.25)
13 – 18 months	11	0.50 (Mis – 1.20)	8	0.68 (0.27)
19 – 24 months	10	0.49 (Mis – 1.00)	8	0.61 (0.28)
> 24 months	17	0.48 (Mis – 2.60)	13	1.07 (0.77)
Total	177***	0.50 (Mis – 3.90)	145	0.67 (0.49)

Mis, melanoma in situ.
* Based on in situ and invasive melanomas; 95% CI, 95% confidence interval.
** Based on invasive melanomas only; SD, standard deviation.
*** One missing value for a noncompliance melanoma.

Detection of interval melanomas

Most interval melanomas (n = 21, 55%) were detected by patients themselves, with a median Breslow thickness of 0.55 mm (range: in situ-1.60 mm), after a median interval of 5 months (range: 1 - 11). Ten interval melanomas (26%) were diagnosed by physicians at an appointment for the excision of another pigmented lesion, judged to be suspicious at the last screen (median thickness: 0.40 mm [in situ - 0.90 mm], interval: 1 month [0-2]). Physicians consulted for another medical condition diagnosed 6 of the interval melanomas (16%, median thickness: 0.38 mm [in situ-3.90 mm], interval: 7.5 months [2-11]). One interval melanoma was detected in a research project (thickness: 2.00 mm, interval 3 months).

Tumor thickness according to mode of detection

The tumor thickness according to mode of detection is shown in Table 4. Regular-screen melanomas were significantly thinner than index melanomas (multiplication factor: 0.53, 95% CI 0.46-0.87, P <.001) and at borderline significance, first-screen melanomas were thinner than index melanomas (multiplication factor: 0.63, 95% CI 0.46-0.87, P = .0053, significance at a = .005, because of multiple testing) (Table 5). The probability of diagnosing

Table 4 Cumulative number and proportion of cases according to Breslow thickness

	Breslow thickness					
Category	**Mis**	**≤ 0.75mm**	**≤ 1.00mm**	**≤ 2.00mm**	**≤ 4.00mm**	**Total**
Index:	0 (0%)	13 (33%)	23 (58%)	32 (80%)	38 (95%)	40
Surveillance:						
- First screening	0 (0%)	10 (77%)	11 (85%)	13 (100%)	-	13
- Regular screening	17 (17%)	88 (86%)	96 (94%)	101 (99%)	102 (100%)	102
- Interval	8 (21%)	30 (79%)	33 (87%)	37 (97%)	38 (100%)	38
- Noncompliance	7 (18%)	24 (63%)	31 (82%)	36 (95%)	38 (100%)	38
- Not categorized	3 (9%)	29 (83%)	30 (86%)	33 (94%)	35 (100%)	35
Surveillance (all):	35 (16%)	181 (80%)	201 (89%)	220 (97%)	226 (100%)	226

Mis, melanoma in situ

a tumor with Breslow thickness greater than 1.00 mm was not significantly different between any of the screening categories and index melanomas (Table 5).

To further investigate possible differences between the different screening categories we performed a subanalysis with a cut-off point of 0.75 mm, as used in older versions of the American Joint Committee on Cancer staging system. The probability of being diagnosed with a tumor thickness greater than 0.75 mm was significantly larger for index melanomas than for regular-screen melanomas (OR 14.6, CI 4.4-48.2, $P < .001$) (Table 5), interval melanomas (OR 7.7, CI 2.0-29.3, $P = .0029$), and first-screen melanomas (OR 6.6, 95% CI 1.8-24.4, $P = .0047$). Noncompliance melanomas had a higher probability of being diagnosed with a Breslow thickness greater than 0.75 mm than regular-screen melanomas (OR 4.8, CI 1.8-13.2, $P = .0021$).

Table 5 Linear and logistic regression analyses

		Linear regression		Logistic regression					
				< 1.00 mm			< 0.75 mm		
Covariate	**MF**	**95% CI**	**p***	**OR**	**95% CI**	**p***	**OR***	**95% CI**	**p***
Screening category									
Index melanomas	1.0	-	-	1.0	-	-	1.0	-	-
First screen	0.63	(0.46 – 0.87)	0.0053	3.4	(0.7 – 16.0)	0.12	6.6	(1.8 – 24.4)	0.0047[$]
Regular screen	0.53	(0.40 – 0.70)	< 0.001[$]	5.7	(1.2 – 28.2)	0.031	14.6	(4.4 – 48.2)	< 0.001[$]
Interval	0.65	(0.44 – 0.96)	0.030	2.1	(0.4 – 11.6)	0.40	7.7	(2.0 – 29.3)	0.0028[$]
Noncompliance	0.69	(0.50 – 0.97)	0.031	2.1	(0.6 – 7.2)	0.27	3.0	(1.1 – 8.7)	0.041
Gender									
Male	1.0			1.0	-	-	1.0	-	-
Female	0.86	(0.73 – 1.01)	0.060	1.3	(0.6 – 2.8)	0.54	1.7	(1.0 – 3.1)	0.063
Age per 10 years	1.05	(1.00 – 1.11)	0.052	0.84	(0.60 – 1.18)	0.32	0.90	(0.75 - 1.10)	0.31
Date of diagnosis per 10 years	0.98	(0.88 – 1.09)	0.68	1.32	(0.79 – 2.23)	0.29	1.21	(0.85 – 1.72)	0.29
Melanoma rank									
Subsequent	1.0			1.0	-	-	1.0	-	-
First	0.93	(0.74 – 1.17)	0.56	1.7	(0.5 – 6.5)	0.43	0.8	(0.3 – 2.0)	0.56

MF, multiplication factor; OR, odds ratio; 95% CI, 95% confidence interval, *, significance level at $p < 0.005$ because of Bonferroni correction; [$], statistically significant

Discussion

We evaluated the effectiveness of our surveillance program for familial melanoma kindred with the p16-Leiden mutation in CDKN2A. The tumor thickness of 226 melanomas of relatives enrolled in the surveillance program was compared with 40 melanomas diagnosed in index patients.

Surveillance melanomas were significantly thinner than index melanomas, indicating that melanomas were detected in an earlier stage during the surveillance program. This is to some degree surprising, given the fact that only 53% of the surveillance melanomas were detected at a regular screen. Of surveillance melanomas, 7% were detected at first screens, 20% between regular screens, and 20% in patients who were not compliant with follow-up instructions at the time of diagnosis. Mode of ascertainment clearly influenced the effectiveness of surveillance. Only first-screen and regular-screen melanomas had a significantly lower Breslow thickness than index melanomas. There were no significant differences in the probability of being diagnosed with a tumor thickness greater than 1.00 mm among melanomas of any of the 4 surveillance melanoma categories and index melanomas. It is likely that this was caused by lack of statistical power, as significance was determined at a = .005 because of multiple testing. In a subanalysis with a cut-off point of 0.75 mm, all surveillance melanoma categories except for noncompliance melanomas were associated with a significantly smaller probability of being diagnosed with a tumor thickness greater than 0.75 mm compared with index melanomas.

The mean tumor thickness of regular-screen melanomas (0.58 mm) was comparable with those of screen-detected melanomas reported in other studies (0.52-0.56 mm).[8,15,16] Hansson et al[17] reported that 93% of 41 melanomas detected in the Swedish national preventive program for melanoma kindred had a tumor thickness less than 1.00 mm, which was comparable to the 89% in our study. These other studies did not specify, however, whether interval melanomas and melanomas in noncompliant patients were included.

First-screen melanomas had a higher mean tumor thickness than regular-screen melanomas, but the difference was not statistically significant. First-screen melanomas did have a significantly lower Breslow thickness than index melanomas, however. These findings are in accordance with earlier studies.[8,15,16]

As much as one fifth of melanomas were diagnosed in patients who were not compliant with follow-up instructions at the time of diagnosis. Moreover, almost half of patients were noncompliant at the time of diagnosis of their first melanoma. Noncompliance had a negative impact on melanoma detection as the probability of being diagnosed with a Breslow thickness greater than 0.75 mm was significantly greater for noncompliance melanomas compared with regular-screen melanomas (OR 4.8). Noncompliance has previously been reported to be a frequent problem in the follow-up of patients with a

primary melanoma,[18] and in the long-term (dermatoscopic) follow-up of patients with atypical pigmented lesions[19,20] as well.

A considerable proportion of melanomas (20%) was diagnosed between scheduled screens. The majority of these interval melanomas was detected by patients themselves after a median interval of 5 months since the last screen. The Breslow thickness of interval melanomas was comparable with that of regular-screen melanomas. This was probably facilitated by the fact that participants of the surveillance program were repeatedly educated about the characteristics of melanoma and instructed to perform regular skin self-examinations and promptly return to the clinic in case of symptomatic, changing, or new fast-growing lesions.

The large number of interval melanomas raises the question whether the standard screening interval of our surveillance program (12 months) is adequate. In this study the median screening interval of regular-screen melanomas was 5 months, because most tumors were diagnosed in patients who were under intensified surveillance because of a previous melanoma. Our results suggest that the majority of melanomas became detectable within 6 months after the preceding screen. Paradoxically we found that tumor thickness was not correlated with the length of the screening interval for intervals less than 24 months. This may have been a result of self-selection bias, however, as patients with a worrisome lesion are more likely to return to the clinic before the scheduled screen (interval melanomas) and are less likely to be noncompliant with follow-up instructions. It may also indicate that health education or increased awareness as a result of earlier melanomas enabled patients to determine themselves when to return. Alternatively this finding could be explained by the growth pattern of melanomas. It has been postulated that most melanomas (except for nodular melanomas) initially only exhibit radial expansion, without substantial vertical expansion.[21]

Based on this theory it could be argued that melanomas can be detectable for a long time, before a substantial increase in their Breslow thickness occurs.
Our study had a retrospective design and as a consequence classification of melanomas into different screening categories was dependent on completeness of data in patient charts. To limit the number of misclassifications we were very restrictive in categorizing doubtful cases and therefore 15% of surveillance melanomas were not further categorized.

Our results suggest a number of ways to improve the surveillance program. First, it is potentially very rewarding to increase efforts to improve patients' compliance with follow-up instructions. Second, early detection of clinically atypical and fast-growing melanomas may be promoted by instructing patients to report to the clinic in case of any changing or new (fast-growing) lesion. As a final point, we believe it is debatable whether our standard screening interval should be shortened from 12 to 6 months. On the one hand the majority of melanomas seemed to be detectable within 6 months after the preceding screen, so a shorter interval would advance melanoma detection. In addition, compliance with follow-up instructions may improve with shorter screening intervals.[19]

On the other hand it is unknown whether shortening of the screening interval would result in detection of tumors in a more favorable stage.[22] Moreover, adequate health education and promotion of skin self-examination may be a more cost-effective alternative than decreasing the screening interval. Further studies will be required to answer these questions.

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