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BENEFITS OF TOTAL BODY PHOTOGRAPHY AND DIGITAL DERMOSCOPY (“TWO-STEP METHOD OF DIGITAL FOLLOW-UP”) IN THE EARLY DIAGNOSIS OF MELANOMA IN HIGH-RISK PATIENTS

Gabriel Salerni, MD^a, Cristina Carrera, MD^{a,b}, Louise Lovatto, MD^a, Joan Anton Puig-Butille, PhD^b, Celia Badenas, PhD^{b,c}, Estel Plana^d, Susana Puig, MD, PhD^{a,b}, and Josep Malvehy, MD, PhD.^{a,b}

Gabriel Salerni: gabrielsalerni@hotmail.com; Cristina Carrera: criscarrer@yahoo.es; Louise Lovatto: loulovatto@hotmail.com; Joan Anton Puig-Butille: jantonpuig@gmail.com; Celia Badenas: cbadenas@clinic.ub.es; Estel Plana: estel.plana@gmail.com; Susana Puig: susipuig@gmail.com; Josep Malvehy: jmalvehy@clinic.ub.es

^aMelanoma Unit, Dermatology Department, Hospital Clinic of Barcelona, IDIBAPS, Barcelona, Spain

^bCIBER de Enfermedades Raras, Instituto de Salud Carlos III, Barcelona, Spain

^cMelanoma Unit, Biochemistry and Molecular Genetics Service, Hospital Clinic of Barcelona, IDIBAPS, Barcelona, Spain

^dNovartis Farmacéutica SA, Barcelona, Spain

Abstract

Background—Early detection of melanoma is the best way to improve prognosis. Digital follow up (DFU) programs of high-risk populations could be an efficient strategy for detecting early melanomas with low morbidity.

Objective—to report the added value of the use of the “two-step method” (digital total-body photography and digital dermoscopy)

Methods—Analysis of the surveillance of 618 high-risk melanoma patients included in our DFU-program from 1999 to 2008.

Results—A total of 11396 lesions were monitored (mean 18.44 per patient) during a median follow-up of 96 months (median 10 visits per patient). 1152 lesions, 1.86 per patient, were excised. Almost 70% (798) were lesions previously registered at least twice, while 356 (30%) were detected and removed in the same visit. During follow-up, 98 melanomas (8.5% of excised lesions) were diagnosed in 78 patients (12.6%). 53 melanomas were *in situ* (53.3%), while invasive (45) showed a Breslow index of less than 1 mm (median 0.5 mm) and none was ulcerated.

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Corresponding author: Susana Puig, MD, Consultant, Melanoma Unit, Dermatology Department, Hospital Clinic Barcelona, Villarroel 170. 08036 Barcelona. Spain, susipuig@gmail.com, spuig@clinic.ub.es, tel.: +34 93 2275400 ext 2893. Fax: +34 93 2275438.

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Limitations—Since there are no control groups we cannot convey if the combined use of total-body photography and digital dermoscopy is more beneficial than these techniques used separately.

Conclusion—DFU with Total-Body Photography and Dermoscopy in a selected high-risk population demonstrated the early detection of melanomas with a low rate of excisions. Long-term follow-up is required to allow the detection of slow growing melanomas. Based on our 10-year experience, melanomas can be diagnosed at any time, suggesting that in high-risk population, DFU should be maintained with time.

Keywords

malignant melanoma; dermoscopy; follow-up; imaging techniques; atypical mole syndrome; outcome

INTRODUCTION

Malignant melanoma (MM) may be clinically and dermoscopically indistinguishable from melanocytic nevi making early recognition a diagnostic challenge, especially in incipient lesions¹ Dermoscopic documentation of melanocytic lesions for the comparison of current and previous images in search of subtle changes over time, known as digital follow-up (DFU), has been shown to be helpful in the diagnosis of early melanomas in which specific criteria for MM may not yet be present².

The use of baseline regional photographs, namely total-body photography (TBP), might facilitate the detection of new lesions, as well as visual changes in pre-existing lesions, by providing a comparative reference point of areas of skin for subsequent examinations³. Nevertheless, it has been suggested that a screening strategy focused solely on atypical nevi will likely misdiagnose MM presenting as new lesions or corresponding to lesions not considered adequate for digital follow-up⁴.

The combined use of total-body photography and digital dermoscopy, called “The two-step method of digital follow-up (DFU)”⁵, has been proposed by our group as an approach for the assessment of high-risk individuals, being potentially more accurate than the two strategies separately.

The present study aims to report our ten-year experience at the Melanoma Unit of Hospital Clinic of Barcelona, using the latter approach in the prospective follow-up of high-risk MM patients included in our specific surveillance program. Our study not only endorses findings from other working groups but also shows new and relevant data derived from the long follow-up period, which is more than twice as long as that reported in previous studies^{6, 7}, of a cohort of more than 600 individuals with more than 11000 lesions evaluated.

METHODOLOGY

Study population

A total of 629 patients included in the surveillance program with Total-Body photography (TBP) and digital dermoscopy at the Melanoma Unit of Hospital Clinic of Barcelona were followed-up between January 1999 and December 2008.

The criteria for patient inclusion in our follow-up program include: moderate to severe atypical mole syndrome (AMS, defined by more than 100 nevi and/or more than 10 clinically atypical according to ABCD criteria, and/or any histologically dysplastic nevi); personal and/or familial history of MM, carriers of high susceptibility for MM gene

mutations, other cancer risk conditions, i.e. presence of congenital nevus of medium to giant size, immunosuppression or genodermatosis (Xeroderma pigmentosum, Gorlin-Goltz Syndrome, etc) associated or not to AMS.

Patients included in the present analysis should have at least two follow-up visits with a minimum of 12 months of surveillance. A total of 11 patients were initially excluded because they did not fulfill these criteria in follow-up.

The study was conducted according to the Declaration of Helsinki and with institutional approval. Patient's written consent was obtained for all invasive procedures.

Examination Procedure: Baseline and Follow-up Registries

In the first visit, a complete clinical history was recorded, including familial history, previous excised melanocytic lesions and other MM associated risk factors.

The baseline digital follow-up (DFU) examination consisted of two steps: the first step, total-body mapping, for clinical examination of the patient and total-body mapping with digital images; and the second step, digital dermoscopy, for clinical and dermoscopic examination in real time of all individual lesions. Digital storage of dermoscopy images of each lesion showing atypical features was performed. Total-body mapping standardized registry was made according to the "two-step method of digital follow-up"⁵ published by our group.

The follow-up examination included: the first step (total-body mapping) for comparison of total-body images with previous registries to detect any changes in shape, color, or surface eventually occurring in any pigmented skin lesions, as well as for identification of new lesions, and the second step (digital dermoscopy follow-up), for dermoscopic comparison and storage of pigmented skin lesions images of lesions with atypical features, as well as for the clinical and dermoscopic examination of eventual new lesions not previously registered.

Follow-up visits performing only the second step, digital dermoscopy follow-up, with no registries of total-body mapping were eventually made in the surveillance of selected patients with low or moderate risk, or for monitoring the progress of specific lesions.

Every examination was performed by an expert in dermoscopy for a total time of 30–45 minutes per patient. Images were obtained using a standardized digital system (MoleMax, Derma Instruments; Vienna, Austria). Patients were scheduled for follow-up in 3, 6 or 12 months according to the judgment of the professional who performed the evaluation. Short-term follow-up (3 months) was considered for individual suspicious melanocytic lesions that do not satisfy the dermoscopic criteria for the diagnosis of melanoma, while medium and long-term (6 and 12) was considered for the surveillance of patients with high or moderate risk respectively according to inclusion criteria.

Inclusion Criteria for melanocytic lesions to DFU

Melanocytic lesions with atypical clinical or dermoscopic features were stored on the digital system. Lesions with clear-cut dermoscopic features of MM (as described in pattern analysis⁸, the ABCD rule of dermoscopy⁹ or the seven-point checklist¹⁰) were not registered for follow-up, as well as lesions with definite dermoscopic features suggestive of benign nevi. Lesions remitted for excision just after our first examinations were excluded from this analysis since they were not part of the follow-up, sixteen MMs were detected in 14 patients in the initial visit.

Lesions considered for excision and histopathological study

Any lesion showing the following changes detected by digital dermoscopy was excised and histopathologically diagnosed: (1) asymmetric enlargement in size; (2) changes in dermoscopic structures (variation in shape; expansion or decrease of pigment network; variation in the distribution or number of dots/globules; modification of depigmented areas or regression structures; appearance of streaks, scar-like areas, blue-whitish veil, and atypical vessels) (3) increase in the number of colors (4) regression features affecting more than 50% of the lesion; and (5) focal pigment modifications. All new or not previously registered lesions observed during follow-up and exhibiting atypical features but no criteria for MM were registered and included in follow-up, lesions displaying criteria for MM were removed.

Twenty-two benign lesions were removed due to practical or aesthetic criteria according to either the patient's or physician's judgment. Since they were not suspicious of atypical melanocytic lesion or MM and therefore, not part of the follow-up, they were excluded from the study. All these lesions were confirmed histopathologically as benign lesions.

Histopathology Procedure

All lesions removed were step-sectioned and processed for standard histopathological examination. Conventional hematoxylin-eosin staining and immunohistochemistry (Melan A, HMB45, Ki67) were performed in lesions that were removed, and whenever it was considered necessary by two pathologists. Histology criteria of atypia were reported according to the National Institutes of Health (NIH) Consensus Conference (1992).

Genetic testing

Genetic studies were performed after informed consent and proper genetic counseling in patients with history of multiple primary and/or familial multiple MM. Exons 1alpha, 1beta, 2, 3; intronic change IVS2-105 and -34G>T at the *CDKN2A* promoter region and Exon 2 from *CDK4* were studied by PCR-SSCP analysis and sequencing. *MC1R* was studied by direct sequencing as previously reported ¹¹.

Compliance

Patient's compliance was assessed according to the continuity in the follow-up program. Patients who were excluded from the program and continued with clinical and dermoscopic examination, left the program or died, were identified.

Statistical analysis

Bi-variate analysis was performed in order to assess differences in patients who were diagnosed with melanoma during follow-up and those who were not; the chi square test was used for the comparison of qualitative variables, applying Fisher's correction according to the sample sizes' need in tables of 2x2 and the T student test was used to compare means of the quantitative variables. Differences were considered to be statistically significant when $p < 0.05$. Multivariable logistic regression analysis was used to obtain the Odds Ratio (OR) using the forward approach, including in the model one by one those variables with a $p < 0.2$ in the bi-variate analysis.

RESULTS

The surveillance program cohort consisted of 618 patients with a mean age of 37 years (mean SD ± 13.3 years) at time of inclusion in the program; 45.5% were men. According to inclusion criteria, the vast majority of the patients (n=556) had atypical mole syndrome

(AMS) and only 7.1 (n=44) had less than 50 nevi associated to other high-risk conditions. Of the patients, 277 had a personal history of MM, including 73 with a history of multiple primary MMs, prior to the beginning of the study; 8 patients with giant congenital melanocytic nevus and 3 patients affected with *xeroderma pigmentosum* were followed-up in our unit. Almost one third of the patients (n=178) also had a familial history of MM. Descriptive data regarding nevi count, skin phototype, eyes and hair color, lentiginosis actinic damage (lentiginosis and solar elastosis) as well as the presence of genetic mutations are shown in table 1.

Patients were followed-up for a median of 96 months (range 13–120 months). Over ten years of follow-up, 6,149 visits (4,155 with total-body photography and digital dermoscopy and 1,994 with digital dermoscopy only) were performed. Each patient was evaluated a median of 10 times (range 2–22) during the course of the study, a median of 7 visits (range 2–17) with total-body photography and digital dermoscopy, and a median of 3 intermediate visits (range 0–11) only with digital dermoscopy. During the study, 78,070 body maps (mean 126.3 per patient, range [9–410]) and 88,283 digital dermoscopy images (mean 142.9 per patient, range [6–726]) were stored.

A total of 11,396 lesions were followed-up, a mean of 18.44 per patient (1–60). Among those 1,152 lesions, a mean of 1.86 lesions per patient, were excised and remitted for histopathological assessment during the study. In 211 patients no excision was required and in 149 only one lesion was excised in ten years of follow-up. So, in almost 60% of the cohort, none or only one lesion required excision. In contrast, only 7 patients required ten or more excisions during surveillance, but they corresponded to patients with personal history of multiple primary MM and familial MM, *CDKN2A* mutations carriers, or patients affected with *xeroderma pigmentosum*.

Among lesions excised during follow-up, 779 (67.6%) corresponded to lesions previously registered and under surveillance, and 373 (32.4%) corresponded to lesions detected in the visits, which were new or, being already present, were not previously counted for register in DFU. Histopathological diagnosis of melanocytic and non melanocytic lesions (initially assumed as melanocytic and thus, registered for DFU) excised in both groups is shown in Figure 1.

During DFU, 98 melanomas (8.5% of excised lesions, benign/MM ratio 10.7:1) were detected in 78 patients; 60 MMs corresponded to monitored lesions (7.7% of registered lesions, benign/MM ratio 11.9:1; Figure 2) and 38 to lesions with no previous digital record (10.2% of new or unregistered lesions, benign/MM ratio 8.8:1; Figure 3). MMs detected due to changes in digital dermoscopy required a median of 4 (range 2–15) consecutive controls and a mean follow-up time of 23.9 months (range 1–77); of these, 16 arose in a previous nevus, but 44 did not show any evidence of a pre-existing nevus upon histopathology.

Histopathologically, 53 MMs were *in situ* (53.3%), among invasive MMs, the median Breslow's index was 0.5 mm (mean 0.62 mm) and no MM detected during follow-up was thicker than 1 mm or ulcerated, that is, all invasive MMs were staged in IA (AJCC 2009).

A total of 1,015 melanocytic nevi were excised during the study, almost half with some degree of histological atypia (18.7% mild, 23.8% moderate and 6% severe). On histological examination, 45.4% exhibited regression, inflammatory changes, Sutton phenomenon or fibrosis that could explain dermoscopic changes during monitoring.

During follow-up, 78 patients, 12.6% of the cohort, were diagnosed with MM. Patients diagnosed with MM during DFU were more frequently men ($p=0.02$), who were older at the beginning of the study ($p<0.001$), with a higher number of lesions monitored ($p<0.001$) and

a higher number of lesions excised during DFU than those who were not diagnosed with MM; no significant differences in length of follow-up between the two groups were observed. History of previous MM and multiple MM were more frequent among patients diagnosed with MM during surveillance ($p < 0.001$ and 0.003 , respectively), but no significant differences were found regarding the number of MM prior to the start. No statistically significant differences were found considering the nevi count in the four pre-established categories (< 50 , $50-100$, $100-200$ and > 200), but patients with > 100 nevus were more frequently diagnosed with MM than those with < 100 nevus ($p 0.007$). As expected, patients with AMS had more MM during follow-up than those without AMS, but differences were not significant ($p=0.636$). No significant differences were found regarding skin phototype, presence and degree of lentiginosis and presence of *CDKN2A* mutation between the two groups (table II).

In the multivariable logistic regression analysis (table III), older age at inclusion and higher number of lesions excised during follow-up, were the variables more associated with melanoma diagnosis during DFU ($p 0.003$ and < 0.001 , respectively); male gender, previous melanoma or the presence of *CDKN2A* mutation, were also associated with melanoma during follow-up but differences were not statistically significant. Skin phototype IV and no indication of *CDKN2A* mutation analysis were associated with a lower risk of melanoma during follow-up ($p=0.033$ and < 0.001 respectively); skin phototype II and III were associated with a lower risk of melanoma than type I, but no statistically significant differences were observed ($p=0.123$ and 0.423 respectively).

Regarding DFU compliance, 519 (84.1 %) patients continue under surveillance in the follow-up program, 47 (7.6%) were excluded from the program and continue clinical and dermoscopic examinations in our Unit, 38 patients (6.1%) left the program or were referred to dermatological follow-up at another centre, and 14 patients (2.2%) died, 12 because of MM progression, one as a consequence of a heart-attack and one related to Duchenne's muscular dystrophy progression.

DISCUSSION

Various strategies have been suggested for MM detection in high risk patients, such as skin self-examination^{12,13}, total cutaneous examination¹⁴, and the use of TBP^{3,15-19}, and dermoscopy^{20,21}. It has been well demonstrated that clinical examination is inaccurate for the diagnosis of incipient MM²² while dermoscopy has been shown to improve the diagnostic accuracy of nearly all cutaneous tumors including melanoma^{20,21,23}.

Over the last few years, increasing evidence has accumulated in favor of digital dermoscopy for the follow-up of atypical melanocytic lesions^{2, 6, 7, 24-30}. Digital Follow-up (DFU) has proven to be useful in the surveillance of high-risk populations by providing the double benefit of not overlooking MM with few dermoscopic criteria while minimizing the excision of benign lesions².

Since dermoscopy is not 100% accurate, a certain percentage of suspicious but benign lesions have to be excised in order to not miss MM. In our study, less than 2 lesions per patient were excised during a median of 8 years of surveillance, with a global MM/benign ratio of 1:10.7 and a MM detection rate of 8.5%, endorsing the fact that DFU is both an efficient and effective strategy for early MM detection in high-risk patients (table III).

The detection of new or clinically changing melanocytic lesions in a high-risk population is difficult and almost impossible in patients with a high nevi count unless total body photography (TBP) is available for comparison. Furthermore, it is well known that MM

often develops *de novo* in clinically normal skin rather than in pre-existing melanocytic nevus³¹.

The “Two-step Method of DFU”, routinely used in our unit in the surveillance of high risk MM patients, consists of the combined performance of TBP and digital dermoscopy in every visit⁵ We believe that our protocol represents a more complete surveillance approach than those from other working groups, in which DFU is solely focused on digital dermoscopy of registered lesions. On the other hand, in protocols of digital dermoscopy in which TBP are performed, body-maps are only registered in the first visits, and in subsequent controls body surface is simply compared with overview images. Already in 2007, Fuller *et al*⁴ highlighted that it is unclear in most previous studies whether any MM was missed because they either presented as new lesions or arose from nevi that were not monitored by dermoscopy, since the total number of MM occurring in those patients was not reported. In the latter study, only one MM was detected by DFU out of 6 MMs detected during a median of 22 months; with a MM/benign lesion ratio of 1:94 and 1:34.4 among lesions with and without previous dermoscopy record respectively. In our study, nearly 40% of MMs detected during follow-up corresponded to lesions that were not previously recorded, either because they were newly assessed by TBP or, being already present, they were not atypical, and hence not included for follow-up. In this MM subgroup, MM/benign ratio was, as in Fullers’ study, lower among lesions with no previous dermoscopy record (1:8.8 vs. 1:11.9).

The ten-year experience in follow-up of patients at increased risk for MM reported by Haenssle *et al*^{6,7} deserves special attention. As seen in table III, general data concerning number of patients, lesions monitored, percentage of lesions excised, malignant/benign ratio, and patients diagnosed with MM during the study, are remarkably similar to our study. Nevertheless, some differences are clear: first, our median follow-up of 96 months (8 years) is more than twice as long, providing more consistent data in terms of long-term follow-up; and second, unlike their study, we decided not to include lesions excised in the first visit examinations, as they were not part of the follow-up, leaving 16 MMs out of the present analysis. Haenssle *et al*. found a higher number of MMs in their study (127); if we exclude 40 MMs, which they report to have diagnosed after the first examination, that would leave 87 MMs detected during follow-up, which is more similar to our experience. Another interesting difference is the percentage of MMs detected due to dynamic changes during DFU, which is 36.7% (32/87) in their experience but 61.2% (60/98) in ours. No further conclusion can be made since the populations are not equivalent.

Recently, Argenziano *et al*³² reported that MM may grow slowly and thus changes can only be seen after long-term follow-up. According to this, we report follow-up as long as 77 months until excision, and being almost half of the MM followed-up for more than 2 years until showing some significant change in initially featureless lesions. Two findings require special attention; first, 75% of MM with more than 2 years of follow-up before excision were *in situ*, and second, almost 65% of MM that required more than 2 years of follow-up showed no pre-existing nevus upon histopathological examination (data not shown). These findings may support the current evidence of the existence of a subgroup of slow-growing MM.

It is well known that the DFU procedure is not only time consuming but also a technique that requires training, experience and specific equipment. Chances of success in DFU depend basically on the proper selection of patients³³. In our study population, with 90% of the patients displaying atypical mole syndrome and almost 45% with previous melanoma, 1 out of 8 developed MM during surveillance, which is more than 1500 times higher than expected in our general population. Not unexpectedly, the percentage of patients diagnosed with MM during follow-up rose from 7% among patients with no personal history of MM,

to 18% and 23% in patients with one primary MM and multiple primary MM prior to the inclusion in follow-up, respectively.

The duration of the DFU or the possibility to exclude a patient included in the program after a period with no excisions required have been a matter of debate. According to our results, MM can be diagnosed at any time once a patient is included in the DFU program, and not just at the beginning within the first follow-up examinations. Furthermore, the risk of diagnosing more than one MM during follow-up is relatively high among high risk populations. In light of these findings, maintained surveillance may be required in high risk individuals.

There is no consensus regarding the most effective melanoma screening strategy in high risk individuals. Since there are no control groups we cannot convey whether the combined use of TBP and digital dermoscopy is more beneficial than the TBP, dermoscopy examination or DFU separately. Recently, Goodson *et al.*¹⁸ compared their results using TBP and digital dermoscopy monitoring of nevi in a similar patient population at risk for melanoma and they found that monitoring patients at risk for melanoma using TBP was associated with a lower biopsy rates and lower benign/melanoma ratios than using digital dermoscopy and facilitated detection of new and changing lesions with a higher MM detection rate during follow-up (4.4% vs. 1.9% respectively). With the use of the “Two-step method of DFU” we achieved a higher melanoma detection rate (8.5%) and a lower nevus:melanoma ratio (9.3 vs. 53 with DFU and 22 with TBP). In our study biopsy rate was higher, but this finding may be due to the fact that our median follow-up period is 4 times longer and our population could be considered of higher risk, since incidence of melanoma per patient during follow-up was six times higher.

In conclusion, TBP and digital dermoscopy (“two-step method of digital follow-up”) in a selected high-risk population was shown to allow the detection of melanomas in early stages with a low rate of excisions. This dual modality is useful not only for the detection of MM with few dermoscopic criteria by DFU of dermoscopy records, but also for the detection of melanoma either presented as new lesions or arising from nevi that were not monitored by dermoscopy. Long-term follow-up is required to allow the detection of slow growing melanomas. Based on our 10-year experience, melanomas can be diagnosed at any time, and not just at the beginning of follow-up, suggesting that in this kind of high-risk population, DFU should be maintained with time.

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ABBREVIATIONS

DFU	digital follow-up
MM	malignant melanoma

TBP	total-body photography
AMS	Atypical mole syndrome
SD	standard deviation

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Capsule summary

1. Digital dermoscopy follow-up is the most reliable and efficient approach in order to detect incipient melanoma.
2. The combined use of total-body photography and digital dermoscopy ("two-step method of digital follow-up") allow the detection of melanomas in early stages with a significant reduction of excisions
3. Long-term follow-up is required to allow the detection of slow growing melanomas. In high-risk population, DFU should be maintained with time

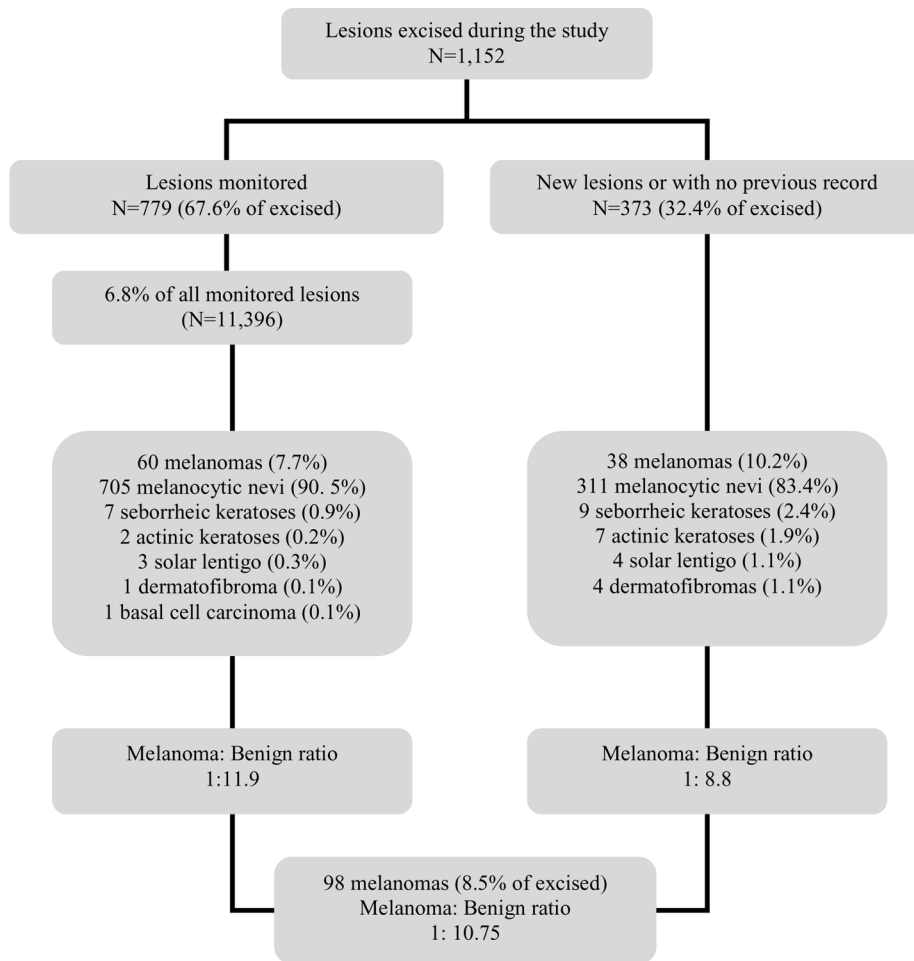


Figure 1.
Lesions excised during the study
* corresponded to 6.8% of all monitored lesions

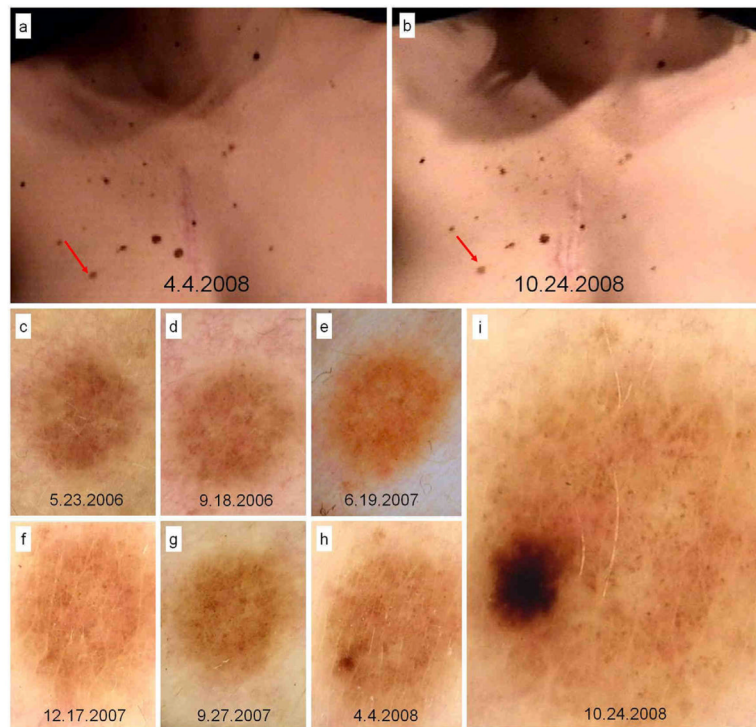


Figure 2. In situ melanoma developed over melanocytic nevus in a 23 year-old patient, with personal and familial history of melanoma, diagnosed due to changes in digital follow-up. Body-mapping images displaying no clinical change (A and B) and dermoscopy records in chronological order until excision after 29 months and 7 visits of follow-up (C to I).

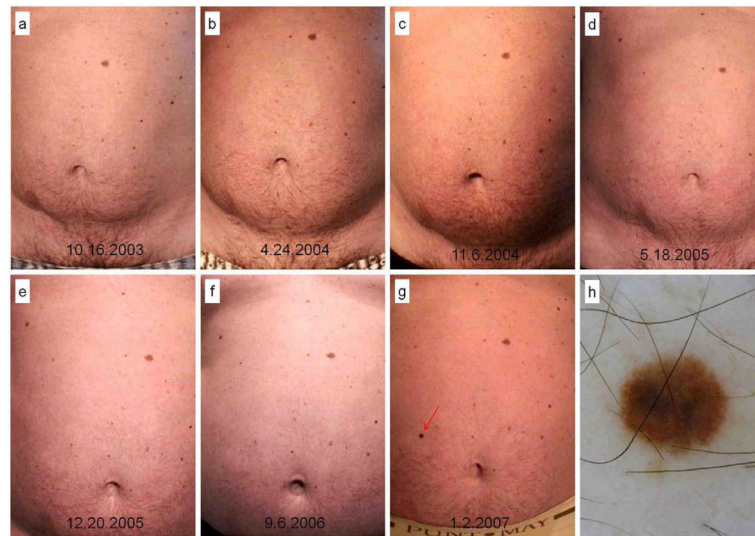


Figure 3. Superficial spreading malignant melanoma, Breslow 0.5 mm, Clark level III detected as a new lesion during total-body mapping comparison in the abdomen of a 48 years-old male, carrier of *CDKN2A* mutation, with history of personal melanoma and familial melanoma and atypical mole syndrome. Body-mapping records showing the appearance of the lesion (A to G), clinically symmetric and with regular borders. Dermoscopy image (H) showing atypical pigment network, inverted pigment network and bluish hue.

Table I

Descriptive data of population

Age at inclusion	37 years (mean SD \pm 13.3 years)
Gender	
male	281 (45.5%)
female	337 (54.5%)
Personal history at inclusion	
melanoma	28 (4.53%)
melanoma & AMS	245 (39.64%)
AMS	311 (50.32%)
Xeroderma pigmentosum (all with previous MM)	3 (0.5%)
Giant congenital nevus (one with previous MM)	8 (1.29%)
Others (only familial history of MM, Gorlin-Goltz syndrome, etc)	23 (3.72%)
Nevi count	
<50	44 (7.11%)
50–100	218 (35.30%)
100–200	241 (38.99%)
>200	115 (18.60%)
Phototype	
I	19 (3.1%)
II	249 (40.3%)
III	327 (52.9%)
IV	23 (3.7%)
V	0
VI	0
Eyes color	
Blue	80 (12.9%)
Green	76 (12.3%)
Brown	445 (72.0%)
Black	17 (2.8%)
Hair color	
Red	26 (4.2%)
Blonde	84 (13.6%)
Brown	463 (74.9%)
Black	45 (7.3%)
Lentiginoses	
mild	209 (33.8%)
moderate	97 (15.7%)
severe	72 (11.7%)
no	240 (38.8%)
CDKN2A mutation	39 (11.5% of studied)
MC1R polymorphism	163 (75.1% of studied)

V60L	42
V92M	17
R151C	28

AMS: Atypical Mole Syndrome

Table II
Differences between patients who were and were not diagnosed with MM during FU

	MM during follow-up				p-value	OR	95% CI
	No (N=540)	Yes (N=78)	n	%			
Sex					0.020		
Female	304	33	42.3			1.00	(Reference)
Male	236	45	57.7			1.76	(1.09–2.84)
Age at inclusion					0.001		
0–20	51	5	6.4			1.00	(Reference)
21–40	295	31	39.7			1.07	(0.40–2.89)
41–60	171	31	39.7			1.85	(0.68–5.00)
>60	23	11	14.1			4.88	(1.52–15.66)
AMS					0.636		
No	53	9	11.5			1.00	(Reference)
Yes	487	69	88.5			0.83	(0.39–1.77)
Previous melanoma					<0.001		
No	317	24	30.8			1.00	(Reference)
Yes	223	54	69.2			3.20	(1.92–5.33)
Previous multiple melanoma					0.003		
No	484	61	78.2			1.00	(Reference)
Yes	56	17	21.8			2.41	(1.32–4.41)
Number of melanoma previous to beginning					0.070		
1	165	37	68.5			1.00	(Reference)
2	49	10	18.5			0.91	(0.42–1.96)
3	5	3	5.6			2.68	(0.61–11.70)
4	2	2	3.7			4.46	(0.61–32.69)
5	1	2	3.7			8.92	(0.79–100.98)
Nevi count					0.058		
<50	40	4	5.1			1.00	(Reference)
50–100	200	18	23.1			0.90	(0.29–2.80)
100–200	204	37	47.4			1.81	(0.61–5.37)

	MM during follow-up				p-value	OR	95% CI
	No (N=540)	Yes (N=78)	n	%			
> 200	96	19	24.4		1.98	(0.63–6.19)	
More than 100 nevi				0.007			
No	240	22	28.2		1.00	(Reference)	
Yes	300	56	71.8		2.04	(1.21–3.43)	
Phototype				0.422			
I	15	4	5.1		1.00	(Reference)	
II	219	30	38.5		0.51	(0.16–1.65)	
III	284	43	55.1		0.57	(0.18–1.79)	
IV	22	1	1.3		0.17	(0.02–1.68)	
Phototype				0.966			
I–II	234	34	43.6		1.00	(Reference)	
III–IV	306	44	56.4		0.99	(0.61–1.60)	
Lentiginous				0.286			
No	214	26	33.3		1.00	(Reference)	
Yes	326	52	66.7		1.31	(0.80–2.17)	
Excised lesions				<0.001			
0	211	0	0.0		-	-	
1	135	14	18.0		1.00	(Reference)	
2	70	14	18.0		1.93	(0.87–4.27)	
3	50	14	18.0		2.70	(1.20–6.06)	
4	35	9	11.5		2.48	(0.99–6.20)	
5	15	5	6.4		3.21	(1.02–10.17)	
6	10	7	9.0		6.75	(2.22–20.52)	
>=7	14	15	19.2		10.33	(4.15–25.74)	
CDKN2A				<0.001			
Negative	239	61	78.2		1.00	(Reference)	
not performed	272	7	9.0		0.10	(0.05–0.22)	
Positive	29	10	12.8		1.35	(0.62–2.92)	
	mean (SD)	mean (SD)	(SD)		p-value	OR	95% CI

	MM during follow-up		p-value	OR	95% CI
	No (N=540)	Yes (N=78)			
	n	%	n	%	
Age at inclusion	36.2	(12.8)	42.4	(15.5)	<0.001 1.03 (1.02–1.05)
Number of controlled lesions	17.6	(8.2)	24.2	(13.0)	<0.001 1.07 (1.04–1.09)
number of excised lesions	1.5	(1.9)	4.3	(3.5)	<0.001 1.50 (1.35–1.66)
Length of follow-up (months)	85.3	(29.9)	88.8	(31.0)	0.348 1.00 (1.00–1.01)

AMS: Atypical Mole Syndrome

Table III

Multivariable logistic regression analysis

	OR	95% CI	p-value
Age at inclusion	1.04	(1.01–1.06)	0.003
Gender			
Female	1.00	(Reference)	
Male	1.23	(0.68–2.22)	0.500
Previous Melanoma			
No	1.00	(Reference)	
Yes	1.55	(0.81–2.97)	0.181
More than 100 nevus			
No	1.00	(Reference)	
Yes	1.37	(0.72–2.60)	0.342
N° of lesions excised	1.55	(1.37–1.75)	<0.001
Skin phototype			
I	1.00	(Reference)	
II	0.33	(0.08–1.35)	0.123
III	0.57	(0.14–2.26)	0.423
IV	0.03	(0.00–0.76)	0.033
CDKN2A mutation			
No	1.00	(Reference)	
Not performed	0.15	(0.06–0.37)	<0.001
Yes	1.39	(0.53–3.68)	0.505

Table IV

Comparison of clinical outcomes of our study and those from other working groups

Authors	Lesions - Patients (number)	Mean lesions/patient	Median follow up (months)	Excisions (%) out of lesions registered	Ratio MM/No MM	MM (%)out of excisions	Patients diagnosed with MM during DFU (%)
Haensle ^{6,7} 2010, Germany	11137-688	16.18	46	10.9	1:8.5	10.4	11.4
Argenziano ²⁹ 2008, Italy	600 – 405	1.48	23	9	1: 3.4	22.2	3
Fuller ⁴ 2007, USA	5945 – 297	20	22m	5.4	1:53	1.9	2
					PRL1:95/NPRL 1:34.4	PRL 1.1/NPRL 2:75	
Haensle ²⁵ 2006, Germany	7001 – 530	13.2	32.2	9.1	1:12	8.3	10
Bauer ²⁶ 2003, Germany (EPL)	2015 – 196	10.28	25m	1.6	1: 15.5	6.1	1
Robinson ²⁷ 2004, USA	3482 - 100	34.82	36.2	5.5	1: 47.3	2.1	4
Malvey ⁵ 2002, Barcelona	3170 – 290	10.93	17.2	1.3	1: 4.2	19	2.8
Menzies ³⁰ 2001, Australia	318 -245	1.29	3m	19.2	1: 7.7	11.5	2.9
Kittler ²⁸ 2000, Austria	1862 – 202	9.21	12.6	4	1: 8.4	10.7	4
Present study	11396-618	18.44	96	10.1	1:10.7	8.5	
					PRL 1:11.9/NPRL 1:8.8	PRL 7.7/NPRL 10.1	12.6

PRL: previously registered lesions; NPRL: non previously registered lesions