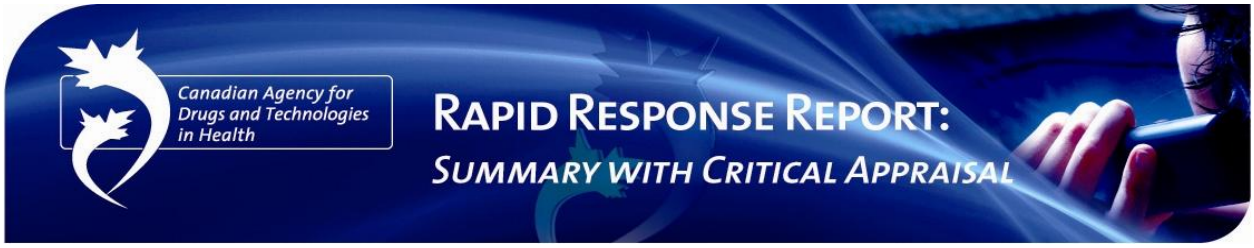

TITLE: Dermoscopy for Patients with Skin Lesions: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Evidence-Based Guidelines

DATE: 26 November 2012

CONTEXT AND POLICY ISSUES

A dermoscope is a non-invasive magnifying device that permits the visualization of structures just below the skin surface.[1] It facilitates examination of the diagnostic features of skin lesions that are not visible with the naked eye, and may assist in determining if lesions require excision or biopsy.[1]

The diagnostic performance of dermoscopy and its impact on the management of suspicious skin lesions is of interest to clinicians and policy makers. Dermoscopy may improve the diagnostic sensitivity if it detects melanomas that would not have been detected based on naked eye exams only. Specificity improves if dermoscopy is better able to identify benign lesions than naked eye examination. From a management perspective, improved sensitivity would result in excision of lesions that would have been left in situ based on the naked eye examination.[2] Improved specificity may mean a reduction in the number of benign lesions excised.[2]

The purpose of this report is to review the literature on the diagnostic accuracy and cost effectiveness of dermoscopy, relative to naked eye examination, for the detection of skin cancer.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of dermoscopy for patients with skin lesions?

2. What is the cost-effectiveness of dermoscopy for patients with skin lesions?

3. What are the evidence-based guidelines for dermoscopy for patients with skin lesions?

KEY FINDINGS

Prospective studies in a clinical setting suggest that dermoscopy may improve the sensitivity, but not specificity in detecting melanoma among patients with suspicious pigmented skin lesions. Due to the absence of evidence, no conclusions can be drawn on the impact of dermoscopy on clinical outcomes, diagnostic accuracy in detecting non-melanoma skin cancers, or cost-effectiveness.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2002 and November 9, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Any age or population Any type of skin cancer with the primary focus on melanoma (other types of skin cancer of interest- squamous cell, basal cell)
Intervention	Dermoscopy (Dermatoscopy, dermatoscopy epiluminescene microscopy)
Comparator	Clinical examination, which may include assessment using the ABCD rule, Menzies Scoring Method, Seven Point Checklist, Pattern Analysis, naked eye examination
Outcomes	Q1: Skin biopsies, clinical benefit, sensitivity, specificity, diagnostic accuracy Q2: Cost-benefit, cost-effectiveness Q3:Guidelines/ Recommendations and all outcomes for Q1,
Study Designs	Systematic review, meta-analysis, health technology assessment, randomized controlled trial, economic evaluation, evidence based guideline, non-randomized study

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, or were described in a systematic review included in this report. Meta-analyses were excluded if they were not based on a systematic review of the literature.

Systematic reviews, health technology assessments, meta-analyses, economic studies and RCTs were included if published in 2002 or later. Due to the volume of literature and the availability of two systematic reviews for question 1, non-randomized studies were included if published in 2007 or later.

Critical Appraisal of Individual Studies

The quality of systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[3] Diagnostic studies were assessed using the QUADAS tool as described in the NICE guidelines manual.[4]

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified 354 potentially relevant articles, of which nine met the inclusion criteria (Appendix 1). Two systematic reviews,[1,5] one RCT,[6] and six non-randomized studies[2,7-11] were included. No relevant health technology assessments or economic analyses were identified.

We identified three potentially relevant clinical guidelines which have been listed in Appendix 2. Due to time constraints these guidelines were not appraised or summarized. One additional review article of potential interest which did not meet the inclusion criteria for this review was listed in Appendix 2.

Summary of Study Characteristics

The characteristics of the systematic reviews and the randomized and non-randomized studies were summarized in Appendix 3 and 5.

All nine studies included in the systematic review by Vestergaard et al. 2008[1] and four studies summarized in this report[2,6-8] used a prospective study design to evaluate the impact of dermoscopy on diagnostic accuracy or intervention decisions, compared to clinical examination alone (i.e. naked eye examination). All studies were conducted in primary care, general dermatology or specialized pigmented lesion clinics. One study enrolled patients at high risk of melanoma, who had a family or personal history of melanoma.[2] All other studies enrolled consecutive patients who were referred to a clinic or were seeking screening for suspicious pigmented lesions. Three of the prospective studies used a sequential intervention design, where clinicians were first asked to diagnose lesions based on clinical assessment, and then based on dermoscopy.[2,7,8] The diagnostic performance of clinical examination and dermoscopy were compared to the reference standard of histology, or a combination of histology, expert diagnosis, or the revised diagnosis after an additional six to 12 month monitoring period.[1,2,6-8] The prevalence of melanoma in the prospective studies ranged from 0.5% to 21%.[1,2,6-8]

The systematic review by Kittler et al. 2002[5] included 27 prospective, retrospective or experimental setting studies. Of these studies, 10 included face-to-face examinations with patients, and in 17 studies clinicians evaluated images of lesions without any patient contact. In two reports non-experts diagnosed lesions, in six studies experts and non-experts were included, and in 19 studies, only experts were used. No information was provided on the selection of patients within these studies other than they had skin lesions. The prevalence of

melanoma ranged from 2% to 49% in the face-to-face studies, and from 16% to 61% in the studies that examined images of lesions only. Fourteen studies directly compared the diagnostic accuracy of dermoscopy with naked eye examination. Histopathology was the reference standard test.

Three other retrospective, non-randomized studies met the inclusion criteria: two cross-sectional studies[9,10] and one controlled before and after study.[11] In two of these studies,[9,10] dermatologists were asked to review digital photographs and dermoscopic images of suspicious pigmented lesions, and record their diagnosis or planned intervention (i.e., excision or no excision). The diagnoses were compared to the histological diagnosis. The third study reviewed the pathology reports from general dermatologists, comparing the malignant to benign ratio of excised lesions for the 2-year period before, and after dermoscopy was adopted into practice. These results were compared to a control group of pigmented lesion specialists who used dermoscopy throughout the same four year study period.[11]

Four studies included in the Kittler et al. 2002[5] review were also included in the report by Vestergaard et al. 2008.[1] The diagnostic accuracy data from the RCT by Carli et al. 2004[6] were included in the review by Vestergaard et al. 2008[1] so only the data on the number of lesions excised have been summarized in this report.

Summary of Critical Appraisal

The critical appraisal of the systematic reviews was summarized in Appendix 4. The review by Vestergaard et al.[1] used robust methods to identify, select and summarize studies. The authors did not report the methods used to assess the validity of the individual studies but had incorporated key methodological aspects into the study inclusion criteria and discussed important limitations when reviewing the findings.

The review by Kittler et al.[5] was limited by the literature search methods (one database searched), and also failed to report methods used to assess study validity. The authors did, however, discuss some key aspects of study validity in the text.[5] Kittler et al.[5] reported that in 22 of 27 studies, there was an independent assessment of the index and reference tests. Five studies did not report data on test independence. The review authors report that most studies were subject to verification bias but provided few details on the characteristics of the individual studies which made it difficult to assess their validity.[5] It is unclear if the meta-analysis of data from heterogeneous study designs was appropriate.

The prospective studies selected patients referred to, or seeking screening for skin cancer.[1,2,7,8] All but one[2] report selected consecutive patients. The prospective studies compared the diagnosis from the clinical exam and dermoscopy to a valid reference test, histology, however, these studies all had some degree of partial verification bias.[1,2,7,8] Verification bias is likely when the decision to perform the reference test (i.e., histology) is influenced by the results of the index test (clinical or dermoscopic diagnosis).[4] Thus, lesions diagnosed as benign by the index test, will not be verified by the reference test. In this situation true and false negative results are less likely to be detected, thereby inflating the sensitivity and decreasing the specificity of dermoscopy.[5] Two studies attempted to reduce the verification bias by monitoring all non-biopsied lesions for six to 12 months to detect false negatives.[2,8] Some studies used a sequential assessment design, where clinicians recorded a diagnosis based on the clinical exam, then perform dermoscopy and recorded a second diagnosis.[2,7,8] This design may be considered inferior to one that allocates clinicians to separate groups, one that uses clinical

examination only, and one that uses a clinical examination plus dermoscopy to make the diagnosis.

Two of the other non-randomized studies included in this report were conducted in an experimental setting, where clinicians were asked to diagnose lesions based on images and without any additional clinical information on the patient.[9,10] There was a high proportion of malignant lesions among the test sample (32% and 46%), and the findings from these studies may be less generalizable to clinical practice.[9,10] The report by Terushkin et al. 2010[11] used a control group with a higher level of expertise in dermoscopy than the intervention group.

Summary of Findings

The results of the included studies were summarized in Appendix 6 and 7. A guide to diagnostic test statistics was included in Appendix 8.

Sensitivity and specificity of dermoscopy was reported in one systematic review,[1] three prospective,[2,7,8] and two retrospective studies (Appendix 6).[9,10] Vestergaard et al.[1] reported a sensitivity of 0.71 (95% confidence interval (CI) 0.59 to 0.82) and specificity of 0.81 (0.48 to 0.95) with naked eye examination alone.[1] Using dermoscopy, the sensitivity was 0.90 (0.80 to 0.95) and specificity was 0.90 (0.57 to 0.98) based on a pooled analysis of nine studies.[1] The increase in sensitivity, but not specificity, was statistically significant for dermoscopy compared to naked eye examination alone.

Among the other included studies, the sensitivity ranged from 0.71 to 1.0, and from 0.70 to 1.0, and specificity ranged from 0.73 to 0.96, and from 0.74 to 0.98, with naked eye and dermoscopy, respectively.[2,7-10]

Kittler et al. 2002[5] pooled the data from 13 studies that directly compared diagnostic accuracy with and without dermoscopy. They reported that accuracy in detecting melanoma improved by 49% (P = 0.001) with dermoscopy [dermoscopy: log odds ratio 4.0 (95% CI 3.0 to 5.1), no dermoscopy: 2.7 (1.9 to 3.4)]. Meta-analysis of all 27 studies yielded similar results.[5]

Three prospective studies[2,6,7] compared the proportion of lesions excised based on clinical examination and dermoscopy (Appendix 7). Based on clinical examination, 16% to 49% of suspicious pigmented lesions were excised compared with 9% to 37% of lesions examined using dermoscopy.[2,6,7] Dermoscopy reduced the number of lesions excised by 4% to 20%.[2,6,7] The malignant to benign ratio of excised lesions ranged from 1:4.6 to 1:18.4 with naked eye examination, and from 1:3.2 to 1:22.5 with dermoscopy.[2,6,7,11]

Limitations

Two systematic reviews,[1,5] one RCT,[6] and six non-randomized studies[2,7-11] were identified in the literature search. All the included studies focused on the use of dermoscopy to diagnose melanoma, and did not include data for other skin cancers. None of the studies reported on clinical outcomes for patients assessed using dermoscopy. No economic evaluations were found in the literature search, and due to time constraints, it was not possible to evaluate the clinical guidelines we found.

A key limitation of the included studies is partial verification bias, where the decision to perform the reference test (i.e., histology) is influenced by the results of the index test (clinical or

dermoscopic diagnosis). Verification bias may increase the sensitivity and decrease the specificity of dermoscopy.

The findings of the systematic review by Kittler et al.[5] should be interpreted with caution due to limitations in the literature search, incomplete reporting of study characteristics and assessment of study validity, and the meta-analysis of heterogeneous study designs. The results from experimental studies, where images of lesion are evaluated with no patient contact, may be less generalizable to clinical practice. The clinician may be influenced by the knowledge that no patients will be affected by their decisions. These studies tend to include a higher proportion of malignant lesions than in practice, and clinicians may not have access to the patient's full clinical history when making the assessment.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Two systematic reviews, one randomized controlled trial, and six non-randomized studies were found that compared dermoscopy to clinical examination for the detection of melanoma.

Prospective studies in clinical settings suggest that dermoscopy improves the sensitivity but not the specificity to detect melanoma compared with clinical (naked eye) examination alone however these findings may be limited by partial verification bias. Dermoscopy may reduce the number of pigmented lesions excised.

Due to the absence of evidence, no conclusions can be drawn on the impact of dermoscopy on clinical outcomes, diagnostic accuracy in detecting non-melanoma skin cancers, or cost-effectiveness.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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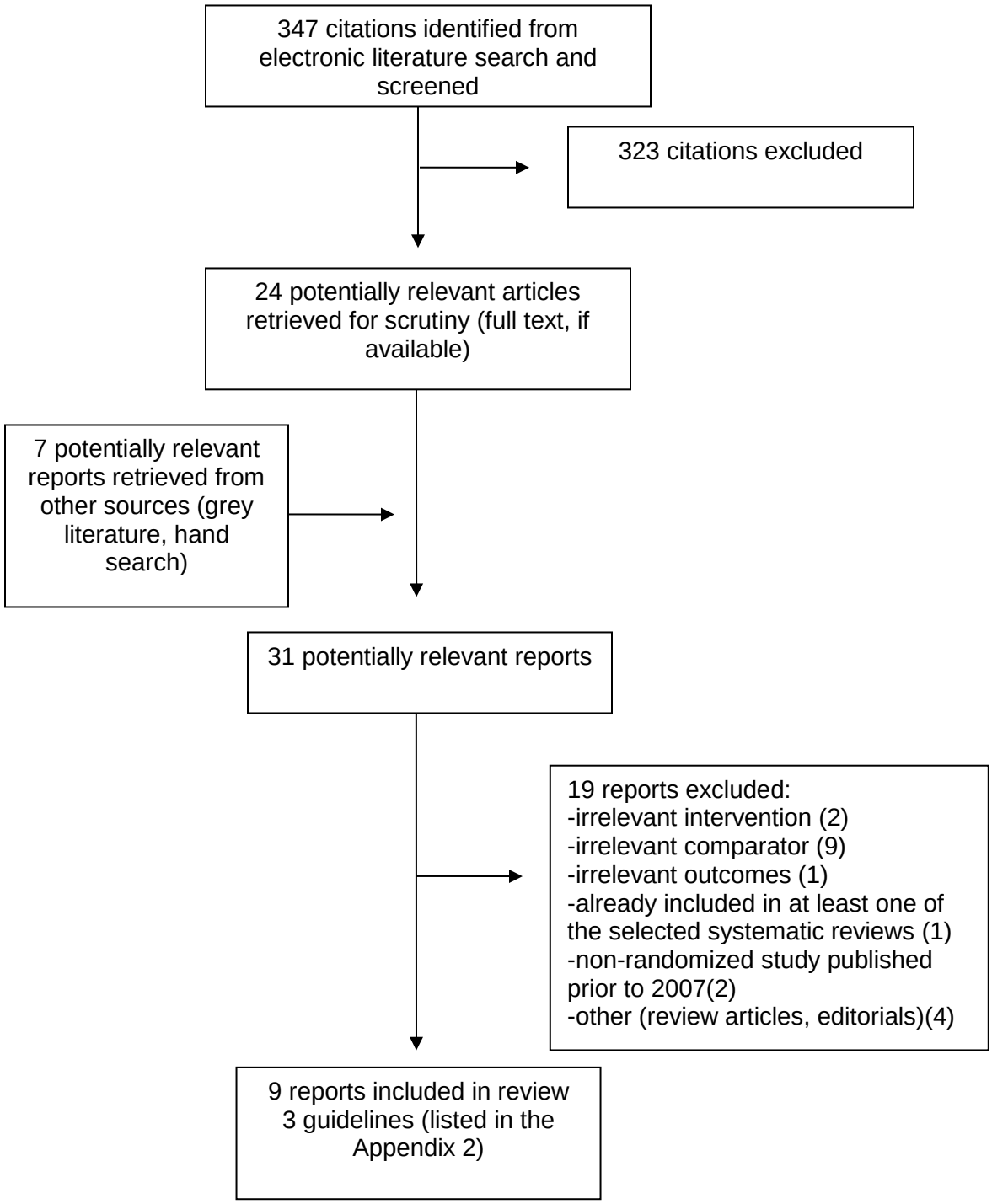
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional Articles of Potential Interest

Guidelines

1. Marsden JR, Newton-Bishop JA, Burrows L, Cook M, Corrie PG, Cox NH, Gore ME, Lorigan P, Mackie R, Nathan P, Peach H, Powell B, Walker C; British Association of Dermatologists (BAD) Clinical Standards Unit. Revised UK guidelines for the management of cutaneous melanoma 2010. J Plast Reconstr Aesthet Surg [Internet]. 2010 Sep [cited 2012 Nov 19];63(9):1401-19. Available from: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Melanoma%20guidelines%202010.pdf

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Melanoma is a malignant tumor that arises from melanocytic cells and primarily involves the skin. The most important exogenous etiological factor is exposure to ultraviolet irradiation. Diagnosis of melanoma is based primarily on its clinical features, and the A-B-C-D rule is useful in identifying pigmented lesions, which are suspicious for melanoma (Asymmetry, Border irregular, Color inhomogeneous and Diameter more than 5 mm). Dermoscopy is very helpful in clarifying the differential diagnosis of pigmented lesions. About 90% of melanomas are diagnosed as primary tumors without any evidence for metastasis. The tumor-specific 10-year survival for all such tumors is about 75-85%. The most important prognostic factors for primary melanoma without metastases are vertical tumor thickness (Breslow depth) as measured on the histological specimen, presence of histopathologically recognized ulceration, invasion level (Clark level) and identification of micrometastases in the regional lymph nodes via sentinel lymph node biopsy. The current tumor node metastasis classification for the staging of primary melanoma is based on these factors. Melanomas can metastasize either by the lymphatic or by the hematogenous route. About two-thirds of metastases are originally confined to the drainage area of regional lymph nodes. A regional metastasis can appear as satellite metastases up to 2 cm from the primary tumor, as intransit metastases in the skin between the site of the primary tumor and the first lymph node and as regional lymph node metastases. In the stage of regional metastasis, the differentiation between micrometastasis and macrometastasis and the number of lymph nodes involved are crucial. As soon as distant metastasis develops, prognosis depends on the site of the metastasis and on the lactate dehydrogenase levels in the blood. The frequency and extent of follow-up examinations is based on the initial tumor parameters. In thin primary melanomas up to 1-mm tumor thickness, clinical examinations at 6-month intervals are sufficient and in thicker primary melanomas, at 3-month intervals. Lymph node sonography as well as determination of the tumor marker protein S100beta are recommended. Additionally, in the stage of regional metastasis, whole body imaging

should be performed every 6 months; in the stage of distant metastasis, surveillance has to be scheduled individually

Review articles

4. Parsons SK, Chan JA, Yu WW, Obadan N, Ratichek SJ, Lee J, et al. Noninvasive diagnostic techniques for the detection of skin cancers. AHRQ Technical Brief 11 [Internet]; 2011 Sep [cited 2012 Nov 19]; Report No.: 11-EHC085-EF. Available from: http://www.ncbi.nlm.nih.gov/books/NBK82493/pdf/TOC.pdf
See page 16-22 for section on dermoscopy

   Cancers of the skin are the most common forms of cancer. Timely diagnosis and treatment are critical to reducing the rates of morbidity and mortality. Newer noninvasive imaging technologies may assist with earlier detection. To provide an objective description of noninvasive imaging modalities in diagnosing cancerous tumors of the skin, to proffer an analytic framework for assessing the applications of the imaging modalities, to summarize the state of ongoing research, and to delineate future research needs. We searched the MEDLINE(R) database for English-language literature published between 1990 and March 2011 for selected noninvasive imaging technologies. We included all publications types and study designs. We extracted data solely from relevant abstracts. Our search also included grey literature (manufacturers' Web sites, Food and Drug Administration's relevant databases, and ClinicalTrials.gov), and incorporated expert input from our key informants. Devices were classified as in general clinical use, limited clinical use, or investigational use, based on all available information. We screened in 629 abstracts that were relevant to the noninvasive imaging technologies of interest. Only 11 abstracts were on randomized controlled trials. Of the devices in general clinical use, we found a total of 51 abstracts on photography and 433 on dermoscopy. Of note, only one abstract reported clinical outcomes. None of the abstracts reported adverse events. Photography is principally used in specialty and subspecialty settings (i.e., oncology) and while widely used by dermatologists, dermoscopy is still not used in primary care. We did not identify any consistent guidelines for the assessment of suspicious skin lesions. Devices in limited clinical use are principally used in research settings. Available literature was limited for these devices as well as those still considered investigational. A review of the literature reveals predominant use of noninvasive devices by dermatologists with limited diffusion of this technology in primary care. When compared with the use of biopsy, future research is needed to evaluate the test accuracies, clinical impact, and the potential adverse events associated with the use of noninvasive imaging technologies

APPENDIX 3: Summary of Systematic Reviews

Author, year / Characteristic	Vestergaard 2008[1]	Kittler 2002[5]
Population	Patients with suspicious skin lesions assessed in a clinical setting	Patients presenting with skin lesions
Intervention (index test)	Compared diagnostic performance of clinical assessment with and without dermoscopy	Compared diagnostic performance of clinical assessment with and without dermoscopy
Comparator (reference test)	Valid reference test defined as histopathological diagnosis or diagnosis made by expert in the field	Histopathology
Outcomes	Sensitivity, specificity	Sensitivity, specificity
Study design	Prospective assessment of consecutive patients evaluated in a clinical setting; Tests performed independent of and blind to the reference test result	No criteria specified
Exclusions	Retrospective studies, assessment of images only (i.e., no direct patient contact), articles with no English abstract; review articles or letters or reports without original data.	Articles not in English or German, unpublished reports or abstracts, computerized image analysis, review articles or letters or reports without original data.
Validity assessment	Methods for validity assessment were not specified however the authors restricted to studies that made direct, independent blinded comparisons between tests.	Methods for validity assessment were not specified; independence of clinical and histological diagnosis, and verification bias were evaluated
Synthesis methods	Conducted a meta-analysis of the studies	Conducted a meta-analysis of the studies
Literature search	Conducted up to January 2008 of multiple databases No grey literature or hand search Screened 3,000 articles for inclusion	Conducted search up to December 2000 of MEDLINE Hand search and consultation with experts Screened 157 articles for inclusion
Included studies	9 (2 RCTs, 7 cross sectional studies) 8,487 lesions examined melanoma prevalence ranged from 0.5% to 21.1%	27 studies 9,821 pigmented lesions examined (median 232/study) melanoma prevalence ranged from 2% to 49% for studies in a clinical setting, and from 16% to 61% for those in an experimental setting (ie, analysis of images) 14 studies directly compared clinical examination to clinical examination with dermoscopy
Comments	Included 4 reports also included in Kittler	Algorithms used included pattern analysis, ABCD rule, and scoring systems (e.g., 7-point checklist, Menzies scoring system).

RCT=randomized controlled trial;

APPENDIX 4: Validity Assessment of Systematic Reviews

AMSTAR checklist item	Vestergaard[1]	Kittler[5]
1. Was an 'a priori' design provided?	Yes	Yes
2. Was there duplicate study selection and data extraction?	Can't answer Duplicate screening of articles; data extraction unclear	Can't answer Duplicate screening of articles; data extraction unclear
3. Was a comprehensive literature search performed?	Yes	No (MEDLINE only database searched)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	Yes
5. Was a list of studies (included and excluded) provided?	No Included studies: yes, Excluded: partial list	No Included studies: yes, Excluded: no
6. Were the characteristics of the included studies provided?	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	Can't answer No mention of validity assessment but key methodological aspects incorporated into inclusion criteria	Can't answer No mention of validity assessment but some methodological aspects discussed in text
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes	Can't answer Appropriateness of combining different study designs (retrospective, prospective & experimental) is unclear
10. Was the likelihood of publication bias assessed?	Can't answer	Yes
11. Was the conflict of interest stated?	Yes	No

APPENDIX 5: Summary of Randomized and Non-randomized Studies

Table 1. Diagnostic studies

Author, year, country,	Study type, Setting	Patient and lesion selection	Criteria for melanoma	Reference test	Risk of verification bias*	Interpretation blinded?†	Clinical data available at assessment‡
Prospective studies in clinical setting							
Van der Rhee 2011[2] Netherlands	Cohort Pigmented lesion clinic	Patients at high risk for melanoma with suspicious lesions	ABCD, ugly duckling sign, pattern analysis	Histology	Yes (however, all lesions not excised were followed for 1 year to detect false negatives)	Yes (sequential examination)	Yes
Van der Rhee 2010[7] Netherlands	Cohort General dermatology clinic	Consecutive patients with suspicious pigmented lesions	ABCDE, ugly duckling sign	Histology	Yes (38% lesions biopsied, no follow up for lesions not biopsied)	Yes (sequential examination)	Yes
Grimaldi 2009[8] Italy	Cross-sectional Primary care	Consecutive patients with suspicious pigmented lesions	ABCD rule	Expert opinion or histology	Yes (however, all patients followed for 6 months to detect false negatives)	Yes (sequential examination)	Yes
Retrospective study or experimental setting							
Samini 2010[9] France	Cross-sectional Analysis of images by dermatologists	Cutaneous blueish lesions suggestive of blue naevus or cutaneous metastasis of melanoma	NS	Histology	No (all lesions had been biopsied previously)	Yes	No

Author, year, country,	Study type, Setting	Patient and lesion selection	Criteria for melanoma	Reference test	Risk of verification bias*	Interpretation blinded?†	Clinical data available at assessment‡
De Giorgi 2010[10] Italy	Cross-sectional Analysis of images by general dermatologists	Small diameter (<8 mm) lesions with atypical characteristics	NS	Histology	No (all lesions had been biopsied previously)	Yes (sequential examination)	No

NS=not specified; RCT=randomized controlled trial

* Verification bias is likely when the decision to perform the reference test (i.e., histology) is influenced by the results of the index test (clinical or dermoscopic diagnosis).

†Were the clinicians unaware of the results of histology when performing the clinical and dermoscopy examinations? In studies using sequential examination procedures, the clinician was asked to record a diagnosis based on the clinical examination, and then use dermoscopy to make a second diagnosis.

‡ Did the clinician have access to all the relevant clinical information on the patient's history, signs and symptoms at the time of assessment?

Table 2. Studies evaluating management practices for suspected malignant skin lesions

Author, year, country,	Study type, Setting	Patient and lesion selection	Intervention	Control	Outcomes
Prospective study in a clinical setting					
Carli 2004[6] Italy	RCT Pigmented lesion clinic	Consecutive patients with suspicious pigmented lesions	Gp2: naked eye + dermoscopy, management options: excise yes/no Gp3: naked eye + dermoscopy, management options: excise, 6 month follow-up, or no action	Gp1: naked eye observation only, management options: excise yes/no	Malignant/benign ratio in excised melanocytic lesions
Retrospective study					
Terushkin 2010[11] US	Controlled before and after study Review of pathology reports from a university hospital dermatology practice	Excised lesions with differential diagnosis of melanoma or dysplastic nevus	General dermatologist in the period before and after adopting dermoscopy into practice	Pigmented lesion specialist using dermoscopy in both periods	Malignant/benign ratio in excised melanocytic lesions

Gp1=group 1; Gp2=group 2; Gp3=group 3; RCT=randomized controlled trial

APPENDIX 6: Summary of Results: Diagnostic Accuracy

First author, study design†	N lesions (% melanoma)	Sensitivity		Specificity	
		Naked eye	Dermoscopy	Naked eye	Dermoscopy
Prospective studies in clinical setting					
Vestergaard[1] SR (pooled data from 9 studies)	8,487 (4%)	0.71 (95% CI 0.59 to 0.82)	0.90 (0.80 to 0.95), p=0.002	0.81 (0.48 to 0.95)	0.90 (0.57 to 0.98), p=NS
van der Rhee 2011[2] Cohort	49 (4%)	1.00	1.00	0.89	0.89
van der Rhee 2010[7] Cohort	207 (7%)	0.79	0.86, p=NS	0.96	0.98, p=NS
Grimaldi 2009[8] Cross-sectional	235 (2%)	1.00*	1.00*	0.73*	0.90*
Retrospective study or experimental setting					
De Giorgi 2010[10] Cross-sectional	200 (32%)	Mean 0.71 (SD 0.15)	0.84 (0.11), p<0.01	0.80 (0.05)	0.80 (0.10), p=NS
Saminini 2010[9] Cross-sectional	39 (46%)	Mean 0.78 (SD 0.10)	0.70 (0.09)	0.77 (0.16)	0.74 (0.09)

*Calculated by CADTH
† Kittler et al.[5] did not present pooled sensitivity and specificity data.

APPENDIX 7: Summary of Results: Impact on Management of Suspicious Lesions

Table 1: Prospective studies in clinical setting

First author, year, study design	N lesions (% melanoma)	Clinical exam		Dermoscopy		Absolute difference in % lesions biopsied†
		N (%) lesions biopsied	Malignant/benign ratio of excised lesions†	N (%) lesions biopsied	Malignant/benign ratio of excised lesions†	
van der Rhee 2011[2] cohort	49 (4%)	24 (49%)	1:11	14 (29%)	1:6	-20%
Van der Rhee 2010[7] cohort	196 (7%)	79 (40%)	1:4.6	72 (37%)	1:4.1	-4%
Carli 2004[6] RCT	913 (1%)	47 (16%)	1:14.7	Gp2*: 28 (9%), p=0.013 Gp3*: 26 (9%), p=NR	Gp2*: 1:13.0 Gp3*: 1:7.7	Gp2*: -7% Gp3*: -7%

Gp2=group 2; Gp3=group 3; N=number; NR=not reported
*Patients in group 2 were examined by naked eye observation, plus dermoscopy if needed. Lesions that were equivocal or suggestive of melanoma were referred for surgery. Patients in group 3 were examined by naked eye observation, plus dermoscopy if needed. Suggestive or equivocal lesions could be referred for surgery or followed for 6 months and re-assessed for melanoma. P values or absolute differences are for group 2 or group 3 compared to clinical exam alone.
†Calculated by CADTH.

Table 2. Retrospective of Experimental Study: Malignant/benign Ratio of Excised Lesions

First author, year, study design	N lesions, (% melanoma)	Year	Malignant/benign ratio of excised lesions			
			General dermatologist (intervention)		Pigmented lesion specialist (control)	
			Period 1 Naked eye exam	Period 2 Dermoscopy	Period 1 Dermoscopy	Period 2 Dermoscopy
Terushkin 2010[11] Controlled before and after study	Intervention: 333 (7%) Control: 105 (18%)	2004	1:10.4	--	1:3.6	--
		2005	1:18.4	--	1:3.2	--
		2006	--	1:22.5	--	1:9.0
		2007	--	1:7.9	--	1:6.0

APPENDIX 8: Guide to Summary Statistics of Diagnostic Tests[12]

In order to test the accuracy of an experimental test, comparison to a reference standard test is required. In this case, histopathology is considered the "gold standard" and is used to determine which patients have or do not have skin cancer. The result of the experimental test is then compared to the reference test to determine the number of true and false, positive and negative results. The results of the reference standard test must be reliable or the performance of the experimental test will be poorly estimated.

	Patients with disease (positive pathology)	Patients without disease (negative pathology)	
Positive dermoscopy	True positive	False positive	Total positive
Negative dermoscopy	False negative	True negative	Total negative
	Total with disease	Total without disease	Total patients

Sensitivity = number of true positives / total number with the disease (ie. the proportion with the disease that has positive test results)
Specificity = number of true negatives / total number without the disease (ie. the proportion without the disease that have negative test results)

Positive predictive value (PPV) = number of true positives/total positive
Negative predictive value (NPV)= number of true negatives/total negative
Positive and negative predictive values are influenced by the prevalence of the disease in the sample population.

Positive likelihood ratio (LR+)is the ratio of the true positive rate to the false positive rate.
Negative likelihood ratio (LR-) is the ratio of the false negative rate to the true negative rate

A positive likelihood ratio >10 or a negative likelihood ratio <0.1 may provide convincing diagnostic evidence. Diagnostic evidence is considered strong if the test shows a positive likelihood ratio >5 or a negative likelihood ratio <0.2.

Example:

	Number of melanomas (positive histology)	Number of benign lesions (negative histology)	
Lesion suspicious based on dermoscopy	15	14	29
Lesion benign based on dermoscopy	1	205	206
	16	219	235

Sensitivity = 15/16 or 94%
LR+ = (15/16)/(14/219) or 14.7
PPV = 15/29 or 52%

Specificity = 205/216 or 94%
LR- = (1/16)/(205/219) or 0.07
NPV = 205/206 or 99.5%