Predictivity of macroscopic changes observed by the patient for melanoma diagnosis

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Running head *(70 characters, max 70 characters)*

New or changing melanocytic lesions observed by older patients predict melanomas

Bulleted statement

What's already known about this topic? *(61 words, max 70 words)*

Half of melanomas are first detected by the patients who notice, according to several studies, changing lesion or pruritus; these observations are documented only for melanomas, but not for suspicious benign lesions. In a single prospective study observing lesions through total body pictures, new or changed lesions were more often melanomas in patients older than 50 years than in younger patients.

What does this study add? *(65 words, max 70 words)*

This study prospectively collected symptoms and signs described by consecutive patients undergoing the excision of lesions clinically diagnosed as melanocytic and considered as suspicious. Dynamic changes observed by the patients were significant for melanoma *versus* non-melanoma diagnosis in all the patients. Dynamic changes and *de novo* appearance were strong predictive values for melanoma *versus* non-melanoma diagnosis in patients older than 41.5 and 44.5 years, respectively.

Abstract *(246 words, max 250 words)*

Background

Around half of melanomas are first detected by the patients but their mean thickness is also higher than when melanomas are diagnosed by physicians. Symptoms and signs described by the patients are a changing lesion and pruritus. The appearance of a new lesion is rarely studied in the literature. These observations are documented for melanomas but it is unknown whether they are common in suspicious benign naevus. A single prospective study examined new and changed melanocytic lesions through total body pictures. The authors concluded that new or changed lesions are more often melanomas in patients older than 50 years than in younger patients.

Objectives

To analyse anamnestic predictors for melanoma *versus* no-melanoma diagnosis according to the age of the patients.

Methods

This study collected prospectively symptoms and signs described by consecutive patients undergoing the excision of lesions clinically diagnosed as melanocytic and considered as suspicious by 46 Belgian dermatologists. The predictive value of the anamnestic predictors for melanoma were analyzed taking into account the age of the patients.

Results

Among 1865 lesions, dynamic changes are significant for melanoma *versus* non-melanoma diagnosis in all the patients. Dynamic changes and *de novo* appearance occurred to be strong predictive values for melanoma diagnosis in patients older than 41.5 and 44.5 years, respectively. Pruritus was not significant for melanoma diagnosis.

Conclusions

When mid-aged or older patients observe melanocytic lesions as recently changed or newly appeared, these lesions should be considered as more suspicious than when observed by young patients.

Manuscript *(Word Count 3000)*

Introduction

Melanoma incidence has been increasing for four decades and this trend is predicted to continue.[1] Likely due to earlier detection, mortality has fortunately stabilized or much less increased than the incidence,[2] but melanoma remains a considerable burden in Caucasian populations.[3] Despite encouraging results with new targeted therapies and immunotherapies developed during the last years, overall survival is still poor for patients with advanced melanomas. Prevention and early detection are therefore essential to improve survival.

Besides physicians, patients have an important role to play as about half of the melanomas are first detected by the patient,[4-9] but percentages vary from 18%[10] to 75%[11] according to the studies. This proportion is higher in females,[4,7-9,12] in patients performing regular skin self-examination[5,7,12,13] as well as in married males, these populations detecting also thinner melanomas, themselves or thanks to their spouses.[12,14] Nevertheless, physician detection is associated with thinner melanomas.[4,5,8,15,] Some studies show that delay in melanoma diagnosis is mostly patient related.[6,16] These observations are explained by inappropriate symptom appraisal by the patients and, in at least some countries, poor information on the disease.[6,17]

A review of studies about skin self-examination concluded that its sensitivity is low (25 to 93%) while its specificity is quite high (83 to 97%).[18] This result is consistent with a systematic review of interventions to promote cancer early detection indicating that melanoma was one of the cancers for which educational campaigns can reduce stage at presentation.[19]

Symptoms and signs observed by the patients with melanomas are lesion's increase in size and/or change in colour and, less frequently, pruritus.[5,8-11,15-17,20] The appearance of a new lesion has seldom been studied . Importantly, most of the aforementioned studies were retrospective and all of them included only melanomas. As a result, it is unknown whether these symptoms and signs are melanoma specific or also common among non-melanoma (NM) lesions.

In the present prospective study conducted in the general population, both melanoma and suspected excised naevi were included in order to collect symptoms (pruritus, anxiety) and signs (*de novo* appearance, dynamic changes and bleeding) noticed by the patient. To the best of our knowledge, this is the first study aiming to analyse anamnestic predictors for melanoma *versus* NM diagnosis.

In a study of patients at high-risk for melanoma, Banky et al.[21] showed that new or changed lesions were more likely to be a melanoma if the patient was older than 50 years. New or changed lesions were diagnosed by the physician through comparison with baseline total body photographs, not by the patient.

The secondary aim of this study was to determine how age influences predictive value of dynamic changes and *de novo* appearance observed by the patient, for melanoma diagnosis.

Materials and methods

The present study was conducted from October 1 October 2009 to 30 September 2010 at the same time as the DEPIMELA study.[22] The study was approved on 28 November 2008 by the Ethical Committee of the Université Catholique de Louvain, Belgium (number B40320085012). Forty-six volunteer French-speaking Belgian dermatologists participated in the study. Among them, 36 worked in hospitals and/or private practices and 10 of them in our academic dermatology department (Cliniques Universitaires Saint-Luc, Brussels, Belgium), of which two (I.T. and P.R.) were involved in the pigmented lesion clinic (PLC).

All the consecutive excised lesions diagnosed as suspicious melanocytic lesions by the participating dermatologists during the inclusion one-year period and for which excision was decided, were included. Those clearly excised for cosmetic or comfort reasons were excluded.

Before excision, the dermatologist filled in a questionnaire to collect the following data: age, gender, changes and symptoms observed by the patient. Patients were questioned about observing dynamic changes (change in colour, size and/or form), *de novo* appearance, and bleeding. New or changed lesions were considered as such according to the patient's observation and not through comparison with photographs which were sometimes available, particularly in the PLC. In addition, patients were interviewed about the presence or absence of two symptoms: pruritus and anxiety (caused by the lesion they consider suspicious).

Histopathological diagnoses were classified into melanoma and NM, the latter including all benign melanocytic lesions and all benign and malignant non-melanocytic lesions. Lesions were examined or reviewed by three independent dermatopathologists.

Lesions excised by the participating dermatologists during the inclusion period, not considered as suspicious melanocytic lesions but for which the pathology concluded in melanoma, were included *a posteriori* and the symptoms and signs observed by the patient were collected retrospectively.

The follow-up took one year. During this period, all participating dermatologists were asked to make a systematic report of lesions examined but left unexcised during the

study period and finally diagnosed as melanoma. The same data were collected *a posteriori* for these lesions, which were also included.

Statistical analysis

Univariate and multivariate logistic regressions were conducted to determine predictive variable for the diagnosis of melanoma *versus* non-melanoma. The studied variables were: gender, age, dynamic changes (change in colour, size and/or form), *de novo* appearance, bleeding, pruritus and anxiety. In addition, three age groups were defined (≤30, 30-50 and ≥50 years) in order to study in which age-group dynamic changes and de novo appearance were more predictive for melanoma diagnosis. P-values were interpreted at the significance alpha level of 5%.

Analyses were completed with classification trees (CT). CT can offer additional insights to those obtained from a logistic regression. Firstly, CT allows handling a large number of explanatory variables as it works with interactions in a flexible way, resulting in a clear division of the original population in high and low risk groups. A CT starts with a parent node, containing the complete sample and then, through successive yes/no questions, creates descendants nodes, each time finding the "best" variable to divide the node into two child nodes, i.e. seeking to obtain the most homogeneous child nodes with respect to the outcome variable (melanoma diagnosis in this study). The splitting is carried on along the child nodes until a terminal node is reached.[23]

To realize the two CT, the parameters age and dynamic changes or *de novo* appearance were introduced in the two models respectively. In addition, the usual methodology for CT was modified and the splitting was forced to start with the parameter dynamic changes or *de novo* appearance. In order to simplify the CT, "no" and "unknown" dynamic changes or *de novo* appearance were pooled. This allowed bringing out the positive information of dynamic changes or *de novo* appearance given by the patient. So, in this study, CT was used to explore the influence of age on predictive value of dynamic changes and *de novo* appearance for melanoma diagnosis. The minimum cost tree with equal costs for false-negatives and false-positives was selected.

By using results obtained through CT in association to those of the logistic regressions, the strengths and advantages of the two methodologies were combined to emphasize

influence of age on predictive value of dynamic changes and *de novo* appearance for melanoma diagnosis. The statistical analyses were performed using Stata 12 and Salford Predictive Model Builder version 6.6 (Salford Systems, San Diego, California).

Results

A total of 1865 lesions, including 231 melanomas, were excised and included in the study. Fifteen melanomas were included *a posteriori* because being examined during the study period, left unexcised and diagnosed during the follow-up (six lesions) or because they were excised during the inclusion period without having been considered as suspicious melanocytic lesions (nine lesions). The 231 melanomas were removed from 1713 patients, of which 37.4% males and 62.6% females. The mean age at excision was 40.6 years (range 3-96). Two hundred and thirteen lesions were excised in the PLC, and among them 62 were melanomas.

Patients had noticed dynamic changes in 639 lesions, of which 105 (16.4%) were melanomas. The appearance of a new lesion was observed by the patients for 230 lesions, of which 41 (17.8%) were melanomas. For 572 lesions, patients had not seen dynamic changes, but 57 (10%) were melanomas. According to the patients, 940 lesions had appeared on a pre-existing lesion; among them 106 (11.3%) were melanomas. The information of dynamic change or not, and *de novo* lesion *versus* lesion arising on a pre-existing naevus was unknown for 654 and 695 lesions respectively (of which 69 and 84 melanomas respectively). For 45.4% of the 231 melanomas diagnosed in this study, dynamic changes had been observed by the patient. Only 17.7% of these same 231 melanomas had appeared *de novo* according to the patients.

The univariate analysis revealed that an excised lesion was more likely to be a melanoma if dynamic changes were observed by the patient or if it appeared *de novo* according to the patient. Elderly compared to young patients were also more likely to develop melanomas (Table 1).

Similarly, the multivariate analysis demonstrated that an excised lesion was significantly more suspicious to be melanoma if observed in an older patient or if dynamic changes were reported by the patient. Conversely, *de novo* appearance according to the patient was not a significant predictor for melanoma diagnosis in the multivariate analysis whereas patient's anxiety appeared as a significant negative predictor (OR < 1, Table 1). Pruritus and bleeding were not significant.

In addition, we searched to determine how exactly age influences predictive value of dynamic changes for melanoma diagnosis (Table 2). In case of dynamic changes

observed by the patient in a suspicious melanocytic lesion, melanoma diagnosis was three times more likely if the patient was older than 50 years ($p<0.05$). In the two other age groups (≤ 30 and 30-50 years), melanoma probability was also higher when dynamic changes were described compared to not, but the differences were not statistically significant.

CT permitted to express similar results in a diagram, using age and dynamic changes observed by the patient as predictor variables for melanoma diagnosis (Figure 1). The study population was first partitioned between lesions with and without dynamic changes observed by the patients. This second group was further split according to age. The CT fixed the cut-off at 41.5 years. In the subgroup older than 41.5 years, melanoma proportion was the highest (27.4 % compared to 8.4 % in the subgroup ≤ 41.5 years), confirming the likelihood of melanoma in presence of changing melanocytic lesions in older patients was higher (+ 67.1%).

Similarly, we attempted to determine whether age influences predictive value of *de novo* appearance for melanoma diagnosis (Table 3). When the suspicious melanocytic lesion had appeared *de novo* in a patient older than 50 years, melanoma diagnosis was nearly three times more likely ($p=0.001$). Within the two other age groups (≤ 30 and 30-50 years), results were not significant.

Figure 2 shows the CT established using age and *de novo* appearance as predictor variables for melanoma diagnosis. Similarly to the first CT, the population study was first split between lesions observed appearing *de novo* and lesions not observed appearing *de novo*. Then, the partition was repeated in the subgroup of *de novo* lesions using age as splitting variable. In this case, the cut-off was fixed by the CT at 44.5 years. This further partition revealed that patient's age higher than 44.5 years was an important determinant of melanoma diagnosis in case of *de novo* melanocytic lesions (32.0 % melanomas compared to 7.5% in the subgroup ≤ 44.5 years).

Discussion

This prospective study collects and analyzes the symptoms (pruritus, anxiety) and signs (*de novo* appearance, dynamic changes and bleeding) observed by the patients operated for melanoma suspicion by 46 Belgian volunteer dermatologists. Consecutive lesions excised for melanoma suspicion in the general population were included. *De novo* appearance and dynamic changes appeared to be the best predictive value for melanoma diagnosis *versus* NM but strongly depending on the age of the patient. Pruritus and bleeding were not significant. Anxiety was a negative predictive value for melanoma diagnosis.

Less than a half (45.5%) of the patients with melanoma had observed dynamic changes and 17.7% had seen the appearance of a new lesion. This was consistent with the literature finding that around half of the melanomas are detected by the patient.[4-9]

Weatherhead et al[24] published a prospective study interviewing 377 melanoma patients. Based on this anamnesis, 34% melanomas appeared *de novo*, 42% arose on a pre-existing naevus, the history of the remaining melanomas could not be assessed. Patients with *de novo* melanomas were significantly older than patients with melanomas arising on a pre-existing naevus and their melanoma was significantly thicker.

In the present and Weatherhead's studies, much less than half (17.7% and 34%) the patients had observed the appearance of a new lesion although only 20 to 30% melanomas were histologically naevus-associated.[25-27] It could be postulated that, when a patient sees a naevus changing, the melanoma has arose on a pre-existing naevus and that, when a patient observes a new lesion appearing, the melanoma is *de novo.* Nevertheless, this assumption has been demonstrated to be false in almost half of 18 (8/18) melanomas.[21] This is, at least partially, explained by the so-called "slow growing melanomas"[28] where a *de novo* melanoma has been present on the skin of the patient for several years and is therefore considered as a changing lesion. A second explanation is the probability that some invasive melanomas destroy or mask the pre-existing naevus.

The negative predictive value of anxiety is probably not significant in practice. In fact, when a patient is very anxious about a melanocytic lesion, excision is more often suggested, in order to reassure the patient, even if the lesion seems to be benign. This

induced a selection bias, which increased the number of NM and therefore decreased de melanoma/NM ratio among anxious patients.

This study demonstrated that, if a melanocytic lesion presented dynamic changes or appeared *de novo* in a patient older than 50 years, this lesion was more likely to be a melanoma (OR = 3.00 and 2.64 respectively) than a lesion without dynamic change or *de novo* appearance. CT allowed to go further by determining an « age limit » for both dynamic changes and *de novo* appearance, above which melanoma probability was much higher. This age limit was 41.5 years and 44.5 years for dynamic changes and *de novo* appearance respectively. Melanoma proportion was 27.4% in the subgroup of patients older than 41.5 years describing dynamic changes in a melanocytic lesion compared to 8.4% if younger than 41.5 years, and 32.0% in the subgroup of patients older than 44. 5 years presenting a melanocytic lesion observed appearing *de novo* compared to 7.5% if younger than 44.5 years.

Banky at al.[21] conducted a study in patients at high risk for melanoma. Naevi were examined in comparison with total body photographies. The incidence rate of appearance of new naevi was 277 per 1000 persons-year, while incidence of changed naevi was 329 per 1000 persons-year, both incidences being more than twice higher in patients younger than 30 years. In another study performed by Oliveira et al. and conducted in adults presenting for naevi follow-up, the incidence rate of appearance of new naevi was 202 per 1000 persons-year, also based on total body photographies.[29] This incidence was 4.3 higher in patients below 25 years of age than in patients older than 75 years.

Banky et al.[21] studied the proportion of naevus and melanomas among changed and new lesions: respectively only 3% and 0.4% were melanomas in patients younger than 50 years, contrasting with respectively 22% and 30% in patients older than 50 years. It is worthwhile noting, when comparing both studies, that populations were different: patients at high risk for melanoma in Banky's study, general population in the present study (except patients consulting in the PLC). Moreover, melanocytic lesions changes or appearance were detected through comparison of the lesions with those observed on baseline total body pictures in Banky's study, whereas dynamic changes and *de novo* appearance were subjectively reported by patients in the present study. Finally, in

Banky's study, only 17% of changing naevus and 7% of new naevus were excised, this decision being based on dermoscopic examination, which can recognize, among others, benign patterns in growing lesions.[30] In the present study, not all new and changing lesions were excised neither, also thanks to dermoscopy, yet with a mean melanoma/NM ratio lower than in the Banky's study.[21,22] Despite these differences in populations and study designs, tendencies are the same in the present and Banky's studies: the older the patient, the higher the risk that a given new or changed lesion is a melanoma.

The explanation is probably multiple. First, the natural history of benign naevus appearing and increasing in size during childhood and young adult life explains the numerous benign *de novo* and changing lesions in young patients.[21,31] Second, the incidence of melanoma increasing with age, and the number of naevi decreasing with age,[21,31] a given lesion has more chance to be a melanoma in an old patient than in a young one. Third, the annual transformation rate of a naevus is higher in old people: it has been calculated to be 0.0005% in males and females younger than 40 years and increases with age in both sexes, to 0.003% in males older than 60 years.[27]

The present study underlines the positive predictive value of dynamic changes and *de novo* appearance of melanocytic lesions in patients from fifteenth decade. According to Askari et al., old patients are less able to identify their melanoma.[10] As, in addition, melanoma incidence is growing in patients older than 60 years, one should conclude that older patients should be more informed that a new or changing skin lesion must be examined by their general practitioner or their dermatologist.

Dynamic changes of a pre-existing lesion in all the patients and *de novo* appearance only in old people were the two major predictive variables for melanoma diagnosis in the present study comparing melanomas and clinically suspicious lesions pathologically diagnosed as NM. Excision of a changing or new melanocytic lesion should be considered especially after the ages of 41.5 and 44.5 years respectively. This enhanced knowledge of changes observed by the patients could help setting up appropriate awareness campaigns, especially intended for mid-aged and older patients.

Tables

Table 1: Univariate and multivariate analysis of the variable « melanoma diagnosis, *versus* non-melanoma diagnosis ».

Predictor variables	**Unadjusted**	**Adjusted**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**
1. Gender		
Female	1	1
Male	1,10 (0,83 – 1,46)	0,99 (0,72 – 1,37)
2. Age	1,04 (1,03 – 1,04)**	1,03 (1,02 – 1,04)**
3. Dynamic changes		
No	1	1
Yes	1,78 (1,26 – 2,51)**	2,35 (1,57 – 3,52)**
Unknown	1,06 (0,72 – 1,55)	0,92 (0,58 – 1,47)
4. De novo lesion		
No	1	1
Yes	1,71 (1,15 – 2,53)**	1,33 (0,85 – 2,10)
Unknown	1,11 (0,81 – 1,52)	1,23 (0,83 – 1,83)
5. Pruritus		
No	1	1
Yes	0,77 (0,48 – 1,26)	0,84 (0,48 – 1,48)
6. Bleeding		
No	1	1
Yes	1,40 (0,61 – 3,20)	0,79 (0,28 – 2,23)
7. Anxiety		
No	1	1
Yes	0,82 (0,59 – 1,15)	0,61 (0,41 – 0,91)*

**p<0,01 ; *p<0,05

Table 2 Dynamic changes, age and melanoma diagnosis (adjusted for gender).

Age	M/NM for lesions with dynamic changes	M/NM for lesions without observed dynamic changes	OR M/NM Dynamic changes/ no dynamic changes observed [95% CI]	p-value
≤ 30y	15/171	11/149	1.14 [0.51 – 2.58]	0.746
30 – 50y	36/239	23/216	1.43 [0.82 – 2.51]	0.207
≥ 50y	54/124	23/150	3.00 [1.73 – 5.21]	**<0.001**

M: melanoma
NM: non-melanoma
OR: odds ratio

Table 3: De novo appearance, age and melanoma diagnosis (adjusted for gender).

Age	M/NM for lesions appeared de novo	M/NM for lesions appeared on a preexisting lesion	OR M/NM De novo lesion/preexisting lesion [95% CI]	p-value
≤ 30y	5/54	19/265	1.24 [0.44 - 3.49]	0.680
30 – 50y	9/84	47/371	0.85 [0.40 - 1.80]	0.663
≥ 50y	27/51	40/198	2.64 [1.48 - 4.70]	**0.001**

M: melanoma
NM: non-melanoma
OR: odds ratio

Figures : titles and legends

Figure 1: Classification Tree with “melanoma diagnosis” as a response variable, dynamics changes and age as predictor variables.

Legend :
Each node is characterised by the number of suspicious melanocytic lesions (n) and their percentage corresponding to melanoma (M). In this figure, patients who did not observe dynamic changes and those who did not know (“unknown”) are pooled as “no dynamic changes observed”.

Figure 2: Classification Tree with “melanoma diagnosis” as a response variable, *de novo* appearance and age as predictor variables.

Legend:
Each node is characterised by the number of suspicious melanocytic lesions (n) and their percentage corresponding to melanoma (M). In this figure, patients who observed the apparition of a new lesion (*de novo* lesion observed) are separated from the patients who did not observe the apparition of a new lesion or did not know (“unknown”) as “preexisting lesion”.

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