Clinical characteristics and management of melanoma families

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Nederlandse Samenvatting

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Summary and Discussion

Introduction

Familial susceptibility is the strongest risk factor (in terms of effect size) for melanoma, and is associated with a very high life-time melanoma risk, especially in the context of the high-penetrance melanoma susceptibility genes CDKN2A, and CDK4. Early melanomas can be cured by an excision with proper resection margins, but prognosis is grim for advanced disease. For these reasons, surveillance of melanoma families has been widely advocated. The studies presented in this thesis focused on 3 related issues: 1. the clinical and histological characteristics of melanoma (patients) from melanoma families with a pathogenic germline mutation in CDKN2A; 2. the effectiveness and yield of surveillance of melanoma families with different CDKN2A mutation status and family characteristics, and 3. the impact of dermoscopy on the management of suspicious lesions in the context of melanoma surveillance. In this concluding chapter, our results will be discussed jointly and in the context of (recent) medical literature.

Part I: Clinical and histological characteristics of melanoma in CDKN2A mutated families.

Several studies have demonstrated that melanoma patients from melanoma families have a different clinical presentation than melanoma patients from the general population. In **chapter 2** we verified and substantiated these differences by comparing the clinical and histological characteristics of 182 patients with 429 CMM from families with a germline mutation in CDKN2A, to a large control population from the Leiden population based cancer registry (7512 patients with 7842 CMM).

We confirmed that melanoma patients from CDKN2A mutated families have a young age of onset and a very high risk of multiple primary melanomas (MPM). We found a mean age of diagnosis of 39.0 years, which is 15 years younger than the general population. Concerning MPM we reported for the first time a difference in concordance with regard to the body site of the first and second melanoma. Where a concordance was seen in MPM patients from the general population, concordance was absent in MPM patients from CDKN2A mutated families. These findings are all in accordance with the high melanoma susceptibility in CDKN2A mutated families, and emphasize the importance of regular skin examinations, starting at a young age and involving the whole skin.

In accordance with earlier studies we found that a relatively high proportion of superficial spreading (≈ 90%) and relatively few lentigo maligna type melanomas (2%) and nodular melanomas (8%) are diagnosed in these families. Contrary to other studies that reported an absence of acrolentiginous melanomas (ALM) in melanoma families, the proportion of ALM in our dataset was similar to the general population.[1,2]

We found that relatively few melanomas from CDKN2A mutated families were located in the head and neck region, but the difference was not statistically significant in a multivariate analysis. However, melanomas that were located in the head and neck region, were diagnosed at a relatively young age compared to melanomas localized elsewhere on the body, whereas, in the general population, melanomas in the head and neck region were diagnosed at a relatively older age compared to melanomas elsewhere on the body. This difference persisted if lentigo maligna melanomas were excluded from the analysis.

Both epidemiological and genetic data suggest that melanoma is a (clinical, histological, epidemiological and molecular) heterogeneous disease, and different pathways to melanoma genesis have been proposed.[3] As described in **chapter 2** our results with regards to the clinical and histological characteristics of melanoma (patients) from families with a germline mutation in CDKN2A suggest that their distribution along these different pathways differs from the general population. From the perspective of the divergent pathway model by Whiteman at all, CDKN2A mutated families tend to follow the nevus pathway, which is associated with a phenotype of multiple nevi and intermittent sun exposure.[4] This supports the notion that prevention of high intermittent sun exposure and sunburn is of great significance within this population. Future studies have to clarify to what extent the natural development and prognosis of melanomas in families with CDKN2A germline mutations differ from sporadic melanomas, as well as the potential implications for preventive and treatment strategies.

Part II: Management of melanoma families

Effectiveness of surveillance

Only few studies have investigated the effectiveness of surveillance of melanoma families.[5-8] We estimated the effect of surveillance on tumour Breslow thickness in: 1. a retrospective data-set of 226 melanomas from relatives of 37 CDKN2A mutated families that were under surveillance at the LUMC pigmented lesion clinic (**chapter 3**), and 2. Fifty-one prospectively detected melanomas in 37 patients among 450 members of 72 melanoma families that were registered at the Netherlands Foundation for the Detection of Hereditary Tumors (NFDHT) and under surveillance throughout the Netherlands (**chapter 4**).

In accordance with previous studies we found that melanomas detected in patients under surveillance (surveillance melanomas) had a significantly thinner Breslow thickness than index melanomas (i.e. the first melanoma of the first two family members diagnosed with melanomas). In both studies the median thickness of surveillance melanomas was 0.50 mm, which is comparable to earlier studies.[5,7,8] On average, index melanomas were approximately 1.5 times as thick as surveillance melanomas. The proportion of surveillance

melanomas with a Breslow thickness > 1.0 mm, was 11% and 22% in **chapter 3 and 4** respectively. In the LUMC PLC setting surveillance melanomas were estimated to be 3 times less likely to have a Breslow thickness > 1.0 mm compared to index melanomas. In **chapter 4** no statistically significant difference was found with respect to the proportion of melanomas with a Breslow thickness > 1.0 mm in the surveillance and index group, but significance may not have been reached due to lack of power (estimate of the odds ratio was 2.5, which is comparable to chapter 3). We did report in **chapter 4** that none of the 37 patients, who were diagnosed with their first melanoma during surveillance, had died after a median follow-up of 4.2 years since diagnosis.

Our findings support the notion from previous studies that surveillance results in earlier detection of melanomas and as such, is likely to improve survival of patients from melanoma families. Acknowledging the limitations of a direct comparison of the two datasets, our studies suggest that surveillance in the setting of a tertiary familial melanoma PLC clinic (chapter 4) was more effective in reducing the proportion of thick melanomas (11% of surveillance melanomas with Breslow thickness > 1.0 mm) than the setting of general dermatology departments (22% of surveillance melanomas with Breslow thickness > 1.0 mm, chapter 5). Effectiveness of surveillance of the highest risk populations may benefit from centralization to highly specialized clinics.

Surveillance interval

There is very little data on the optimal length of the interval between two skin examinations for melanoma. In **Chapter 3** we report that the majority of surveillance melanomas were detected within 6 months since the previous surveillance skin examination. The current 2012 Dutch melanoma guideline recommends patients should be seen at least annually.[9] In order to determine the appropriate surveillance interval it is important to know the natural history of melanoma. Several studies have attempted to approximate the melanoma growth rate based on patients recall of the moment the lesion was first noticed or started changing. Even though this approach has considerable theoretical as well as practical limitations, it was demonstrated that (this measurement of) growth rate is prognostic of survival, independent of Breslow thickness.[10-12] Consequently, three types of melanomas have been defined: slow growth melanoma (< 0.1 mm/month), intermediate growth (0.1 – 0.49 mm / month) and fast-growing melanoma (≥ 0.5 mm/month). It was reported that all three types represent approximately one-third of CMM.[13] This is in line with the fact that most melanomas in **chapter 3** were detected within 6 months since the previous skin examination, and suggest that, if one is to advance the detection of those melanomas that are most likely to have an unfavourable outcome, surveillance may need to be performed at least biannually.

However, we found no correlation between tumour thickness and the length of the surveillance interval for melanomas detected within 24 months since the previous skin examination. A possible explanation for this contra-intuitive finding may be that it is more

likely that patients will present intermediate and fast growing melanomas to their physician in between their regular surveillance appointments, as these melanomas are more noticeable than slow growing melanomas. In our study (**chapter 3**) 20% of surveillance melanomas were so-called interval tumors, i.e. detected in between regular surveillance visits. The majority of these were identified by patients themselves, in an early stage. Patients that participate in our surveillance program, are instructed to perform monthly skin self-examinations (SSE). The performance of SSE has been demonstrated to be associated with detection of melanomas in an early stage, and improved melanoma survival, and is therefore a valuable addition to surveillance by physicians.[14]

Compliance

In **chapter 3** we studied adherence to surveillance recommendations at the time of melanoma diagnosis. Noncompliance was defined as a diagnosis of melanoma later than 2 months after the recommended surveillance date. We found that 20% of surveillance melanomas were detected in noncompliant patients. The median surveillance interval at the time of diagnosis was 24 months. When we limited the analysis to individuals who were diagnosed with their first melanoma the proportion of noncompliant patients was 46%. These results are in accordance with two earlier studies, that reported that adherence to surveillance recommendations was approximately 50% among members of CDKN2A mutated families, and higher for individuals with a history of melanoma compared to individuals without a history of melanoma.[15,16]

We found that melanomas of patients that were noncompliant, were 5-times more likely to have a tumor thickness > 0.75 mm compared to melanomas of compliant patients. These findings are of great concern because they suggest that current health-education to high-risk patients is ineffective in communicating the importance of regular surveillance, particularly for individuals without a personal history of melanoma. Several interventions to improve compliance have been described; these include: 1. clear recommendations on surveillance, 2. psycho-education, 3. skill-based training (related to SSE), 4. time and space for individuals to explore and express their feelings and concerns about melanoma with a caring and attentive professional, 5. genetic testing, 6. shortening surveillance intervals.[15] A more detailed description of the management of health behavioral change processes is beyond the scope of this chapter.

Yield of surveillance

Members of melanoma families are invited to participate in surveillance based on the assessment of their melanoma risk. Few studies have evaluated the yield of surveillance in relation to patient and family characteristics on which risk assessment is based. In **chapters 4 and 5** we assessed the yield of surveillance in family members with different personal and family characteristics. Additional data on melanoma detection rates came from **chapters 2 and 8**.

History of melanoma

In accordance with an earlier study, we found that family members with a history of melanoma have a considerable higher melanoma detection rate then their first degree relatives (HR 3.9, **chapter 4**). [17] As melanoma patients are probable carriers of the genetic risk factor in their family, it was anticipated that this subpopulation is at a particularly high risk of developing (additional) melanomas. In **chapter 2** we performed a quantitative analysis of the risk to be diagnosed with a second melanoma in (single) melanoma patients from families with the p16-Leiden mutation, and found the 5 and 10 year cumulative melanoma incidence to be 23.4% and 34.8% respectively. This is considerably higher than the risk of second melanoma in the general population. We found that the increased risk was age dependent, with a HR of 15.8 for patients with melanoma diagnosed before the age of 40 years and 7.5 for patients diagnosed above age of 40 years respectively.

Both in **chapter 2 and 4** we computed the occurrence of only the first subsequent melanoma for each patient. As melanoma counts as high as 19 (**chapter 2**) have been reported, the overall melanoma detection rate in melanoma patients is expected to be considerable higher.

CDKN2A mutation status

In **chapter 4** we compared the melanoma detection rate in families with different CDKN2A mutation status. In a multivariate analysis we demonstrated that the melanoma risk in p16-Leiden mutated families was statistically significant higher than in CDKN2A wild-type families, independent of the families' number of melanoma patients and youngest age of melanoma diagnosis, with a HR of 3.6. Given the fact that CDKN2A (and CDK4) is the only known high risk melanoma susceptibility genes, it was expected that families with these mutations are at a particularly high melanoma risk. It should be noted however that CDKN2A/CDK4 wild-type families, are very heterogenic. As discussed in the introduction, melanoma risk in the majority of these families is probably attributable to (a combination of) low (e.g. MC1R) and moderate (e.g. MITF) risk modifier genes, and presumably to some extent environmental, as well as behavioral aspects.[18,19] It cannot be excluded however that rare high penetrance genes play a role in a small proportion of these families. It is likely that such families have similar characteristics as CDKN2A mutated families, i.e. larger numbers of melanoma patients, young age of diagnosis and patients with multiple melanomas. In **chapter 4** we found a borderline non-significant difference in melanoma detection rate between families with 2 melanoma patients and families with 3 or more melanoma patients (HR 2.2, 95% CI: 0.9 – 5.0), which is in accordance with the notion that number of affected relatives is positively correlated with melanoma risk.

Second degree relatives

In the Netherlands, historically all first and second degree relatives from melanoma families have been recommended to undergo regular skin examinations. The subject of

surveillance of second degree relatives has received hardly any attention in the medical literature and foreign melanoma guidelines. In **chapter 5** we performed a study to investigate the yield of surveillance of second degree relatives from P16-Leiden families. We found a melanoma incidence rate of 2.2 / 1000 person years if all available data on second degree relatives was included in the analysis. In a sub-analysis of second degree relatives under surveillance we found a melanoma detection rate of 8.5 / 1000 person years. Differences in these outcome are most likely related to selection bias, i.e. persons at high risk were more likely to participate in surveillance, difference in age distribution and possible under-reporting and under-detection in unscreened individuals. Standardized morbidity ratio for second degree relatives compared to the general population was 12.9.

Risk stratification

As was discussed in the introduction, the surveillance recommendations in the 2005 melanoma guidelines were independent of CDKN2A (and CDK4) mutation status and family characteristics. Based on **Chapter 2, 4, 5 (and 8)** figure 1 proposes a risk stratification diagram for members of melanoma families.

Our studies were restricted to families with the p16-Leiden mutation in CDKN2A. Although melanoma risk may vary to some extent, previous studies suggest that similar estimations probably apply to other pathogenic mutations in CDKN2A, as well as CDK4 mutations.[20-22]

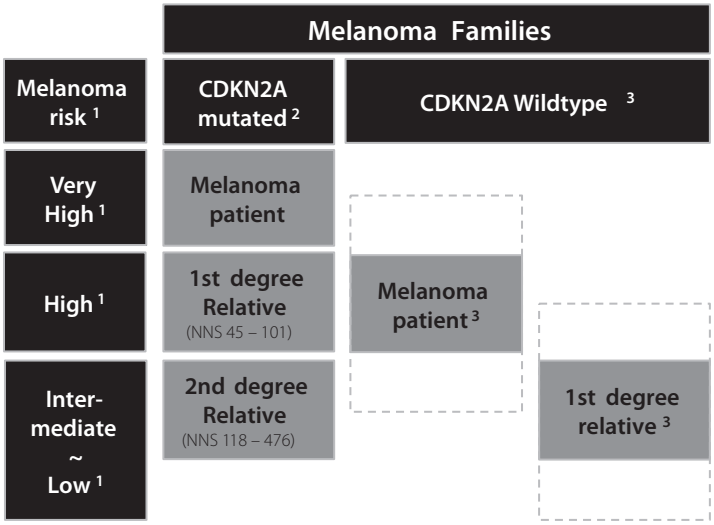
It is important to stress that the proposed risk categorization has its limitations. Families with CDKN2A (and CDK4) wild-type or unknown mutation status are very heterogeneous. The majority of these families will have a considerable lower melanoma risk than CDKN2A mutated families, but in some families yet unknown high risk susceptibility genes may be present. As described above, family characteristics can provide additional information that may justify an upgrade to a higher risk category (this issue will be addressed in more detail below, where its practical implications are discussed).

The NNS in figure 1 are based on **chapter 5** in which melanoma incidence was calculated in two ways. The lower NNS represent actual NNS in the LUMC PLC surveillance program. The higher NNS were based on calculations in which patients that were not under surveillance in this institution, were included as well. We expect actual NNS to be nearer to the lower margin.

Management recommendations

Based on this thesis a number of recommendations can be given concerning the management of melanoma families. Our data from **chapter 3 and 4** is in accordance with previous data that surveillance results in early diagnosis and a reduction in the proportion of melanomas with a Breslow thickness > 1mm. This finding supports the notion that surveillance should be recommended to family members at a significant risk of melanoma.

Figure 1 Proposed risk categories based on melanoma detection rates during surveillance of melanoma patients, first- and second degree relatives from mutated and wildtype CDKN2A families



NNS = Numbers Needed to Screen to detect one melanoma (numbers based on chapter 5)

[1] Risk categories are approximations based on hazard ratio's calculated in chapter 4 and 5: HR (melanoma patients versus first degree relatives) ≈ 4, HR (CDKN2A mutated versus CDKN2A wild-type families) ≈ 3.5, and HR (CDKN2A mutated first degree relatives versus second degree relatives) ≈ 2.5 – 5.0. NNS give an indication of the quantitative risk.

[2] Our studies were only conducted in families with the P16-Leiden mutation, the predominant CDKN2A mutation in the Netherlands.

[3] CDKN2A/CDK4 wild-type families are heterogeneous; dotted lines are used to emphasize the variance in melanoma risk. Based on chapter 4, risk of melanoma (recurrence) in families with ≥ 3 melanoma patients is expected to be higher than risk in families with only 2 affected relatives.

The data from **chapter 4** indicate that families with pathogenic mutations in CDKN2A have a considerable higher melanoma risk than CDKN2A wild-type families. Melanoma patients from these families have a very high risk of multiple melanoma, the majority of which (≈75%) were diagnosed in the first 10 years after diagnosis. Intensified surveillance of these relatives, at least during the first 10 to 15 years after melanoma diagnosis, is therefore recommendable. As we found (**chapter 2**) that the majority of melanomas were detectable within 6 months since the previous skin examination, at least biannual surveillance of this highest risk population should be considered. Given the fact that we did not find a correlation between Breslow thickness and surveillance interval, a switch from annual (2005 melanoma guideline) to biannual surveillance in this risk population, may be introduced in the context of a randomized prospective study. We estimated (**chapter 5**)

that the melanoma risk of second degree relatives from CDKN2A mutated families is considerable higher than the risk of the general population (Standerdized Morbidity Ratio ≈ 13). Based on results from **chapter 4 and 5**, we estimate that melanoma risk of second degree relatives from CDKN2A mutated families is comparable to melanoma risk of first degree relatives from CDKN2A wild-type families. These findings support the continuation of offering surveillance to second degree relatives from these very high melanoma risk families.

Families with an unknown CDKN2A mutation status took an intermediate melanoma risk position, which is likely attributable to a proportion of these families having a mutation in CDKN2A or CDK4. Genetic testing of these families is desirable in order to estimate melanoma risks, and facilitation of adequate surveillance recommendations. Because CDKN2A wild-type families are heterogeneous, melanoma risk estimation in these families should be accompanied by a critical appraisal of family characteristics. **Chapter 4** gives support to the notion that the number of melanoma patients in a family is positively correlated with melanoma risk in these families. With regards to the classification in figure 1, it should be considered to "upgrade" CDKN2A wild-type families with many affected relatives to a higher risk category. Melanoma risk of first degree relatives from families with only two affected relatives, and with a single melanoma, diagnosed at an older age (e.g. > 50 years) is expected to be relatively low, but still higher than the general population. The yield of surveillance of second degree relatives from (the majority of) CDKN2A wild-type families is expected to be very small, and cessation of the offering of surveillance to this population should be considered.

In **chapter 3** we reported that interval melanomas detected by patients were diagnosed after a median surveillance interval of 5 months and had a favorable tumor thickness. These findings supports the growing evidence that SSE is a key factor in effective melanoma surveillance. Instruction to perform monthly SSE should therefore be given to all patients. Formalization of these instructions may enhance patients adherence to SSE recommendations.

We found that noncompliance with the surveillance program was considerable, being close to 50% at the time of melanoma diagnosis for patients without a history of melanoma. Noncompliance was associated with thicker melanomas and is therefore a considerable threat to the effectiveness of surveillance. Compliance should therefore be one of the targets of surveillance and strategies to improve compliance should be developed.

In table 1, age at diagnosis (in percentiles) of the first melanoma in members of melanoma families with different CDKN2A mutation status as were found in **chapter 2, 4 and 5** are presented.

Table 1 shows that approximately 80% of melanomas were diagnosed before age 50 years, and 90% of melanomas were diagnosed before age 60 years. These findings suggest that

Table 1 Age of diagnosis of first melanoma in members of melanoma families (based on **studies 2, 4 and 5**)

Percentiles[1]	**Age of diagnosis (first melanoma)**				
	Chapter 2[2]	**Chapter 5**[2]	**Chapter 4**		
	P16-Leiden (n = 182)	P16-Leiden (n = 56)[3]	P16-Leiden (n = 44)	Wild-type (n = 57)	Unknown (n = 102)
Minimum	11.7	15.6	16.5	16.4	19.7
10	21,7	20,5	21,6	24,3	25,7
20	27,2	23,8	26,0	29,9	29,8
30	31,7	27,6	28,5	35,9	33,7
40	35,5	35,0	32,6	38,6	38,4
50	38,6	37,8	38,1	42,5	43,3
60	41,1	40,0	41,0	46,7	46,5
70	45,1	43,4	45,1	49,1	49,6
80	50,5	51,5	49,2	54,4	54,3
90	57,5	60,4	56,4	61,0	59,7
Maximum	72.3	72.3	69.3	78.2	75.6

[1] Percentiles represent the proportion of melanoma patients that were diagnosed with melanoma at the given age in the right columns; e.g. in Chapter 2, 40% of melanoma patients were diagnosed with their melanoma at age ≤ 35.5 years.

[2] All cases in chapter 5 are included in chapter 2 as well.

[3] These are all incident cases.

upper age limits on (intensified) surveillance, especially in patients with an intermediate risk, may improve the cost-effectiveness of surveillance, without considerable loss of effectiveness.

Over-diagnosis

Over-diagnosis of melanomas has been a recurring point of discussion. It became an issue as a result of the observation that, whereas melanoma incidence has been increasing considerably over the last decades, mortality has increased relatively little. Some have argued that the increase of melanoma incidence is largely attributable to indolent melanocytic tumors, that are diagnosed as a result of increasing attention and screening for melanoma.

In **chapter 6** we report an observation related to over-diagnosis/misclassification in 10 CDKN2A wild-type members of melanoma families with the p16-Leiden mutation. In this group 73% (7 in situ and one invasive) of 11 melanocytic lesions that were initially classified as melanomas, were reclassified as benign lesions after histological revision. This implied that 7 out of 10 of these CDKN2A wild-type family members were unnecessarily burdened with a diagnosis of melanoma.

This observation illustrates that if populations with a low *a priori* melanoma risk participate in surveillance, the positive predictive value of a histological diagnosis of melanoma decreases. In order to limit misclassification of benign lesions as melanoma (false positives), it is important to make an adequate selection of risk populations for surveillance. In addition, this finding challenges the reported increased melanoma incidence among mutation negative relatives, which has caused doubt on the value of genetic testing for mutations in CDKN2A.[23]

Table 2 Recommendations

Recommendations for the development of surveillance strategies for melanoma families *
1. Intensified surveillance of melanoma patients from (CDKN2A mutated) melanoma families, at least up to 10 years after melanoma diagnosis is recommended. *(Chapter 2, 4)*
2. Genetic testing helps identifying those families and individuals at highest risk of melanoma. Melanoma family members should therefore be encouraged to be tested (i.e. melanoma patients from families with unknown CDKN2A mutation status and first degree relatives in case of families with a pathogenic CDKN2A mutation). *(Chapter 2, 4, 5 and 6)*
3. Surveillance should start at an early age (preferably before age 15 years). Discontinuation of surveillance above age 60 years may improve the cost-effectiveness of surveillance, without considerable loss of effectiveness, especially in case of family members without a history of melanoma from intermediate to low risk families. *(Chapter 2,4 and 5)*
4. Given the fact that most melanomas in our studies were detected within 6 months since the previous skin-examination, biannual skin-examinations should be considered, especially for those at highest risk of melanoma (i.e. melanoma patients and proven CDKN2A mutation carriers). *(Chapter 3)*
5. The favourable Breslow thickness of interval melanomas, underlines the importance of health education for melanoma family members concerning the signs of melanoma and skin self-examination. *(Chapter 3)*
6. Noncompliance has a considerable impact on the effectiveness of surveillance. Strategies need to be developed to improve patients' compliance. *(Chapter 3)*
7. The probability of melanoma detection in CDKN2A mutated families is higher than in (most) CDKN2A wildtype families. CDKN2A mutated families therefore require more stringent surveillance strategies. *(chapter 4)*
8. Surveillance of second degree relatives should be considered for CDKN2A mutated families, but the yield of surveillance of second degree relatives from CDKN2A/CDK4 wildtype families appears to be very limited, especially in case of few affected relatives. *(chapter 4 and 5)*
9. The use of dermoscopy in the surveillance of melanoma families reduces the number of unnecessary excisions. Dermoscopy is therefore likely to reduce the burden of surveillance, improve cost-effectiveness and decrease the risk of overdiagnosis. The use of dermoscopy is therefore recommended. *(chapter 6 and 7)*

* Except for recommendation 6, all recommendations in this table are (fully or in part) reflected in the 'new' 2012 Dutch melanoma guideline.

Part III: Impact of dermoscopy on clinical practice

Several meta-analysis have concluded that dermoscopy improves the diagnostic accuracy of the clinical diagnosis of melanoma with the unaided eye.[24-26] We investigated how this is reflected in the impact of dermoscopy on management in two different clinical settings:

1. The specialized pigmented lesion clinic of the LUMC in which two dermoscopy experts identified and evaluated in consensus 49 suspicious lesions including 2 melanomas, in 132 consecutive FAMMM patients with a history of melanoma and/or a pathogenic mutation in CDKN2A (**chapter 8**).
2. The general dermatology clinics of 17 dermatologists, that evaluated a total of 209 suspicious pigmented lesions, including 14 melanomas (**chapter 7**).

The impact of dermoscopy on clinical diagnosis

In neither of the clinical settings the addition of dermoscopy to naked eye evaluation (NEE) resulted in a statistically significant improvement of sensitivity or specificity of the clinical diagnosis of melanoma with the unaided eye. However, we did find an (not statistically significant) increase in sensitivity from 0.79 to 0.86 and in specificity from 0.96 to 0.98 for dermatologists working in general dermatology clinics (**chapter 7**), which is very similar to a meta-analysis of dermoscopy studies performed in a clinical setting, reporting that dermoscopy improves sensitivity rather than specificity.[26]

In the expert dermoscopists / familial melanoma surveillance setting, dermoscopy did not result in an improvement of sensitivity (1.0) or specificity (0.89) (**chapter 8**). We believe that this finding is related to the fact that only 49 suspicious lesions with only 2 melanomas could be included in our study, as suspicious lesions necessitating the use of dermoscopy were detected in only 37% of the 132 patients that were recruited. This could be attributed to the highly variable nevus phenotype of familial melanoma patients (gene carriers can have very few (atypical) nevi), and the fact that patients were under regular surveillance, implicating that (suspicious) lesions may have already been removed in the past.

The impact of dermoscopy on clinical practice

Dermoscopy was associated with a considerable reduction in the number of lesions that were excised, both in the expert dermoscopists / familial melanoma surveillance setting (42% reduction, statistically significant) and general dermatology clinics setting (9%, not statistically significant) **(chapter 7 & 8)**. Our findings on the impact of dermoscopy on management in the expert dermoscopists setting are very similar to the only randomized controlled trial in a (dermoscopy expert) dermatologists setting that has ever been conducted, reporting a 38% reduction in excisions.[27] The reduction of excisions was considerably lower in the general dermatologists setting. Some confirmation of this findings comes from two recent studies. First, a study investigating the impact of

dermoscopy on management of pigmented lesions by general dermatologists based on photographic images, found dermoscopy actually resulted in a slight increase in the intention to excise lesions.[28] An important limitation of this study however was the fact that it only included excised lesions. Second, an international study reported that between 1998 and 2007 the number needed to excise to detect one melanoma almost halved in specialised clinical settings, but remained unchanged in non-specialised clinical settings (including general dermatologists and general practitioners).[29] The authors of this study suggested that the difference is most likely related to differences in the uptake of dermoscopy.[25] Our results suggest that, in addition to differences in the uptake of dermoscopy, dermoscopy may be less effective in reducing the numbers needed to excise in the hands of non-expert dermoscopists and/or in the patient population setting of non-specialised clinics.

In summery chapter 7 and 8 suggest that the main effect of dermoscopy in the dermoscopy expert / familial melanoma surveillance setting, was a significant improvement of specificity (from a management, but not from a clinical diagnosis standpoint), and a decreased burden of unnecessary excision. Dermoscopy is therefore likely to improve the cost effectiveness of familial melanoma surveillance, and in addition may decrease the risk of 'overdiagnosis'. The impact of dermoscopy in the general dermatology setting was considerably smaller, and no statistically significant improvement of sensitivity or specificity were noticed. Possible explanations for the differences between the two clinical settings may be related to the degree of dermoscopy expertise as well as differences in the population under study. Differences in lesion ascertainment between the two clinical settings may have resulted in an underestimation of the reduction of the number of excisions in the general dermatology setting.

An important issue that has been suggested before, but has now been clearly demonstrated in our studies, is the fact that prior studies that evaluated dermoscopy from a clinical diagnosis perspective, give an inaccurate picture of its impact in clinical practice. The just mentioned meta-analysis by Vestergaard et al. concluded that dermoscopy rather improves sensitivity than specificity and the promotion of dermoscopy has benefitted considerably from the proclamation that it advances melanoma diagnosis.[26] Our studies confirm an earlier randomized controlled trial, that dermoscopy primarily results in the reduction of excisions. Our studies were considerably limited in their ability to detect an improvement of sensitivity due to the small number of melanomas. Still, it appears logical that dermoscopy predominantly reduces the proportion of excisions (i.e. improve specificity rather/more than sensitivity), as the majority of clinicians use dermoscopy predominantly for the evaluation of lesions that have been judged to be suspicious by naked eye examination. Dermoscopy can be applied in several ways however (table 3); first of all dermoscopic evaluation can be performed only once or sequentially in case of

dermoscopic follow-up; secondly lesion selection for dermoscopic evaluation can be limited to lesions that appear suspicious by NEE evaluation, or include lesions that are regarded inconspicuous by NEE. The impact of dermoscopy on sensitivity and specificity are expected to be highly dependent on the way in which it is used. This aspect has had limited attention in the literature so far.

Table 3 Different applications of dermoscopy

		TIME-FRAME	
		SINGLE EVALUATION	FOLLOW-UP
LESION APPRAISAL BY NAKED-EYE EVALUATION	SUSPICIOUS	**Single evaluation of suspicious lesions***	Follow-up of suspicious lesions
	INCONSPICUOUS	Single evaluation of inconspicuous lesions	Follow-up of inconspicuous lesions

* method of dermoscopy in chapter 8 & 9, as well as the majority of studies evaluating dermoscopy.

If the primary effect of dermoscopy in clinical practice is a reduction of the number of excisions, this implies that, as an effect, sensitivity could be compromised. This danger is illustrated in **chapter 7** by a histologically proven melanoma that was diagnosed as melanoma prior to dermoscopy, but as a benign lesion after dermoscopy. In this case the change in clinical diagnosis had no impact on the decision to excise this particular lesion, but it clearly illustrates the possible drawback of dermoscopy. In accordance with a few other studies, we found (**chapter 8**) that the increase of specificity does not result in a loss of sensitivity in case of dermoscopy experts.[27,30,31] This cannot be stated with certainty for the non-expert dermatologists because we had no follow-up data with respect to lesions that were not excised as a result of dermoscopy. Data on the safety of dermoscopy performed by non-expert dermoscopists is limited.[25,32] This issue, as well as the issue concerning the amount of training that is necessary to develop optimal dermoscopy skills (reflected in its impact on lesion management), may be a subject of future studies.

Summary and concluding remarks

In the first part of this thesis it was shown that clinical and histological characteristics of melanoma (patients) from CDKN2A mutated families differ from the general population in several ways. As evidence on the existence of distinct melanoma subtypes is increasing, our data suggest that there may be overrepresentation of certain subtype(s) in these families, which may impact future preventive and treatment strategies.

In the second part of this thesis we confirmed previous reports that surveillance of melanoma families results in early diagnosis. We showed that noncompliance is a major concern, especially for family members without a history of melanoma. The favourable tumour stage of self-detected (interval) melanomas and the observation that the majority of melanomas were detected within 6 months since the previous skin-examination stress the importance of monthly self-examination as a key element in successful melanoma surveillance. Based on our data we propose a risk classification system for members of melanoma families, that supports the development of a more tailored and cost-effective surveillance program. Our findings support the surveillance of second degree relatives from CDKN2A mutated families. Further studies are needed in order to optimize current surveillance strategies, including optimal surveillance intervals and to facilitate the assessment of melanoma risk in CDKN2A wild-type families.

In the third part of this thesis we demonstrated that dermoscopy in the context of an expert / high melanoma risk PLC setting, resulted in a considerable reduction of unnecessary excisions. Dermoscopy is therefore likely to reduce the burden of surveillance, improve cost-effectiveness and decreases the risk of overdiagnosis. The impact of dermoscopy on management in the expert PLC setting was considerably higher than in the general dermatology setting. These findings confirm and clarify the value of dermoscopy for the PLC setting and suggest that more studies are needed to clarify and optimize the role of dermoscopy in a non-expert dermoscopist, general dermatology settings.

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