Original Investigation

Detection of Primary Melanoma in Individuals at Extreme High Risk

A Prospective 5-Year Follow-up Study

Fergal J. Moloney, MD; Pascale Guitera, MD, PhD; Elliot Coates, MB, BS; Nikolas K. Haass, MD, PhD; Kenneth Ho, MB, BS; Ritta Khoury, BMedSci; Rachel L. O'Connell, PhD; Leo Raudonikis; Helen Schmid, MPH; Graham J. Mann, MB, BS, PhD; Scott W. Menzies, MB, BS, PhD

IMPORTANCE The clinical phenotype and certain predisposing genetic mutations that confer increased melanoma risk are established; however, no consensus exists regarding optimal screening for such individuals. Early identification remains the most important intervention in reducing melanoma mortality.

OBJECTIVE To evaluate the impact of full-body examinations every 6 months supported by dermoscopy and total-body photography (TBP) on all patients and sequential digital dermoscopy imaging (SDDI), when indicated, on detecting primary melanoma in an extreme-risk population.

DESIGN, SETTING, AND PARTICIPANTS Prospective observational study from February 2006 to February 2011, with patients recruited from Sydney Melanoma Diagnostic Centre and Melanoma Institute Australia who had a history of invasive melanoma and dysplastic nevus syndrome, history of invasive melanoma and at least 3 first-degree or second-degree relatives with prior melanoma, history of at least 2 primary invasive melanomas, or a *CDKN2A* or *CDK4* gene mutation.

EXPOSURES Six-month full-body examination compared with TBP. For equivocal lesions, SDDI short term (approximately 3 months) or long term (≥6 months), following established criteria, was performed. Atypical lesions were excised.

MAIN OUTCOMES AND MEASURES New primary melanoma numbers, characteristics, and cumulative incidence in each patient subgroup; effect of diagnostic aids on new melanoma identification.

RESULTS In 311 patients with a median (interquartile range [IQR]) follow-up of 3.5 (2.4-4.2) years, 75 primary melanomas were detected, 14 at baseline visit. Median (IQR) Breslow thickness of postbaseline incident melanomas was in situ (in situ to 0.60 mm). Thirty-eight percent were detected using TBP and 39% with SDDI. Five melanomas were greater than 1 mm Breslow thickness, 3 of which were histologically desmoplastic; the other 2 had nodular components. The benign to malignant excision ratio was 1.6:1 for all lesions excised and 4.4:1 for melanocytic lesions. Cumulative risk of developing a novel primary melanoma was 12.7% by year 2, with new primary melanoma incidence during the final 3 years of follow-up half of that observed during the first 2 years (incidence density ratio, 0.43 [95% CI, 0.25-0.74]; $P = .002$).

CONCLUSIONS AND RELEVANCE Monitoring patients at extreme risk with TBP and SDDI assisted with early diagnosis of primary melanoma. Hypervigilance for difficult-to-detect thick melanoma subtypes is crucial.

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Author Affiliations: Author affiliations are listed at the end of this article.

Melanoma incidence is increasing annually in Australia, where it is the fourth most common cancer.[1] The most important predictors of future melanoma, apart from possession of a predisposing high-penetrance germline mutation, are a history of melanoma and multiple atypical nevi.[2-4] Guidelines recommend that individuals at highest risk be selected for closer surveillance.[5] Whereas encouraging vigilance and self-skin examination is important, there is increasing evidence that interventions such as dermoscopy, sequential digital dermsocopic imaging (SDDI), and baseline total-body photography (TBP) can aid early detection of melanoma.[6-8]

Meta-analysis indicates improved diagnosis of melanoma with dermoscopic vs naked eye evaluation in the clinic.[9] The use of SDDI enhances earlier detection of featureless melanomas and reduces excisions of benign pigmented lesions.[10,11] Dermatologists with access to SDDI demonstrate improved sensitivity and specificity of melanoma diagnosis when compared with dermatologists using dermoscopy only in their practice.[12] Combining SDDI and TBP improves diagnosis of clinically featureless and de novo melanomas that might be missed with dermoscopy alone.[13]

We recruited a cohort at extreme high risk of melanoma and evaluated the impact of full-body examinations every 6 months supported by dermoscopy and TBP, with SDDI where indicated, on the detection of primary melanoma in this population.

Methods

Study Population

The study was approved by the ethics committee of Royal Prince Alfred Hospital, with recruitment by written informed consent. Patients (≥18 years of age) fulfilling at least 1 of the following 4 inclusion criteria were recruited from outpatient clinics of the Sydney Melanoma Diagnostic Centre and the Melanoma Institute Australia.

Group 1: Personal history of at least 1 invasive melanoma and dysplastic nevus syndrome (DNS). Dysplastic nevus syndrome was defined as at least 100 nevi, at least 6 of which showed atypical dermoscopic features consistent with dysplastic nevus as previously described,[14(pp79-128)] and at least 1 of which was at least 8 mm in greatest dimension.

Group 2: Personal history of at least 1 invasive melanoma and a family history of at least 3 first-degree or second-degree relatives with a confirmed history of malignant melanoma.

Group 3: Personal history of at least 2 primary invasive melanomas, with at least 1 occurring in the 10 years prior to recruitment for patients with only 2 melanomas.

Group 4: Confirmed *CDKN2A* (OMIM 600160) or *CDK4* (OMIM 123829) gene mutation (the highest-penetrance susceptibility gene mutations for melanoma). No history of invasive melanoma was required for this group, although 12 of 17 patients had such a history.

Certain patients satisfied more than 1 inclusion criterion and were analyzed in each category. Family history was validated by recruitment, where necessary, to the University of Sydney GenoMEL study center at Westmead Millennium Institute,[15] from which, in turn, confirmed *CDKN2A* mutation carriers were referred to the melanoma high-risk clinic. All participants in category 4 carried confirmed pathogenic *CDKN2A* mutations; none had *CDK4* mutations.[15]

Study Design

Key patient data were recorded at each visit and stored on a purpose-built Filemaker Pro database (Filemaker Inc). Each patient was reviewed on a 6-month basis by a dermatologist (F.J.M., P.G., N.K.H., K.H.) or, in a small proportion of visits, by dermatology registrars.

Initial Visit

Baseline data obtained included age, sex, Fitzpatrick skin type, eye color, hair color, and childhood freckling history. The attending physician performed a mole count documenting the patient's total nevus and dysplastic nevus count. Each patient underwent a full skin examination and contact dermoscopic evaluation of suspicious lesions using a Heine Delta 20 dermatoscope (Heine Optotechnik). Lesions of concern were excised, referred for SDDI, or compared with images if previously monitored.

SDDI

Macular or slightly raised melanocytic lesions considered suspicious because of dermoscopic appearance or history of change but lacking any positive features of melanoma were monitored using short-term SDDI (SolarScan, Polartechnics Ltd) as previously described.[11] A baseline dermoscopic image was repeated at 3 months with excision of lesions showing any morphological change, as previously described.[16] Substantially raised suspicious lesions were excluded from SDDI and excised. For melanocytic lesions undergoing SDDI over longer intervals (long-term monitoring ≥6 months), such as in patients with multiple dysplastic nevi, lesions were excised according to the clinically significant morphological changes as previously described.[17,18] Long-term SDDI was performed on less suspicious atypical nevi (compared with those undergoing short-term SDDI) or in some nevi previously monitored by short-term SDDI.

TBP

Each patient underwent baseline digital TBP following standard protocols, according to which between 12 and 24 high-resolution digital photographs of their skin surface were recorded[19] (Polartechnics Pty Ltd and MoleMap Pty Ltd). The photographs were provided on a DVD to the patient, and a copy of the images was stored. Patients were instructed in the use of TBP and asked to perform a full self-skin examination at 3 months and again the day before their 6-month follow-up visit.

Follow-up Visits

At each follow-up visit, patients were initially asked about changes that they had noted either with or without TBP assistance. Patients then underwent a full clinical and dermoscopic skin examination. The clinician then compared the pa-

tient with baseline TBP images. Any lesion noted as changed from baseline was recorded. If the lesion was also earmarked during the clinical and/or dermoscopic examination as being of concern, it was coded as "detected with the aid of TBP." If the lesion had not been previously earmarked, it was coded as "detected exclusively with TBP."

Again, lesions of concern were excised or referred for SDDI (short term or long term). For all lesions excised, the reason for the decision was recorded: (1) excised only because of patient request, (2) self-detected without TBP, (3) self-detected with TBP, (4) clinician detected without TBP, (5) clinician detected with aid of TBP, (6) clinician detected exclusively with TBP, (7) change under short-term SDDI, or (8) change under long-term SDDI.

Statistical Methods

Data were expressed as frequencies (percentages) for categorical variables and as mean and standard deviation or median and interquartile range (IQR) for normally and nonnormally distributed continuous variables, respectively. A cumulative incidence curve of the time to first new melanoma event during the follow-up period was calculated with the Kaplan-Meier method.[20] eFigure 1 (in Supplement) shows the number at risk at the beginning of each year of follow-up (ie, the number still under follow-up [not censored] who had not yet experienced an event).

For multiple-event analysis, a Poisson regression model using generalized estimating equations[21(pp162-168)] was used with 2 time intervals per person: 0 to 2 years from registration (ie, early [0-2]) and after 2 years (ie, late [>2-5]). The model used an offset to adjust for patient exposure within each interval and an exchangeable correlation structure between intervals.

Median follow-up time was obtained by using the reverse Kaplan-Meier method, in which deaths were treated as censored and censored observations as failures.[22] The Poisson generalized estimating equations analysis produced an incidence density ratio (analogous to the hazard ratio) that reflected the relative change in event rate per unit time for late (after 2 years) vs early (within 2 years) incidence of new primary melanoma. SAS software, version 9.3 (SAS Institute), was used for the analysis.

Results

Baseline Demographic Characteristics

A total of 311 patients were recruited between 2006 and 2009. Of these, 219 had a history of invasive melanoma and DNS (DNS cohort); 52, a history of invasive melanoma and 3 or more first-degree or second-degree relatives with melanoma (strong family history cohort); 146, a history of multiple previous primary invasive melanomas (multiple primary melanomas cohort); and 17, a documented *CDKN2A* gene mutation (gene mutation carrier cohort). The median (range) age at baseline was 53 (21-85) years (**Table 1**).

Ten patients did not attend as per protocol after baseline assessment, 7 of whom were lost to follow-up. There was no statistical difference in follow-up duration for the 4 groups, with a median follow-up for the study population as a whole of 41.8 months (3.5 years) (IQR, 29.0-50.8 months [2.4-4.2 years]). Nine patients died during the course of the study, 7 from metastatic melanoma, of whom only 1 developed a new primary melanoma during the study period. In this latter case, it was not possible to determine whether metastases developed from the pretrial or trial melanoma.

Fitzpatrick skin type was also consistent across each of the study groups. Approximately two-thirds of patients were Fitzpatrick skin type I or II. Only 2 patients (0.6%) were skin type IV, and none were V or VI (Table 1). Approximately two-thirds of patients (70%) had 100 or more nevi at baseline counting, whereas approximately one-third (36%) had 200 or more nevi.

Lesions Excised

During the study period, 770 lesions were excised from the patient cohort (**Table 2**), of which 291 (38%) were malignant, for a benign to malignant ratio of 1.6:1 for all lesions. The benign to malignant ratios were 2.2:1 in the DNS cohort, 1.8:1 in the strong family history cohort, 1.1:1 in the multiple primary melanomas cohort, and 1.6:1 in the gene mutation carrier cohort. Of the 770 excised lesions, 441 were melanocytic, including 82 melanomas, representing a 4.4:1 benign melanocytic to melanoma ratio. Of the 359 benign melanocytic lesions excised, 251 (70%) were reported as dysplastic nevi. Of the 291 excised malignant skin lesions, 209 were nonmelanoma skin cancers, comprising 143 basal cell carcinomas, 35 squamous cell carcinomas, 29 squamous cell carcinomas in situ, and 2 keratoacanthomas. The basal cell carcinoma to squamous cell carcinomas ratio was 2.2:1 in the study population overall.

A high proportion of the melanoma-associated nevi were dysplastic (37 of 38 [97%]). Of the nevi excised and not associated with melanoma, 251 of 337 (74%) were dysplastic.

The 82 melanomas detected during the study included 75 primary tumors and 7 locally recurrent or cutaneous metastases (**Table 3**). Fifty-one of the primary melanomas (68%) occurred in the 179 men, compared with 24 primary melanomas (32%) in the 132 women. The median (IQR) Breslow thickness for all primary melanomas identified, including at baseline, was in situ (in situ to 0.60 mm). Body site and histological subtype are detailed in Table 3.

Fourteen primary melanomas were identified at the baseline visit. Sixty-one additional primary melanomas diagnosed during follow-up monitoring visits (Table 3) were found in 48 patients, 74% of whom had multiple primary melanomas and 67%, 16%, and 5% in the DNS, strong family history, and gene mutation carrier cohorts, respectively. The overall rate of melanomas identified during follow-up per study year was 0.08, with the highest rate in the multiple primary melanoma cohort (0.11), followed by the strong family history cohort (0.08), DNS cohort (0.07), and the gene mutation cohort (0.06), allowing for the fact that certain patients were included in more than 1 subgroup. The median (range) time from baseline visit to primary melanoma detection was 17.9 months (2.9-53.2 months).

Thirty-eight postbaseline incident melanomas (62%) were identified on pathological analysis as nevus-associated (junctional n = 23, with 22 dysplastic and 1 nondysplastic; 15 com-

Table 1. Characteristics of Patients at Extreme High Risk of Melanoma by Subgroup[a]

Characteristic	All Patients (N = 311)	DNS and History of Melanoma (n = 219)	Strong Family and Personal History of Melanoma (n = 52)	Multiple Primary Melanomas (n = 146)	Gene Mutation (n = 17)
Age at baseline, median (range), y	53 (21-85)	51 (21-77)	50 (27-81)	59 (29-85)	48 (30-81)
Sex, No. (%)					
Male	179 (58)	125 (57)	17 (33)	86 (59)	7 (41)
Female	132 (42)	94 (43)	35 (67)	60 (41)	10 (59)
Follow-up, months					
Total	11 998	8750	1703	5802	565
Median (range)	41.8 (29.0-50.8)	43.0 (31.2-51.1)	31.9 (24.9-44.3)	45.0 (29.0-52.1)	40.5 (6.2-50.5)
Phenotype, No. (%)					
I	49 (16)	34 (16)	8 (15)	24 (16)	3 (18)
II	165 (53)	116 (53)	28 (54)	80 (55)	7 (41)
III	92 (30)	67 (31)	14 (27)	40 (27)	6 (35)
IV	2 (0.6)	1 (0.5)	1 (2)	1 (0.7)	1 (6)
V	0	0	0	0	0
VI	0	0	0	0	0
No value	3 (1)	1 (0.5)	1 (2)	1 (0.7)	0
Eye color, No. (%)					
Blue/gray	177 (57)	114 (52)	26 (50)	94 (64)	13 (76)
Hazel/green	97 (31)	77 (35)	19 (37)	34 (23)	2 (12)
Brown	32 (10)	25 (11)	6 (12)	15 (10)	2 (12)
No value	5 (2)	3 (1)	1 (2)	3 (2)	0
Hair color, No. (%)					
Red	52 (17)	29 (13)	12 (23)	32 (22)	4 (24)
Blond	137 (44)	102 (47)	19 (37)	59 (40)	8 (47)
Brown	112 (36)	82 (37)	19 (37)	49 (34)	5 (29)
Black	4 (1)	2 (0.9)	0	2 (1)	0
No value	6 (2)	4 (2)	2 (4)	4 (3)	0
Childhood freckling, No. (%)					
None	103 (33)	81 (37)	9 (17)	48 (33)	2 (12)
Very few	83 (27)	56 (26)	15 (29)	37 (25)	5 (29)
Few	60 (19)	41 (19)	14 (27)	30 (21)	6 (35)
Some	30 (10)	19 (9)	4 (8)	15 (10)	2 (12)
Many	20 (6)	13 (6)	6 (12)	11 (8)	2 (12)
Very many	12 (4)	8 (4)	3 (6)	4 (3)	0
No value	3 (1)	1 (0.5)	1 (2)	1 (1)	0
Total nevi, No. (%)					
0-49	43 (14)	0	7 (13)	38 (26)	3 (18)
50-99	25 (8)	0	8 (15)	19 (13)	6 (35)
100-199	106 (34)	98 (45)	17 (33)	40 (27)	5 (29)
≥200	111 (36)	109 (50)	14 (27)	37 (25)	2 (12)
No value	26 (8)	12 (6)	6 (12)	12 (8)	1 (6)
Nevus count, median (IQR)					
Total	167 (104-253)	202 (150-294)	143 (76-225)	112 (38-202)	78 (60-173)
Dysplastic	8 (6-13)	10 (7-15)	6 (3-12)	6 (3-12)	5 (2-7)

Abbreviations: DNS, dysplastic nevus syndrome; IQR, interquartile range.

[a] Patients may satisfy inclusion criteria for more than 1 subgroup.

pound, all of which were dysplastic), compared with 23 (38%) developing de novo. The median (IQR) Breslow thickness was in situ (in situ to 0.60 mm) when only melanomas detected following the baseline visit were considered. Five of the 61 melanomas diagnosed after the baseline visit had a Breslow thickness of greater than 1 mm (**Table 4**). Three of the 5 thick melanomas were desmoplastic (none associated with a nevus) and occurred in 2 siblings (eFigure 2 in Supplement). Two of these were morphologically amelanotic on dermoscopy, and the other, tan. The 2 other lesions had both superficial spread-

Table 2. Melanomas, Nonmelanoma Skin Cancers (NMSCs), and Benign Melanocytic and Nonmelanocytic Lesions Excised During Follow-up in Total and by Patient Subgroup[a]

Lesion	No.				
	All Patients (N = 311)	DNS and History of Melanoma (n = 219)	Strong Family and Personal History of Melanoma (n = 52)	Multiple Primary Melanomas (n = 146)	Gene Mutation (n = 17)
Melanoma					
SSM	25	18	1	16	0
Nodular	6	4	3	4	2
Lentigo maligna melanoma	1	0	0	1	0
Lentigo maligna (HMF)	9	4	1	8	0
Desmoplastic	3	3	3	3	0
In situ	30	19	3	21	1
Invasive, not classified	1	1	0	1	0
Local recurrence or cutaneous metastasis[b]	7	2	0	6	0
Total	**82**	**51**	**11**	**60**	**3**
NMSC					
BCC	143	93	8	77	3
SCC	35	14	3	23	3
SCC in situ	29	12	5	20	2
Keratoacanthoma	2	0	1	1	0
Total	**209**	**119**	**17**	**121**	**8**
Benign melanocytic					
Ephelis	3	3	0	1	0
Lentigo	19	14	1	12	1
Lentiginous nevus	5	4	2	1	0
Junctional nevus	19	14	3	10	0
Compound nevus	40	39	5	9	3
Intradermal nevus	21	17	1	7	0
Blue nevus	1	0	0	1	0
Dysplastic junctional nevus	130	102	12	63	4
Dysplastic compound nevus	121	108	10	39	3
Total	**359**	**301**	**34**	**143**	**11**
Benign nonmelanocytic					
Dermatofibroma	12	9	1	8	0
Capillary hemangioma	3	1	2	1	1
Seborrheic keratosis	21	13	1	12	0
Actinic keratosis	21	12	4	13	3
Granuloma	1	0	0	1	0
Inflammatory and/or pigment incontinence	2	1	0	2	0
Other	53	33	9	25	3
Total	**113**	**69**	**17**	**62**	**7**
No pathology report obtainable	7	6	0	1	0
Total lesions excised	**770**	**546**	**79**	**387**	**29**

Abbreviations: BCC, basal cell carcinoma; DNS, dysplastic nevus syndrome; HMF, Hutchinson melanocytic freckle; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma; SSM, superficial spreading melanoma.

[a] Patients may satisfy inclusion criteria for more than 1 subgroup.

[b] Nonprimary melanomas.

ing and nodular components. Both lesions were described clinically as amelanotic, although a dermoscopic image was not available to confirm this. Importantly, of the 6 predominantly nodular melanomas detected postbaseline, only 1 had a Breslow thickness greater than 1 mm. Four of 6 of these nodular melanomas were associated with a nevus (2 dysplastic compound, 2 dysplastic junctional).

Cumulative Incidence

eFigure 1 (in Supplement) shows the cumulative incidence of new primary melanomas for the study population for each year of the study. Forty-four of the primary melanomas identified after the baseline visit (72%) were diagnosed in the first 2 years of follow-up. The curve illustrates an increased cumulative incidence for melanoma in the first 2 years of inclusion in the

Table 3. All Primary Melanomas Diagnosed During the Intervention

Characteristic	All Primary Melanomas (n = 75)[a]	Nonbaseline Incident Primary Melanomas (n = 61)
Sex, No. (%)		
Male	51 (68)	41 (67)
Female	24 (32)	20 (33)
Inclusion criteria,[b] No. (%)		
DNS + melanoma	49 (65)	41 (67)
Strong family history + melanoma	11 (15)	10 (16)
Multiple primary melanomas	54 (72)	45 (74)
Gene mutation	3 (4)	3 (5)
Melanomas per year of follow-up		
DNS + melanoma	...	0.07
Strong family history + melanoma	...	0.08
Multiple primary melanomas	...	0.11
Gene mutation	...	0.06
Tumor site, No. (%)		
Head and neck	11 (15)	11 (18)
Trunk	35 (47)	26 (43)
Upper limbs	18 (24)	16 (26)
Lower limbs	11 (15)	8 (13)
Detection time, median (range), months	...	17.9 (2.9-53.2)
Breslow thickness		
Median (IQR)		
All	In situ (in situ to 0.60 mm)	In situ (in situ to 0.60 mm)
TBP detected	...	0.33 (in situ to 0.83 mm)
SDDI detected	...	In situ (in situ to 0.15 mm)
No. (%)		
In situ	38 (51)	32 (52)
≤1 mm	30 (40)	24 (39)
>1 mm	7 (9)	5 (8)
Nevus associated, No. (%)		
Yes	...	38 (62)
No	...	23 (38)
Histological subtype, No. (%)		
Lentigo maligna	9 (12)	8 (13)
Lentigo maligna melanoma	1 (1)	1 (2)
In situ	30 (40)	25 (41)
SSM	25 (33)	17 (28)
Nodular	6 (8)	6 (10)
Desmoplastic	3 (4)	3 (5)
Invasive, not histologically classified	1 (13)	1 (2)
Excision and detection reason,[c] No. (%)		
Excision reason unclear	...	0
Excised at patient's request	...	0
Excised after self-detection without TBP	...	5 (8)
Excised after self-detection with TBP	...	0
Excised after clinician detection without TBP	...	10 (16)
Excised after clinician detection with TBP		
With the aid of TBP	...	20 (33)
Exclusively with TBP	...	3 (5)
Excised because of change on lesion monitoring		
Short-term monitoring	...	10 (16)
Long-term monitoring	...	14 (23)

Abbreviations: IQR, interquartile range; SDDI, sequential digital dermoscopy imaging; SSM, superficial spreading melanoma; TBP, total-body photography.

[a] The categories of melanomas per year of follow-up, detection time, method, and reason for detection were relevant for nonbaseline incident primary melanomas only.

[b] Patients may satisfy inclusion criteria for more than 1 subgroup.

[c] Certain melanomas were detected with more than 1 method.

study, with continued new primary melanoma identification out to year 5. The risk of new primary melanoma development for all patients was 12.7% by year 2 and 18.2% by year 4, with an incidence of new primary melanoma during the final 3 years of follow-up noted to be half of that observed during the first 2 years (incidence density ratio, 0.43 [95% CI, 0.25-0.74]; $P = .002$).

Effect of Diagnostic Aids on New Melanoma Identification

Melanomas detected with SDDI and TBP did not differ significantly (χ^2 test, $P = .75$) with respect to whether they originated in nevi or de novo. Twenty-four of the postbaseline incident melanomas (39%) were detected using SDDI (Table 3). A total of 1697 lesions were monitored by SDDI; that is, 70.7 lesions were monitored for each melanoma detected. Changes in 10 melanomas (16%) were detected on short-term monitoring whereas 14 (23%) were detected on long-term monitoring. The median (IQR) Breslow thickness for melanomas detected by SDDI was in situ (in situ to 0.15 mm). Twenty-three of the postbaseline incident melanomas (38%) were excised after the clinician-detected change on the TBP. The median (IQR) Breslow thickness for melanomas detected with TBP was 0.33 (in situ to 0.83 mm). Twenty of the 23 melanomas were detected with the aid of TBP, whereas 3 were diagnosed exclusively as a result of a change identified on TBP. Ten of the melanomas diagnosed (16%) were lesions identified dermoscopically by the examining physician as suspicious, without any change noted on TBP or with SDDI. No melanoma diagnosed could be exclusively attributed to changes on the TBP identified by the patient, although 5 melanomas (8%) were noted by the patient to be changing—without reference to the TBP—and were subsequently brought to the physician's attention. Finally, of the 5 melanomas of greater than 1 mm Breslow thickness, 2 were self-detected by patients and only 1 of

Table 4. Melanomas Diagnosed During Follow-up (Postbaseline Incident) Measuring Greater Than 1 Millimeter Breslow Thickness

Breslow thickness, mm	Histopathologic Subtype	Dermoscopic Appearance	Location
21.0	Desmoplastic	Amelanotic	Left buttock
8.5	Desmoplastic	Amelanotic	Right upper arm
1.6	Desmoplastic	Tan colored	Nose
2.3	SSM and nodular	Not able to confirm	Right neck
1.4	SSM and nodular	Not able to confirm	Left shoulder

Abbreviations: IQR, interquartile range; SDDI, sequential digital dermoscopy imaging; SSM, superficial spreading melanoma.

the 5 was detected with the aid of TBP. Of the 6 predominantly nodular melanomas detected postbaseline, 3 were detected with the aid of TBP, 2 were detected without TBP, and 1 was self-detected.

When patients with DNS were compared with patients without DNS, there was no significant difference between the proportion of postbaseline incident melanomas detected by TBP (15 of 41 [37%] in the DNS group vs 8 of 20 [40%] in the non-DNS group; χ^2 P = .80) or SDDI (17 of 41 [41%] in the DNS group vs 7 of 20 [35%] in the non-DNS group; χ^2 P = .63). Finally, there was no significant difference between the proportion of postbaseline incident melanomas associated with a nevus in the DNS group (28 of 41 [68%]), compared with the non-DNS group (10 of 20 [50%]; χ^2 P = .17).

Discussion

Patients with a history of melanoma have a 9-fold increased risk of developing a new primary melanoma compared with the general population.[23] This risk is further amplified in patients with melanoma who have multiple dysplastic nevi, a history of multiple primary melanomas, 3 or more first-degree relatives with melanoma, or a predisposing gene mutation.[2,15,24,25] To our knowledge, this study is the first to prospectively follow a patient cohort at extreme high risk of melanoma with the primary aim of determining the relative efficacy of diagnostic interventions.

Our study's inclusion criteria generated patients at extreme melanoma risk, hence the high rate of melanomas detected (75 new primary melanomas in 311 individuals over a median 3.5-year period). Other studies have prospectively followed populations at increased melanoma risk. Haenssle et al[7] detected 127 melanomas in 688 patients over 10 years using naked eye, dermoscopic analysis, and SDDI. Their patient population was at increased risk, but not all patients were high risk. Malvehy and Puig[26] focused on high-risk patients (45% of whom had a prior melanoma), identifying 98 melanomas from 1152 lesions excised in 618 patients monitored over 10 years with combined SDDI and TBP surveillance.[6] Our study also demonstrated high rates of nonmelanoma skin cancer in a relatively young melanoma-prone population (median age, 53 years), with 72% (209 of 291) of biopsied malignant lesions demonstrating nonmelanoma skin cancer.

Although the subgroups in our study were not mutually exclusive, the number of new melanomas per year of follow-up was highest in patients possessing a personal history of multiple primary invasive melanoma. In Australia, 1 study estimated the 10-year risk for developing a second primary melanoma as 12.7%, and for those who had 2 primary melanomas, the estimated 10-year risk of developing a third was 28%.[27] Ferrone et al[24] calculated an estimated 11.4% cumulative risk of second primary melanoma within 5 years in patients with a history of melanoma.

The cumulative incidence of postbaseline incident melanomas diagnosed was significantly higher in the first 2 years following inclusion despite standard 6-monthly reviews stretching out to 5 years. We do not report our incidence from first melanoma but rather from entry into our intervention. In previous studies observing patients with multiple primary melanomas, 51% to 59% of subsequent primary melanomas identified occurred within the first year following initial melanoma diagnosis, although these percentages must be evaluated in the context of the short duration of follow-up in these studies.[23,28,29] Identifying a preponderance of subsequent melanomas in the initial years following melanoma diagnosis is an observation in part attributed to increased surveillance after diagnosis. Alternatively, those melanomas may have been present at initial surveillance but without features of melanoma and were therefore only diagnosable by subsequent change identified on SDDI or noted from comparisons with baseline TBP.

Ninety-one percent of postbaseline incident melanomas excised in this cohort were thin melanomas of no more than 1 mm Breslow thickness. A median Breslow thickness of in situ confers an optimal prognosis for most of the melanomas that were excised. It is well documented that subsequent melanomas in patients with multiple primary melanomas tend to be thinner at diagnosis than the patient's first melanoma.[23,28,29] Body site location of melanomas detected in our high-risk population showed a similar body site distribution (primarily on the limbs in women and the trunk in men) and histological subtype (superficial spreading melanoma and melanoma in situ most common) compared with melanomas diagnosed in the general population.[30]

All 5 melanomas more than 1 mm thick detected were diagnostically challenging because of lack of pigment or rare pathological subtypes. Whereas 8% of the melanoma subtypes in our study were nodular and 4% desmoplastic, no such lesions were reported in the Spanish cohort, in which all melanomas detected were 1 mm or less.[6] Our findings demonstrate the need for high awareness of rare melanoma subtypes in extreme high risk populations. Desmoplastic melanoma is frequently diagnosed late because of absent pigmentation and minimal specific identifying features.[31] Hypervigilance for nodular lesions using dermoscopic criteria[32] with prompt biopsy of longstanding or changing atypical lesions is vital.

Only 8.2% of melanomas were self-detected by patients; however, 2 of 5 thick melanomas (>1 mm) and 1 of 6 nodular melanomas were self-detected. Importantly, in our study, only 1 of 6 postbaseline incident nodular melanomas had a Breslow thickness greater than 1 mm, indicating that these rapidly growing tumors were detected early using our protocol. We did not assess patients' compliance with TBP self-examination during the trial. However, following the trial with the same cohort under the same examination protocol, 46.6% of patients undertook self-skin examination with TBP prior to their consultation and 71.7% reported TBP self-examination at least once during the previous 12 months (interim analysis of an ongoing study).

In the present study, 39% of melanomas were diagnosed either exclusively or aided by SDDI. This compares with the 25% (32 of 127) of melanomas that were detected exclusively by SDDI by Haenssle et al[7] and the 61% (60 of 98) of melanomas that were identified by SDDI by Salerni et al[6] in their high-risk populations. There is increasing use of TBP in academic pigmented lesion clinics but few studies demonstrating its efficacy as a screening adjunct for melanoma.[33] In this extreme-risk population, 38% of melanomas were diagnosed either exclusively or aided by TBP. The median Breslow thickness was in situ for melanomas diagnosed with the aid of either SDDI or TBP.

There are certain limitations to this study. Many patients satisfied inclusion criteria for more than 1 subgroup, so we were unable to test for differences in characteristics or outcomes across nonmutually exclusive groups. Although the nature of the study precluded a control arm, comparison of surrogate markers such as benign to malignant ratio and median Breslow thickness compares favorably with other studies. It is possible that skin cancer incidence was underestimated because of excisions by practitioners outside our clinic, although every effort was made to capture these events. It is also recognized that the study design includes a greater time allocation for TBP comparative examination than is provided for in a routine clinic setting. Approximately one-third of study patients had more than 200 nevi, monitoring of which is time consuming and challenging for both patients and physicians. It could be argued that this study in part demonstrates the value of allocating additional clinic time for examination of patients at higher risk. There were few nonattendances, with most patients expressing high levels of satisfaction with the service. Finally, the nevus-associated melanomas were reported from the synoptic histopathology reports. Because the focus of this research was early detection of primary melanoma, histopathological review of all excised lesions was not undertaken. Whereas there may be difficulty in distinguishing true dysplastic nevi within melanoma in some cases, the diagnosis of melanoma is not in doubt.

Conclusions

Our study highlights the diagnostic importance of both TBP and SDDI in the follow-up of high-risk patients for primary melanoma. Despite this, hypervigilance for difficult-to-detect thick melanoma subtypes is crucial.

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Author Affiliations: Discipline of Dermatology, University of Sydney at the Sydney Cancer Centre, Sydney, New South Wales, Australia (Moloney, Guitera, Coates, Haass, Ho, Menzies); Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia (Moloney, Guitera, Coates, Haass, Ho, Khoury, Menzies); Sydney Melanoma Diagnostic Centre, Sydney Cancer Centre, Sydney, New South Wales, Australia (Moloney, Guitera, Coates, Haass, Ho, Khoury, Menzies); now with Department of Dermatology, Mater Misericordiae University Hospital, Dublin, Ireland (Moloney); now with University of Queensland Diamantina Institute, Translational Research Institute, Woolloongabba, Queensland, Australia (Haass); National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia (O'Connell); Raudonikis Database Services, Mount Colah, New South Wales, Australia (Raudonikis); University of Sydney at the Westmead Millennium Institute, Westmead, New South Wales, Australia (Schmid, Mann); Melanoma Institute Australia, Westmead, New South Wales, Australia (Schmid, Mann).

Corresponding Author: Scott W. Menzies, MB,BS, PhD, Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Camperdown, New South Wales 2050, Australia (scott.menzies@sswahs.nsw.gov.au).

Author Contributions: Drs Moloney and Coates had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Guitera, Mann, Menzies.
Acquisition, analysis, or interpretation of data: Moloney, Coates, Haass, Ho, Khoury, O'Connell, Raudonikis, Schmid, Mann, Menzies.
Drafting of the manuscript: Moloney, Coates, O'Connell, Mann, Menzies.
Critical revision of the manuscript for important intellectual content: Moloney, Guitera, Coates, Haass, Ho, Khoury, Raudonikis, Schmid, Mann, Menzies.
Statistical analysis: Coates, O'Connell.
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Study supervision: Mann, Menzies.

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