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Efficiency of Detecting New Primary Melanoma Among Individuals Treated in a High-risk Clinic for Skin Surveillance

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IMPORTANCE A previous single-center study observed fewer excisions, lower health care costs, thinner melanomas, and better quality of life when surveillance of high-risk patients was conducted in a melanoma dermatology clinic with a structured surveillance protocol involving full-body examinations every 6 months aided by total-body photography (TBP) and sequential digital dermoscopy imaging (SDDI).

OBJECTIVE To examine longer-term sustainability and expansion of the surveillance program to numerous practices, including a primary care skin cancer clinic setting.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study recruited 593 participants assessed from 2012 to 2018 as having very high risk of melanoma, with a median of 2.9 years of follow-up (interquartile range, 1.9-3.3 years), from 4 melanoma high-risk clinics (3 dermatology clinics and 1 primary care skin cancer clinic) in New South Wales, Australia. Data analyses were conducted from February to September 2020.

EXPOSURES Six-month full-body examination with the aid of TBP and SDDI. For equivocal lesions, the clinician performed SDDI at 3 or 6 months.

MAIN OUTCOMES AND MEASURES All suspect monitored or excised lesions were recorded, and pathology reports obtained. Outcomes included the incidence and characteristics of new lesions and the association of diagnostic aids with rates of new melanoma detection.

RESULTS Among 593 participants, 340 (57.3%) were men, and the median age at baseline was 58 years (interquartile range, 47-66 years). There were 1513 lesions excised during follow-up, including 171 primary melanomas. The overall benign to malignant excision ratio, including keratinocyte carcinomas, was 0.8:1.0; the benign melanocytic to melanoma excision ratio was 2.4:1.0; and the melanoma in situ to invasive melanoma ratio was 2.2:1.0. The excision ratios were similar across the 4 centers. The risk of developing a new melanoma was 9.0% annually in the first 2 years and increased with time, particularly for those with multiple primary melanomas. The thicker melanomas (>1-mm Breslow thickness; 7 of 171 melanomas [4.1%]) were mostly desmoplastic or nodular (4 of 7), self-detected (2 of 7), or clinician detected without the aid of TBP (3 of 7). Overall, new melanomas were most likely to be detected by a clinician with the aid of TBP (54 of 171 [31.6%]) followed by digital dermoscopy monitoring (50 of 171 [29.2%]).

CONCLUSIONS AND RELEVANCE The structured surveillance program for high-risk patients may be implemented at a larger scale given the present cohort study findings suggesting the sustainability and replication of results in numerous settings, including a primary care skin cancer clinic.

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The incidence of melanoma has been increasing in many countries.[1] Australia has the highest incidence rates, and together with other nonmelanoma (keratinocyte) skin cancers, melanoma represents the most expensive cancer for the health care system.[2-4] Those who develop an in situ or invasive primary melanoma are at much greater risk of developing subsequent melanoma compared with the general population,[5] especially for those with additional risk factors, such as multiple primary melanomas, dysplastic nevi, family history, or a melanoma-predisposing gene variant.[6,7] Early detection is associated with better survival,[8] less morbidity from treatment, and fewer health system costs.[9-12]

Australian clinical practice guidelines recommend that individuals at very high risk of melanoma be checked regularly by a clinician, with full skin examinations every 6 months supported by dermoscopy and using the aids of sequential digital dermoscopy imaging (SDDI) and total-body photography (TBP).[13] This recommendation was based partly on a previous Australian study that showed a structured surveillance program was less expensive and associated with more quality-adjusted life-years of survival than standard care.[14,15] The use of surveillance technologies, including dermoscopy, short-term and long-term SDDI, and TBP,[16] facilitated the detection of changing lesions and minimized the excision of benign lesions that add considerably to health system costs.[11,15] A Spanish study[17] also showed a favorable Breslow thickness distribution among a high-risk cohort followed up with a structured surveillance protocol, albeit with a higher ratio of excised benign to malignant melanocytic lesions (10.7:1) than the Australian study (4.4:1).[14,15]

As highlighted in clinical practice guidelines for the diagnosis and management of melanoma,[13] there are some key gaps and limitations that hinder the wider implementation of these recommendations in routine clinical practice, such as the single-center design of the previous studies, limited replication, and uncertainty around the extent to which reduced rates of excisions for benign lesions can be sustained in the longer term and achieved in other dermatology clinics and in primary care settings, such as primary care skin cancer clinics, that diagnose approximately 17% of early-stage melanoma cases in Australia.[18] The present study addresses these gaps.

Key Points

Question Are the favorable excision rates and melanoma early detection outcomes from a previously implemented structured surveillance program for people at high risk of melanoma sustained in the longer term and replicated in other centers, including a primary care skin cancer clinic?

Findings Of 171 new melanomas detected among 593 participants in this cohort study, 96% had a Breslow thickness of 1 mm or less, and 67% of melanomas were found with the assistance of total-body photography or sequential digital dermoscopy imaging. The overall benign to malignant excision ratio was 0.8:1.0, and the benign melanocytic to melanoma excision ratio was 2.4:1.0, both of which were similar across centers.

Meaning The findings of this cohort study suggest that the structured surveillance program may be implemented on a larger scale, including at primary care skin cancer clinics, with consistent and sustainable benefits observed.

Methods

Study Design and Population

We used a cohort study design. Melanoma high-risk clinics (HRCs) were established at 4 centers in New South Wales, Australia (**Table 1**). The Sydney Melanoma Diagnostic Centre (SMDC) at Royal Prince Alfred Hospital, a tertiary referral center, had a dedicated trained resident medical officer or general practice physician (S.W.M., E.C.) under specialist supervision. Dermatologists (P.F.-P., R.L.) led the HRCs at Westmead Hospital, an outpatient clinic in a major teaching hospital, and at Melanoma Institute Australia (P.G., H.C.), a major tertiary referral center. Newcastle Skin Check is a primary care skin cancer clinic (A.A., A.L.). Skin cancer clinics are staffed by general practice physicians; however, they focus solely on skin cancer. The study was approved by the human research ethics committees of the Sydney Local Health District at Royal Prince Alfred Hospital. All participants provided written informed consent that was obtained in a manner consistent with the Australian National Statement on Ethical Conduct in Human Research. No one received compensation or was offered any incentive for participating in this study.

Patients 18 years of age or older were invited to attend the HRC for their skin surveillance as part of this research study if they were considered to be at very high risk of cutaneous melanoma, assessed as meeting at least 1 of 4 eligibility criteria (eMethods in the Supplement).[14] The HRC study initially started as a single-center study with recruitment of participants from 2006 to 2009 at the Sydney Melanoma Diagnostic Centre; follow-up data collected at that center from 2006 to 2011 as part of the initial study have been previously reported.[14] Thus, only data from 2012 onward are included in this analysis from that center. This study reports the outcomes from the expansion of the HRC study, which involved continuation of the existing cohort and recruitment of new participants at the Sydney Melanoma Diagnostic Centre and at the 3 other centers.

The median follow-up time for participants in this expanded cohort was 2.9 years (interquartile range [IQR], 1.9-3.3 years), and there was a median of 2.7 (IQR, 2.3-3.2) clinic visits per year per participant (Table 1). The length of follow-up was based on available research funding.

HRC Skin Surveillance Protocol and Data Collection

The HRC skin surveillance protocol has been previously described.[14] A clinician conducted a full-body skin examination every 6 months with the aid of a handheld dermoscopy device and a comparison of the skin with baseline TBP. In addition, SDDI of some lesions, either short term (>3 months) or long term (≥6 months), was scheduled as required. Table 1 shows the surveillance equipment used. More details are in the eMethods in the Supplement.

Table 1. Description of Each Melanoma HRC Study Center and Surveillance Technology Used

Center	Location	No. of participants in analysis	Recruitment period	Follow-up period[a]	Follow-up time, median (IQR), y	No. of HRC visits per year, median (IQR)	Surveillance technologies	
							Sequential digital dermoscopy imaging	Total-body photography
Sydney Melanoma Diagnostic Centre at Royal Prince Alfred Hospital	Major teaching hospital and tertiary referral center, metropolitan Sydney	307[b]	Initial cohort: January 2006 to November 2009; expansion cohort: February 2012 to June 2014	February 2012 to June 2016	2.8 (1.8-3.2)	2.7 (2.3-3.1)	Polartechnics Ltd, SolarScan	Polartechnics Pty Ltd, MoleMap Pty Ltd
Newcastle Skin Check	Primary care skin cancer clinic, in a coastal region of New South Wales	113	June 2012 to November 2015	June 2012 to June 2016	3.0 (2.5-3.2)	2.6 (2.4-3.2)	Canon 5D Mark II SLR camera with Dermlite Foto II Pro lens	Canon 5D Mark II SLR camera with 50-mm lens and Apple Aperture software
Melanoma Institute Australia	Major tertiary referral center, metropolitan Sydney	90	March 2012 to June 2016	March 2012 to August 2018	2.8 (1.7-3.4)	2.8 (2.5-3.2)	Canon EOS 700D camera with Heine Delta 20 Dermatoscope and Dermoscopix software	Canon EOS 700D camera with 60-mm macro lens and Dermoscopix software
Westmead Hospital	Major teaching hospital, metropolitan Sydney	83	August 2014 to March 2018	August 2014 to August 2018	1.8 (1.1-2.9)	3.0 (2.6-3.4)	Fotofinder	Fotofinder

Abbreviations: HRC, high-risk clinic; IQR, interquartile range; SLR, single-lens reflex.

[a] The HRC study initially started as a smaller single-center study with recruitment of participants from 2006 to 2009 at the Sydney Melanoma Diagnostic Centre; follow-up data collected at that center from 2006 to 2011 have been previously reported[14]; thus, only data from 2012 onward were included in the present analysis.

[b] Included 243 from the initial cohort and 64 from the expansion cohort.

Statistical Analysis

In total, 593 participants from 4 centers were included in the analysis (Table 1) after excluding 100 of 693 individuals (14.4%) lost to follow-up (eMethods in the Supplement). Participants' follow-up times were censored at the end of the specified follow-up time (Table 1), or earlier if there were more than 12 months between HRC visits, or at the time of death (n = 11).

The patient's first HRC visit during the specified follow-up dates was considered the baseline visit, except for the initial cohort at the Sydney Melanoma Diagnostic Centre and patients from the Melanoma Institute Australia, who were already following a photography surveillance protocol similar to the HRC and were thus considered not to have a baseline visit for this analysis.

Descriptive data are shown as frequencies and percentages for categorical variables and as mean (SD) values or median values with IQRs for normally and nonnormally distributed continuous variables, respectively. The *P* values for differences across centers or subgroups were calculated using the χ^2 test or the Mantel-Haenszel test for trend. A 2-sided value of $P < .05$ was considered statistically significant. Poisson regression models using generalized estimating equations were used to estimate incidence rate ratios and 95% CIs for excisions and new primary melanomas after 2 years compared with within the first 2 years of follow-up. The analysis was conducted using SAS software, version 9.4 (SAS Institute Inc). Data analyses were performed from February to September 2020.

Results

Characteristics of Participants

The characteristics of the participants are shown in **Table 2** for the cohort overall and in eTable 1A, B, C, and D in the Supplement for each of the 4 centers. The majority of 593 participants met the eligibility criteria for multiple primary melanoma (n = 546), followed by dysplastic nevus syndrome (DNS) and previous melanoma (n = 332), with fewer participants having a strong family history and previous melanoma (n = 83) or a *CDKN2A* gene variant (no requirement of previous melanoma was made; n = 16). The overlap of participants in the 4 eligibility criteria subgroups, overall and by center, is shown in eFigure 1 in the Supplement. The distribution of participants in the different subgroups differed across centers. The median age at first visit to the HRC was 58 years (IQR, 47-66 years). The sample of 593 participants was predominately men (340 [57.3%]), but this differed by subgroup, with more women (50 of 83 [60.2%]) in the strong family history subgroup ($P = .001$ compared with no strong family history) and the *CDKN2A* subgroup (10 of 16 [62.5%] were women; $P = .17$). Participants with a strong family history had a higher proportion of high-risk phenotypic characteristics (red hair, many freckles).

Lesions Excised at Baseline

Among 261 participants who were not already under close photography surveillance, there were 78 lesions excised at the base-

Table 2. Characteristics of High-risk Clinic Participants From All Centers Combined, by Subgroup[a]

Participant characteristic	No. (%) of participants				
	Total (n = 593)[b]	DNS and previous melanoma (n = 332)	Strong family history and previous melanoma (n = 83)[c]	Multiple primary melanomas (n = 546)	*CDKN2A* variant (n = 16)
Center					
SMDC	307 (51.8)	215 (64.8)	46 (55.4)	291 (53.3)	11 (68.8)
Newcastle	113 (19.1)	67 (20.2)	17 (20.5)	98 (17.9)	0
Melanoma Institute Australia	90 (15.2)	38 (11.4)	4 (4.8)	83 (15.2)	1 (6.3)
Westmead	83 (14.0)	12 (3.6)	16 (19.3)	74 (13.6)	4 (25.0)
Age at first visit, median (IQR), y	58 (47-66)	54 (44-61)	56 (43-63)	58 (47-66)	52 (45-60)
Sex					
Male	340 (57.3)	182 (54.8)	33 (39.8)	319 (58.4)	6 (37.5)
Female	253 (42.7)	150 (45.2)	50 (60.2)	227 (41.6)	10 (62.5)
Skin type					
Always burns, never tans	111 (19.2)	49 (15.0)	18 (21.7)	101 (19.0)	3 (18.8)
Usually burns, sometimes tans	318 (55.1)	182 (55.8)	50 (60.2)	292 (55.0)	8 (50.0)
Sometimes burns, usually tans	145 (25.1)	94 (28.8)	15 (18.1)	135 (25.4)	5 (31.3)
Never burns, always tans	3 (0.5)	1 (0.3)	0	3 (0.6)	0
Eye color					
Light blue, blue gray, blue	317 (56.0)	171 (53.3)	44 (54.3)	293 (56.0)	10 (66.7)
Green, hazel	181 (32.0)	107 (33.3)	26 (32.1)	167 (31.9)	2 (13.3)
Light or dark brown	68 (12.0)	43 (13.4)	11 (13.6)	63 (12.0)	3 (20.0)
Hair color					
Red	81 (14.3)	31 (9.6)	19 (23.8)	72 (13.7)	2 (13.3)
Blond	252 (44.4)	150 (46.6)	26 (32.5)	234 (44.6)	7 (46.7)
Brown	225 (39.6)	139 (43.2)	33 (41.3)	210 (40.0)	6 (40.0)
Black	10 (1.8)	2 (0.6)	2 (2.5)	9 (1.7)	0
Childhood freckling					
None	126 (22.1)	86 (26.5)	10 (12.2)	121 (23.0)	1 (6.7)
Very few	146 (25.6)	83 (25.6)	22 (26.8)	135 (25.6)	5 (33.3)
Few	142 (24.9)	79 (24.4)	24 (29.3)	127 (24.1)	4 (26.7)
Some	82 (14.4)	46 (14.2)	7 (8.5)	78 (14.8)	3 (20.0)
Many	55 (9.6)	23 (7.1)	11 (13.4)	50 (9.5)	1 (6.7)
Very many	20 (3.5)	7 (2.2)	8 (9.8)	16 (3.0)	1 (6.7)
Total nevi					
0-49	124 (20.9)	0	26 (31.3)	108 (19.8)	3 (18.8)
50-99	51 (8.6)	0	13 (15.7)	38 (7.0)	6 (37.5)
100-199	208 (35.1)	175 (52.7)	21 (25.3)	203 (37.2)	4 (25.0)
≥200	159 (26.8)	149 (44.9)	15 (18.1)	158 (28.9)	1 (6.3)
Missing	51 (8.6)	8 (2.4)	8 (9.6)	39 (7.1)	2 (12.5)
Nevus count, median (IQR)					
Total	135 (60-214)	190 (142-275)	91 (33-180)	143 (74-220)	79 (53-169)
Dysplastic	7 (3-12)	10 (7-14)	6 (1-8)	8 (5-12)	4 (2-7)

Abbreviations: DNS, dysplastic nevus syndrome; IQR, interquartile range; SMDC, Sydney Melanoma Diagnostic Centre at Royal Prince Alfred Hospital.

[a] Criteria assessed at first high-risk clinic visit. Participants could be in more than 1 subgroup if they met the relevant criteria.

[b] The sum of the numbers for some variables do not add to the total number owing to some missing values.

[c] At least 3 first- or second-degree relatives with a confirmed history of melanoma.

line HRC visit (or within 8 weeks), of which 10 (12.8%) were melanomas, 34 (43.6%) were nonmelanoma skin cancer, 17 (21.8%) were benign melanocytic lesions, and 17 (21.8%) were benign nonmelanocytic lesions (eTable 2 in the Supplement).

Lesions Excised and Excision Ratios During Follow-up Surveillance

There were 1513 lesions excised during follow-up surveillance in the HRCs (**Table 3**). Of the excised lesions, 171 (11.3%) were melanomas, 690 (45.6%) were nonmelanoma skin cancer, 410 (27.1%) were benign melanocytic lesions, and 234 (15.5%) were benign nonmelanocytic lesions. The probability of an excised lesion being melanoma (positive predictive value) was 11.3% overall and 29.4% for melanocytic lesions. Of 593 participants, 114 (19.2%) had 1 or more primary melanomas excised during the median 2.9-year follow-up surveillance period (IQR, 1.9-3.3 years), 214 (36.1%) had 1 or more nonmelanoma skin cancer lesions, 213 (35.9%) had 1 or more benign melanocytic lesions, and 142 (23.9%) had 1 or more benign nonmelanocytic lesions. The occurrence of a new primary melanoma was less common in the DNS subgroup (14.8%, $P = .03$).

The mean excision rate for all lesions was 0.9 (95% CI, 0.8-1.0) excisions per person-year of follow-up in the first 2 years of HRC surveillance, and the mean excision rate was 1.2 (95% CI, 1.0-1.4) excisions per person-year of follow-up in years 2 to 4 (eFigure 2 in the Supplement). Thus, the excision rate was 1.3 times as high (95% CI, 1.1-1.5; $P = .002$) in years 2 to 4 compared with years 0 to 2. When compared across centers, the mean excision rates in years 0 to 2 ranged from 0.6 to 1.5, and the incidence excision rate ratios ranged from 1.0 to 1.8.

For all centers combined, the total benign to malignant excision ratio was 0.8:1.0, and the benign melanocytic to melanoma ratio was 2.4:1.0 (Table 3). The excision ratios were higher for the DNS subgroup and lower for the strong family history subgroup. The total excision ratios were similar across the 4 centers (Table 3). The lesions excised for each center are shown in eTable 3 in the Supplement. The melanoma in situ to invasive melanoma ratio was 2.2:1.0.

Melanomas Detected During Follow-up Surveillance

The 171 melanomas detected during follow-up surveillance occurred among 114 participants. Although most participants (479 of 593 [80.8%]) experienced no melanomas during follow-up, some participants had multiple (up to 6) primary melanomas detected (**Table 4**). Male participants were more likely than female participants to develop another melanoma (82 of 340 [24.1%] vs 32 of 253 [12.6%]; $P < .001$).

The mean melanoma incidence rate was 0.09 (95% CI, 0.08-0.12) per person-year of follow-up in the first 2 years of HRC surveillance (equivalent to a 9.0% annual risk of melanoma in each of the first 2 years) and 0.15 (95% CI, 0.11-0.20) per person-year of follow-up in years 2 to 4 (equivalent to a 15.0% annual risk of melanoma in years 2-4) (Table 4). Thus, the incidence rate of new primary melanomas was 1.6 times as high (95% CI, 1.2-2.2; $P = .004$) in years 2 to 4 compared with years 0 to 2. The increase over time was more pronounced for the Melanoma Institute Australia center than for the other centers (Table 4) and for the subgroup with multiple primary melanomas than for the other subgroups (eFigure 3 in the Supplement).

The lesion characteristics of the incident primary melanomas diagnosed during follow-up surveillance in the HRCs are shown in **Table 5**. Melanomas occurred most frequently on the trunk (56 of 171 [32.7%]) and the upper limb and shoulder (56 of 171 [32.7%]). The median Breslow thickness was in situ (IQR, in situ to 0.40 mm); of 171 melanomas, 117 (68.4%) were in situ, 37 (21.6%) had a Breslow thickness of 0.1 to less than 0.8 mm, 10 (5.8%) had a Breslow thickness of 0.8 to 1.0 mm, and 7 (4.1%) had a Breslow thickness of more than 1.0 mm. There were some differences by center, such as a higher proportion of lentigo maligna diagnoses at Westmead Hospital (8 of 24 melanomas [33.3%]). Only 9 of 171 melanomas (5.3%) were of a nodular or desmoplastic subtype, but they represented 4 of the 7 thicker (>1 mm) melanomas detected (eTable 4 in the Supplement). Two of the thicker melanomas were self-detected, and 5 were detected by a clinician, of which 2 were detected with the aid of TBP. Overall, new primary melanomas were most likely to be detected by a clinician with the aid of TBP (54 of 171 [31.6%]) followed by SDDI (50 of 171 [29.2%], of which 32 [18.7%] were short term and 18 [10.5%] were long term), but there were differences across centers (Table 5).

Discussion

Using a structured surveillance protocol aided by TBP and SDDI for optimizing the detection of new primary melanoma among individuals at very high risk, we observed favorable long-term early detection and excision results sustained for more than 10 years at the original center (SMDC) and replicated at 3 other centers. The clinicians following the surveillance protocol included dermatology specialists, trained dedicated residents, and primary care physicians in hospital outpatient clinics and in a primary care skin cancer clinic.

The sustained long-term results at SMDC are reassuring because they indicate that thick melanomas were unlikely to be missed despite a low benign to malignant excision ratio. The overall benign to malignant excision ratio of 0.8:1.0 and the overall benign melanocytic to melanoma ratio of 2.4:1.0 in this cohort were better than the commonly accepted benign to malignant excision ratios of 5:1 for dermatology specialists and 20:1 for generalists.[19] Australia often has lower excision ratios than other countries because skin cancer is common.[20] A recent international meta-analysis on the number needed to excise or biopsy to diagnose melanoma concluded that pigmented lesion specialists have the lowest number (5.9), followed by dermatologists (9.6) and primary care doctors (22.6).[21] Nevertheless, our results showed similar outcomes across centers, indicating that the diagnostic tools and structured surveillance protocol were more important than the clinical specialty. The low number needed to excise or biopsy was associated with the use of photography surveillance affecting the threshold for biopsy and would also be expected to be lower for clinicians experienced in skin cancer detection and for regions with higher incidence of melanoma, as was the case in the present study.

Based on the original study,[14] Watts et al[15] reported the cost-effectiveness of this structured surveillance protocol (mean savings per patient of A$6828 [approximately $5205] during 10 years), showing that the main factor associated with the savings was the detection of melanoma at an earlier stage, resulting in less extensive treatment (mean quality-adjusted

Table 3. Incidence of Melanoma, NMSC, Benign Melanocytic, and Nonmelanocytic Lesions Excised During Follow-up Surveillance in High-risk Clinics, by Subgroup[a,b]

Lesion excised	No. of lesions				
		Melanoma			
	Total	DNS and previous	Strong family history and previous	Multiple primary	*CDKN2A* variant
Participants, No.	593	332	83	546	16
Lesions	1513	608	15	1401	28
Melanoma					
In situ					
Lentigo maligna (MFH)	28	10	6	25	1
Other in situ	89	36	13	86	1
Invasive melanomas					
Superficial spreading melanoma	37	13	4	36	2
Nodular	5	2	0	5	0
Lentigo maligna melanoma	3	1	0	3	0
Spindle cell or desmoplastic	4	2	1	4	0
Not classified	5	1	1	4	0
Total primary melanomas, No. (%)	171 (11.3)	65 (10.7)	25 (16.6)	163 (11.6)	4 (14.3)
Participants with ≥1 primary melanoma, No. (%)	114 (19.2)	49 (14.8)	18 (21.7)	108 (19.8)	3 (18.8)
Intradermal, subcutaneous or local recurrence	4	1	0	4	0
NMSCs					
Basal cell carcinoma	465	155	45	430	6
Squamous cell carcinoma	157	22	24	137	4
Squamous cell carcinoma in situ	59	11	4	56	1
Keratoacanthoma	9	1	1	9	0
Total NMSC, No. (%)	690 (45.6)	189 (31.1)	74 (49.0)	632 (45.1)	11 (39.3)
Participants with ≥1 NMSC, No. (%)	213 (35.9)	85 (25.6)	23 (27.7)	195 (35.7)	7 (43.8)
Benign melanocytic lesions					
Ephelis	2	1	0	2	0
Lentigo	27	12	2	23	0
Lentiginous or junctional nevus	83	46	6	75	2
Compound nevus	76	53	1	73	0
Intradermal nevus	16	9	6	15	0
Blue nevus	3	1	1	2	0
Dysplastic nevus	188	125	13	179	4
Spitz nevus	3	2	1	3	0
Nevus, not otherwise specified	11	9	0	10	1
Dermal nevus	1	0	0	1	0
Total benign melanocytic lesions, No. (%)	410 (27.1)	258 (42.4)	30 (19.9)	383 (27.3)	7 (25.0)
Participants with ≥1 benign melanocytic lesion, No. (%)	214 (36.1)	131 (39.5)	19 (22.9)	198 (36.3)	4 (25.0)
Benign nonmelanocytic lesions					
Dermatofibroma	12	7	1	12	0
Hemangioma	4	2	0	4	0
Seborrheic keratosis	38	17	2	35	0

(continued)

Table 3. Incidence of Melanoma, NMSC, Benign Melanocytic, and Nonmelanocytic Lesions Excised During Follow-up Surveillance in High-risk Clinics, by Subgroup[a,b] (continued)

Lesion excised	No. of lesions				
		Melanoma			
	Total	DNS and previous	Strong family history and previous	Multiple primary	*CDKN2A* variant
Actinic or solar keratosis	85	22	12	74	5
Inflammatory or pigment incontinence	25	14	2	23	1
Other	70	30	4	67	0
Total benign nonmelanocytic lesions, No. (%)	234 (15.5)	92 (15.1)	21 (13.9)	215 (15.3)	6 (21.4)
Participants with ≥1 benign nonmelanocytic lesion, No. (%)	142 (23.9)	60 (18.1)	12 (14.5)	131 (24.0)	4 (25.0)
No pathology report obtainable[c]	4	3	0	4	0
Excision ratios, overall and by center[d]					
Benign to malignant ratio[e]					
Overall	0.8:1.0	1.4:1.0	0.5:1.0	0.8:1.0	0.9:1.0
Sydney Melanoma Diagnostic Centre	0.9:1.0	1.3:1.0	0.6:1.0	0.9:1.0	0.5:1.0
Newcastle Skin Check	0.7:1.0	1.5:1.0	0.3:1.0	0.8:1.0	Not estimable
Melanoma Institute Australia	0.7:1.0	1.4:1.0	2.0:1.0	0.7:1.0	3.0:1.0
Westmead Hospital	0.6:1.0	4.0:1.0	1.7:1.0	0.5:1.0	1.7:1.0
Benign melanocytic to melanoma ratio					
Overall	2.4:1.0	4.0:1.0	1.2:1.0	2.3:1.0	1.8:1.0
Sydney Melanoma Diagnostic Centre	2.3:1.0	3.1:1.0	0.7:1.0	2.3:1.0	0.7:1.0
Newcastle Skin Check	2.2:1.0	3.9:1.0	0.7:1.0	2.2:1.0	Not estimable
Melanoma Institute Australia	2.9:1.0	6.0:1.0	Not estimable	2.7:1.0	Not estimable
Westmead Hospital	2.19:1.0	16.0:1.0	3.3:1.0	2.0:1.0	3.0:1.0

Abbreviations: DNS, dysplastic nevus syndrome; IQR, interquartile range; MFH, melanocytic freckle of Hutchinson; NMSC, nonmelanoma skin cancer.

[a] Data in this table exclude lesions excised at baseline, defined as the first 8 weeks from the initial high-risk center study visit at Newcastle, Westmead, and for those recruited from 2012 to 2014 at the Sydney Melanoma Diagnostic Centre. No baseline visit was assigned to the Melanoma Institute Australia or to participants recruited from 2006 to 2009 at the Sydney Melanoma Diagnostic Centre because they were already under photography surveillance.

[b] The subgroup criteria were assessed at their first high-risk center visit. Participants could be in more than 1 subgroup if they met the relevant criteria and may have undergone more than 1 excision of any type.

[c] No reports obtainable for 4 lesions: 3 at Sydney Melanoma Diagnostic Centre and 1 at Westmead Hospital.

[d] Numbers of different lesions at each center, overall, and by subgroup are given in eTable 3 in the Supplement.

[e] For the benign to malignant ratio, malignant lesions include melanomas and NMSCs, and benign lesions include benign melanocytic and nonmelanocytic lesions and those with no reports.

life-year gain of 0.31) and a low annual mean excision rate (0.81 vs 2.55 in standard care). In the present expanded cohort, the mean excision rate was 0.9 per person-year of follow-up in the first 2 years and 1.2 per person-year in years 2 to 4. However, this rate also corresponded with an overall 1.6 times as high melanoma incidence rate in years 2 to 4 vs the first 2 years. This result is a distinct difference from the initial study in which the melanoma incidence rate decreased with time.[14] The melanoma incidence rate was also higher in the present expanded cohort (9.0% annual risk in each of the first 2 years and 15.0% annual risk thereafter) compared with 12.7% cumulative 2-year risk in the original study. This higher and increasing incidence rate may be because 46.9% of participants had multiple primary melanomas at baseline in the first cohort, whereas 92.1% did so in the expanded cohort, and multiple primary melanomas are a strong determinant of subsequent melanoma risk (mean 5-year risk of 8% after 1 melanoma and 47% after 2 melanomas[6]). Another possible explanation is that the protocol relied heavily on photographic change to detect melanoma, shifting the diagnosis to later time points. Yet this shift did not appear to be meaningfully associated with the stage at diagnosis, probably because measuring the change allows detection of incipient melanoma that may not yet have developed dermoscopic features.[13] The increased incidence rate was more pronounced for the Melanoma Institute Australia than for the other centers; this finding may be partly due to a higher proportion of male patients at the Melanoma Institute Australia because male patients were twice as likely as female patients to develop new primary melanoma during the surveillance period. Male patients also have a higher risk of melanoma mortality.[22]

The Breslow thickness distribution was even more favorable in the expanded cohort; in the initial cohort, the median Breslow thickness was in situ (IQR, in situ to 0.60 mm), and there were 4 of 61 lesions (6.6%) that had a Breslow thickness of more than 1 mm, compared with the expanded cohort in which the median was in situ (IQR, in situ to 0.40 mm), and 7 of 171 lesions (4.1%) had a Breslow thickness of more than 1 mm. Thus, these results, together with substantially increasing health system costs for melanoma treatment,[11] suggest that cost-effectiveness may be higher than previously estimated and provide impetus to scale up the program. This was, however, an observational study; more definitive evidence on mortality reduction or rates of thicker melanoma

Table 4. Incidence of New Primary Melanoma Diagnosed During Follow-up Surveillance, by Center

Participant characteristic	No. (%) of participants				
	All centers	Sydney Melanoma Diagnostic Centre	Newcastle Skin Check	Melanoma Institute Australia	Westmead Hospital
Total No. of participants	593	307	113	90	83
No. of melanomas (per person) diagnosed during follow-up surveillance [a]					
0	479 (80.8)	263 (85.7)	89 (78.8)	64 (71.1)	63 (75.9)
1	81 (13.7)	32 (10.4)	16 (14.2)	16 (17.8)	17 (20.5)
2	18 (3)	7 (2.3)	4 (3.5)	5 (5.6)	2 (2.4)
3	10 (1.7)	3 (1.0)	2 (1.8)	4 (4.4)	1 (1.2)
4	2 (0.3)	0	1 (0.9)	1 (1.1)	0
5	2 (0.3)	1 (0.3)	1 (0.9)	0	0
6	1 (0.2)	1 (0.3)	0	0	0
No. of new primary melanomas per person-year of follow-up, mean (95% CI)					
0-2 y	0.09 (0.08-0.12)	0.07 (0.05-0.10)	0.12 (0.07-0.18)	0.13 (0.07-0.22)	0.13 (0.08-0.21)
2-4 y	0.15 (0.11-0.20)	0.09 (0.06-0.14)	0.17 (0.08-0.33)	0.40 (0.27-0.60)	0.17 (0.07-0.40)
Incidence rate ratio (95% CI)[b]	1.6 (1.2-2.2)	1.3 (0.8-2.0)	1.4 (0.7-2.9)	3.2 (1.8-5.7)	1.3 (0.5-3.7)
P value[c]	.004	.40	.30	<.001	.60
Patients diagnosed as having ≥1 melanoma during surveillance					
Participants, No.	114	44	24	26	20
Sex[d]					
Male	82 (71.9)	32 (72.7)	17 (70.8)	22 (84.6)	11 (55.0)
Female	32 (28.1)	12 (27.3)	7 (29.2)	4 (15.4)	9 (45.0)

[a] Excludes melanomas detected at baseline, and does not take into account differences in follow-up time by center.

[b] Incidence rate ratios compare melanoma incidence rates from years 2 to 4 with years 0 to 2, and take into account follow-up time.

[c] Showing whether the incidence rate ratio differs from 1.0.

[d] Proportion of participants at all high-risk centers who developed 1 or more melanomas during the surveillance period was 24.1% for male patients and 12.6% for female patients ($P < .001$).

requires a randomized clinical trial. In addition, second primary melanomas and familial melanomas tend to be thinner than sporadic melanomas.[23,24]

One concern of increased surveillance is for overdiagnosis and overtreatment, particularly for in situ melanoma, such that some melanomas left undetected (and untreated) would never transform into invasive disease causing symptoms or harm.[25] We diagnosed 2.2 in situ melanomas to each invasive melanoma in this study, compared with a ratio of 1.6:1.0 in the general population.[4] The harm associated with overdiagnosis in the HRCs is likely lower relative to the benefits obtained from attending the clinic because previous work by members of our group have shown fewer excisions compared with usual care,[15] and the psychological impact of a new diagnosis may be less given that most people have already had a previous melanoma. Patients are also reassured by expert care,[26] and there was minimal loss to follow-up (14.0%). In addition, two-thirds (66.7%) of melanomas in our cohort were found because of changes on photography (SDDI or TBP) indicating biological activity.

Participants with DNS had a higher benign to malignant excision ratio but fewer new primary melanomas developed compared with the other subgroups, and this highlights the difficulty in correctly distinguishing melanomas from dysplastic nevi masquerading as melanomas. Nodular and desmoplastic melanomas are particularly difficult to diagnose, and these were overrepresented in the thicker (>1 mm) melanomas detected. Only 2 of the 7 thicker melanomas detected were identified using photography, and 2 were self-detected, showing that educating patients and physicians to recognize these difficult lesions remains a priority.

Limitations

Our data were limited to the Australian population and may not be generalizable to regions with lower melanoma incidence or to all Australian centers. Melanomas in Australia are routinely detected in dermatology settings and primary care (general practice and skin cancer clinics).[18] Most primary care physicians in Australia use dermoscopy, whereas TBP and particularly SDDI are more commonly used in primary care skin cancer clinics than in generalist primary care (Victoria Mar, PhD, Director of the Victorian Melanoma Service, written personal communication, September 2020). In the primary care skin cancer clinic in our study, TBP and SDDI were routinely used prior to the study. Hence, significant uncertainty exists when

Table 5. Lesion Characteristics of Incident Primary Melanoma Diagnosed During Follow-up Surveillance in High-risk Clinics, by Center[a]

Melanoma characteristic	No (%) of melanomas					*P* value for differences between centers[b]
	All centers	Sydney Melanoma Diagnostic Centre	Newcastle Skin Check	Melanoma Institute Australia	Westmead Hospital	
Melanomas, No.	171	66	39	42	24	
Anatomical site						
External ear	6 (3.5)	3 (4.5)	1 (2.6)	1 (2.4)	1 (4.2)	.50
Face	16 (9.4)	11 (16.7)	1 (2.6)	1 (2.4)	3 (12.5)	
Scalp and neck	12 (7.0)	4 (6.1)	3 (7.7)	2 (4.8)	3 (12.5)	
Trunk	56 (32.7)	18 (27.3)	15 (38.5)	17 (40.5)	6 (25.0)	
Upper limb and shoulder	56 (32.7)	19 (28.8)	15 (38.5)	14 (33.3)	8 (33.3)	
Lower limb and hip	25 (14.6)	11 (16.7)	4 (10.3)	7 (16.7)	3 (12.5)	
Breslow thickness, median (IQR), mm						
All	In situ (in situ to 0.40)	In situ (in situ to 0.40)	In situ (in situ to 0.40)	In situ (in situ to 0.52)	In situ (in situ to in situ)	
Detected by TBP	In situ (in situ to 0.40)	In situ (in situ to 0.40)	In situ (in situ to 0.45)	0.20 (in situ to 0.50)	In situ (in situ to in situ)	
Detected by SDDI	In situ (in situ to in situ)	In situ (in situ to in situ)	In situ (in situ to 0.20)	In situ (in situ to 0.15)	In situ (in situ to in situ)	
Range	In situ to 12	In situ to 3.5	In situ to 12	In situ to 1.5	In situ to 3	
In situ	117 (68.4)	47 (71.2)	28 (71.8)	22 (52.4)	20 (83.3)	
0.1 to <0.8	37 (21.6)	14 (21.2)	9 (23.1)	13 (31.0)	1 (4.2)	.07
0.8 to 1.0	10 (5.8)	2 (3.0)	1 (2.6)	6 (14.3)	1 (4.2)	
>1.0	7 (4.1)	3 (4.5)	1 (2.6)	1 (2.4)	2 (8.3)	
Histologic subtype						
In situ						
Lentigo maligna	28 (16.4)	18 (27.3)	0	2 (4.8)	8 (33.3)	<.001
Other in situ	89 (52.0)	29 (43.9)	28 (71.8)	20 (47.6)	12 (50.0)	
Invasive melanomas						
Superficial spreading melanoma	37 (21.6)	14 (21.2)	5 (12.8)	16 (38.1)	2 (8.3)	
Nodular	5 (2.9)	3 (4.5)	0	1 (2.4)	1 (4.2)	
Lentigo maligna melanoma	3 (1.8)	1 (1.5)	0	2 (4.8)	0	
Spindle cell or desmoplastic	4 (2.3)	0	3 (7.7)	0	1 (4.2)	
Invasive, not classified	5 (2.9)	1 (1.5)	3 (7.7)	1 (2.4)	0	
Excision reason						
No reason provided	9 (5.3)	5 (7.6)	0	3 (7.1)	1 (4.2)	<.001
Patient request	7 (4.1)	5 (7.6)	0	2 (4.8)	0	
Self-detected without TBP	5 (2.9)	0	2 (5.1)	1 (2.4)	2 (8.3)	
Clinician detection without TBP	35 (20.5)	4 (6.1)	9 (23.1)	15 (35.7)	7 (29.2)	
Clinician detection with aid of TBP	54 (31.6)	24 (36.4)	15 (38.5)	5 (11.9)	10 (41.7)	
Clinician detection exclusively with TBP	11 (6.4)	5 (7.6)	5 (12.8)	1 (2.4)	0	
Short-term SDDI	32 (18.7)	16 (24.2)	8 (20.5)	7 (16.7)	1 (4.2)	
Long-term SDDI	18 (10.5)	7 (10.6)	0	8 (19.0)	3 (12.5)	

Abbreviations: IQR, interquartile range; SDDI, sequential digital dermoscopy imaging; TBP, total body photography.

[a] Excludes melanomas detected at baseline.

[b] For differences across centers calculated using the χ^2 test or for Breslow thickness using the Mantel-Haenszel test for trend.

generalizing the findings to all primary care clinics. However, nearly everyone in this cohort had a previous melanoma, which is consistently a strong predictor for developing a subsequent melanoma in other countries,[27] and close surveillance is recommended.[28] People at low or average risk may benefit less from this surveillance program. Use of risk prediction al-

gorithms may help to accurately select people at high risk and tailor surveillance intervals according to personal risk.[6,29] Advanced diagnostic photographic tools and high-quality, low-cost dermatoscopes provide an opportunity for primary care physicians and even patients to equip themselves with this technology. Incorporating artificial intelligence to enhance melanoma diagnosis may further change this paradigm of skin surveillance.

Conclusions

The structured surveillance program for individuals at high risk of new primary melanoma may be implemented on a larger scale, including primary care skin cancer clinics, given the study findings suggesting consistent and sustainable benefits.

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