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Total Body Photography for the Diagnosis of Cutaneous Melanoma in Adults: A Systematic Review and Meta-Analysis

Total Body Photography for the Diagnosis of Melanoma

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What's already known about this topic?

- Early detection of melanoma is essential to reduce morbidity and mortality.
- Total body photography (TBP) can facilitate the detection of melanoma in high-risk individuals.
- The accuracy of TBP in diagnosing melanoma is unknown.

What does this study add?

- Best current estimates suggest that the use of TBP for the diagnosis of melanoma has an acceptable number needed to biopsy in patients at high risk of melanoma.
- There is heterogeneity in the design and delivery of studies evaluating TBP in high-risk patients.
- There is a need for robustly designed prospective diagnostic test accuracy studies, in order to accurately assess the diagnostic accuracy of TBP.

Summary

Background

Early detection of melanoma is essential to reduce mortality. Total body photography (TBP) can facilitate the detection of melanoma in high-risk individuals. However, the accuracy of TBP in diagnosing melanoma remains unclear.

Objectives

To determine the diagnostic accuracy of TBP for the detection of melanoma in adults.

Methods

MEDLINE, EMBASE, Cochrane, and Centre for Reviews databases were searched from inception to 26 May 2020. Studies using TBP for diagnosing melanoma with at least one follow-up appointment were eligible if they provided data to calculate at least one diagnostic accuracy measure. Two authors independently screened articles, extracted data, and assessed quality. Disagreements were resolved by a third reviewer.

Results

Ten studies were included, comprising 41703 patients who underwent TBP and 6203 biopsies. Melanoma *in situ* (MIS) was diagnosed in 315 (5.1%) lesions and invasive melanoma in 187 (3.0%) lesions biopsied. Summary estimates for TBP in diagnosing melanoma were calculated: mean percentage of biopsies positive for MIS or melanoma was 16% (95% CI, 11%-20%), NNB was 8.6 (range 2.3-19.6), naevus:melanoma ratio was 7.6 (range 1.3-18.6), and MIS:melanoma ratio was 1.7 (1.0-3.5). Regression analysis showed a negative correlation between NNB and MIS:melanoma ratio.

Conclusions

Available data regarding the diagnostic accuracy of TBP are heterogeneous, due to variability in the risk profile of cohorts and TBP protocols. Best current estimates suggest that TBP for diagnosing melanoma has an acceptable NNB in high-risk patients. However, prospective diagnostic test accuracy studies are needed to accurately gauge the diagnostic accuracy of TBP.

Introduction

Melanoma accounts for 5% of skin cancer cases but is responsible for up to 75% of skin cancer deaths.[1] Early detection of melanoma can reduce morbidity and mortality.[2] In high-risk individuals, total body photography (TBP) is used to aid in screening and detection, with surveys of US dermatologists reporting that 67-71% use TBP regularly.[3,4] TBP can help identify new or changing naevi through comparison of baseline TBP images with subsequent skin examinations or comparison of sequential TBP images over time, either by clinicians or computer-assisted algorithms.

The use of TBP has been associated with improved detection of thin melanomas[5] and greater overall survival.[6] Several studies suggest that TBP can reduce the number of biopsies per patient which can reduce patient anxiety and waiting times.[7,8] TBP can be particularly useful in patients at high risk of melanoma by confirming that suspicious lesions remain stable,[9] and has been shown to reduce patient anxiety regarding melanoma recurrence.[10] However, there are conflicting data regarding whether TBP results in fewer biopsies in all patient cohorts, with one study showing that TBP had no effect on number of biopsies when compared to no TBP imaging.[11]

The diagnostic accuracy of TBP for melanoma is unclear. There are limited data regarding the sensitivity or specificity of TBP, likely due to difficulty in defining and confirming true negatives or false negatives in clinical settings. Evaluations of TBP instead focus on lesions selected for biopsy, reporting metrics such as the percentage of melanomas diagnosed, number needed to biopsy (NNB) or the naevus:melanoma ratio. However, these data have been conflicting, with studies yielding variable NNBs and naevus:melanoma ratios.[7,12,13]

To our knowledge, there have been no systematic reviews assessing accuracy of TBP for detecting cutaneous melanoma. With the current drive to increase digital technologies in this arena, this information is vital to robustly test new technologies that claim superiority to standard TBP. Our aim was therefore to determine diagnostic accuracy of TBP for melanoma in adults, focusing on the use of TBP in high-risk individuals requiring long-term skin surveillance.

Materials and methods

The review protocol was prospectively registered with PROSPERO (ID: CRD42020186675). The review was conducted in accordance to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[14] Findings are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for diagnostic test accuracy studies.[15]

Data sources

Searches were conducted from inception of the databases to 26 May 2020. Databases searched included MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Database of Abstracts of Reviews of Effects, and the CRD Health Technology Assessment database. The search strategy is presented in Supplementary Figure S1. Only studies published in English were considered. Reference lists of included studies were screened for additional relevant studies.

Study selection

Two independent reviewers (AJX and RM) screened articles using titles and abstracts, and subsequently reviewed full texts of relevant articles for eligibility. Any disagreements were resolved by a third independent reviewer (JD). Studies of participants who received TBP with at least one follow-up visit were eligible for inclusion, if they provided sufficient data for estimation of at least one measure of diagnostic accuracy: sensitivity, specificity, positive predictive value (PPV or 1/NNB) or negative predictive value (NPV). The primary target condition was detection of melanoma. The preferred reference standard was histopathological diagnosis with follow-up of clinically benign lesions. Additional eligible standards included cancer registry follow-up or expert diagnosis.

Studies were excluded if smartphones were used to take TBP images. Studies were also excluded if more than 50% of participants were aged 16 or under. Conference abstracts were excluded, but attempts were made to identify full papers for relevant abstracts. When one parameter was missing for the estimation of a measure of diagnostic accuracy, we contacted authors to attempt to obtain the data.

Data extraction, analysis, and quality assessment

Two authors independently extracted data for each study using a piloted data extraction form. We aimed to extract all data required to populate a 2x2 diagnostic contingency table for TBP. However,

as anticipated, data for lesions that were not biopsied (i.e. true and false negatives) were not reported by any of the studies. Data extraction therefore focused on extraction of number of lesions biopsied and of melanomas diagnosed. Additional outcomes collected included number of biopsies per patient, the MIS:melanoma ratio of lesions detected by TBP, and reasons for biopsy. Risk of bias and concerns for applicability were assessed using a modified QUADAS-2 checklist[16] tailored to the review (Supplementary Figure S2). Quality assessment was carried out independently by two authors, with any disagreements resolved by referral to a third independent author.

Statistical analysis

Source study data were used to calculate summary estimates and aggregate means weighted by study size. To aid in the estimation of variance, data were structured as a proportion, i.e. the number of melanomas per total number of biopsies (1/NNB). Summary effect size and Wilson 95% confidence intervals (CIs) of 1/NNB were calculated with a random-effects model meta-analysis, using the metaprop function.[17] The I^2 statistic was used to quantify heterogeneity. Regression analysis was used to assess relationships between quantitative variables. Pearson correlation coefficients (r) were calculated to evaluate the strength and direction of linear relationships between variables. Coefficients of determination (r^2) were obtained to measure the degree of statistical dependence between variables. *P* values < 0.05 were considered significant. Statistical analyses were conducted using Stata, Release 15.

Results

Study selection

The search identified 317 unique references, of which 35 were selected for full text assessment (Figure 1). Twenty-five studies were excluded (reasons detailed in Figure 1). We contacted one author to clarify cohort characteristics, and excluded the study as the cohort was duplicated from a previous study.[18] We contacted another author to obtain the total number of biopsies, but as these data were not collected, this study was also excluded.[6]

Characteristics of included studies

Ten (3.2%) studies met eligibility criteria[5,7,8,11–13,19–22] (Table 1). Included studies were from the United States (n = 6),[5,7,8,11,12,21] Australia (n = 1),[22] New Zealand (n = 1),[20] Greece (n =1),[13] and Spain (n = 1).[19] Seven studies were retrospective[5,8,11,12,19–21] and 3 were prospective,[7,13,22] with data collection ranging from 1998 to 2018. Median follow-up periods ranged from 12-96 months.

Protocols used for TBP in each of the studies examined varied widely, with 5 studies complementing TBP with sequential dermoscopic images[12,13,19,20,22] (Table 1). One study used computer-assisted automation to aid serial acquisition of TBP images.[12] No studies reported using artificial intelligence algorithms to classify images as benign versus malignant. All studies reported clinical examination, and 8 studies included dermoscopic examination of lesions.[5,7,12,13,19–22] TBP was reviewed in-person by a dermatologist in all studies except one, where expert review was undertaken remotely using a store-and-forward telemedicine service.[20] Two studies reported a median number of TBPs per patient of 2[11] and 7.[19] Three studies reported median intervals between baseline TBP and diagnosis of 18,[5] 23,[20] and 24[12] months.

Patient demographics and tumour characteristics

Included studies comprised total of 41703 patients undergoing TBP, of which 3224 had a biopsy. All patients were at high risk of melanoma (Table 2). The number of patients receiving TBP ranged from 64 to 36832. The proportion of males ranged from 45.3-58.4%, with ages ranging from 11-89 years old.

All studies aimed to detect melanoma. In one study, the target condition was dysplastic naevi but information regarding melanoma was available.[11] Six studies restricted inclusion to pigmented lesions only, and 4 studies included information regarding non-melanoma skin cancer (NMSC).[5,19,21,22] The reference standard was histopathology in all studies.

A total of 6203 biopsies were performed in patients undergoing TBP, resulting in a diagnosis of MIS in 315 (5.1%) lesions, and invasive melanoma in 187 (3.0%) lesions. Mean Breslow thickness (BT) ranged from 0.04-0.62mm for 5 studies reporting data as mean BT.[5,7,13,19,21] Median BT ranged from 0.33-0.50 for 3 studies reporting median BT.[8,20,22] Only 3 studies reported body location for melanoma: 180 (48.1%) were located on extremities, 160 (43.3%) on the trunk, and 32 (8.6%) on the head or neck.[5,20,22] Only 2 studies reported melanoma subtype.[12,22] Reasons for biopsy were reported in 5 studies (including 2572 lesions), and included diagnostic uncertainty (n=1063, 41.3%), changing lesion (n=948, 36.9%), new lesion (n=454, 17.7%), and patient concern or poor photographic quality (n=107, 4.2%).[5,7,12,19,20] In 3 studies, the origin of new melanomas was reported; *de novo* in 101 (59.4%), and naevus-derived in 69 (40.6%).[7,19,22]

Four studies collected data regarding NMSC,[5,19,21,22] reporting a total of 224 NMSCs (10 basal cell carcinomas, 5 squamous cell carcinomas, 209 not specified) diagnosed during TBP monitoring.

Assessment of risk of bias and applicability concerns using QUADAS-2

Six studies were rated low risk of bias for participant selection,[7,11–13,19,20] and 2 were rated unclear due to lack of detail regarding the recruitment process[5,22] (Table 3). Two studies were rated high risk of bias because only data from patients who had a biopsy were recorded, without recording follow-up data for those patients who underwent TBP and did not require a biopsy.[8,21] Concerns for applicability of participants were low in 6 studies,[11–13,19,21,22] and high in one study, because inclusion was not restricted to populations who would be most likely to be eligible for TBP in usual practice.[20]

All studies were rated low risk of bias for the index test, as TBP was always conducted prior to obtaining histopathological diagnosis, and the decision to biopsy was always predetermined. Concerns about applicability of the index test were rated high in one study using a highly automated and computer-assisted array of 25 cameras[23], as this system is not widely available, and unclear in 4 studies due to lack of details regarding the TBP protocol.[8,11,13,20]

Risk of bias for reference standards in all studies was rated unclear, because information was not provided on whether histopathologists were blinded to whether requests were from patients who underwent TBP or not. Applicability concerns for the reference standard were low for all studies as all used histopathology. Most studies had high risk of bias for flow and timing due to short follow-up periods and lack of data regarding outcomes for non-excised lesions.[7,8,11,21,22] In one study, 57% patients were lost to follow-up.[7] Three studies did not provide sufficient information to assess flow and timing.[5,12,20]

Diagnostic accuracy data

The reported mean number of biopsies per patient ranged from 0.6 to 6.4, with an aggregate mean of 1.6 biopsies per patient (total biopsies/total patients receiving TBP) (Table 4). As anticipated, studies only reported data on true positives (TP, clinically suspicious lesion on TBP diagnosed as MIS or melanoma with histology, n = 721) and false positives (FP, clinically suspicious lesion on TBP diagnosed as neither MIS nor melanoma with histology, n = 5482), but no data on true or false negatives. The percentage of biopsies positive for MIS or melanoma ranged from 0%[11] to 43%[13], with a summary estimate of 16.0% (effect size, 0.16; 95% CI, 0.11-0.20) (Figure 2), after excluding one study that detected no MIS or melanomas.[11]

The NNB (number of biopsies/number of MIS and melanoma) ranged from 2.33[13] to 19.6[7], with an aggregate mean of 8.6. The naevus:melanoma ratio, an alternative measure of relative benefit reported in some studies which correlates with NNB, ranged from 1.33[13]-18.57[7], with an aggregate mean of 7.6.

The MIS:melanoma ratio ranged from 0.98[8]-3.50[5], with an aggregate mean of 1.68. Regression analysis revealed that NNB was strongly and negatively correlated with MIS:melanoma ratio (r = -0.76, r^2 = 0.58, P = 0.04), suggesting that the lower the NNB (i.e. higher relative benefit), the higher the proportion of MIS diagnosed. Length of follow-up and mean number of biopsies per patient did not significantly correlate with BT, NNB, or MIS:melanoma ratio.

Discussion

TBP is increasingly recommended for skin monitoring for individuals at high risk of melanoma,[3,4,24] despite unclear accuracy and relative benefits.[25,26] Furthermore digital technologies are rapidly being developed as diagnostic tools to improve melanoma diagnosis and the accuracy of our current diagnostic aids is therefore essential to determine what additional benefit these new technologies may provide. To our knowledge, this is the first systematic review to evaluate diagnostic accuracy of TBP for melanoma. We evaluated 10 studies of high-risk patients who were monitored using TBP in addition to standard clinical examination. We show that in cohorts using TBP for high-risk individuals, on average 16% (95% CI, 11-20%) of lesions were MIS or melanoma, with an aggregate NNB of 8.6. An average of 1.68 MIS were diagnosed for every invasive melanoma.

A clinically important comparison is whether the addition of TBP to standard care is associated with improved diagnostic accuracy compared to standard care alone. However, the lack of controlled studies precludes our ability to estimate added benefits from TBP.[27,28] A recent meta-analysis assessed accuracy of clinicians diagnosing melanoma, comprising 455 496 biopsies and 29 257 melanomas from 46 studies. They calculated a mean 4-12% of lesions biopsied demonstrated melanoma, with an aggregate NNB of 14.8.[29] Since most (44/46) of the studies in that meta-analysis used standard clinical examination without TBP for diagnosing melanoma, this provides the best available baseline comparison, suggesting that the addition of TBP in a standard clinical pathway is potentially associated with higher mean percentage of positive biopsies and lower NNB.

Cohort studies can also provide a crude estimate of the relative additional benefit of TBP in diagnosing melanoma. In Goodson *et al.*, which compared a cohort before and after introduction of TBP, the naevus:melanoma ratio post-TBP introduction was 17, compared to a naevus:melanoma ratio of 45 in a pre-TBP historical cohort.[7] However, the post-TBP group had a longer follow-up period and more follow-up visits, and studies have shown that dermatologists have higher thresholds for biopsy when clinical follow-up is used as an alternative strategy.[5,30] Truong *et al.* reported that TBP imaging reduced the mean number of biopsies per patient over a median follow-up period of 7.2 years, however the naevus:melanoma ratio paradoxically increased from 7.7 pre-TBP to 14.3 post-TBP.[8] Additionally, Risser *et al.* documented that use of TBP did not influence mean number of biopsies per patient or the naevus:melanoma ratio.[11]

Several sources could account for the observed variability in accuracy in the included studies. Although all studies included patients at high risk of melanoma, differences in the risk profile of cohorts alter the percentage of positive biopsies and NNB, which depend on the underlying prevalence of melanoma in each cohort. Adjusting for other factors, cohorts at higher risk have higher percentage of positive biopsies and lower NNBs, as exemplified by the 2 studies in our review with the highest percentage of positive biopsies; in one study, all included patients had a personal history of melanoma,[13] whereas in the other study a significant proportion had a personal (75%) and/or family history (33%) of melanoma.[5]

Conversely, the included studies with the lowest percentage of positive biopsies (0%[12] and 5.1%[7]) identified a large number of dysplastic naevi on histopathology, but these were not accounted for when estimating diagnostic accuracy.[32,33] Similarly, NMSCs excised are not accounted for in accuracy estimates focusing on MIS or melanoma. In one included study, the NNB was 9.39 for MIS or melanoma, but decreased to 2.64 when calculated for any malignant lesion.[22] Studies provided limited data regarding degree of clinical suspicion required to recommend lesion biopsy. Moreover, factors not related to diagnostic accuracy, such as poor photograph quality[7] and patient anxiety,[8,10] may influence decision to biopsy.[7] Finally, the use of different comparators and TBP protocols used are additional sources of variability.

Strengths of this review include a comprehensive literature search, quality assessment, and stringent systematic review methods. To maximise generalisability to clinical practice, we excluded studies that did not include high-risk patients that typically undergo TBP,[34] and studies where TBP was not conducted in a clinical setting.

Limitations included lack of data regarding lesions that were not biopsied, which precluded us from estimating summary sensitivities and specificities for TBP. This was partly related to the challenge in defining a false negative, given that malignant lesions not selected for biopsy at one TBP visit have a higher chance of being identified as a true positive at the subsequent visit. Other limitations include the variable quality and wide heterogeneity of the included studies. Only 3 studies were prospective.[7,13,22] No studies had a contemporaneous control group, and only one attempted comparison with a historical cohort.[13] We did not evaluate studies assessing benefits of TBP for patient-related outcomes[10,35–37] or disease-related outcomes.[6,18,38] Finally, access to TBP systems remains limited in developing countries, limiting the applicability of our findings to resource-rich settings.[39]

Future studies should focus on prospective comparative diagnostic test accuracy studies, whereby eligible patients have baseline TBP, and at each subsequent visit, clinicians conduct clinical assessment without TBP and record their decisions, and are then provided with TBP images and record any changes in their decisions. Details of TBP equipment used and the TBP protocols applied, including exactly how TBP is used to inform a clinical decision within a patient pathway, should be explicitly stated in publications to allow for valid comparisons. Lesions identified on TBP but which are not biopsied (e.g. benign-appearing lesions) should be included in the data and followed-up to allow longitudinal estimation of false negative rates, which in turn would allow for calculation of sensitivity. A combined reference standard of histopathology and long-term clinical follow-up should be used, as it has higher reliability than histopathology alone. Studies should record risk factors to determine how diagnostic accuracy correlates with risk profiles, report melanoma characteristics (BT, melanoma subtype, body location) and disease-related outcomes (locoregional recurrence, distant metastasis, melanoma-specific survival, overall survival), to establish the impact of TBP. The use of artificial intelligence (AI) is increasingly applied in skin cancer diagnostics,[40,41] and has the potential to optimise clinical pathways for high-risk patients. Future studies of TBP are likely to use new technologies such as 3D imaging in combination with AI.[42] In order to demonstrate the additive benefit from AI, it is essential that future prospective studies assess the diagnostic accuracy of TBP alone, in addition to assessing the combined diagnostic accuracy of AI in conjunction with TBP.

In summary, available studies regarding the diagnostic accuracy of TBP in melanoma report highly variable estimates, which are likely related to heterogeneity in patient cohorts, TBP comparators, and TBP protocols. Best current estimates suggest that in patients at high risk of melanoma, TBP has an acceptable NNB, when compared to previous studies using standard clinical examination without

TBP. However, our review highlights the need for prospective comparative trials, to provide robust estimates of diagnostic accuracy of TBP. Given the current evolving digital landscape in healthcare, these studies will most likely be designed in conjunction with an AI intervention.

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Figure Legends

Figure 1. PRISMA Flow Diagram.

Figure 2. Proportions of Melanoma *in Situ* or Invasive Melanoma Diagnosed in All Lesions Biopsied After TBP.

Tables

Table 1. Characteristics of studies reporting diagnostic accuracy of total body photography.

Study	Study design	Data collection period	Follow-up, months, median (range)	Inclusion criteria	Type of TBP
Drugge (2020)	RC	2015-2016	NS	Patients with risk factors for melanoma (personal or family history, 4 or more dysplastic naevi, or 100 or more naevi)	Automation of TBP using a 25-camera array and computer-assisted comparison of serial images with dermoscopic photography of new and changing lesions
Feit (2004)	RC	NS	30 (12-118)	Patients with melanoma biopsied at least 3 months after their TBP session participating in photographic follow-up examination	Digitally acquired photographs, with a standardized series of poses and computer workstations in examination rooms to view patients' images during follow-up examinations. New and ∕ or changing lesions with a benign clinical and dermoscopic appearance are re-photographed and tracked over time.
Goodson (2010)	PC	2004-2009	24 (2-54)	Patients attending Mole Mapping clinic with at least one of the following: 3 or more clinically atypical naevi, >50 naevi, personal history of melanoma, and 3 or more family members with history of melanoma. A small number did not have one of these risk factors but had extensive lentiginosis or were referred by dermatologists who deemed them high risk	27 regional photographs were taken based on standard poses to capture naevus-bearing and naevus-free areas of skin. Some additional images in other locations (such as the scalp, pubic area, between toes) or on curved surfaces (such as the shoulder or hip). All clinically suspicious lesions were assessed using hand-held non-contact dermoscopy.
Greenwald (2020)	RC	2015-2016	NS	MoleMap NZ teledermatology program: Any lesion either 6 mm or more in diameter or 3 mm or more in diameter with asymmetry, border irregularity, colour variability, evolution, or elevation, or 1 or more dermoscopic criteria suspicious for melanoma, or any lesion about which the patient or referring physician is concerned	Store and forward telemedicine service, with expert review of TBP and close-up and dermoscopic images of suspicious skin lesions
Lallas (2020)	PC	2013-2018	NS	Patients with a recently diagnosed primary cutaneous melanoma of any stage	TBP and sequential digital dermoscopic documentation were performed with the use of a commercially available digital device that includes a standardized protocol for capturing clinical images and were repeated at all follow-up visits. All the images (clinical and dermoscopic) were captured and evaluated by specialist clinicians
Mintsoulis (2016)	RC	2010-2014	NS (6-12)	Patients attending a PLC (history of melanoma (single or multiple) or high risk of developing melanoma i.e. strong family history of melanoma, presence of numerous (>100) nevi, mutation that predisposes to melanoma (e.g. CDKN2A mutation), or numerous atypical /dysplastic naevi) who had a biopsy as a result of TBP images taken, and compared	Digital dermoscopy and TBP (details NS) in PLC clinic versus handheld dermoscopy in GDC

				to patients with a history of melanoma followed up in a general dermatology clinic (GDC)	
Moloney (2014)	PC	2006-2009	42 (29-51)	Group 1: History of >1 invasive melanoma and dysplastic naevus syndrome (>100 naevi, at least 6 dysplastic and >1 greater than 8mm diameter); Group 2: history of >1 invasive melanoma and at least 3 first-degree or second-degree relatives with prior melanoma; Group 3: history of > 2 primary invasive melanomas; Group 4: Confirmed CDKN2A or CDK4 mutation	Baseline digital TBP following standard protocols (12-24 images) high resolution digital photographs recorded (Polartechnics and MoleMap). Images provided to patients and a copy stored. Patients instructed in the use of TBP and asked to perform a full self-skin examination at 3 and 6 months
Risser (2007)	RC	1998-2003	12 (NS)	Patients who had attended a PLC at least 3 times, had multiple atypical moles, and had at least 1 year of follow-up after the initial visit	Patient had regional photographs taken by one of two experienced technicians, but no close-up photographs or dermoscopy
Salerni (2012)	RC	1999-2008	96 (13-120)	Patients at high risk of melanoma defined as moderate to severe atypical mole syndrome (defined by >100 nevi and/or >10 clinically atypical according to ABCD criteria, and/or any histologically dysplastic naevi), personal or family history of melanoma, genetic predisposition, or other cancer risk conditions (congenital naevus of medium to giant size, immunosuppression, or genodermatoses) enrolled in a TBP and digital dermoscopy surveillance program	Baseline: TBP with clinical exam and digital images, followed by digital dermoscopy using a standardized digital system (MoleMax). Dermoscopy images of lesions with atypical features were stored digitally. Total body mapping standardized registry according to the two-step method of digital follow-up. Follow-up: TBP comparing total body images with previous registries, plus dermoscopic comparison of images of atypical lesions and new atypical lesions not previously registered.
Truong (2016)	RC	2012-2014	56, 86* (24-194)	Patients attending two pigmented lesion clinics who underwent TBP and had 2 or more follow-up visits over a period of 2 years or longer	NS

TBP = total body photography; RC = retrospective cohort; PC = prospective cohort; PLC = pigmented lesion clinic; NS = not specified.
*Median follow-up for Salt Lake City and Boston cohorts, respectively.

Table 2. Patient demographics and tumour characteristics for included studies.

Study	Patients receiving TBP	Patients with risk factors, n (%)	Males, n (%)	Age, median (range)	MIS, n (%)‡	MM, n (%)‡	BT, mm, median (range)
Drugge (2020)	218	All patients were high risk (defined as personal or family history, 4 or more dysplastic nevi, or 100 or more nevi)	NS	NS	44 (20.2)	23 (10.6)	NS
Feit (2004)	567	Personal history of melanoma: 9 (75), Family history of melanoma: 4 (33), History of non-melanoma skin cancer: 3 (25)	6§ (50)	39.5 (22-77)	21 (3.7)	6 (1.1)	0.51* (0.20-1.10)
Goodson (2010)	1076	Personal history of melanoma: 280 (26), Family history of melanoma: 108 (10), More than 2 atypical naevi: 829 (77), More than 50 naevi: 732 (68)	NS	NS	15 (1.4)	13 (1.2)	Initial visit: 0.83*, Follow-up: 0.38* (0.25 to >3)
Greenwald (2020)	36832	Personal history of melanoma: 417 (31), More than 5 atypical naevi: 425 (31), Red hair: 63 (5), Early sunburns: 802 (84), Sunbed use: 133 (14)	694¶ (50)	52 (15-87)	101 (0.3)	36 (0.1)	0.50 (0.20-3.10)
Lallas (2020)	977	All patients had a personal history of melanoma	520 (53.2)	54.7* (15-89)	35 (3.6)	17 (1.7)	0.49* (0.20-0.90)
Mintsoulis (2016)	114	All patients either had history of melanoma (PLC and GDC) or were at high risk of melanoma (PLC only)	51 (44.7)	46.1* (17-75)	NS	NS	0.04* (NS)
Moloney (2014)	311	Personal and family history of melanoma: 52 (17), AMS and history of melanoma: 219 (70), Multiple primary melanoma: 146 (47), More than 50 naevi: 217 (70), Fitzpatrick skin type I: 49 (16), Red hair: 52 (17), CDKN2A mutation: 17 (5)	179 (57.6)	53 (21-85)	NS	NS	0.33 (in situ to 0.15)
Risser (2007)	64	Personal history of melanoma: 22 (34), Family history of melanoma: 16 (25%), Mean number of severe dysplastic naevi: 1.4	29 (45.3)	33.7	0	0	NA
Salerni (2012)	618	Personal history of melanoma: 277 (45), More than 50 naevi: 574 (93), AMS: 556 (90), Fitzpatrick skin type I: 19 (3), Red hair: 26 (4), CDKN2A mutation: 39 (6), MC1R polymorphism: 163 (26)	281 (45.5)	37*	53 (8.6)	45 (7.3)	0.62* (all <1)
Truong (2016)	926	Personal history of melanoma: 60 (38), Family history of melanoma: 30 (19), More than 50 naevi: 117 (75)	541 (58.4)	38, 39† (11-76)	46 (5.0)	47 (5.1)	0.38, 0.51† (0.10-2.10)
Total	41703	NA	NA	NA	315	187	NA
Range	NA	NA	45.3-58.4%	11-89	NA	NA	In situ to >3

TBP = total body photography; MIS = malignant melanoma in situ; MM = malignant melanoma; BT = Breslow thickness; AMS = atypical mole syndrome; PLC = pigmented lesion clinic; GDC = general dermatology clinic; NS = not specified; NA = not applicable.

*Mean values instead of median values shown.

†Values for Salt Lake City and Boston cohorts, respectively.

‡Percentages expressed as a proportion of total number of biopsies.

§Demographic data available only for patients with MIS or MM on biopsy.

¶Demographic data available only for patients with at least one biopsied lesion.

Table 3. Overview of the risk of bias and concerns about applicability for included studies.

Study	Risk of bias				Concerns about applicability		
	Participant selection	**Index test**	**Reference standard**	**Flow and timing**	**Participant selection**	**Index test**	**Reference standard**
Drugge (2020)	Low	Low	Unclear	Unclear	Low	High	Low
Feit (2004)	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Goodson (2010)	Low	Low	Unclear	High	Unclear	Low	Low
Greenwald (2020)	Low	Low	Unclear	Unclear	High	Unclear	Low
Lallas (2020)	Low	Low	Unclear	Low	Low	Unclear	Low
Mintsoulis (2016)	High	Low	Unclear	High	Low	High	Low
Moloney (2014)	Unclear	Low	Unclear	High	Low	Low	Low
Risser (2007)	Low	Low	Unclear	High	Low	Unclear	Low
Salerni (2012)	Low	Low	Unclear	Low	Low	Low	Low
Truong (2016)	High	Low	Unclear	High	Unclear	Unclear	Low

Table 4. Summary statistics of diagnostic accuracy for included studies.

Study	Patients receiving TBP	Total number of biopsies	Mean biopsies per patient	True positives	False positives	Number needed to biopsy	Naevus: melanoma ratio	MIS:MM ratio
Drugge (2020)	218	225	2.0	67	158	3.36	2.36	1.91
Feit (2004)	567	77	6.4	27	50	2.85	1.85	3.50
Goodson (2010)	1076	548	0.6	28	520	19.57	18.57	1.15
Greenwald (2020)	36832	1571	1.1	260	1311	6.04	5.04	2.81
Lallas (2020)	977	121	NS	52	69	2.33	1.33	2.06
Mintsoulis (2016)	114	267	2.3	14	253	19.10	18.07	NA
Moloney (2014)	311	770	NS	82	688	9.39	8.39	NA
Risser (2007)	64	53	1.9	0	53	NE	NA	NA
Salerni (2012)	618	1152	1.9	98	1054	11.76	10.76	1.18
Truong (2016)	926	1419	1.6	93	1326	15.26	14.26	0.98
Total	41703	6203	NA	721	5482	NA	NA	NA
Range			0.6-6.4			2.33-19.6	1.33-18.57	0.98-3.50
Weighted mean			1.6			8.6	7.6	1.68

MIS = melanoma in situ; MM = malignant melanoma; NA = not applicable; NE = not estimable.

Values were calculated from source study data when not directly provided in the manuscript.

Mean biopsies per patient = number of lesions biopsied/number of patients biopsied.

True positives (MIS or MM on histopathology), false positives (neither MIS nor MM on histopathology), and number needed to biopsy (lesions biopsied for 1 MIS or MM) are shown for combined MIS and MM.