Benefits of total body photography and digital dermatoscopy ("two-step method of digital follow-up") in the early diagnosis of melanoma in patients at high risk for melanoma

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

Objective: We sought to report the added value of the use of the "two-step method" (digital total body photography and digital dermatoscopy).

Methods: This was an analysis of the surveillance of 618 patients at high risk for melanoma included in our DFU program from 1999 to 2008.

Results: A total of 11,396 lesions were monitored (mean 18.44/patient) during a median follow-up of 96 months (median 10 visits/patient). A total of 1152 lesions, 1.86 per patient, were excised. Almost 70% (798) were lesions previously registered at least twice, whereas 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%). In all, 53 melanomas were in situ (53.3%), whereas invasive (45) showed a Breslow index of less than 1 mm (median 0.5 mm) and none were ulcerated.

Limitations: Because there are no control groups we cannot determine if the combined use of total body photography and digital dermatoscopy is more beneficial than these techniques used separately.

Conclusion: DFU with total body photography and dermatoscopy in a selected population at high risk 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 a population at high risk for melanoma, DFU should be maintained over time. (J Am Acad Dermatol 2012;67:e17-27.)

Key words: atypical mole syndrome; dermatoscopy; follow-up; imaging techniques; malignant melanoma; outcome.

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Malignant melanoma (MM) may be clinically and dermatoscopically indistinguishable from melanocytic nevi making early recognition a diagnostic challenge, especially in incipient lesions.[1] Dermatoscopic 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 for which specific criteria for MM may not yet be present.[2]

The use of baseline regional photographs, namely total body photography (TBP), might facilitate the detection of new lesions, and visual changes in pre-existing lesions, by providing a comparative reference point of areas of skin for subsequent examinations.[3] 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 DFU.[4]

CAPSULE SUMMARY

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

The combined use of TBP and digital dermatoscopy, called the "two-step method" of DFU,[5] has been proposed by our group as an approach for the assessment of individuals at high risk, being potentially more accurate than the two strategies separately.

This study aims to report our 10-year experience at the Melanoma Unit of Hospital Clinic of Barcelona, Spain, using the latter approach in the prospective follow-up of patients at high risk for melanoma 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 11,000 lesions evaluated.

METHODS

Study population

A total of 629 patients included in the surveillance program with TBP and digital dermatoscopy at the Melanoma Unit of Hospital Clinic of Barcelona, Spain, 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 >100 nevi and/or >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, and other cancer risk conditions, ie, presence of congenital nevus of medium to giant size, immunosuppression, or genodermatosis (eg, xeroderma pigmentosum, Gorlin-Goltz syndrome) associated or not to AMS.

Patients included in this 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 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 dermatoscopy, for clinical and dermatoscopic examination in real time of all individual lesions. Digital storage of dermatoscopy images of each lesion showing atypical features was performed. Total body mapping standardized registry was made according to the two-step method of DFU[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, and for identification of new lesions, and the second step (digital dermatoscopy follow-up), for dermatoscopic comparison and storage of lesions with atypical features, and for the clinical and dermatoscopic examination of eventual new lesions not previously registered.

Follow-up visits performing only the second step, digital dermatoscopy follow-up, with no registries of

Abbreviations used:

AMS: atypical mole syndrome
DFU: digital follow-up
MM: malignant melanoma
TBP: total body photography

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 dermatoscopy for a total time of 30 to 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 did not satisfy the dermatoscopic criteria for the diagnosis of melanoma, whereas medium- and long-term follow-up (6 and 12 months) 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 dermatoscopic features were stored on the digital system. Lesions with clear-cut dermatoscopic features of MM (as described in pattern analysis,[8] the ABCD rule of dermatoscopy,[9] or the 7-point checklist[10]) were not registered for follow-up, nor were lesions with definite dermatoscopic features suggestive of benign nevi. Lesions remitted for excision just after our first examinations were excluded from this analysis because they were not part of the follow-up; 16 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 dermatoscopy was excised and histopathologically diagnosed: (1) asymmetric enlargement in size; (2) changes in dermatoscopic 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, scarlike 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.

In all, 22 benign lesions were removed because of practical or aesthetic criteria according to either the patient's or physician's judgment. Because they were not suggestive 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, human melanoma black 45, 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 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 1alfa, 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 dermatoscopic examination, left the program, or died were identified.

Statistical analysis

Bivariate analysis was performed to assess differences in patients who were given the diagnosis of melanoma during follow-up and those who were not; the χ^2 test was used for the comparison of qualitative variables, applying Fisher correction according to the sample sizes' need in tables of 2×2 and the Student t test was used to compare means of the quantitative variables. Differences were considered to be statistically significant when P was less than .05. Multivariable logistic regression analysis was used to obtain the odds ratio using the forward approach, including in the model one by one those variables with P less than .2 in the bivariate 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 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, before 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, eye and hair color, lentiginosis, and the presence of genetic mutations are shown in Table I.

Patients were followed up for a median of 96 months (range 13-120 months). During 10 years of follow-up, 6149 visits (4155 with TBP and digital dermatoscopy and 1994 with digital dermatoscopy 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 TBP and digital dermatoscopy, and a median of 3 intermediate visits (range 0-11) only with digital dermatoscopy. During the study, 78,070 body maps (mean 126.3/patient, range 9-410) and 88,283 digital dermatoscopy images (mean 142.9/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, 1152 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 10 years of follow-up. So, in almost 60% of the cohort, none or only one lesion required excision. In contrast, only 7 patients required 10 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 nonmelanocytic lesions (initially assumed as melanocytic and thus, registered for DFU) excised in both groups is shown in Fig 1.

Table I. Descriptive data of population

Age at inclusion, y	37 (mean SD ± 13.3)
Gender	
Male	281 (45.5%)
Female	337 (54.5%)
Personal history at inclusion	
Melanoma	28 (4.53%)
Melanoma and AMS	245 (39.64%)
AMS	311 (50.32%)
Xeroderma pigmentosum (all with previous MM)	3 (0.5%)
Giant congenital nevus (1 with previous MM)	8 (1.29%)
Others (eg, only familial history of MM, Gorlin-Goltz syndrome)	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; *MM*, malignant melanoma.

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) (Fig 2) and 38 to lesions with no previous digital record (10.2% of new or unregistered lesions, benign/MM ratio 8.8:1) (Fig 3). MMs detected as a result of changes in digital dermatoscopy required

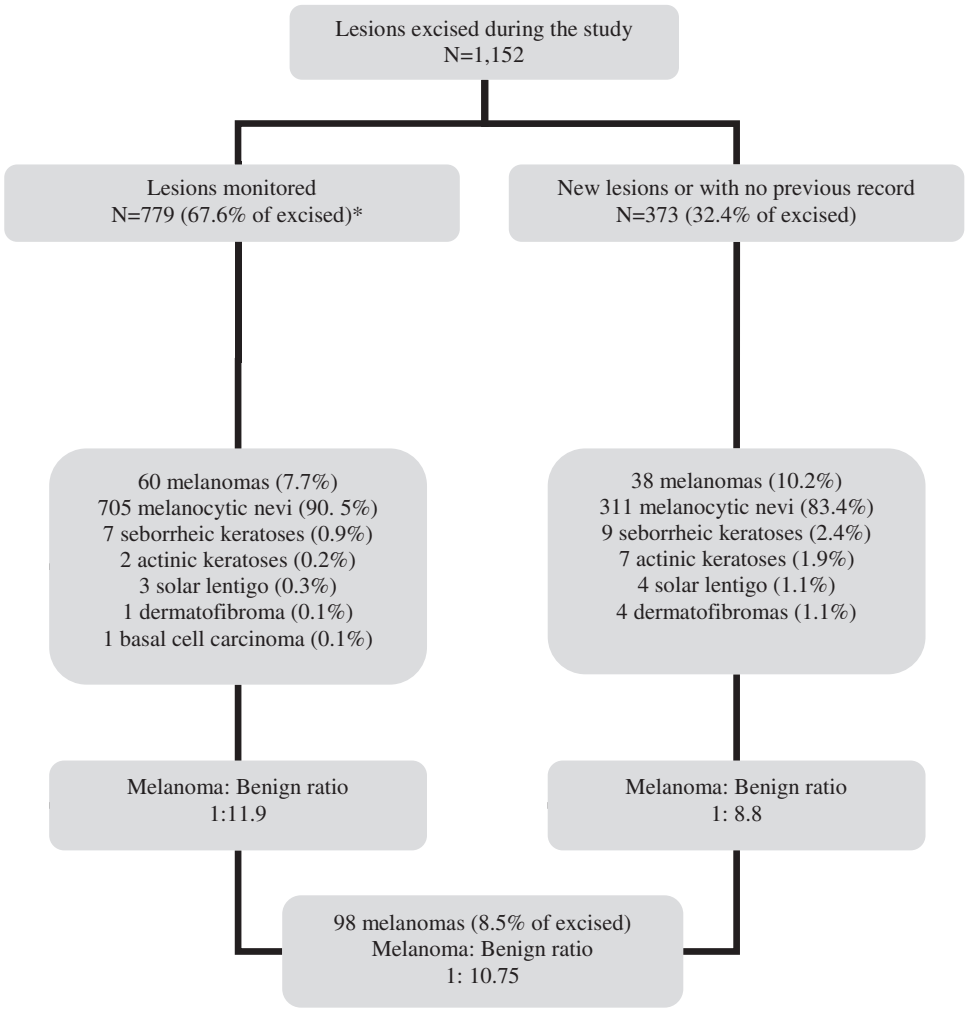

Fig 1. Lesions excised during study. *Corresponded to 6.8% of all monitored lesions.

a median of 4 (range 2-15) consecutive controls and a mean follow-up time of 23.9 months (range 1-77 months); 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 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 (American Joint Committee on Cancer 2009).

A total of 1015 melanocytic nevi were excised during the study, almost half with some degree of histologic atypia (18.7% mild, 23.8% moderate, and 6% severe). On histologic examination, 45.4% exhibited regression, inflammatory changes, Sutton phenomenon, or fibrosis that could explain dermatoscopic changes during monitoring.

During follow-up, 78 patients, 12.6% of the cohort, were given the diagnosis of MM. Patients given the diagnosis of MM during DFU were more frequently men (P = .02), who were older at the beginning of the study (P < .001), with a higher number of lesions monitored (P < .001), and a higher number of lesions excised during DFU than those who were not given the diagnosis of MM; no significant differences in length of follow-up between the two groups were observed. History of MM and multiple MM was more frequent among patients given the diagnosis of MM during surveillance (P < .001 and = .003, respectively), but no significant differences were found regarding the number of MM before the start. No statistically significant differences were found considering the nevi count in the 4 pre-established categories (<50, 50-100, 100-200, and >200), but patients with more than 100 nevi were more frequently given the diagnosis of MM than those with less than 100 nevi (P = .007). As expected, patients with AMS had more MM during follow-up than those without AMS, but differences were not significant (P = .636). No significant differences were found regarding skin phototype, presence

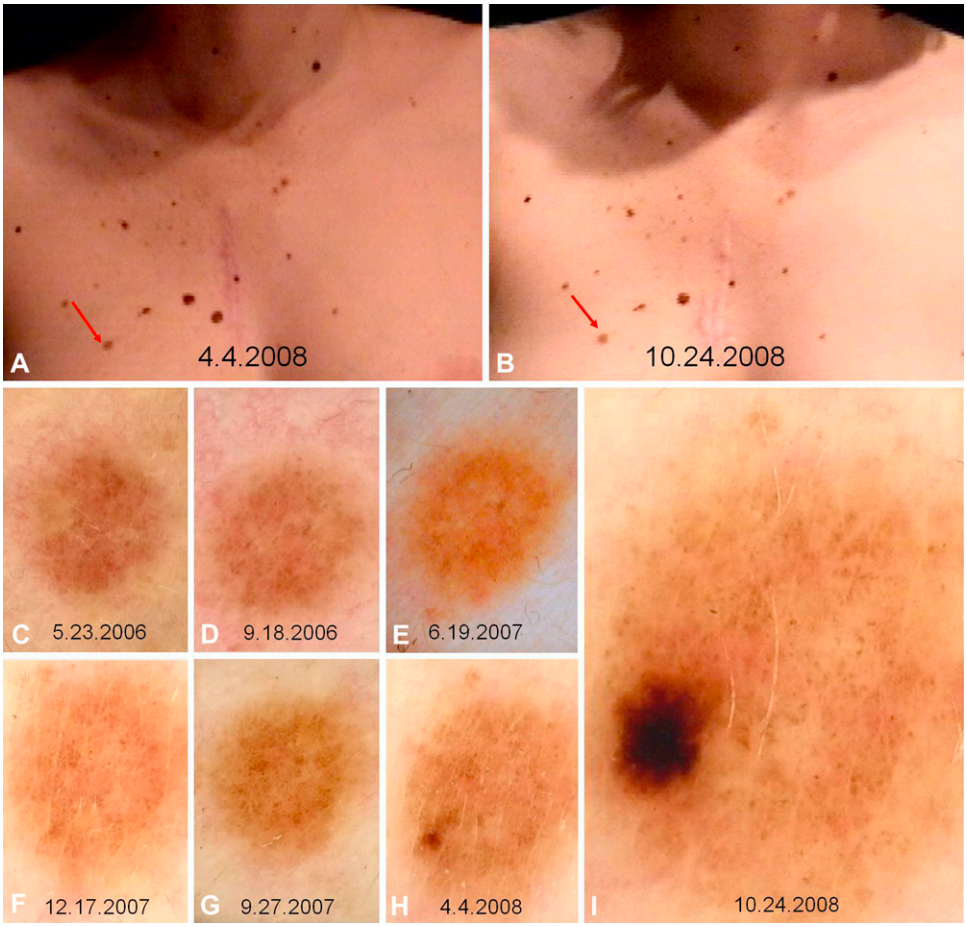

Fig 2. In situ melanoma developed over melanocytic nevus in 23-year-old patient, with personal and familial history of melanoma, given diagnosis as result of changes in digital follow-up. Body mapping images displaying no clinical change (**A** and **B**) and dermatoscopy records in chronological order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

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 = .003 and <.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 = .033 and <.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 = .123 and = .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 dermatoscopic examinations in our unit, 38 patients (6.1%) left the program or were referred to dermatologic follow-up at another center, and 14 patients (2.2%) died, 12 because of MM progression, one as a consequence of a heart attack, and one related to Duchenne muscular dystrophy progression.

DISCUSSION

Various strategies have been suggested for MM detection in patients at high risk, such as skin self-examination,[12,13] total cutaneous examination,[14] and the use of TBP[3,15-19] and dermatoscopy.[20,21] It has been well demonstrated that clinical examination is inaccurate for the diagnosis of incipient MM[22] whereas dermatoscopy has been shown to improve the diagnostic accuracy of nearly all cutaneous tumors including melanoma.[20,21,23]

During the last few years, increasing evidence has accumulated in favor of digital dermatoscopy for the follow-up of atypical melanocytic lesions.[2,6,7,24-30]

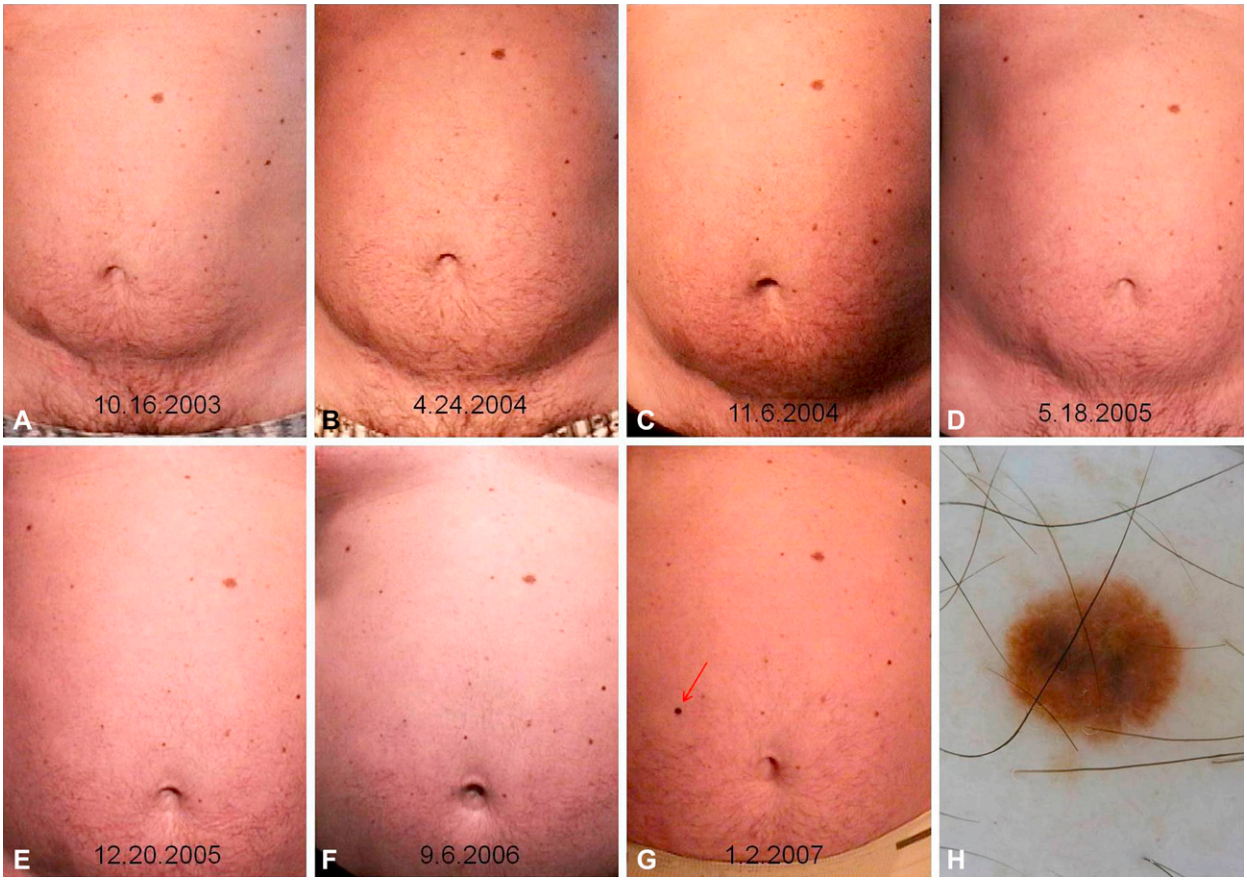

Fig 3. Superficial spreading malignant melanoma, Breslow 0.5 mm, Clark level III, detected as new lesion during total body mapping comparison in abdomen of 48-year-old man, carrier of *CDKN2A* mutation, with history of personal melanoma and familial melanoma and atypical mole syndrome. Body mapping records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

DFU has proven to be useful in the surveillance of populations at high risk by providing the double benefit of not overlooking MM with few dermatoscopic criteria while minimizing the excision of benign lesions (Table IV).[2]

Because dermatoscopy is not 100% accurate, a certain percentage of suspicious but benign lesions have to be excised to not miss MM. In our study, less than two 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 patients at high risk.

The detection of new or clinically changing melanocytic lesions in a population at high risk for melanoma is difficult and almost impossible in patients with a high nevi count unless TBP is available for comparison. Furthermore, it is well known that MM often develops de novo in clinically normal-appearing skin rather than in pre-existing melanocytic nevus.[31]

The two-step method of DFU, routinely used in our unit in the surveillance of patients at high risk for melanoma, consists of the combined performance of TBP and digital dermatoscopy in every visit.[5] 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 dermatoscopy of registered lesions. On the other hand, in protocols of digital dermatoscopy in which TBP is 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 MMs were missed because they either presented as new lesions or arose from nevi that were not monitored by dermatoscopy, because the total number of MM

Table II. Differences between patients who were and were not given diagnosis of malignant melanoma during follow-up

	MM during follow-up						
	No (N = 540)		Yes (N = 78)				
	n	%	n	%	*P* value	OR	(95% CI)
Sex					.020		
Female	304	56.3	33	42.3		1.00	(Reference)
Male	236	43.7	45	57.7		1.76	(1.09-2.84)
Age at inclusion, y					.001		
0-20	51	9.4	5	6.4		1.00	(Reference)
21-40	295	54.6	31	39.7		1.07	(0.40-2.89)
41-60	171	31.7	31	39.7		1.85	(0.68-5.00)
>60	23	4.3	11	14.1		4.88	(1.52-15.66)
AMS					.636		
No	53	9.8	9	11.5		1.00	(Reference)
Yes	487	90.2	69	88.5		0.83	(0.39-1.77)
Previous melanoma					<.001		
No	317	58.7	24	30.8		1.00	(Reference)
Yes	223	41.3	54	69.2		3.20	(1.92-5.33)
Previous multiple melanoma					.003		
No	484	89.6	61	78.2		1.00	(Reference)
Yes	56	10.4	17	21.8		2.41	(1.32-4.41)
No. of melanoma previous to beginning					.070		
1	165	74.3	37	68.5		1.00	(Reference)
2	49	22.1	10	18.5		0.91	(0.42-1.96)
3	5	2.3	3	5.6		2.68	(0.61-11.70)
4	2	0.9	2	3.7		4.46	(0.61-32.69)
5	1	0.5	2	3.7		8.92	(0.79-100.98)
Nevi count					.058		
<50	40	7.4	4	5.1		1.00	(Reference)
50-100	200	37.0	18	23.1		0.90	(0.29-2.80)
100-200	204	37.8	37	47.4		1.81	(0.61-5.37)
>200	96	17.8	19	24.4		1.98	(0.63-6.19)
>100 Nevi					.007		
No	240	44.4	22	28.2		1.00	(Reference)
Yes	300	55.6	56	71.8		2.04	(1.21-3.43)
Phototype					.422		
I	15	2.8	4	5.1		1.00	(Reference)
II	219	40.6	30	38.5		0.51	(0.16-1.65)
III	284	52.6	43	55.1		0.57	(0.18-1.79)
IV	22	4.1	1	1.3		0.17	(0.02-1.68)
Phototype					.966		
I-II	234	43.3	34	43.6		1.00	(Reference)
III-IV	306	56.7	44	56.4		0.99	(0.61-1.60)
Lentigines					.286		
No	214	39.6	26	33.3		1.00	(Reference)
Yes	326	60.4	52	66.7		1.31	(0.80-2.17)
Excised lesions					<.001		
0	211	39.1	0	0.0		—	—
1	135	25.0	14	18.0		1.00	(Reference)
2	70	13.0	14	18.0		1.93	(0.87-4.27)
3	50	9.3	14	18.0		2.70	(1.20-6.06)
4	35	6.5	9	11.5		2.48	(0.99-6.20)
5	15	2.8	5	6.4		3.21	(1.02-10.17)
6	10	1.9	7	9.0		6.75	(2.22-20.52)
≥7	14	2.6	15	19.2		10.33	(4.15-25.74)

Continued

Table II. Cont'd

	MM during follow-up						
	No (N = 540)		Yes (N = 78)				
	n	%	n	%	*P* value	OR	(95% CI)
CDKN2A					<.001		
Negative	239	44.3	61	78.2		1.00	(Reference)
Not performed	272	50.4	7	9.0		0.10	(0.05-0.22)
Positive	29	5.4	10	12.8		1.35	(0.62-2.92)
	Mean	(SD)	Mean	(SD)	*P* value	OR	(95% CI)
Age at inclusion, y	36.2	(12.8)	42.4	(15.5)	<.001	1.03	(1.02-1.05)
No. of controlled lesions	17.6	(8.2)	24.2	(13.0)	<.001	1.07	(1.04-1.09)
No. of excised lesions	1.5	(1.9)	4.3	(3.5)	<.001	1.50	(1.35-1.66)
Length of follow-up, mo	85.3	(29.9)	88.8	(31.0)	.348	1.00	(1.00-1.01)

AMS, Atypical mole syndrome; *CI*, confidence interval; *MM*, malignant melanoma; *OR*, odds ratio.

Table III. Multivariable logistic regression analysis

	OR	(95% CI)	*P* value
Age at inclusion	1.04	(1.01-1.06)	.003
Gender			
Female	1.00	(Reference)	
Male	1.23	(0.68-2.22)	.500
Previous melanoma			
No	1.00	(Reference)	
Yes	1.55	(0.81-2.97)	.181
>100 Nevi			
No	1.00	(Reference)	
Yes	1.37	(0.72-2.60)	.342
No. of lesions excised	1.55	(1.37-1.75)	<.001
Skin phototype			
I	1.00	(Reference)	
II	0.33	(0.08-1.35)	.123
III	0.57	(0.14-2.26)	.423
IV	0.03	(0.00-0.76)	.033
CDKN2A mutation			
No	1.00	(Reference)	
Not performed	0.15	(0.06-0.37)	<.001
Yes	1.39	(0.53-3.68)	.505

CI, Confidence interval; *OR*, odds ratio.

occurring in those patients was not reported. In the latter study, only one MM was detected by DFU 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 dermatoscopy 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. MM/benign ratio was, as in the study of Fuller et al,[4] lower among lesions with no previous dermatoscopy record (1:8.8 vs 1:11.9).

The 10-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 IV, general data concerning number of patients, lesions monitored, percentage of lesions excised, malignant/benign ratio, and patients given the diagnosis of 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 of the current analysis. Haenssle et al[6,7] 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 as a result of 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 because 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, 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 MMs 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

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

Authors	Lesions-patients, No.	Mean lesions/ patient	Median follow-up, mo	Excisions (%) of lesions registered	Ratio MM/no MM	MM (%) of excisions	Patients given diagnosis of MM during DFU, %
Haenssle et al,[6,7] 2010, Germany	11,137-688	16.18	46	10.9	1:8.5	10.4	11.4
Argenziano et al,[29] 2008, Italy	600-405	1.48	23	9	1:3.4	22.2	3
Fuller et al,[4] 2007, USA	5945-297	20	22	5.4	1:53 PRL 1:95/NPRL 1:34.4	1.9 PRL 1.1/NPRL 2.75	2
Haenssle et al,[25] 2006, Germany	7001-530	13.2	32.2	9.1	1:12	8.3	10
Bauer et al,[26] 2005, Germany (EPL)	2015-196	10.28	25	1.6	1:15.5	6.1	1
Robinson and Nickoloff,[27] 2004, USA	3482-100	34.82	36.2	5.5	1:47.3	2.1	4
Malvehy and Puig,[5] 2002, Barcelona	3170-290	10.93	17.2	1.3	1:4.2	19	2.8
Menzies et al,[30] 2001, Australia	318-245	1.29	3	19.2	1:7.7	11.5	2.9
Kittler et al,[28] 2000, Austria	1862-202	9.21	12.6	4	1:8.4	10.7	4
Current study	11,396-618	18.44	96	10.1	1:10.7 PRL 1:11.9/ NPRL 1:8.8	8.5 PRL 7.7/ NPRL 10.1	12.6

DFU, Digital follow-up; *EPL*, epiluminiscence; *MM*, malignant melanoma; *NPRL*, nonpreviously registered lesions; *PRL*, previously registered lesions.

requires training, experience, and specific equipment. Chances of success in DFU depend basically on the proper selection of patients.[29] In our study population, with 90% of the patients displaying AMS and almost 45% with previous melanoma, one 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 given the diagnosis of MM during follow-up increased from 7% among patients with no personal history of MM, to 18% and 23% in patients with one primary MM and multiple primary MM before 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 populations at high risk for melanoma. In light of these findings, maintained surveillance may be required in individuals at high risk.

There is no consensus regarding the most effective melanoma screening strategy in individuals at high risk. Because there are no control groups we cannot convey whether the combined use of TBP and digital dermatoscopy is more beneficial than the TBP, dermatoscopy examination, or DFU separately. Recently, Goodson et al[18] compared their results using TBP and digital dermatoscopy 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 dermatoscopy 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 because of the fact that our median follow-up period is 4 times longer and our population could be considered of higher risk, because incidence of melanoma per patient during follow-up was 6 times higher.

In conclusion, TBP and digital dermatoscopy (two-step method of digital follow-up) in a selected population at high risk for melanoma 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 dermatoscopic criteria by DFU of dermatoscopy records, but also for the detection of melanoma either presented as new lesions or arising from nevi that were not monitored by dermatoscopy. 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 over time.

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