Exfoliative cytology for the diagnosis of basal cell carcinoma and other skin cancers in adults

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Abstract

Background

Early accurate detection of all skin cancer types is essential to guide appropriate management and to reduce morbidity and improve survival. Basal cell carcinoma (BCC) is usually localised to the skin with potential to infiltrate and damage surrounding tissue, while cutaneous squamous cell carcinoma (cSCC) and melanoma have a much higher potential to metastasise and ultimately lead to death. Exfoliative cytology is a non–invasive test that uses the Tzanck smear technique to identify disease by examining the structure of cells obtained from scraped samples. This simple procedure is a less invasive diagnostic test than a skin biopsy, and for BCC has the potential to provide an immediate diagnosis that avoids an additional visit to clinic to receive skin biopsy results. This may benefit patients scheduled for either Mohs micrographic surgery or non–surgical treatments such as radiotherapy. A cytology scrape can never give the same information as a skin biopsy, however, so it is important to know more about which skin cancer situations it may be helpful.

Objectives

The primary objective was to determine the diagnostic accuracy of exfoliative cytology for the detection of basal cell carcinoma (BCC) in adults. Secondary objectives were to determine diagnostic accuracy for the detection of i) cutaneous

squamous cell carcinoma, ii) invasive melanoma and atypical intraepidermal melanocytic variants, and iii) any skin cancer, including keratinocyte skin cancer, invasive melanoma and atypical intraepidermal melanocytic variants, or any other skin cancer.

Search methods

We undertook a comprehensive search of the following databases from inception up to August 2016: Cochrane Central Register of Controlled Trials; MEDLINE; EMBASE; CINAHL; CPCI; Zetoc; Science Citation Index; US National Institutes of Health Ongoing Trials Register; NIHR Clinical Research Network Portfolio Database; and the World Health Organization International Clinical Trials Registry Platform. We also studied the reference lists of published systematic review articles.

Selection criteria

Studies evaluating exfoliative cytology in adults with lesions suspicious for BCC, cSCC or melanoma, compared with a reference standard of histological confirmation.

Data collection and analysis

Two review authors independently extracted all data using a standardised data extraction and quality assessment form (based on QUADAS-2). Where possible we estimated summary sensitivities and specificities using the bivariate hierarchical model.

Main results

This review reports on nine studies with a total of 1655 lesions including 1120 BCCs (14 datasets), 401 lesions with 44 cSCCs (two datasets), and 200 lesions with 10 melanomas (one dataset). Three of these datasets (one each for BCC, melanoma, and any malignant condition) were derived from one study which also performed a direct comparison with dermoscopy. Studies were of moderate to poor quality providing inadequate descriptions of participant selection, thresholds used to make cytological and histological diagnoses, and blinding. Reporting of patients' prior referral pathways was particularly poor, as were descriptions of the cytodiagnostic criteria used to make diagnoses. No studies evaluated the use of exfoliative cytology as a primary diagnostic test for detecting BCC or other skin cancers in lesions suspicious for skin cancer. Pooled data from seven studies using standard cytomorphological criteria (but various stain methods) to detect BCC in patients with a high clinical suspicion of BCC estimated the sensitivity and specificity of exfoliative cytology as 97.5% (95% CI: 94.5 to 98.9%) and 90.1% (95% CI: 81.1 to 95.1%) respectively. When applied to a hypothetical population of 1000 clinically suspected BCC lesions with a median observed BCC prevalence of 86%, exfoliative cytology would miss 21 BCCs and would lead to 14 false positive diagnoses of BCC. No false positive cases were histologically confirmed to be melanoma. Insufficient data are available to make summary statements regarding the accuracy of exfoliative cytology to detect melanoma or cSCC, or its accuracy compared to dermoscopy.

Authors' conclusions

The utility of exfoliative cytology for the primary diagnosis of skin cancer is unknown, as all included studies focused on the use of this technique for confirming strongly suspected clinical diagnoses. For the confirmation of BCC in lesions with a high clinical suspicion, there is evidence of high sensitivity and specificity for exfoliative cytology. Since decisions to treat low risk BCCs are unlikely in practice to require diagnostic confirmation given that clinical suspicion is already high, exfoliative cytology might be most useful for cases of BCC where the treatments being contemplated require a tissue diagnosis (e.g. radiotherapy). The small number of included studies, poor reporting and varying methodological quality means that no strong conclusions can currently be drawn to guide clinical practice. Despite insufficient data on the use of cytology for cSCC or melanoma, it is unlikely that cytology would be useful in these scenarios since preservation of the architecture of the whole lesion that would be available from a biopsy provides crucial diagnostic information. Given the paucity of good quality data, appropriately designed prospective comparative studies may be required to evaluate both the diagnostic value of exfoliative cytology by comparison to dermoscopy, and its confirmatory value in adequately reported populations with a high probability of BCC scheduled for further treatment requiring a tissue diagnosis.

Plain language summary

What is the diagnostic accuracy of exfoliative cytology ('skin scrape' cytology) for the detection of BCC in adults?

Why is improving the diagnosis of skin cancer important?

There are a number of different types of skin cancer. The most common is basal cell carcinoma (BCC). BCC is a localised cancer that can grow and destroy the skin around it. They do not spread into the body like other cancers can. Very small or superficial low risk BCCs can generally be treated with treatments such as creams rather than surgery, while BCCs which are more likely to grow and spread are best removed using surgery. Radiotherapy (a treatment where radiation is used to kill cancer cells) can also be used if BCCs are very large, or cannot be removed by surgery. Cutaneous squamous cell carcinoma (cSCC) is also usually a localised skin cancer. In a small proportion of cases it can spread to other parts of the body, so the best treatment is to remove it using surgery. Melanoma is one of the most dangerous forms of skin cancer as it has a higher potential to spread to other parts of the body, and so it is vital that it is recognised early so that it can be removed using surgery. If BCC is not diagnosed correctly (known as a false negative test result) treatment can be delayed and this makes the surgical procedure more complicated. Diagnosing BCC when it is actually something else (a false positive result) may result in unnecessary treatment, surgery or other investigations and can cause stress and anxiety to the patient. If BCC is incorrectly diagnosed in an individual who actually has an cSCC or melanoma, effective treatment can be

delayed and this might lead to a greater chance that the cSCC or melanoma spreads to other organs in the body which can be very serious.

What is the aim of the review?

The aim of this Cochrane review was to find out how accurate a technique called 'exfoliative cytology' is for diagnosing skin cancer. Researchers in Cochrane included nine studies to answer this question. Nine studies were concerned with the diagnosis of BCC, two with the diagnosis of cSCC and one with the diagnosis of melanoma.

What was studied in the review?

Exfoliative cytology means scraping the surface of a possible skin cancer with a knife, and then spreading a small layer of the scrape onto a glass slide so that the cells in the scrape can be stained and looked at under a microscope. It is less invasive than skin biopsy, and quick to perform with results available immediately and so could save patients an additional clinic visit to receive skin biopsy results.

What are the main results of the review?

The review examined nine studies with a total of 1655 lesions including 1120 BCCs, 44 cSCCs and 10 melanomas.

For identifying BCC, seven studies show the effect of using exfoliative cytology to confirm BCC in lesions that doctors already suspected were BCCs. In a group of 1000 such lesions, of which 860 (86%) actually do have BCC, then:

- An estimated 853 people will have an exfoliative cytology result confirming that a BCC is present. Of these 14 (1.6%) will not actually have a BCC (false positive result).

- Of the 147 people with an exfoliative cytology result indicating that no BCC is present, 21 (14%) will in fact actually have a BCC (false negative result).

One study compared the accuracy of exfoliative cytology to using a hand-held microscope (dermoscopy) for making a diagnosis of BCC, but used a different method of removing cells and included patients with a higher risk of melanoma than found in the other eight studies.

There was not enough evidence to determine the accuracy of exfoliative cytology for diagnosing cSCC or melanoma.

How reliable are the results of the studies of this review?

The small number of studies included in this review, poor description of how patients were selected to be included in the study, and limited information on how the test results were used to make diagnoses, reduces the reliability of our results.

The studies did not explain how patients had been referred to have the exfoliative cytology test. Most important of all, the test was only used in people in whom doctors had already diagnosed a BCC just by looking at the skin lesion. In other words, the test was being used to confirm a doctor's diagnosis. Most studies did not include enough people with skin lesions that are similar in appearance to a BCC to be sure that this test correctly identifies a BCC. This may cause exfoliative cytology to appear more accurate than it would be in actual practice.

Who do the results of this review apply to?

Studies were conducted in the UK, across Europe and in Australia. Patient characteristics, such as age and location of the lesion, were very poorly reported. The percentage of people included in the studies with a final diagnosis of BCC ranged from 18% to 90% (nine studies). For cSCC it was 4% and 18% (two studies), and for melanoma it was 5% (one study). It was not possible to tell from the studies how clinicians had decided that study participants had lesions which they felt were suspicious of a skin cancer.

What are the implications of this review?

No research has been done using exfoliative cytology to diagnose a skin cancer when a patient is first seen by a doctor. The results of this review suggest that exfoliative cytology can help to **confirm** BCC in patients with skin lesions that a doctor already suspects of being a BCC. This test could be useful for patients with BCCs that need non–surgical treatments, such as radiotherapy, where a tissue diagnosis is needed before the treatment can be given.

Background

This review is one of a series of Cochrane Diagnostic Test Accuracy (DTA) reviews on the diagnosis and staging of melanoma and keratinocyte skin cancers conducted for the National Institute for Health Research (NIHR) Cochrane Systematic Reviews Programme. Appendix 1 shows the content and structure of the programme.

Target condition being diagnosed

The commonest skin cancers in Caucasian populations are keratinocyte skin cancers, namely basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) (Gordon 2013; Madan 2010). BCC is the more common of the two keratinocyte carcinomas, and approximately one third of people with a BCC will develop at least a second BCC over time (Flohill 2013). In 2003, the World Health Organization estimated that between two and three million 'non-melanoma' skin cancers (of which BCC and cSCC are estimated to account for around 80% and 16% of cases respectively) and 132,000 melanoma skin cancers occur globally each year (WHO 2003). Rather than defining BCC and cSCC by what they are not (i.e. non-melanoma skin cancer), we collectively refer to these conditions using the preferred and more accurate term of 'keratinocyte carcinoma' in this diagnostic test accuracy review (Karimkhani 2015).

Exfoliative cytology is a simple procedure designed to detect the presence of malignancy through analysis of cell structure. Since its main benefit would be to replace histology, basal cell carcinoma has been chosen as the primary target condition for this review since this is the condition for which exfoliative cytology could potentially have the clearest role (see Role of index test(s) and Rationale below). Secondary target conditions include: i) cSCC, ii) invasive melanoma and atypical intraepidermal melanocytic variants, and iii) any skin cancer, including keratinocyte skin cancer, invasive melanoma and atypical intraepidermal melanocytic variants, or any other skin cancer. Table 1 provides a glossary of terms used.

Basal cell carcinoma

BCC can arise from multiple stem cell populations, including from the bulge and interfollicular epidermis (Grachtchouk 2011). Growth is usually localised, but it can infiltrate and damage surrounding tissue, which if left untreated can cause considerable destruction and disfigurement, particularly when located on the face (Figure 1). The four main subtypes of BCC are superficial, nodular, morphoeic or infiltrative, and pigmented. They typically present as slow-growing asymptomatic papules, plaques, or nodules which may bleed or form ulcers that do not heal (Firnhaber 2012). People with a BCC often present themselves to healthcare professionals with a non-healing lesion rather than specific symptoms such as pain. The diagnosis is often made incidentally rather than by people presenting with symptoms (Gordon 2013).

BCCs most frequently occur on sun-exposed areas of the head and neck (McCormack 1997), and are more common in men and in people over 40 years of age. A rising incidence of BCC in younger people has been attributed to increased recreational sun exposure (Bath-Hextall 2007a; Gordon 2013; Musah 2013). Other risk factors include Fitzpatrick skin types I and II (Fitzpatrick 1975; Lear 1997; Maia 1995); previous skin cancer history; immunosuppression; arsenic exposure; and genetic predisposition, such as in basal cell naevus (Gorlin) syndrome (Gorlin 2004; Zak-Prelich 2004). Annual incidence is increasing worldwide; Europe has experienced an average increase of 5.5% per year over the last four decades, the USA 2% per year, while estimates for the UK show incidence appears to be increasing more steeply at a rate of an additional 6 / 100,000 persons per year (Lomas 2012). The rising incidence has been explained by an ageing population, changes in the distribution of known risk factors, particularly ultraviolet radiation, and improved detection due to the increased awareness amongst both practitioners and the general population (Verkouteren 2017). Hoorens 2016 points to evidence for a gradual increase in the size of BCCs over time, with delays in diagnosis ranging from 19 to 25 months.

According to the National Institute for Health and Care Excellence (NICE) guidance (NICE 2010), low-risk BCCs that may be considered for excision include nodular lesions occurring in patients older than 24 years old who are not immunosuppressed and do not have Gorlin syndrome. Furthermore, lesions should be located below the clavicle; should be small (< 1 cm) with well-defined margins; not recurrent following incomplete excision; and not in awkward or highly visible locations (NICE 2010). Superficial BCCs are also typically low risk and may be amenable to medical treatments such as photodynamic therapy or topical chemotherapy (Kelleners-Smeets 2017). Assigning BCCs as low or high risk influences the management options (Batra 2002; Randle 1996).

It is recognised that basosquamous carcinoma (more like a high risk SCC in behaviour and not considered a true BCC) is likely to have accounted for many cases of apparent metastases of BCC hence the spuriously high reported incidence in some studies of up to 0.55% which is not seen in clinical practice (Garcia 2009).

Advanced locally destructive BCC can arise from long-standing untreated lesions or from a recurrence of a basal cell carcinoma after primary treatment (Lear 2012). Very rarely, BCC metastasises to regional and distant sites resulting in death, especially cases of large neglected lesions in those who are immunosuppressed or those with Gorlin syndrome (McCusker 2014). Rates of metastasis are reported at 0.0028% to 0.55% (Lo 1991), with very poor survival rates.

Squamous cell carcinoma of the skin (cSCC)

Primary cSCC arises from the keratinising cells of the outermost layer of the skin. People with cSCC often present with an ulcer or firm (indurated) papule, plaque, or nodule (Firnhaber 2012; Griffin 2016) sometimes with an adherent crust and poorly defined margins (Madan 2010). cSCC can arise in the absence of a precursor lesion or it can develop from pre-existing actinic keratosis or Bowen's disease (squamous cell carcinoma *in situ*) with an estimated annual risk of progression of <1% to 20% (Alam 2001) and 5% respectively (Kao 1986). It remains locally invasive for a variable length of time, but has the potential to spread to the regional lymph nodes or via the bloodstream to distant sites, especially in immunosuppressed individuals (Lansbury 2010). High risk lesions are those arising on the lip or ear, recurrent cSCC, lesions arising on non-exposed sites, scars or chronic ulcers, tumours more than 20mm in diameter and depth of invasion more than 4mm and poor differentiation on pathological examination (Motley 2009).

Chronic ultraviolet light exposure through recreation or occupation is strongly linked to cSCC occurrence (Alam 2001). It is particularly common in people with fair skin and in less common genetic disorders of pigmentation, such as albinism, xeroderma pigmentosum, and recessive dystrophic epidermolysis bullosa (RDEB) (Alam 2001). Other recognised risk factors include immunosuppression; chronic wounds; arsenic or radiation exposure; certain drug treatments, such as voriconazole and BRAF inhibitors; and previous skin cancer history (Baldursson 1993; Chowdri 1996; Dabski 1986; Fasching 1989; Lister 1997; Maloney 1996; O'Gorman 2014). In transplant recipients, cSCC is the most common form of skin cancer, with estimates of the risk of developing cSCC 65 to 253 times that of the general population (Hartevelt 1990; Jensen 1999; Lansbury 2010). Overall, local and metastatic recurrence of cSCC at five years is estimated at 8% and 5% respectively. Five-year survival rate following metastatic recurrence is only 25% to 40% (Rowe 1992).

Melanoma

Melanoma arises from uncontrolled proliferation of melanocytes - the epidermal cells that produce pigment or melanin. Cutaneous melanoma refers to skin lesions with malignant melanocytes present in the dermis, and includes superficial spreading, nodular, acral lentiginous, and lentigo maligna melanoma variants. Melanoma *in situ* describes malignant melanocytes that lay within the epidermis without invasion of the dermis, but are at risk of progressing to melanoma if left untreated. Lentigo maligna, a subtype of melanoma-in-situ in chronically sun-damaged skin, can progress to invasive melanoma if its growth breaches the dermo-epidermal junction during a vertical growth phase (when it becomes known as 'lentigo maligna melanoma'), however its malignant transformation is both lower and slower than for melanoma *in situ* (Kasprzak 2015). Melanoma *in situ* and lentigo maligna are both atypical intraepidermal melanocytic variants. Melanoma is one of the most dangerous forms of skin cancer, with the potential to metastasise to other parts of the body via the lymphatic system and blood stream. It accounts for only a small percentage of skin cancer cases but is responsible for up to 75% of skin cancer deaths (Boring 1994; Cancer Research UK 2017).

The incidence of melanoma rose to over 200,000 newly diagnosed cases worldwide in 2012 (Erdmann 2013; Ferlay 2015), with an estimated 55,000 deaths (Ferlay 2015). In the UK, melanoma has one of the fastest rising incidence rates of any cancer, and has had the biggest projected increase in incidence between 2007 and 2030 (Mistry 2011). In the decade leading up to 2013, age standardised incidence increased by 46%, with 14,500 new cases in 2013 and 2,459 deaths in 2014 (Cancer Research UK 2017). Rates are higher in women than in men; however, the rate of incidence in men is increasing faster than in women (Arnold 2014). This rising incidence is thought to be primarily related to an increase in recreational sun exposure, tanning bed use and an increasingly ageing population with higher lifetime recreational ultraviolet (UV) exposure, in conjunction with possible earlier detection (Belbasis 2016; Linos 2009). Putative risk factors are reviewed in detail elsewhere (Belbasis 2016).

A database of over 40,000 US patients from 1998 onwards which assisted the development of the 8th American Joint Committee on Cancer (AJCC) Staging System indicated a five-year survival of 97% to 99% for stage I melanoma, dropping to between 32% and 93% in stage III disease depending on tumour thickness, the presence of ulceration and number of involved nodes (Gershenwald 2017). While these are substantial increases relative to survival in 1975 (Cho 2014), mortality rates have remained static during the same period. This observation coupled with increasing incidence of localised disease, suggests that improvements in survival may be due to earlier detection and heightened vigilance (Cho 2014). Targeted therapies for stage IV melanoma (e.g. BRAF inhibitors) have improved survival expectation and immunotherapies are evolving such that long term survival is being documented (see below).

Treatment

Treatment for BCC and cSCC includes surgery, other destructive techniques and topical chemotherapy. A Cochrane systematic review of 27 randomised controlled trials (RCTs) of interventions for BCC found very little good quality evidence for any of the interventions used (Bath-Hextall 2007b). Complete excision of primary BCC has a reported five-year recurrence rate of < 2% (Griffiths 2005; Walker 2006), leading to significantly fewer recurrences than treatment with radiotherapy (Bath-Hextall 2007b). After apparent clear histopathological margins (serial vertical sections) after standard excision biopsy with 4mm surgical peripheral margins taken there is a 5-year reported recurrence rate of around 4% (Drucker 2017). Mohs micrographic surgery, whereby horizontal sections of the tumour undergo histological analysis and re-excisions are made until the margins are tumour-free, can be considered for high risk lesions such as on the centre of the face where standard wider excision margins might lead to considerable functional impairment (Bath-Hextall 2007b; Lansbury 2010; Motley 2009; Stratigos 2015). Bath-Hextall and colleagues (Bath-Hextall 2007b) found a single trial comparing Mohs micrographic surgery with complete excision in BCC, showing non-significantly lower recurrence at 30 months with Mohs micrographic surgery (Smeets 2004).

Destructive techniques other than excisional surgery include electrodesiccation and curettage, and cryotherapy (Alam 2001; Bath-Hextall 2007b). Alternatively, non-surgical (or non-destructive) treatments may be considered (Bath-Hextall 2007b; Kim 2014; Drew 2017), including topical chemotherapy such as imiquimod (Williams 2017), 5-fluorouracil (Arits 2013), ingenol mebutate (Nart 2015) and photodynamic therapy (Bath-Hextall 2007b; Roozeboom 2016). These non-surgical approaches are increasingly used for the superficial subtypes of BCC, for multiple lesions on low risk sites, where there are relevant comorbidities, or where surgery would be associated with risk of poor wound healing or significant scarring (Marsden 2010). However, non-surgical techniques do not allow histological confirmation of tumour clearance, and their use is dependent on accurate characterisation of the histological subtype and depth of tumour. The 2007 systematic review of BCC interventions found limited evidence from very small RCTs for these approaches (Bath-Hextall 2007b), which have only partially been filled by subsequent studies (Bath-Hextall 2014; Kim 2014; Roozeboom 2012). Most BCC trials have compared interventions within the same treatment class, and few have compared medical versus surgical treatments (Kim 2014).

A systematic review of interventions for primary cSCC found only one RCT eligible for inclusion (Lansbury 2010). Current practice therefore relies on evidence from observational studies, as reviewed in Lansbury 2013, for example. Surgical excision with predetermined margins is usually the first-line treatment (Motley 2009; Stratigos 2015). Observational studies suggest low recurrence rates for small, low risk lesions treated with cryotherapy or curettage and electrodesiccation (recurrence rates < 2%). Estimates of recurrence after Mohs micrographic surgery, surgical excision, or radiotherapy, which are likely to have been evaluated in higher risk populations, have shown pooled recurrence rates of 3%, 5.4% and 6.4%, respectively with overlapping confidence intervals; the review authors advise caution when comparing results across treatments (Lansbury 2013)

For primary melanoma, the mainstay of definitive treatment is wide local excision of the lesion, to remove both the tumour and any malignant cells that might have spread into the surrounding skin (Garbe 2016; Marsden 2010; NICE 2015a;

SIGN 2017; Sladden 2009). Recommended surgical margins vary according to tumour thickness (Garbe 2016) and stage of disease at presentation (NICE 2015a). Following histological confirmation of diagnosis, the lesion is pathologically staged from 0 (referring to melanoma *in situ*) to IV (indicating the presence of distant metastasis) according to the American Joint Committee on Cancer (AJCC) Staging System to guide treatment (Balch 2009). The main prognostic indicators can be divided into histological and clinical factors. Histologically, Breslow thickness is the single most important predictor of survival, as it is a quantitative measure of tumour invasion which correlates with the propensity for metastatic spread (Balch 2001). Independent of tumour thickness, prognosis is worse in older people, males, those with recurrent lesions, and in those with distant lymph node involvement (micro or macroscopic) and/or metastatic disease at the time of primary presentation.

Further details of treatment options beyond these primary therapies is provided in Appendix 2

Index test(s)

Exfoliative cytology is a non–invasive test that uses the Tzanck smear technique (Tzank 1949) to identify disease through the examination of the structure of cells. It is also known as 'skin scrape cytology', which is perhaps a better description of the technique than 'exfoliative' which traditionally refers to the removal of superficial dead cells from the skin surface. Skin lesions are cleaned, any surface crust removed, and they are then scraped with a scalpel or curette to collect cell material, which is subsequently smeared onto one or more glass slides (Chandra 2009). The material is then fixed using alcohol or air–drying, and stained using one of several methods recommended by the British Society of Cytopathology, namely the Papanicolaou (Pap) and May-Grünwald Giemsa (MGG; also called Romanowsky) methods (Chandra 2009). Slides are immediately examined under a microscope to determine the presence of malignant cells, either by a dermatologist with experience of the technique, or by a cytopathologist (Bakis 2004). Superficial shave biopsy differs from a cytological scrape in that it slices off a superficial (largely epidermal) section from a BCC that protrudes above the skin surface. The specimen retains the architecture of the part of lesion that is shaved off. Shave biopsy typically contains only tumour tissue rather than the interface between BCC and normal tissue, which provides important information on the depth and pattern of tumour invasion. Shave biopsy specimens are processed using normal paraffin block histopathology. Shave biopsy is only suitable for elevated/protruding BCCs and does not provide the immediate results that cytology can provide (Russell 1999).

Exfoliative cytology may be used for confirming the presence of clinically diagnosed BCC with a view to definitive treatment such as radiotherapy. The cellular appearance of BCC is characteristic (Figure 2), with ‘palisade’ arrangements of typically basal cells positioned around the margins of densely packed masses of larger and intensely stained cells (Figure 3 and Figure 4) (Ruocco 2011). Cytological features differ for the detection of cSCC, tending to show larger cells with less coherence that are more atypical in appearance with a more varied shape and size (pleomorphic) and abnormal nuclei (Bocking 1987; Fortuno-Mar 2013; Ruocco 2011). The cytological appearance of melanoma is much more varied, but can include larger cells than those observed which are typical of BCC, with prominent and often multiple large nuclei, large nuclear inclusions of cytoplasm, and often a presence of melanin pigment in tumour cells (Bocking 1987; Fortuno-Mar 2013).

Clinical Pathway

The diagnosis of skin lesions occurs in primary, secondary, and tertiary care settings by both generalist and specialist healthcare providers. In the UK, people with concerns about a new or changing lesion will either present to their general practitioner or directly to a specialist in secondary care, which could include a dermatologist, plastic surgeon, general surgeon or other specialist surgeon (such as an ear, nose, and throat (ENT) specialist or maxillofacial surgeon), or ophthalmologist (Figure 5). Current UK guidelines recommend that all suspicious pigmented lesions presenting in primary care should be assessed by taking a clinical history and visual inspection using the seven-point checklist (MacKie 1990); lesions suspected to be melanoma or cSCC (London Cancer Alliance 2013) should be referred for appropriate specialist assessment within two weeks (Chao 2013; Marsden 2010; NICE 2015b). In the UK, low risk BCC are usually recommended for routine referral, with urgent referral reserved for those in whom a delay could have a significant impact on outcomes, for example due to large lesion size or critical site (NICE 2015b). Appropriately qualified generalist care providers increasingly undertake management of low risk BCC in the UK (NICE 2010) and Australia (CCAAC Network 2008).

For referred lesions, the specialist clinician will use history-taking, visual inspection of the lesion (in conjunction with other skin lesions), and often dermoscopy to inform a clinical decision. If melanoma or cSCC is suspected, then urgent excision is recommended. Equivocal lesions for which a definitive diagnosis cannot be reached may undergo surveillance to identify any lesion changes that would indicate biopsy or reassurance and discharge for those that remain stable over a period of time. Low risk BCC and pre-malignant skin lesions potentially eligible for nonsurgical treatment may undergo a diagnostic biopsy before initiation of therapy.

Prior test(s)

The diagnosis of skin cancer is based on history-taking and clinical examination. In the UK, this is typically undertaken at two decision points – first in the GP surgery where a decision is made to refer or not to refer, and then a second time by a dermatologist or other secondary care clinician where a decision is made to biopsy/excise or not. A range of technologies have emerged to aid diagnosis to reduce the number of diagnostic biopsies or inappropriate surgical procedures. Dermoscopy using a hand-held microscope, has become the most widely used tool for clinicians to improve diagnostic accuracy of pigmented lesions, in particular melanoma, following visual inspection (Argenziano 1998; Argenziano 2012; Haenssle 2010; Kittler 2002), although is less well

established for the diagnosis of BCC or cSCC (Dinnes 2018a). The diagnostic accuracy, and comparative accuracy, of visual inspection and dermoscopy have been evaluated in a further three reviews in this series (Dinnes 2018a, Dinnes 2018b, Dinnes 2018c).

Visual inspection of the skin is undertaken iteratively, using both implicit pattern recognition (non-analytical reasoning) and more explicit 'rules' based on conscious analytical reasoning (Norman 2009), the balance of which will vary according to experience and familiarity with the diagnostic question. Various attempts have been made to formalise the "mental rules" involved in analytical pattern recognition, ranging from a setting out of lesion characteristics that should be considered (Friedman 1985; Sober 1979) to formal scoring systems or algorithms with explicit numerical thresholds of skin cancer.

Role of index test(s)

For the diagnosis of BCC, the potential role of exfoliative cytology could be to confirm a strong clinical suspicion of malignancy. If shown to be sufficiently accurate, this simple procedure could avoid the need for an invasive diagnostic skin biopsy in those who might be more suitable for non–surgical treatment. In ulcerated lesions (such as BCC), the removal of overlying dead cells or dried exudate is easily achieved, and the procedure is therefore potentially less invasive than shave or punch biopsy (though more invasive than dermatoscopic examination). Thus, exfoliative cytology could replace histology or allow treatment to be initiated prior to biopsy results in some patients. The test might also be of value to confirm a clinical suspicion of cSCC in recurrent lesions, or those that are critically located around the eyes, nose, lips, ears and neck, since these are suitable sites for Mohs micrographic surgery. The potential role for exfoliative cytology to detect melanoma is less clear, given the optimal treatment in these patients is excision (Murali 2009). Melanomas are frequently solid skin lesions for which scraping is likely to be more invasive as removal of the dead layer alone is difficult to achieve. In these cases, histological biopsy is likely to be equally traumatic, and is more likely to provide thorough and reliable diagnostic information.

Although skin is the largest and most accessible organ in the body, cutaneous cytology is not standard practice in the diagnosis of skin cancer lesions (NICE 2015a; SIGN 2014; Stratigos 2015; Telfer 2008). Although cytology is occasionally used in practice to confirm a clinical diagnosis of BCC when planning radiotherapy or surgery, the nature of the sample obtained lacks the additional histological information, such as pathological subtype and interaction with surrounding skin and structures, which is readily available following biopsy of suspicious lesions (Barr 1984; Ruocco 2011) and is required by clinicians to decide on best treatment. Nonetheless, the simplicity, immediacy and non–invasive nature of exfoliative cytology are clearly desirable attributes, which could benefit both health services and patients, albeit in a limited number of circumstances. This is true for confirming a clinical diagnosis of BCC which can present as multiple lesions, and commonly occur on the face, head and neck which are cosmetically critical sites (Powell 2000). Once diagnosed, superficial BCC can be treated using non–invasive treatments (listed in Target condition being diagnosed). Excisional surgery and Mohs micrographic surgery are the most successful treatments for nodular BCC, although smaller nodular BCCs in low risk areas can also be treated with topical treatments (Williams 2017); therefore, the ability to confirm a diagnosis in these patients using a fast and non–invasive approach is attractive (Ruocco 2011). The test can be performed during a consultation, with negative results in the presence of clinical concerns for malignancy indicating the need to proceed to a definitive biopsy (Ozden 2013). However, such potential benefits may be outweighed by mistaking more aggressive forms of BCC for a low-risk BCC, and cytology will never be able to match the additional pathological information regarding cellular behaviour and interaction with surrounding tissues provided by routine histopathology.

In order for exfoliative cytology to realise its potential in low-risk BCC, it would need to have a high positive predictive value (from a high specificity) to be sure that patients receiving positive results could safely proceed to treatment without biopsy. Any patients with negative cytology findings would still require biopsy to be sure that another malignancy had not been missed. A delay in the diagnosis of a BCC as a result of a false-negative test is usually not so serious as for melanoma because BCC is typically slow-growing and very unlikely to metastasise. However, delayed diagnosis can result in a larger and more complex excision. Very sensitive tests for BCC however are likely to result in a compromise on lower specificity leading to a higher false-positive rate, and an enormous burden of skin surgery, such that a balance between sensitivity and specificity is needed. The situation for cSCC is more similar to melanoma in that the consequences of falsely reassuring a person that they do not have skin cancer can be serious and potentially fatal. Thus, a good diagnostic test for cSCC should demonstrate high sensitivity and a corresponding high negative predictive value. A test that can reduce false positive diagnoses without missing true cases of disease has patient and resource benefits. False-positive diagnoses not only cause unnecessary morbidity from the biopsy, but could lead to initiation of inappropriate therapies and also increase patient anxiety. Notwithstanding these advantages, cytology does not allow the diagnostician to observe the tumour's histologic growth pattern, a characteristic which can influence management decisions since more aggressive growth patterns require more aggressive treatment (Oram 1997). For melanoma, high test sensitivity is a key requirement, as the cost of missing an early, thin curable lesion can make the difference between life and death.

Alternative test(s)

Standard practice for suspected skin cancer diagnosis in specialist settings involves visual and dermatoscopic examination by a dermatologist, and these tests are therefore considered as the comparators in this review. The direct alternative to cytopathology is histopathologic analysis of biopsy or excision specimens. This review uses histopathology as the reference standard for definitive diagnosis, and does not review it as an index test. We have also omitted alternative methods of exfoliative cytology, in particular imprint or 'touch imprint' methods

which involve pressing cytology slides directly onto the surface of suspicious lesions (Christensen 2008).

A number of other tests are being reviewed as part of our series of Cochrane DTA reviews on the diagnosis of skin cancer, including visual inspection and dermoscopy, teledermatology, mobile phone applications, reflectance confocal microscopy (RCM), optical coherence tomography (OCT) and computer-aided diagnosis techniques applied to dermoscopic and other types of image (Chuchu 2018a; Chuchu 2018b; Dinnes 2018a; Dinnes 2018b; Dinnes 2018c; Dinnes 2018d; Dinnes 2018e; Dinnes 2018f; Ferrante di Ruffano 2018a; Ferrante di Ruffano 2018b). RCM and OCT both provide depth-resolved optical reflectance imaging, and are emerging as noninvasive adjuncts to dermoscopy in a specialist setting, and RCM potentially as an alternative to dermoscopy for skin cancer diagnosis (Edwards 2016). Both methods are resource intensive and require specialist training in comparison to exfoliative cytology. High frequency ultrasound may prove to be an additional tool to assist in the diagnosis of melanoma however evidence to date is scarce and generally of poor quality (Dinnes 2018a).

Computer-aided diagnosis or artificial intelligence-based techniques use predefined algorithms to process and manipulate acquired data to identify the features that discriminate malignant from benign lesions, and may be applied to any types of image or spectra (e.g. Wallace 2000; Wallace 2000a). They have most commonly been applied to digital dermoscopy images (Esteva 2017; Rajpara 2009), with further developments in diffuse reflectance spectroscopy such as SIAscopy™ (Moncrieff 2002; Walter 2012), MelaFind® (Hauschild 2014; Monheit 2011; Wells 2012), and Electrical Impedance Spectroscopy, e.g. the Nevisense™ system (Malvehy 2014).

Evidence permitting, the accuracy of available tests will be compared in an overview review, exploiting within-study comparisons of tests and allowing the analysis and comparison of commonly used diagnostic strategies where tests may be used singly or in combination.

Rationale

This review is part of a series of reviews of diagnostic tests used to assist clinical diagnosis that aims to identify the most accurate approaches to diagnosis and provide clinical and policy decision-makers with the highest possible standard of evidence on which to base diagnostic and treatment decisions. With increasing rates of skin cancer and the push towards the use of dermoscopy and other high resolution image analysis in primary care, the anxiety around missing early cases needs to be balanced against sending too many people with benign lesions for a specialist opinion. Although its role for the diagnosis of melanoma is unconvincing because of the loss of vital additional histological information needed for optimal treatment, exfoliative cytology has the potential to improve the health of BCC patients through less invasive and more accessible diagnosis that avoids an additional visit for a skin biopsy result. These benefits must be weighed carefully against the potential limitations of exfoliative cytology to detect the additional pathological features seen on histological examination that help to differentiate lesions into those requiring immediate attention. For the subgroup of patients who will go on to receive non–invasive treatments, the technique could also enable quicker treatment with the potential for better cosmetic results: key objectives from patient groups (NICE 2010) whilst saving health services the costs of unnecessary biopsies. Treatment of BCCs currently requires diagnostic confirmation using histopathology (NICE 2010), so it is important to assess whether these potential benefits could be attained by comparing the accuracy of exfoliative cytology against that of the reference standard, histological diagnosis.

Since assessing the appearance of a cytological smear is essentially a subjective one that depends on adequate material, the diagnostic performance of exfoliative cytology is likely to be influenced by the experience and training of the individual collecting the sample, as well as the diagnostician. Reproducibility is a known issue in other areas of cytopathology, for example cervical cytology where the ability to make a diagnosis is influenced by the technician's proficiency in retrieving a sufficient cell sample from scraping (Baena 2017). Evidence from other tests involving the analysis of visual images, such as histopathology, often show variation in diagnosis according to the experience of diagnosticians (Farmer 1996; Shoo 2010) as well as the availability of clinical data used at the time of diagnosis (Ferrara 2009). This review will therefore also aim to evaluate the impact of clinician experience and training on the adequate retrieval of cell material for cytopathological analysis, as well as on the accuracy of diagnosis.

A single meta–analysis published in 2004 was identified which considered the accuracy of exfoliative cytology for differentiating between BCC and other conditions (Bakis 2004). Synthesising eight studies, it incorporated three studies not eligible for our review including those conducted on eyelid lesions and evaluating imprint techniques. It also found no studies evaluating the effect of clinician experience. Given that it only included studies published up to 2000, there is a need for an up-to-date analysis of the accuracy of exfoliative cytology for the diagnosis of BCCs as well as cSCCs and melanoma skin cancer.

This is one of a series of Cochrane Diagnostic Test Accuracy (DTA) reviews on the diagnosis and staging of melanoma and keratinocyte skin cancers as part of the National Institute for Health Research (NIHR) Cochrane Systematic Reviews Programme. Appendix 1 shows the content and structure of the programme. As several reviews for each topic area followed the same methodology, generic protocols were prepared in order to avoid duplication of effort, one for diagnosis of melanoma (Dinnes 2015a) and one for diagnosis of keratinocyte skin cancers (Dinnes 2015b). The Background and Methods sections of this review therefore use some text that was originally published in those protocols, and text that overlaps some of our other reviews (Dinnes 2018a; Dinnes 2018b; Dinnes 2018d; Ferrante di Ruffano 2018a). Table 1 provides a glossary of terms used.

Objectives

To determine the diagnostic accuracy of exfoliative cytology for the detection of basal cell carcinoma in adults, and to

compare its accuracy with that of standard diagnostic practice.

Secondary objectives

To determine the diagnostic accuracy of exfoliative cytology for the detection of cutaneous squamous cell carcinoma, and to compare its accuracy with that of standard diagnostic practice.

To determine the diagnostic accuracy of exfoliative cytology for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, and to compare its accuracy with that of standard diagnostic practice.

For each of the target conditions:

- i. To compare the accuracy of exfoliative cytology to dermoscopy where both tests have been evaluated in the same studies (direct test comparisons)
- ii. To determine the effect of observer experience.

Investigation of sources of heterogeneity

We set out to address a range of potential sources of heterogeneity for investigation across our series of reviews, as outlined in our generic protocols (Dinnes 2015a; Dinnes 2015b), and described in Appendix 3. Our ability to investigate these and other sources of heterogeneity was necessarily limited by the available data on each individual test reviewed.

Methods

Criteria for considering studies for this review

Types of studies

We included test accuracy studies that allow comparison of the result of the index test with that of a reference standard, including the following:

- studies where all participants receive a single index test and a reference standard;
- studies where all participants receive more than one index test(s) and reference standard;
- studies where participants are allocated (by any method) to receive different index tests or combinations of index tests and all receive a reference standard (between-person comparative studies (BPC));
- studies that recruit series' of participants unselected by true disease status (referred to as case series for the purposes of this review);
- diagnostic case-control studies that separately recruit diseased and non-diseased groups (see Rutjes 2005), however we did not include studies that compared results for malignant lesions to those for healthy skin (i.e. with no lesion present); and
- both prospective and retrospective studies.

We excluded studies from which we could not extract 2x2 contingency data or if they included fewer than five disease positive (for each of BCC, cSCC or melanoma) or five disease negative (i.e. benign) cases.

Participants

We included studies in adults with lesions suspicious for BCC, cSCC or melanoma. We excluded studies that recruited only participants with malignant diagnoses. We excluded studies conducted in children or where it was clearly reported that more than 50% of participants were aged 16 years old and under.

Index tests

Studies evaluating exfoliative cytology alone, or exfoliative cytology in comparison to visual inspection and/or dermoscopy were included. All techniques involving scraping of skin lesions in vivo and subsequent cytological analysis of material were considered eligible. Swabbed lesions, tape stripping, use of ex vivo specimens, imprint cytodiagnosis and fine needle aspiration were therefore excluded.

Studies evaluating the accuracy of subjective assessment of the presence or absence of individual cytomorphological features (with no overall diagnosis of malignancy) were also excluded, as were those using the test in intraoperative settings, such as for margin control during excision.

No exclusions were made according to test observer.

Target conditions

The target conditions were defined as the detection of:

- basal cell carcinoma (all types).

This decision reflected our assessment that the clearest role of exfoliative cytology would be to replace histological confirmation of disease (see Role of index test(s) and Rationale sections above).

Three additional definitions of the target condition were considered in secondary analyses, the detection of:

- cutaneous squamous cell carcinoma
- any form of invasive cutaneous melanoma or atypical melanocytic intraepidermal variants (i.e. including melanoma in situ, or lentigo maligna, which have a risk of progression to invasive melanoma)
- Any skin cancer

Reference standards

The ideal reference standard was histopathological diagnosis of the excised lesion or biopsy sample in all eligible lesions. All biopsy methods were eligible. A qualified pathologist or dermatopathologist should perform histopathology. Ideally, reporting should be standardised detailing a minimum dataset to include the histopathological features of BCC, cSCC or melanoma to determine the American Joint Committee on Cancer (AJCC) Staging System (e.g. Slater 2014a; Slater 2014b; Slater 2014c). We did not apply the reporting standard as a necessary inclusion criterion, but extracted any pertinent information.

We also accepted clinical follow-up of benign-appearing lesions as an eligible reference standard, whilst recognising the risk of differential verification bias (as misclassification rates of histopathology and follow up will differ) in our quality assessment of studies. 'Expert diagnosis' of benign lesions with no histology or clinical follow-up was also accepted as long as at least 50% of all participants with benign lesions had a histological diagnosis. We required all study participants with a final diagnosis of malignancy to have a histological diagnosis, either subsequent to the application of the index test or after a period of clinical follow-up.

Search methods for identification of studies

Electronic searches

The Information Specialist (SB) carried out a comprehensive search for published and unpublished studies. A single large literature search was conducted to cover all topics in the programme grant (see Appendix 2 for a summary of reviews included in the programme grant). This allowed for the screening of search results for potentially relevant papers for all reviews at the same time. A search combining disease-related terms with terms related to the test names, using both text words and subject headings was formulated (Appendix 4). The search strategy was designed to capture studies evaluating tests for the diagnosis or staging of skin cancer. As the majority of records were related to the searches for tests for staging of disease, a filter using terms related to cancer staging and to accuracy indices was applied to the staging test search, to try to eliminate irrelevant studies, for example, those using imaging tests to assess treatment effectiveness. A sample of 300 records that would be missed by applying this filter was screened and the filter adjusted to include potentially relevant studies. When piloted on MEDLINE, inclusion of the filter for the staging tests reduced the overall numbers by around 6000. The final search strategy, incorporating the filter, was subsequently applied to all bibliographic databases as listed below. The final search result was cross-checked against the list of studies included in five systematic reviews; our search identified all but one of the studies, and this study is not indexed on MEDLINE. The Information Specialist devised the search strategy, with input from the Information Specialist from Cochrane Skin. No additional limits were used.

We searched the following bibliographic databases to 29 August 2016 for relevant published studies:

- MEDLINE via OVID (from 1946);
- MEDLINE In-Process & Other Non-Indexed Citations via OVID; and
- EMBASE via OVID (from 1980).

We searched the following bibliographic databases to 30 August 2016 for relevant published studies:

- the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7, 2016, in the Cochrane Library;
- the Cochrane Database of Systematic Reviews (CDSR) Issue 8, 2016 in the Cochrane Library;
- Cochrane Database of Abstracts of Reviews of Effects (DARE) Issue 2, 2015;
- CRD HTA (Health Technology Assessment) database Issue 3, 2016;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature via EBSCO from 1960).

We searched the following databases for relevant unpublished studies:

- CPCI (Conference Proceedings Citation Index) via Web of Science™ (from 1990);
- Zetoc (from 1993)
- SCI Science Citation Index Expanded™ via Web of Science™ (from 1900, using the "Proceedings and Meetings Abstracts" Limit function).

We searched the following trials registers:

- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov);
- NIHR Clinical Research Network Portfolio Database (http://www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/);
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We aimed to identify all relevant studies regardless of language or publication status (published, unpublished, in press, or in progress). No date limits were applied. Update searches will be time and resource dependent.

Searching other resources

No potentially ongoing studies have been identified at the time of publication. We screened relevant systematic reviews identified by our searches for their included primary studies, and included any missed by our searches. We checked the reference lists of all included papers, and subject experts within the author team have reviewed the final list of included studies. No citation searching has been conducted.

Data collection and analysis

Selection of studies

Titles and abstracts were screened by at least one author (JDi or NC), with any queries discussed and resolved by consensus. A pilot screen of 539 MEDLINE references showed good agreement (89% with a kappa of 0.77) between screeners. Primary test accuracy studies and test accuracy reviews (for scanning of reference lists) of any test used to investigate suspected melanoma, BCC, or cSCC were included at initial screening. Inclusion criteria (Appendix 5) were applied independently by both a clinical reviewer (from one of a team of twelve clinician reviewers) and a methodologist reviewer (JDi or NC) to all full text articles, disagreements were resolved by consensus or by a third party (JDe, CD, HW, and RM). Authors of eligible studies were contacted when insufficient data were presented to allow for the construction of 2x2 contingency tables.

Data extraction and management

One clinical (as detailed above) and one methodologist reviewer (JDi, NC or LFR) independently extracted data concerning details of the study design, participants, index test(s) or test combinations and criteria for index test positivity, reference standards, and data required to populate a 2x2 diagnostic contingency table for each index test using a piloted data extraction form. Diagnostic thresholds were all qualitative, with cytopathology criteria used to indicate the target condition presence or absence. Some studies used a third diagnostic category for 'possible disease', and for these studies two datasets were extracted: one grouping 'possible' cases with index test positives (used for the primary analysis), and another grouping 'possible' cases with index test negatives. Disagreements were resolved by consensus or by a third party (JDe, CD, HW, and RM).

Authors of conference abstracts published from 2013 to 2015 were contacted to ask whether full data were available. If no full paper was identified, we marked conference abstracts as 'pending' and will revisit them in a future review update. It was not necessary to contact authors of included studies due to missing information regarding the target condition or diagnostic threshold.

Dealing with multiple publications and companion papers

We did not identify multiple publications for any of our included studies.

Assessment of methodological quality

We assessed risk of bias and applicability of included studies using the QUADAS-2 checklist (Whiting 2011), tailored to the review topic (see Appendix 6). The modified QUADAS-2 tool was piloted on a small number of included full text articles. One clinical and one methodologist reviewer (JDi, NC or LFR) independently assessed quality for the remaining studies; any disagreement was resolved by consensus or by a third party where necessary (JDe, CD, HW, and RM).

Statistical analysis and data synthesis

Due to paucity of data and differences in patient populations and thresholds used to define test positivity, no meta-analysis was undertaken for the diagnosis of melanoma or for the diagnosis of cSCC. Statistical pooling was, however, undertaken for the diagnosis of BCC.

For the diagnosis of BCC, any other skin cancers (for example melanomas or cSCCs) in the ‘disease negative’ group that were incorrectly identified by exfoliative cytology as BCCs were considered false positive results. This decision was taken on the basis that the clinical management of a lesion considered to be a BCC (for example, initiation of Mohs micrographic surgery, destructive techniques or non-surgical treatments) could be quite different to that for a melanoma or cSCC and could potentially lead to a negative outcome for those concerned. For the diagnosis of melanoma, however, any other skin cancers (BCC, cSCC etc) that were incorrectly identified as melanomas (i.e. positive on exfoliative cytology) were considered as true negative test results rather than as false positives, on the basis that excision of such lesions may still have been appropriate for the participants concerned.

Our unit of analysis was the lesion rather than the person. This is because (i) in skin cancer initial treatment is directed to the lesion rather than systemically (thus it is important to be able to correctly identify cancerous lesions for each person), and (ii) it is the most common way in which the primary studies reported data. Although there is a theoretical possibility of correlations of test errors when the same people contribute data for multiple lesions, most studies include very few people with multiple lesions and any potential impact on findings is likely to be very small, particularly in comparison with other concerns regarding risk of bias and applicability. For each analysis, only one dataset was included per study to avoid multiple counting of lesions. We conducted separate analyses according to the definition of the target condition, i.e. detection of BCC, melanoma or cSCC, and detection of any skin lesion requiring excision, as defined under Target condition being diagnosed. We used Review Manager 5.3 (RevMan 2014) for preliminary analyses of the data by plotting estimates of sensitivity and specificity on coupled forest plots and in receiver operating characteristic (ROC) space. We used the bivariate model to obtain summary estimates of sensitivity and specificity (Macaskill 2010). We fitted the bivariate models using the meqrlogit command in STATA 15.

Comparison with standard diagnostic practice was made by comparing with the accuracy of visual inspection or dermoscopy. Direct comparisons using data on the accuracy of visual inspection and/or dermoscopy were included only if reported in the included studies of exfoliative cytology due to the known substantial unexplained heterogeneity in all studies of the accuracy of dermoscopy (Dinnes 2018b). Comparative meta-analysis was not performed because of the limited number of studies.

Investigations of heterogeneity

We examined heterogeneity between studies by visually inspecting forest plots and summary ROC plots. Due to the limited number of studies in each analysis, we were unable to formally assess heterogeneity using meta-regression.

Sensitivity analyses

We were unable to perform sensitivity analyses due to limited data.

Assessment of reporting bias

Because of uncertainty about the determinants of publication bias for diagnostic accuracy studies and the inadequacy of tests for detecting funnel plot asymmetry (Deeks 2005), we did not test for publication bias.

Results

Results of the search

A total of 34,080 unique references were identified and screened for inclusion. Of these, 959 full text papers were reviewed for eligibility for any one of the suite of reviews of tests to assist in the diagnosis of melanoma or keratinocyte skin cancer. Figure 6 documents a PRISMA flow diagram of search and eligibility results. A total of 40 full text publications were tagged as potentially eligible for this review; ultimately 9 publications were included. Studies were excluded due to: not being primary studies (n = 6), including too few (≤ 5) benign lesions (n = 8), insufficiently reporting test accuracy data (n = 1), using an ineligible index test (n = 10, including swabbing (Bocking 1987), tape–stripping (Berardi 1992), imprint cytology (Hering 1970; Melek 1970; Urbach 1957) and fine needle aspiration (Jakasa 1976; Korabiec 1977; Rojo 1998; von Gizycki-Nienhaus 1992; Yu 2005)), using exfoliative cytology in an ineligible context (n = 2, for intraoperative care or margin control) or in an ineligible patient population (n = 4), or using an ineligible reference standard (n = 4). Three studies were excluded for multiple reasons. A list of the 31 studies excluded from this review with reasons for exclusion is provided in Characteristics of excluded studies, with a list of all studies excluded from the full series of reviews available as a separate pdf.

Across all skin cancer DTA reviews, the corresponding authors of 86 studies were contacted and asked to supply further information to allow study inclusion (n = 37) to clarify diagnostic thresholds (n = 18) or target condition definition (n = 30). It was not necessary to contact any authors for the current review.

Characteristics of included studies

We included nine studies evaluating the use of exfoliative cytology in participants with lesions suspected of skin cancer, providing 25 datasets (14 for BCC, 2 for cSCC, 1 for melanoma, and 8 for any malignant condition). One of these also performed a direct comparison between exfoliative cytology and dermoscopy (3 datasets: one each for melanoma, BCC and any malignant condition). A total of 1655 lesions were included with 1120 BCCs for the detection of BCC, 401 lesions with 44 cSCCs for the detection of cSCC, and 200 lesions with 10 melanomas for the detection of melanoma.

A description of thresholds used for diagnosis across the studies is provided in Appendix 7, along with summary study details.

Most studies (n = 6) recruited series of lesions with clinically suspected BCCs that also underwent histological evaluation by excision or biopsy. Two were prospective (Berner 1999; Gordon 1984), two retrospective (Powell 2000; Ruocco 1992) and two unclear (Brown 1979; Derrick 1994). Two case–control studies selectively included a mix of histologically confirmed lesions (Christensen 2008; Nauth 1988) and a single prospective case series was conducted in participants with pigmented skin lesions (Durdu 2011) considered to be difficult to diagnose on clinical grounds. No studies provided further details regarding the degree of investigation prior to receiving exfoliative cytology. Four were conducted in the UK (Berner 1999; Brown 1979; Derrick 1994; Powell 2000), one in Italy (Ruocco 1992), one in Norway (Christensen 2008), one in Germany (Nauth 1988), one in Australia (Gordon 1984) and one in Turkey (Durdu 2011). None reported being funded by manufacturers of diagnostic technology.

The number of included patients ranged from 30 to 240 with a median of 101 (interquartile range (IQR) 73 – 188) patients, but was not reported by one study (Ruocco 1992). Studies included a median of 150 lesions (range 37–578, IQR 83 –224). In the BCC studies, disease prevalence ranged from 52% (Gordon 1984) to 95% (Derrick 1994) in the 6 case series, and was pre–set at 19% (Nauth 1988) and 64% (Christensen 2008) in the two case–control studies. In the series evaluating pigmented skin lesions, the prevalence of melanoma was 5% and BCC 17% (Durdu 2011). This was the only study to include significant numbers of melanocytic benign lesions (Durdu 2011), whilst the remaining eight studies included mainly non–melanocytic benign lesions including actinic keratoses, seborrhoeic keratoses, Bowens Disease, and keratoacanthoma. Four studies that did not contribute datasets for the analysis of cSCC included small numbers of cSCCs (Berner 1999; Brown 1979; Derrick 1994; Ruocco 1992). Two studies did not report specific benign diagnoses (Berner 1999; Nauth 1988). A full breakdown of differential diagnoses for each study is listed in Appendix 7.

A variety of staining methods were used, chiefly Papanicolau (Christensen 2008; Gordon 1984; Nauth 1988) and May-Grünwald Giemsa (MGG; Christensen 2008; Derrick 1994; Durdu 2011). Only one study used Diff–Quick (Berner 1999). Three studies used more than one technique but failed to report which had been used in particular participants (Ruocco 1992; Brown 1979), and a fourth failed to report the stain method (Powell 2000). The impact of varying stain methods was investigated in one study which performed a direct comparison of diagnoses made using Pap, MGG, and both Pap and MGG (Christensen 2008).

All studies based their index diagnoses on cytomorphological findings, though three failed to outline the diagnostic criteria used (Christensen 2008; Brown 1979; Powell 2000). Features diagnostic for BCC were similar across the remaining studies, except for Nauth 1988 who clearly implemented a different approach by using a classification developed

from vaginal cytology (the 'Munchener scheme', a modification of the original Papanicolaou classification) to decide whether a lesion was malignant. For the diagnosis of melanoma, Durdu 2011 provided a basic definition of disease, defining melanoma as the presence of 'Epithelioid or spindle-type atypical nevoid cells' (Durdu 2011). Durdu 2011 also reported dermoscopic diagnoses for all patients, which followed a two–step method, differentiating melanocytic from non-melanocytic lesions before applying the ABCD algorithm. Specific diagnostic criteria are listed for each study in Appendix 7.

Skin scrapes were performed by the dermatologist in one study (Durdu 2011), but the operating clinician was not described in the remaining studies. Experience of the clinician performing cytodiagnosis was described as the cytologist (Gordon 1984), cytopathologist (Berner 1999; Christensen 2008), pathologist (Derrick 1994) or dermatologist (Durdu 2011), but was not reported by 4 studies (Brown 1979; Nauth 1988; Powell 2000; Ruocco 1992). No study evaluated interobserver variability.

In eight studies the reference standard diagnosis was made by histology alone, while Brown 1979 used expert opinion to overrule the histological diagnosis in two lesions whose clinical and cytological appearance was 'characteristic' of BCC.

Test failures

Four studies reported instances of insufficient cellular material to make a cytological diagnosis (Christensen 2008; Durdu 2011; Gordon 1984; Nauth 1988), listed in Table 2. Comprising between 1% and 8% of slides evaluated in each study, these were considered as test failures and excluded from analysis of accuracy. One study excluded inadequate slides at study entry (Berner 1999) and the remaining four studies did not report the adequacy of cellular material suggesting this may have been an implicit eligibility criterion (Brown 1979; Derrick 1994; Powell 2000; Ruocco 1992).

Methodological quality of included studies

Overall study quality was low or unclear, particularly in terms of the clinical applicability of results (Figure 7 and Figure 8).

Three of the nine studies were at low risk of bias for participant selection (Gordon 1984; Powell 2000; Ruocco 1992); three were at high risk of bias because studies recruited non–consecutively and selected participants according to histological diagnosis (Christensen 2008; Nauth 1988) or excluded lesions inappropriately (Derrick 1994). Three did not clearly describe consecutive patient recruitment or exclusions. Concern was high for the applicability of setting and included participants (n = 6) due to poor reporting regarding the composition of study populations (n = 5), inclusion of narrowly defined study groups (Berner 1999; Derrick 1994) and inclusion of multiple lesions per patient (Berner 1999; Christensen 2008; Durdu 2011; Gordon 1984; Powell 2000). The clinical applicability of participant populations could not be determined in two studies due to insufficient reporting of study populations (Nauth 1988; Ruocco 1992).

Risk of bias for the index test was low in two studies (Berner 1999; Gordon 1984) but could not be determined in the remaining seven studies due to poor reporting of diagnostic thresholds and whether cytology slides were interpreted without knowledge of the lesion's histology results. More than half of studies (5/9) were of high concern regarding the applicability of the index test, since examiners did not did have access to the clinical diagnosis during review of cytology slides (Christensen 2008; Gordon 1984), and not report cytodiagnostic criteria in sufficient detail to allow replication (Brown 1979; Christensen 2008; Gordon 1984; Powell 2000; Ruocco 1992); two studies could not be assessed due to poor reporting of the diagnostician's cytological expertise (Durdu 2011; Nauth 1988), and the remaining two studies were of low concern (Berner 1999; Derrick 1994).

All studies reported the use of an acceptable reference standard with one exception: Nauth 1988 failed to state the reference standard used to confirm the absence of disease in 14 of 224 included diseased participants (Nauth 1988). Only two studies clearly blinded the reference standard diagnosis to the cytology results (Berner 1999; Brown 1979), while in the remaining studies a failure to clearly report this aspect meant that the risk of bias due to conduct of the reference standard was unclear in these seven studies. In most studies (7/9) we were unclear as to whether the reference standard was used in a clinically applicable way, largely due to inadequate description of the conduct and interpretation of histology; only one study reported histopathology interpretation by an experienced dermatopathologist (Derrick 1994). Brown 1979 was judged to be of high concern due to use of expert opinion (discipline and qualifications not reported) to overrule the reference standard diagnosis in two of 85 cases.

All but one study (Durdu 2011) were judged at high risk (Brown 1979; Christensen 2008; Nauth 1988) or unclear risk of bias (Berner 1999; Derrick 1994; Gordon 1984; Powell 2000; Ruocco 1992) for flow and timing domain due to use of different reference standard tests (Brown 1979; Nauth 1988), exclusion of slides 'unavailable for examination' (Christensen 2008), and failure to report the time interval between exfoliative cytology and histology examinations (Berner 1999; Christensen 2008; Derrick 1994; Gordon 1984; Nauth 1988; Powell 2000; Ruocco 1992).

The single study comparing exfoliative cytology with dermoscopy (Durdu 2011) reported blinding the diagnoses of the two index tests, however did not describe the time interval between both tests, nor did it give sufficient details on the conduct of both tests, thus its risk of bias and applicability in the comparative domain remain unclear.

Findings

Detection of BCC

Seven of the nine studies provided data eligible for pooling. The remaining two studies were not pooled in the meta–analysis due to their use of a different diagnostic classification system (the Munchener Scheme, Nauth 1988) or to the evaluation of exfoliative cytology in a distinct patient group (pigmented skin lesions, Durdu 2011).

The seven pooled studies were conducted in participants with clinically suspect BCC lesions, and used standard

cytomorphology to investigate 1264 lesions with 1045 BCCs using MGG stain (Derrick 1994), Pap stain (Gordon 1984), Diff–Quick (Berner 1999), a mixture of stain techniques (Brown 1979; Ruocco 1992), or did not report the stain method (Powell 2000). Christensen 2008 used two slides per lesion, one MGG and the other Pap stain, selecting the slide showing greatest degree of cytological atypia for the final diagnosis. These were pooled regardless of stain method used, giving a summary sensitivity of 97.5% (95% CI: 94.5, 98.9%) with a summary specificity of 90.1% (95% CI: 81.1, 95.1%). A summary of all results is provided in Table 3.

Common diagnoses mistaken for BCC were actinic keratosis (Christensen 2008; Gordon 1984) and trichoepithelioma (Derrick 1994; Ruocco 1992). Only three of the 22 false positive cases (listed in Table 4) were malignant lesions, all 3 were confirmed carcinomas but histological type could not be classified due to insufficient biopsy material (Berner 1999). No false positive cases were melanomas. Six of the seven false positive cases in Gordon 1984 were 'possible but not diagnostic for BCC' lesions, histologically diagnosed as marked atypia (n = 4) and seborrhoeic keratosis (n = 2). Consideration of these uncertain diagnoses as test negatives did not impact on pooled sensitivity (97.3% (95% CI: 93.5, 98.9%)) but raised the specificity estimate to 94.2% (95% CI: 88.7, 97.1%) (Figure 9 and Figure 10). All 16 cSCCs were correctly identified as true negative cases (Berner 1999; Brown 1979; Derrick 1994; Gordon 1984; Ruocco 1992), however two studies misdiagnosed 3 BCCs as cSCCs (Brown 1979; Gordon 1984).

The study using the Munchener scheme (Nauth 1988) identified fewer BCCs and incorrectly diagnosed 42 lesions as having BCC, giving a sensitivity of 80.5% (95% CI: 66.0, 89.8%) and specificity of 74.6% (95% CI: 67.4, 80.6%). Misdiagnosis by lesion type was not reported.

The study in pigmented skin lesions (MGG stain) reported no false diagnoses amongst slides for 185 lesions, giving a sensitivity of 100% (95% CI: 89.9, 100%) and specificity of 100% (95% CI: 97.5, 100%) for the diagnosis of BCC (Durdu 2011); however 15 lesions were excluded from analysis due to the retrieval of insufficient cell material. Results for dermoscopy, conducted on the full sample of 200 lesions, demonstrated a lower sensitivity of 94.1% (95% CI: 80.9, 98.4%) and higher specificity 98.2% (95% CI: 94.8, 99.4%), but the differences could be explained by chance.

Christensen 2008 found no difference in sensitivity or specificity between the three stain techniques (Pap versus MGG versus Pap+MGG), with each method identifying the same number of false positive (n = 1) and false negative (n = 2) cases to give a sensitivity of 96% and specificity of 96%.

Detection of cSCC

Two studies included adequate numbers of cSCC cases (≥ 5) amongst their 347 lesions to be included for this target condition, however they are likely to have used different diagnostic criteria and so their results have not been pooled. Using standard cytomorphological criteria to diagnose 5 cSCC slides from 141 lesions, Gordon 1984 report a sensitivity of 100% (95% CI: 56.6, 100%) and specificity of 98.5% (95% CI: 94.8, 99.6%) with two false positive results, both showing squamous differentiation with cellular pleomorphism and a histological diagnosis of pleomorphic BCC. Nauth 1988's use of the Munchener scheme to diagnose 38 cSCC slides from 206 lesions resulted in a lower sensitivity of 88.9% (95% CI: 74.7, 95.6%) and lower specificity of 74.7% (95% CI: 67.7, 80.6%), reporting the only false negative cSCCs of any included study. Two were diagnosed as 'questionable dyskeratoses and/or questionable anaplastic tumour cells', one as mild dysplasia and the fourth as severe dysplasia.

No data were available to compare exfoliative cytology for detection of cSCC with routine diagnostic practice.

Detection of invasive melanoma and atypical intraepidermal melanocytic variants

The single study evaluating exfoliative cytology for the detection of 10 melanomas in 185 lesions (Durdu 2011) reported sensitivity of 100% (95% CI: 72.3, 100%) and specificity of 100% (95% CI: 97.6, 100%); dermoscopic diagnosis in the full sample (200 lesions, 10 melanomas) produced a sensitivity of 80.0% (95% CI: 49.0, 94.3%) and specificity of 97.4% (95% CI: 94.0, 98.9%).

Detection of any skin cancer

Four studies in 573 clinically suspect BCC lesions provided data for detection of any skin cancer (Berner 1999; Brown 1979; Derrick 1994; Gordon 1984); 495 histologically confirmed malignant lesions were included (476 BCCs, 13 cSCCs, 1 melanoma, 4 carcinomas of unspecified histological type (Berner 1999) and 1 apocrine carcinoma (Derrick 1994)). Pooled sensitivity was estimated to be 97.3% (95% CI: 93.5, 98.9%) with a pooled specificity of 86.0% (95% CI: 73.5, 93.1%). Consideration of uncertain diagnoses (Berner 1999; Gordon 1984) as test negatives did not impact on pooled estimates of sensitivity (96.6% (95% CI: 90.3, 98.9%)) or specificity (94.7% (95% CI: 80.2, 98.7%)) (Figure 11 and Figure 12).

The Munchener scheme was less sensitive in its detection of 36 cSCCs and 41 BCCs amongst 206 included cases, with a sensitivity of 84.4% (95% CI: 74.7, 90.8%) and specificity of 92.3% (95% CI: 86.3, 95.7%) (Nauth 1988).

The study in pigmented skin lesions included 10 Melanoma, 34 BCC, 1 pigmented mammary Paget disease and 1 pigmented metastatic mammary carcinoma (Durdu 2011). In 185 lesions, exfoliative cytology was able to differentiate between these and benign conditions with a sensitivity of 100% (95% CI: 92.3, 100%) and specificity of 100% (95% CI: 97.3, 100%). Whilst this was marginally more accurate when compared to dermoscopy alone (sensitivity 97.8% (95% CI: 88.7, 99.6%), specificity 98.1% (95% CI: 94.4, 99.3%)), the difference could be explained by chance. Also, dermoscopy was conducted on the full sample of 200 lesions (Durdu 2011).

Effect of observer experience

No included studies evaluated the effect of observer experience on the accuracy of exfoliative cytology in any skin cancer.

Investigations of heterogeneity

We were unable to undertake formal investigations of heterogeneity due to insufficient study numbers.

Discussion

Summary of main results

This review aimed to assess the accuracy of exfoliative cytology for diagnosing BCC, cSCC or melanoma in adults, yet most studies focus on its use for confirming the clinical diagnosis in lesions with a high clinical suspicion of BCC. Studies were poorly reported and of uncertain to poor methodological quality, particularly in terms of the applicability of their results to the current clinical setting in the UK, thus limiting the strength of conclusions that can be drawn. The Summary of findings table 1 presents key results for the primary target condition of BCC.

Pooled results from seven studies with 1264 clinically suspected BCC lesions that included 1045 BCCs provided a sensitivity of 97.5% (95%CI: 94.5 to 98.9%) and specificity 90.1% (95%CI: 81.1 to 95.1%). The Summary of findings table 1 translates these estimates to a hypothetical cohort of 1000 lesions clinically suspected of being BCC. At the median BCC prevalence of 86%, exfoliative cytology would miss 21 BCCs and would result in 14 false positive diagnoses. As BCCs are usually relatively slow growing, delayed treatment of 21 out of 860 BCCs may not have serious consequences. However if the test was used as a basis for initiation of nonsurgical treatment and any of the false positive results were lesions requiring excision, such as melanomas or cSCCs, the consequences could be potentially fatal. At the lower and upper quartile prevalence of BCC of 63% and 88%, 16 and 22 BCCs would be missed, with 37 and 12 false positive diagnoses. While evidence for the ability of exfoliative cytology to detect cSCC is scarce (with only one study using a clinically relevant application of exfoliative cytology), it is worth noting that all 17 cSCCs included in the primary analysis were correctly identified using standard cytomorphology, albeit with some difficulty in discriminating BCCs from cSCC correctly in the presence of pleomorphic features. This suggests that in populations with very high clinical suspicion of BCC, and therefore high prevalence of disease, exfoliative cytology could have a potential role in guiding the use of non-surgical therapy and avoiding biopsy. Decisions to start some non–surgical treatments in patients with superficial BCC, for example topical imiquimod, are in practice unlikely to require additional confirmation when clinical suspicion is already high, and thus cytodiagnosis is likely to have minimal utility in these cases. Conversely, exfoliative cytology may be most valuable to the management of patients with BCC lesions considered for radiotherapy, since a tissue diagnosis is typically required for confirmation before the therapy can proceed.

The ‘perfect’ results for the detection of both BCC and melanoma from the single study recruiting only pigmented lesions is likely to be explained by the unique case–mix of patients (Durdu 2011), with high proportions of benign melanocytic nevi and of benign non melanocytic lesions such as seborrhoeic keratosis, warts and dermatofibroma (Durdu 2011). The high rate of uninterpretable benign slides in this study (8%) may also have influenced its specificity. In the absence of additional studies and greater numbers of lesions, these data did not provide sufficient evidence on the performance of exfoliative cytology to detect melanomas, in populations with pigmented skin lesions, or by using other cytological classification approaches.

Observed limitations of primary studies

Studies were limited by universally poor reporting and poor methodological quality. In addition to scarce reporting of participant selection, studies failed to outline the prior referral pathway of eligible patients, including description of which clinical methods had been used to arrive at enough of a clinical suspicion of BCC to determine the patient’s eligibility for study inclusion. For the purposes of our BCC analysis we have assumed that all approaches resulted in similar population groups, however in reality the spectrum of disease in included groups remains unclear and could differ considerably.

Similarly, very limited reporting of the diagnostic criteria used to define the cytomorphologic presence of disease could obscure actual differences in diagnostic thresholds. Along with missing descriptions of how histopathological diagnoses were made and the experience of clinicians performing or interpreting scrapes, these limitations of the primary studies limit the generalisability of our findings to current clinical practice, as well as our understanding of the efficacy of exfoliative cytology to distinguish between skin cancers.

There was a similar lack of clarity in description of most items necessary to determine the risk of bias, including: recruitment methods, study design, threshold selection, blinding of the reference standard to the index test result and the time interval between exfoliative cytology and definitive histology. When these details were reported, studies were often at high risk of bias and so their accuracy estimates may not adequately reflect the true sensitivity and specificity of exfoliative cytology.

Strengths and weaknesses of the review

The strengths of this review include an in-depth and comprehensive electronic literature search, systematic review methods including double extraction of papers by both clinicians and methodologists, and contact with authors to allow study inclusion or clarify data. A clear analysis structure was planned to allow test accuracy to be estimated in discrete study populations using only scrape techniques to gather a cell sample for cytopathology. A detailed and replicable assessment of methodologic quality was undertaken. It is the only review we are aware of to have examined the accuracy of exfoliative cytology for detecting cSCC, melanoma, or any skin cancer.

Published in 2004, an earlier meta–analysis of exfoliative cytology based on eight studies including 1261 BCCs arrived at very similar pooled estimates (97% sensitivity and 86% specificity) (Bakis 2004), despite including three studies that did not meet our inclusion criteria due to differing target condition (Barton 1996), ineligible method of exfoliation (Bocking 1987) and insufficient numbers of individuals with benign disease (Vega-Memije 2000). By comparison, the present

review provides an updated estimate of the accuracy of exfoliative cytology to detect BCC using a larger number of studies (3 published after 2004), evaluating the same target conditions, and all of which have used scrape techniques to gather a cell sample for cytopathology. Ours has included a non–English language study (Nauth 1988) that was excluded from the Bakis 2004 review (whose article could not be located), and so can be considered a more current and more comprehensive summary of the accuracy of exfoliative cytology to detect BCC.

The main concerns for this review are the small number of studies and their poor reporting of patients' prior referral pathways, criteria used to arrive at cytopathological or histopathological diagnoses, observer experience, and other aspects relating to participant selection or methods of performing exfoliative cytology. The ability of cytopathology to provide sufficient discrimination of skin cancer subtypes has been questioned (INSERT REF HERE), however this topic was not addressed in the current review. Thus, echoing the findings of Bakis 2004, the main weakness of this review is the poor reporting of primary studies which has limited our appraisal of study quality and, critically, impedes our understanding of whether summary estimates are applicable to current clinical settings.

Applicability of findings to the review question

Not all data included in this review are likely to be generally applicable to the current clinical setting. In particular, one study used exfoliative cytology in a clearly different population to that in which the test is likely to be used in clinical practice (Durdu 2011), whilst another used a diagnostic classification used for vaginal cytology (the Munchener Scheme) to grade the degree of cell dysplasia from normal to anaplastic (Nauth 1988), an approach which is clearly different to the other seven studies that sought to determine whether a lesion was a BCC, cSCC, or melanoma. The remaining seven studies were pooled and summary accuracy estimates do appear to show that exfoliative cytology does confirm clinically suspected BCC with a high sensitivity and specificity, however poor reporting limits any further statements regarding a detailed description of which patient populations these results would be replicated in. Furthermore, the lack of description in all studies regarding the diagnostic criteria used for both index test and reference standard may restrict applicability and transferability of results in practice.

Authors' conclusions

Implications for practice

The utility of exfoliative cytology for the primary diagnosis of skin cancer is unknown, as all included studies have focused on the use of this technique for confirming strongly suspected clinical diagnoses. Whilst our review has provided some data regarding the potential usefulness of confirming the clinical diagnosis of BCC, the small number of included studies, poor reporting and varying methodological quality of seven included studies means that no strong conclusions can currently be drawn to guide practice. For the confirmation of BCC in lesions with a high clinical suspicion, there is evidence of high sensitivity and specificity for exfoliative cytology. As such, the test might be useful for cases of BCC that can be diagnosed confidently where treatments such as radiotherapy are being contemplated which require a tissue diagnosis. However, as the main potential advantage of the test would be initiation of non–surgical treatment and avoidance of unnecessary biopsy in confirmed cases of low-risk BCC, even the high rates of specificity observed will lead to a number of false positive diagnoses, including in populations with a high prevalence of BCC. The critical question is whether patients and clinicians are willing to accept the potential for misdiagnosis of some lesions with a worse prognosis that require excision. While none of the false positive diagnoses in these studies were melanomas or cSCCs, three carcinomas were misdiagnosed in one study, though unfortunately their precise type could not be confirmed due to the presence of inadequate sample sent for histology (Berner 1999). Even if cytology confirms a clinically suspected BCC, it can never give the same quality of histological information on parameters such as lesion architecture and infiltration or perineural invasion as does an entire skin biopsy. It is possible therefore that some of the true positives in our studies included more infiltrative forms of BCC that would have been better treated by wide excision or Mohs micrographic surgery. Exfoliative cytology poses another potential limitation in cases which require a subsequent excision, since measurement of total lesion depth could be distorted by the previous scraping process and because a cytological scrape may induce ulceration which would alter the prognostic classification.

Insufficient data are available to provide conclusive comments on the accuracy of exfoliative cytology to detect melanoma or cSCC. While only one study reported that exfoliative cytology missed cSCC diagnoses, not all studies included an adequate range of differential diagnoses known to present difficulties in being differentiated from cSCC using cytomorphology. It is therefore unlikely that the accuracy estimates reflect the true discriminatory power of exfoliative cytology. As for BCC, superficial scrapings of squamatous lesions cannot provide information regarding the lesion's pattern of invasion hence the technique is potentially very limited unless it is used to confirm lesions which already have a very high clinical suspicion. For similar reasons exfoliative cytology is very unlikely to be useful in the diagnosis of melanoma: an absence of malignant cells would require a biopsy since superficial scrapings cannot be relied upon to rule out invasion, while the presence of malignant cells would still require a further biopsy to confirm the diagnosis of melanoma and to determine depth of invasion which guides future excision margins for definitive management. Cytology is unlikely to avoid the need for a biopsy of a new lesion suspected to be melanoma. Conversely, performing an adequate scrape in these lesions risks introducing inflammation and ulceration which would alter the histopathological characteristics of the lesion that inform prognosis and treatment. On this basis we caution against the use of exfoliative cytology in non–ulcerated lesions suspected to be melanoma.

Implications for research

Whilst some evidence exists (albeit low quality) for evaluating the use of exfoliative cytology for confirming a BCC that has been diagnosed clinically i.e. a *confirmatory test*, the use of exfoliative cytology as a primary *diagnostic test* for suspected skin cancer at different points in the care pathway remains unknown. Given the absence of studies that

evaluate the diagnostic value of exfoliative cytology in discriminating between BCC and other skin cancers and other benign lesions, studies are needed to provide a full and proper evaluation of the accuracy and ability of the test. Such studies should prospectively evaluate exfoliative cytology in comparison to an alternative diagnostic test such as dermoscopy in a standard healthcare setting, for which the most rigorous design would be a multiple test comparison study (Takwoingi 2013) in which study participants are given both diagnostic tests followed by an acceptable reference standard. Study participants should be recruited consecutively from a clearly defined population that is representative of patients who would receive the test in practice and should include sufficient numbers of participants with cSCC as well as key benign differential diagnoses.

There is also scope for further research that adequately reports its evaluation of exfoliative cytology for confirming the diagnosis of BCC in whom a clinical diagnosis has indicated a high probability of BCC in order to plan further treatment such as radiotherapy.

Whether new research examines the use of exfoliative cytology as a primary diagnostic or confirmatory treatment-planning test, the target patient group in such studies needs to be clearly defined. Such studies should include a full description of the clinical pathway (referral process), including prior testing. A multi-centred approach would allow confirmation that results are replicable across centres and that the technology can be implemented across a health service. Patient's views of the test should also be explored in such studies, as well as costs to the health service. Prospective recruitment of a consecutive series of participants, with test interpretation blinded to the reference standard diagnosis with pre-specified and clearly defined diagnostic thresholds for determining test positivity is easily achieved. Clear identification of qualifications and practitioner/diagnostician training and experience is also required. Systematic follow-up of non-excised lesions avoids over-reliance on a histological reference standard and allows results to be more generalisable to routine practice. These studies would benefit from evaluating standardized techniques for performing and interpreting Tzank smears, which have yet to be developed. Developing diagnostic criteria would be useful for clinicians, facilitating ease of interpretation and ensuring that the results of future studies are fully transferable to clinical practice. Any future research study needs to be clear about the diagnostic pathway followed by study participants prior to study enrolment, and reporting should conform to the updated Standards for Reporting of Diagnostic Accuracy (STARD) guideline (Bossuyt 2015).

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Contributions of authors

JDi was the contact person with the editorial base.
SB was the information specialist and performed the review searches.
LFR wrote the final draft of the review and co-ordinated contributions from the co-authors.
All authors reviewed and contributed to the final draft.
JDi, NC screened papers against eligibility criteria.
LFR obtained data on ongoing and unpublished studies.
LFR, JDi appraised the quality of papers.
LFR, JDi, NC, extracted data for the review and sought additional information about papers.
LFR entered data into RevMan.
YT, LFR, JDi analysed and interpreted data.
LFR, JDi, YT worked on the methods sections.
LFR drafted the clinical sections of the background and responded to the clinical comments of the referees.
LFR responded to the methodology and statistics comments of the referees.
CO'S was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.
JDi is the guarantor of the update.

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Differences between protocol and review

The primary target condition and primary objective have been changed from the detection of BCC and cSCC to the detection of BCC, since exfoliative cytology has a clearer potential role for this condition.

Secondary target conditions were added for the detection of cSCC and for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants.

Secondary objectives have been tailored to the individual test, with two objectives added for each primary and secondary target condition: to compare the accuracy of exfoliative cytology to dermoscopy where both tests have been evaluated in the same studies; and to determine the effect of observer experience. Heterogeneity investigations were limited by the data available.

We proposed to supplement the database searches by searching the annual meetings of appropriate organisations (e.g., British Association of Dermatologists Annual Meeting, American Academy of Dermatology Annual Meeting, European Academy of Dermatology and Venereology Meeting, Society for Melanoma Research Congress, World Congress of Dermatology, European Association of Dermato Oncology), however due to volume of evidence retrieved from database searches and time restrictions we were unable to do this.

For quality assessment, the QUADAS-2 tool was further tailored according to the review topic. In terms of analysis, restriction to analysis of per patient data was not performed due to lack of data. Sensitivity analyses were not performed as planned due to lack of data.

Published notes

Characteristics of studies

Characteristics of included studies

Berner 1999

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection:** NR **Country:** Norway **Funding:** none declared
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Lesions clinically suspected of being nodular BCCs **Setting:** Secondary (unspecified) **Prior testing:** Clinical suspicion of BCC (no further details) **Exclusion criteria:** Lesions thinner than 2mm, with inadequate material retrieved for cytological or histological analysis **Sample size (patients): No. eligible:** 90; **No. included:** 90 **Sample size (lesions): No. eligible:** 112; **No. included:** 107 **Participant characteristics:** None reported **Lesion characteristics:** All were nodular lesions, located on the head, thorax or abdomen
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Exfoliative Cytology:** Initial removal of epidermal or keratin layer; scalpel or curette to obtain sample; stain method Diff-Quick. **Diagnostic threshold:** Qualitative - microscopic appearance of cellular scraping. Diagnosis of BCC was based on a cellular smear with the presence of small dissociated hyperchromatic cells in cohesive sheets **Prior test data available:** Clinical diagnosis (no further details) **Diagnosis based on single or consensus observation:** NR (3 examiners) **Observer qualifications:** NR - 'Cytopathologists' **Experience in practice:** NR **Experience with index test:** NR

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology (shave biopsy) **Details:** Minute tumour fragments of sizes 1 - 3 mm were removed from the lesions with a curette and placed in a Shandon cytoblock cassette before fixation in 4% buffered formalin. The tumour fragments were removed without damaging neighbouring skin and without the use of anaesthesia. The histological specimens were examined by one pathologist (AB). The minute tissue fragments were fixed in 4% buffered formalin before embedding in paraffin. Sections 5 mm thick were cut at 3 levels and stained with haematoxylin and eosin. The histological diagnosis of BCC was based on the criteria defined by WHO (study reference #6). **Disease positive:** 101**; Disease negative:** 6 **Final diagnoses:** **Target condition:** 96 BCC; 1 cSCC; 4 carcinoma (type not specified) **Benign diagnoses**: 6 (3 'benign'; 3 atypical)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Consecutive; "tumour fragments...were subsequently removed from the lesions". **Interval between index tests:** N/A **Exclusions:** None reported.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	-

Brown 1979

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** NR **Period of data collection:** NR **Country:** UK **Funding:** none declared
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Localised lesions for which a histological diagnosis was required to confirm clinical diagnosis of BCC, or in a minority to exclude BCC **Setting:** Secondary (unspecified) **Prior testing:** Clinical suspicion of BCC (no further details) **Exclusion criteria:** None reported **Sample size (patients): No. eligible:** NR; **No. included:** 81 **Sample size (lesions): No. eligible:** NR; **No. included:** 85 **Participant characteristics:** None reported **Lesion characteristics:** None reported
Are the included patients and chosen study setting appropriate?	Yes
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**Exfoliative Cytology** - Initial removal of surface crust; scalpel or curette to obtain sample; Stain method short May-Grunwald-Giemsa technique or rapid method (sample treated with 0.1% aqueous toluidine blue for 2 minutes followed by brief washing in water). **Diagnostic threshold:** NR, presumably based on qualitative appearance of scraping material Interpretation of smears includes: form of cell clusters, variation in cell size and outline, presence of squamous differentiation. **Prior test data available:** Clinical diagnosis (no further detail) **Diagnosis based on single or consensus observation:** NR **Observer qualifications:** NR **Experience in practice:** NR **Experience with index test:** NR

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology (biopsy) in all, plus expert opinion in 2/85 with discordant cytological and histological findings **Details:** The biopsy tissue was fixed in 10% formalin in normal saline and processed routinely for histology. When biopsy disagreed with clinical and cytological diagnosis, expert opinion used to overrule histological diagnosis. **Disease positive:** 76; **Disease negative:** 9 **Final diagnoses:** **Target condition:** 73 BCC; 2 cSCC; 1 Malignant melanoma **Benign diagnoses:** 9 (5 seborrhoeic keratosis; 4 actinic keratosis)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	No
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Consecutive; "Biopsy undertaken immediately after exfoliative cytology". **Interval between index tests:** N/A **Exclusions:** None reported.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	High risk

Notes

Notes	-

Christensen 2008

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case-control **Data collection:** Retrospective **Period of data collection:** NR **Country:** Norway **Funding:** None declared
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Histologically confirmed BCC or AK lesions **Setting:** Secondary (General Dermatology) **Prior testing:** NR **Exclusion criteria:** None reported **Sample size (patients): No. eligible:** NR**; No. included:** 64 **Sample size (lesions): No. eligible:** NR**; No. included:** 78 **Participant characteristics:** None reported **Lesion characteristics:** 10 were recurrences; Mean lesion size 9.0mm (range 2.0–41.0 mm); Mean BCC tumour thickness (n–30) 1.6 mm (range 0.5–4.0 mm); BCC types: 16 superficial, 23 nodular, 3 microdocular, 2 infiltrating, 2 basosquamous, 4 morphoeic. Lesions located on head or neck (56,72%), trunk (15,19%), extremities (7,10%)
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Exfoliative Cytology:** Curette to obtain sample; 3 smears for each lesion: 1) modified Pap technique, 2) MGG technique, 3) Touch Imprint stained with MGG. **Diagnostic threshold:** Qualitative appearance of cell material. Cytological results grouped into four categories: BCC, AK, non-BCC/non-AK and non-evaluable (smears showing only keratin and/or cellular debris or inadequate cellular material). Final diagnosis for the combined diagnostic result from Pap and MGG stains determined from the slide showing the greatest degree of cytological atypia. Cytological diagnosis of BCC: "based on fragments of closely packed cells which tend to present in monolayers or a club-like formations, demonstrating smooth external contours and peripheral palisading of nuclei. There is little dissociation of cells. The malignant basal cells have small, oval, hyperchromatic nuclei. The nucleus to cytoplasmic ratio is extremely high. Smears from AK lesions show greater cellular dissociation and individual as well as clumps of dysplastic keratinocytes, often with ragged edges. These cells show a polyhedral or spindle-shaped configuration. The nucleus to cytoplasmic ratio is moderately high....Each specimen was considered independently even if taken from the same patient." **Prior test data available:** None; blinded to clinical exam **Diagnosis based on single or consensus observation:** NR (2 examiners participated) **Observer qualifications:** 'Pathologists' **Experience in practice:** NR **Experience with index test:** High; extensive experience in cytology without specific training in skin scrape cytology. **Other details:** Within-patient comparison of stain methods conducted

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology alone **Details:** Punch biopsies (2 or 3 mm) fixed in 10% formaldehyde, routinely processed and embedded in paraffin. Sections of 4 microns were cut at three levels and stained with haematoxylin–eosin–saffron. Cases of BCC were subtyped according to the World Health Organization guidelines: (1) superficial type; (2) nodular/micronodular type; and (3) infiltrating type, basosquamous type or morphoeic type. **Disease positive:** 50**; Disease negative:** 28 **Final diagnoses:** **Target condition:** 50 BCC **Benign diagnosis:** 28 Actinic keratosis
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Not reported for 50 (67%) cases, Consecutive in 28 cases; "In cases where no former histology report existed, a diagnostic punch biopsy was obtained approximately 3–5 minutes before cytological sampling **Interval between index tests:** N/A **Exclusions:** 3 slides 'unavailable for investigation'
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Notes

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Derrick 1994

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** NR **Period of data collection:** NR **Country:** UK **Funding:** none declared
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Clinically suspected BCC on head or neck **Setting:** Secondary (Unspecified) **Prior testing:** Clinical examination (no further details) **Exclusion criteria:** None reported **Sample size (patients): No. eligible:** NR; **No. included:** 240 **Sample size (lesions): No. eligible:** NR; **No. included:** 240 **Participant characteristics:** None reported **Lesion characteristics:** BCC types: ulcerative (116, 48%), nodulocystic (101, 42%), morphoeic (19, 8%) and superficial (4, 2%); Located on the head or neck.
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Exfoliative Cytology:** Scalpel to obtain sample; MGG staining method. **Diagnostic threshold:** Qualitative appearance of cell material. Cytological diagnosis of a BCC based on: "the presence or tight groups of uniform small cells and the presence of pink amorphous material in MGG-stained preparations. Squamous cell lesions showed less cellular adhesion, much more nuclear pleomorphism and no pink material." **Prior test data available:** Clinical diagnosis **Diagnosis based on single or consensus observation:** NR **Observer qualifications:** Consultant pathologists **Experience in practice:** NR **Experience with index test:** NR

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology (punch biopsy) **Details:** 3-mm biopsy punch, with total surgical excision if cytology and biopsy diagnoses disagreed (n=4). Biopsies fixed in formaldehyde, routinely processed, and embedded in paraffin. Sections of 5 microns cut and stained with haematoxylin and eosin. **Disease positive:** 234**; Disease negative:** 6 **Final diagnoses:** **Target condition:** 229 BCC; 4 cSCC; 1 apocrine carcinoma **Benign diagnoses:** 6 (1 Actinic keratosis, 1 Bowen disease, 1 Trichoepithelioma, 3 no abnormality)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** NR **Interval between index tests:** N/A **Exclusions:** None reported
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

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Durdu 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series, within-person comparison **Data collection:** Prospective **Period of data collection:** January 2006 to January 2009 **Country:** Turkey **Funding:** none declared
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Pigmented skin lesions that could not be diagnosed with only dermatologic physical examination **Setting:** Secondary (general dermatology) **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion **Exclusion criteria:** None reported **Sample size (patients): No. eligible:** NR; **No. included:** 176 **Sample size (lesions): No. eligible:** NR; **No. included:** 200 **Participant characteristics:** Mean age 48 (range 4-85); 64 (36.4%) males **Lesion characteristics:** 100% Pigmented; 9% Ulcerated; 56% papular; 17% macular; 10% nodular; 8% plaque.
Are the included patients and chosen study setting appropriate?	Yes
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Exfoliative cytology: Slit-skin exfoliation using scalpel;** MGG stain; evaluated with a light microscope (310 and 340 magnifications and then 3100 magnification with immersion oil). **Prior test data:** Clinical examination and/or case notes Dermoscopy was conducted by a different dermatologist **Diagnostic threshold:** Qualitative - microscopic appearance of cellular scraping. Cytologic diagnoses were made according to findings reported previously (several studies referenced and criteria used were tabulated). Criteria for BCC: Clusters of basaloid cells containing pigment granules (Powell 2000; Vega-Memije 2000). Criteria for melanoma: Epithelioid or spindle-type atypical nevoid cells (Canti 1984). **Diagnosis based on single or consensus observation:** Single (1 examiner) **Observer qualifications:** Dermatologist **Experience in practice:** NR **Experience with index test:** NR **2. Dermoscopy** **Method of diagnosis:** In person diagnosis **Prior test data:** Clinical examination and/or case notes **Diagnostic Threshold:** NR Two step process: step 1 melanocytic and non melanocytic were differentiated (Braun 2005; Zalaudek 2008); step 2 ABCD applied to melanocytic lesions only 1. melanocytic and non melanocytic were differentiated (Braun 2005) 2. ABCD applied to melanocytic only **Diagnosis based on single or consensus observation:** Single (1 examiner) **Observer qualifications:** Dermatologist **Experience in practice:** NR **Experience with index test:** NR

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology (excision 166; punch biopsy 34) **Details:** Biopsy specimens were stained with hematoxylin and eosin. Immunohistochemical (anti-S-100 and human melanoma black [HMB]-45) and histochemical (Fontana-Masson) stains were also applied, if necessary. **Disease positive:** 46; **Disease negative:** 154 **Final diagnoses:** **Target condition :** 34 BCC; 10 Melanoma (in situ and invasive, or not reported); 1 pigmented mammary Paget disease; 1 pigmented metastatic mammary carcinoma; 1 apocrine carcinoma **Benign diagnoses:** 154 (24 Sebhorrheic keratosis, 100 benign melanocytic naevus, 30 other benign melanocytic lesions).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Consecutive; exact interval not reported **Interval between index tests:** Consecutive **Exclusions:** 15 slides with inadequate material for cytological diagnosis; no exclusions for dermoscopy
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

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Gordon 1984

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection:** NR **Country:** Australia **Funding:** none declared
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients with cutaneous neoplasms undergoing diagnostic biopsy or definitive excision at a routine clinic. **Setting:** Secondary (General dermatology) **Prior testing:** Selected for excision (no further details) **Exclusion criteria:** Lesions too small to retrieve adequate material for cytological or histological analysis, suspected melanomas, **Sample size (patients): No. eligible:** NR; **No. included:** 112 **Sample size (lesions): No. eligible:** NR; **No. included:** 150 **Participant characteristics:** None reported **Lesion characteristics:** Not reported for whole sample; BCCs included 4 pleomorphic BCCs
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Exfoliative Cytology:** Initial removal of ulcerated crust or keratotic surface; scalpel to obtain sample; stan method Papanicolaou. **Diagnostic threshold:** Qualitative appearance of cell material. Smears of BCC reported to be characterised by "many cohesive epithelial fragments composed of tightly packed small cells with uniform, oval, dark nuclei. The nuclear chromatin is dense, but granular and evenly distributed; nucleoli are small and indistinct. Cytoplasm is scanty and cyanophilic. Usually, some fragments show the marginal palisading arrangement of tumour cells familiar to the histopathologist (Figs. I and 2). Squamous differentiation may be present within BCC (keratotic BCC and metatypical epithelioma). When this is prominent and associated with nuclear enlargement and pleomorphism, the cytologic differentiation between SCC and pleomorphic BCC is difficult or impossible. Strong cohesiveness, uniformly high nuclear/cytoplasmic ratio, and evenly distributed nuclear chromatin favour a diagnosis of pleomorphk BCC (Fig. 3)." **Prior test data available:** None; blinded to clinical exam **Diagnosis based on single or consensus observation:** Single **Observer qualifications:** NR 'Cytologists' **Experience in practice:** NR **Experience with index test:** NR

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology (excisional or incisional biopsy) **Details:** Biopsy specimens were stained with hematoxylin and eosin. Immunohistochemical (anti-S-100 and human melanoma black [HMB]-45) and histochemical (Fontana-Masson) stains were also applied, if necessary. **Disease positive:** 84; **Disease negative:** 57 **Final diagnoses:** **Target condition:** 78 BCC; 6 cSCC; Severe dysplasia: 4 marked squamous atypia **Benign diagnoses:** 62 (9 Seborrhoeic keratosis; 53 Actinic keratosis)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** NR **Interval between index tests:** N/A **Exclusions:** None reported 9 lesions with inadequate material for cytological diagnosis (1 BCC, 1cSCC, 7 AK).
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	-

Nauth 1988

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control **Data collection:** NR **Period of data collection:** NR **Country:** Germany **Funding:** none declared
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** NR **Setting:** Secondary (unspecified) **Prior testing:** NR **Exclusion criteria:** NR **Sample size (patients): No. eligible:** NR; **No. included:** 224 **Sample size (lesions): No. eligible:** NR; **No. included:** 224 **Participant characteristics:** Age range 11-100; 132 (59%) male **Lesion characteristics:** NR
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	**Exfoliative cytology:** Method of exfoliation not reported; Papanicolaou stain used. **Prior test data:** NR **Diagnostic threshold:** Qualitative threshold - assessment of the cell images was based on the findings and measures already obtained in earlier studies on vulva cytology, using the Munchener classification scheme (study reference #24). Cut-off of V (malignancy present) used. **Diagnosis based on single or consensus observation:** NR **Observer qualifications:** NR **Experience in practice:** NR **Experience with index test:** NR

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology (punch biopsy 210/224), not reported for 14/224 (inflammatory conditions) **Details:** Not described **Disease positive:** 145; **Disease negative:** 65 **Final diagnoses:** **Target condition:** 42 BCC; 38 cSCC; 34 Severe dysplasia; 31 Moderate dysplasia **Benign diagnoses:** 51 benign (not further specified), 28 inflammatory lesions
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Unclear
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** NR **Interval between index tests:** N/A **Exclusions:** None reported.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	High risk

Notes

Notes	-

Powell 2000

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective **Period of data collection:** January 1999 - September 1999 **Country:** UK **Funding:** none declared
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** All cytology smears taken over a 9–month period to confirm a diagnosis of BCC **Setting:** Secondary (unspecified) **Prior testing:** Clinical suspicion of BCC (no further details) **Exclusion criteria:** No histological specimen available **Sample size (patients): No. eligible:** 72; **No. included:** 30 **Sample size (lesions): No. eligible:** 82; **No. included:** 37 **Participant characteristics:** NR **Lesion characteristics:** NR
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Exfoliative Cytology:** Scalpel or curette to obtain sample; stain method not reported. **Diagnostic threshold:** Qualitative - microscopic appearance of cellular scraping. Diagnosis of BCC was based on a cellular smear with the presence of small dissociated hyperchromatic cells in cohesive sheets **Prior test data available:** Clinical diagnosis (no further details) **Diagnosis based on single or consensus observation:** NR **Observer qualifications:** NR - 'histopathologist' **Experience in practice:** NR **Experience with index test:** NR

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology (excisional or incisional biopsy) **Details:** NR - 'routine histological analysis of the lesion' **Disease positive:** 22; **Disease negative:** 11 **Final diagnoses:** **Target condition:** 22 BCC **Benign diagnoses:** 11 (5 Actinic keratosis, 1 Bowenoid actinic keratosis, 4 Bowen's disease, 1 benign lesion (type NR))
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** NR **Interval between index tests:** N/A **Exclusions:** None reported.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	-

Ruocco 1992

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective **Period of data collection:** January 1971 - July 1991 **Country:** Italy **Funding:** none declared
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Nodular, papular or erythematous-infiltrative lesions for which the most likely clinical diagnosis was BCC **Setting:** Secondary (general dermatology) **Prior testing:** Clinical suspicion of BCC without dermatoscopic suspicion **Exclusion criteria:** No histology slide or result, insufficient material for histology and cytology, patient undergoing treatment (diathermal coagulation, cryotherapy, radiotherapy, local chemotherapy with 5–fluorouracile or interferon a–2b), or patient treated elsewhere **Sample size (patients): No. eligible:** NR; **No. included:** NR **Sample size (lesions): No. eligible:** NR; **No. included:** 578 **Participant characteristics:** NR **Lesion characteristics:** Solid (162, 28%), cystic (83, 14%), keratinous (71, 12%), superficial (63, 11%), pigmented (57, 10%), intermediate (baso–squamous: 18, 3%), morfeiform (12, 2%), aggressive or pleomorphic (6, 1.2%), adamantinoid (1, 0.2%), other (25, 4%).
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	Unclear
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	**Exfoliative Cytology:** Initial removal of surface crust; scalpel to obtain sample; 3 slides per lesion stained using the May Grunwald-Giemsa method, and either the Papanicolaou method or with pure undiluted Giemsa. **Diagnostic threshold:** Qualitative - microscopic appearance of cellular scraping. Characteristics suggestive of BCC: basaloid cells arranged in groups, clumped in the centre and at times arranged as ‘fences/palisades’ around the periphery (as found in histological specimens), slightly increased compared to normal epidermal basal keratinocytes, but in a single dimension, with an elongated shape, oval nucleus, intensely basophilic , occupying 4/5 of the entire cell with weak/thin cytoplasm, sometimes containing coarse melanin granules **Prior test data available:** Clinical diagnosis without dermoscopy (no further details) **Diagnosis based on single or consensus observation:** NR **Observer qualifications:** NR **Experience in practice:** NR **Experience with index test:** NR

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Exfoliative Cytology

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology (excisional or punch biopsy) **Details:** Fixed at 10% formalin, initiated to the standard histological method (coloration with hematoxylin-cosine) and observed at the same microscope **Disease positive:** 507**; Disease negative:** 71 **Final diagnoses:** **Target condition:** 498 BCC; 4 cSCC; 3 Cutaneous metastasis from visceral malignancy; 2 Merkel Cell Carcinoma. **Benign diagnoses:** 67 (19 Actinic keratosis, 11 seborrhoeic keratosis, 8 senile sebaceous hyperplasia, 6 Bowen's disease, 4 keratoacanthoma, 3 molluscum contagiosum, 3 psoriasis, 3 Trichoepithelioma, 2 Syringocystadenoma papilliferum, 2 lichen planus, 2 localised scleroderma, 1 sebaceous adenoma, 1 cylindroma, 1 pilomatricoma) Other: 4 'LED' (abbreviation not defined)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** NR **Interval between index tests:** N/A **Exclusions:** None reported.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	-

Footnotes

ABCD - Asymmetry/Border/Colour/Diameter; AK - actinic keratosis; BCC - basal cell carcinoma; cSCC - cutaneous squamous cell carcinoma; H/N - Head and neck; LED - disease type, acronym not provided by study; MGG - May-Grünwald Giemsa stain technique; N/A - not applicable; NR - not reported; Pap - Papanicolaou stain technique; SK - seborrhoeic keratosis;

Characteristics of excluded studies

Baba 2010

Reason for exclusion	Index test - margin control; Study population - confirmed BCC cases only

Bakis 2004

Reason for exclusion	Not primary study - systematic review and meta-analysis

Barton 1996

Reason for exclusion	Target condition - periocular suspected BCCs

Berardi 1992

Reason for exclusion	Index test - tape stripping cytology

Bilen 2000

Reason for exclusion	sample size - <5 benign lesions

Bocking 1987

Reason for exclusion	Index test - ineligible method: use of swabbing

David 1971

Reason for exclusion	Target condition - intraocular tumours

Eryilmaz 2014

Reason for exclusion	Reference standard – unclear if all disease positive based on histology

Hajdu 1973

Reason for exclusion	Study population - metastatic melanoma

Hatvani 1974

Reason for exclusion	Study population - Includes intra-ocular disease

Hering 1970

Reason for exclusion	Index test - imprint cytology

Jakasa 1976

Reason for exclusion	Index test – Includes data for FNA; unclear whether data disaggregated by type of test

Korabiec 1977

Reason for exclusion	Index test – Includes FNA as well as scrape cytology; results cannot be differentiated

Melek 1970

Reason for exclusion	Index test - imprint cytology

Norris 2008

Reason for exclusion	Not primary study

Oram 1997

Reason for exclusion	Sample size - <5 benign cases

Ozden 2013

Reason for exclusion	Sample size - <5 benign cases

Rojo 1998

Reason for exclusion	Index test – fine needle aspiration

Scanagatta 1981

Reason for exclusion	Study population - only confirmed BCCs included

Schmid-Wendtner 1999

Reason for exclusion	Not primary study

Sharifi 2007

Reason for exclusion	Sample size - <5 benign cases

Spinowitz 1986

Reason for exclusion	Not primary study

Strokowska 1981

Reason for exclusion	Reference standard – unclear if all disease positive based on histology

Tzanck 1951

Reason for exclusion	Not primary study

Urbach 1957

Reason for exclusion	Index test – exfoliative cytology from ex vivo biopsy samples

Vakhturova 1995

Reason for exclusion	Index test – intraoperative use of cytology

Vega-Memije 2000

Reason for exclusion	Sample size - <5 benign cases

Veselovskaia 1984

Reason for exclusion	Reference standard – No reference standard for index test negatives

Viglioglia 1955

Reason for exclusion	Not primary study

von Gizycki-Nienhaus 1992

Reason for exclusion	Index test - fine needle aspiration; Study population - includes recurrences

Yu 2005

Reason for exclusion	Index test – three different cytological tests used, cannot disaggregate

Footnotes

BCC - basal cell carcinoma; FNA - fine needle aspiration.

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of results tables

1 Summary of findings table

Question:	**What is the diagnostic accuracy of exfoliative cytology for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults?**				
Population:	Adults with lesions suspicious for BCC, cSCC or for melanoma				
Index test:	Exfoliative cytology				
Comparator test:	Dermoscopy				
Target condition:	BCC				
Reference standard:	Histology, any method				
Action:	If accurate, positive diagnosis by exfoliative cytology would reduce the need for biopsies in suspected BCC and help to appropriately select lesions for excision				
Quantity of evidence					
Number of studies	**9**	Total lesions with test results	**1655**	Total with BCC	**1120**
				Total with cSCC	**55**
				Total with melanoma	**11**

Question:	**What is the diagnostic accuracy of exfoliative cytology for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults?**			
Limitations				
Risk of bias:	High risk for patient selection due to case-control study design (2/9) or inappropriate exclusion of lesions (1/9), and unclear due to poor reporting of recruitment and exclusion criteria (3/9). Unclear risk for the index test due to lack of reporting diagnostic thresholds and blinding from the reference standard diagnosis (7/9). Unclear risk of bias due to inadequate reporting of blinding the reference standard (7/9) or the index test (7/9). High risk of bias in flow and timing domain from differential verification (2/9) and exclusion of slides from analysis (1/9); timing of tests was not mentioned in 7/9.			
Applicability of evidence to question:	High concern due to narrowly defined populations and multiple lesions per patient (6/9), and unclear concern due to poor reporting of patient groups (2/9), so may not be representative of populations eligible for exfoliative cytology. High concern for clinical applicability of exfoliative cytology from lack of reporting cytodiagnostic criteria in adequate detail (5/9). Little information was given concerning the expertise of the cytopathologist or histopathologist.			
Detection of BCC: pooled analysis[a]				
Datasets	**Lesions**	**BCCs**	**Sensitivity (95%CI)**	**Specificity (95%CI)**
7	1264	1045	97.5% (94.5, 98.9)	90.1% (81.1, 95.1)
Numbers observed in a cohort of 1000 people being tested				
	True positive	**False negative**	**False positive**	**True negative**
	(appropriately do not receive excision)	(inappropriately receive excision or undertreated)	(inappropriately do not receive excision, or overtreated)	(receive appropriate management – excision or other)
At prevalence 63%	614	16	37	333
At prevalence 86%	839	21	14	126
At prevalence 88%	858	22	12	108
Detection of BCC: pooled analysis[b]				
Datasets	**Lesions**	**BCCs**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
7	1264	1045	97.3% (93.5, 98.9)	94.2% (88.7, 97.1)
Detection of cSCC, Melanoma, any skin cancer				
Findings	Studies also evaluated cSCC (2), melanoma (1) or any skin cancer (6). • cSCC – studies could not be pooled due to different diagnostic approaches, sensitivity ranged from 89 – 100% and specificity from 75 – 99% • melanoma – only study (10 melanoma) conducted in 185 pigmented skin lesions, also providing a comparison with dermoscopy: sensitivity and specificity 100%. • any skin cancer – 4 studies pooled 573 suspicious lesions, with 495 malignant lesions (476 BCCs, 13 cSCCs, 1 melanoma, 4 carcinomas of unspecified histological type, 1 apocrine carcinoma). Pooled sensitivity 97.3% (93.5, 98.9) and specificity 86.0% (73.5, 93.1) (uncertain diagnoses classified as test positives). When uncertain diagnoses classified as test negatives, pooled sensitivity became 96.6% (90.3, 98.9) and specificity 94.7% (80.2, 98.7).			

Footnotes

[a]'possible BCC' cases classified as index test positive

[b]'possible BCC' cases classified as index test negative

BCC - basal cell carcinoma; cSCC - cutaneous squamous cell carcinoma; CI - confidence interval.

Additional tables

1 Glossary of terms

Term	Definition
Atypical intraepidermal melanocytic variant	Unusual area of darker pigmentation contained within the epidermis that may progress to an invasive melanoma; includes melanoma *in situ* and lentigo maligna

Term	Definition
Atypical naevi	Unusual looking but noncancerous mole or area of darker pigmentation of the skin
BRAF V600 mutation	BRAF is a human gene that makes a protein called B-Raf which is involved in the control of cell growth. BRAF mutations (damaged DNA) occur in around 40% of melanomas, which can then be treated with particular drugs.
BRAF inhibitors	Therapeutic agents which inhibit the serine-threonine protein kinase BRAF mutated metastatic melanoma.
Breslow thickness	A scale for measuring the thickness of melanomas by the pathologist using a microscope, measured in mm from the top layer of skin to the bottom of the tumour.
Congenital naevi	A type of mole found on infants at birth
Dermoscopy	Whereby a handheld microscope is used to allow more detailed, magnified, examination of the skin compared to examination by the naked eye alone
Excisional biospy	One of four types of skin biospy used to retrieve cells for histological analysis, in which a scalpel is used to cut out the whole lesion.
Exfoliative cytology	The microscopic examination of cells desquamated from the surface of a lesion obtained by scraping
False negative	An individual who is truly positive for a disease, but whom a diagnostic test classifies them as disease-free.
False positive	An individual who is truly disease-free, but whom a diagnostic test classifies them as having the disease.
Histopathology/Histology	The study of tissue, usually obtained by biopsy or excision, for example under a microscope.
Incidence	The number of new cases of a disease in a given time period.
Incisional biopsy	One of four types of skin biospy used to retrieve cells for histological analysis, in which a scalpel is used to cut out the whole lesion (excisional), part of a lesion, or part of the affected skin plus part of the normal skin.
Index test	A diagnostic test under evaluation in a primary study
Lentigo maligna	Unusual area of darker pigmentation contained within the epidermis which includes malignant cells but with no invasive growth. May progress to an invasive melanoma
Lymph node	Lymph nodes filter the lymphatic fluid (clear fluid containing white blood cells) that travels around the body to help fight disease; they are located throughout the body often in clusters (nodal basins).
Melanocytic naevus	An area of skin with darker pigmentation (or melanocytes) also referred to as ‘moles’
Meta-analysis	A form of statistical analysis used to synthesise results from a collection of individual studies.
Metastases/metastatic disease	Spread of cancer away from the primary site to somewhere else through the bloodstream or the lymphatic system.
Micrometastases	Micrometastases are metastases so small that they can only be seen under a microscope.
Mitotic rate	Microscopic evaluation of number of cells actively dividing in a tumour.
Mohs micrographic surgery	Microscopically controlled surgery to remove skin cancer lesions, involving the examination of removed tissue for cancer cells during surgery
Morbidity	Detrimental effects on health.
Mortality	Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1000, 10,000 or 100,000 people.
Multidisciplinary team	A team with members from different healthcare professions and specialties (e.g. urology, oncology, pathology, radiology, and nursing). Cancer care in the National Health Service (NHS) uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for that patient.
Prevalence	The proportion of a population found to have a condition.
Prognostic factors/indicators	Specific characteristics of a cancer or the person who has it which might affect the patient’s prognosis.

Term	Definition
Punch biopsy	One of four types of skin biospy used to retrieve cells for histological analysis, in which a blade is pushed into the skin to retrieve a core of tissue.
Receiver operating characteristic (ROC) plot	A plot of the sensitivity and 1 minus the specificity of a test at the different possible thresholds for test positivity; represents the diagnostic capability of a test with a range of binary test results
Receiver operating characteristic (ROC) analysis	The analysis of a ROC plot of a test to select an optimal threshold for test positivity
Recurrence	Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body.
Reference Standard	A test or combination of tests used to establish the final or 'true' diagnosis of a patient in an evaluation of a diagnostic test
Sensitivity	In this context the term is used to mean the proportion of individuals with a disease who have that disease correctly identified by the study test
Shave biopsy	One of four types of skin biospy used to retrieve cells for histological analysis, in which a small fragment of protruding tumour is shaved off with a blade.
Specificity	The proportion of individuals without the disease of interest (in this case with benign skin lesions) who have that absence of disease correctly identified by the study test
Staging	Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories.
Subclinical (disease)	Disease that is usually asymptomatic and not easily observable, e.g. by clinical or physical examination.
Systemic treatment	Treatment, usually given by mouth or by injection, that reaches and affects cancer cells throughout the body rather than targeting one specific area.

Footnotes

2 Test failures due to insufficient cellular material

Study	Stain technique	Slides with inadequate material n (%)		Histological diagnosis
Gordon 1984	Papanicolaou	9	(6)	BCC: 1 cSCC: 1 Actinic keratosis: 7
Christensen 2008 [a]	Papanicolaou	1	(1)	Actinic keratosis: 1
	MGG	3	(4)	BCC: 1 Actinic keratosis: 2
Durdu 2011	MGG	15	(8)	Melanocytic benign: 6 Nonmelanocytic benign: 9
Nauth 1988	Papanicolaou	18	(8)	BCC: 1 cSCC: 2 Severe precancerous disease: 2 Mild precancerous disease: 6 Benign tumour: 5 Inflammation: 2

Footnotes

[a]When diagnosis was made using both papanicolaou and MGG stained slides, all lesions could be diagnosed cytologically

BCC - basal cell carcinoma; cSCC - cutaneous squamous cell carcinoma; MGG - May-Grünwald Giemsa stain technique.

3 Summary of main results

Analysis	Target condition Test	Studies (n)	Lesions with cytology results (n)	Diseased lesions (n)	Sensitivity (95% CI)	Specificity (95% CI)
Detection of Basal cell carcinoma (BCC)						
All studies	Studies with cases of BCC	9	1655	1120	-	-
Pooled studies	Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC ('possible BCC' cases classified as BCC test positive)	7	1264	1045	97.5 [94.5, 98.9]	90.1 [81.1, 95.1]
	Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC ('possible BCC' cases classified as BCC test negative)	7	1264	1045	97.3 [93.5, 98.9]	94.2 [88.7, 97.1]
Studies not pooled		2				
	Nauth 1988: Different diagnostic criteria - Munchener scheme (class V = malignant)	1	206	42	80.5 [66.0, 89.8]	74.6[67.4, 80.6]
	Durdu 2011: Different patient group - pigmented skin lesions (Exfoliative Cytology)	1	185[a]	34	100 [89.9, 100]	100 [97.5, 100]
	Durdu 2011: Different patient group - pigmented skin lesions (Dermoscopy)	1	200	34	94.1 [80.9, 98.4]	98.2 [94.8, 100]
Detection of cutaneous squamous cell carcinoma (cSCC)						
All studies	Studies with cases of cSCC	6	1357	55	-	-
Studies not pooled		2	401	44		
	Gordon 1984: Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC	1	141	5[b]	100 [56.6, 100]	98.5 [94.8, 99.6]
	Nauth 1988: Different diagnostic criteria - Munchener scheme (class V = malignant)	1	206	38	88.9 [74.7, 95.6]	74.7 [67.7, 80.6]
Studies not included in dataset	< 5 cSCC cases	4	1010	11	-	-
Detection of invasive melanoma and atypical intraepidermal melanocytic variants (MM)						
All studies	Studies with cases of MM	2	270	11	-	-
Studies not pooled		1	185[a]	10		
	Durdu 2011: Different patient group - pigmented skin lesions (Exfoliative Cytology)	1	185[a]	10	100 [72.3, 100]	100 [97.6, 100]
	Durdu 2011: Different patient group - pigmented skin lesions (Dermoscopy)	1	200	10	80.0 [49.0, 94.3]	97.4 [94.0, 98.9]
Studies not included in dataset	< 5 MM cases	1	85	1	-	-
Detection of any potential skin cancer (BCC or other skin cancer)						
All studies	Studies with any skin cancer lesions	9	1655	1200	-	-
Pooled studies	Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC ('possible BCC' cases classified as BCC test positive)	4	573	495	97.3 [93.5, 98.9]	86.0 [73.5, 93.1]
	Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC ('possible BCC' cases classified as BCC test negative)	4	573	495	96.6 [90.3, 98.9]	94.7 [80.2, 98.7]

Analysis	Target condition Test	Studies (n)	Lesions with cytology results (n)	Diseased lesions (n)	Sensitivity (95% CI)	Specificity (95% CI)
Studies not pooled		2	391	123	-	-
	Nauth 1988: Different diagnostic criteria - Munchener scheme (class V = malignant)	1	206	77	84.8 [74.4, 90.8]	92.3 [86.3, 95.7]
	Durdu 2011: Different patient group - pigmented skin lesions (Exfoliative Cytology)	1	185[a]	46	100 [92.3, 100]	100 [97.3, 100]
	Durdu 2011: Different patient group - pigmented skin lesions (Dermoscopy)	1	200	46	97.8 [88.7, 99.6]	98.2 [94.4, 99.3]
Studies not included in dataset	No skin cancer other than BCC (Powell 2000; Christensen 2008)	2	113	72	-	-
	Data not reported (Ruocco 1992)	1	578	507	-	-

Footnotes

[a]From a total population of 200 lesions (15 excluded from exfoliative cytology analysis due to insufficient cell material, all 200 examined by dermoscopy).

[b]Only 5 of 6 cSCC lesions were included for examination by exfoliative cytology, one was excluded due to inadequate cell material.

BCC - basal cell carcinoma; 95%CI - 95% confidence interval; cSCC - cutaneous squamous cell carcinoma; MM - invasive melanoma and atypical intraepidermal melanocytic variants.

4 Exfoliative cytology for the detection of BCC: False positive diagnoses

Study	False positive n (%)		Histological diagnosis
Berner 1999	5	(4.6)	Carcinoma, type not specified: 3 atypia: 2
Brown 1979	0	(–)	–
Christensen 2008 [a]	1	(1.3)	Actinic keratosis: 1
Derrick 1994	1	(0.4)	Trichoepithelioma: 2
Durdu 2011	0	(–)	–
Gordon 1984	7	(5.0)	Actinic keratosis: 1 Marked atypia: 4 Sebhorroeic keratosis: 2
Nauth 1988	18	(8)	BCC: 1 cSCC: 2 Severe precancerous disease: 2 Mild precancerous disease: 6 Benign tumour: 5 Inflammation: 2
Powell 2000	2	(5.4)	Bowenoid actinic keratosis: 1 Bowen’s disease: 1
Ruocco 1992	6	(1)	Trichoepithelioma: 3 Syringocystadenoma papilliferum: 2 Pilomatricoma: 1

Footnotes

[a]Diagnosis made using both Papanicolaou and May-Grünwald Giemsa stained slides

BCC - basal cell carcinoma; 95%CI - 95% confidence interval; cSCC - cutaneous squamous cell carcinoma

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Classification pending references

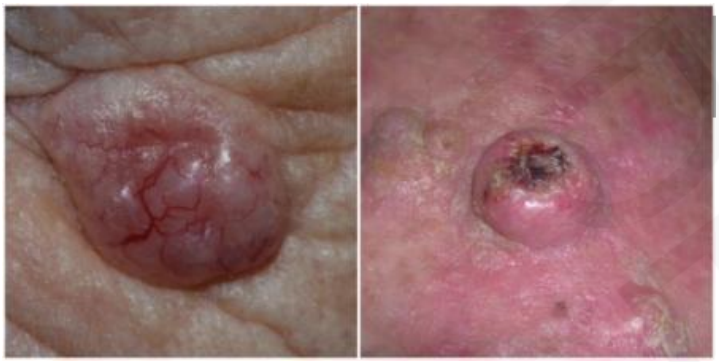
Data and analyses

Data tables by test

Test	Studies	Participants
1 Exfoliative Cytology - BCC (possible BCCs classified as test positives)	7	1264
2 Exfoliative Cytology - BCC (possible BCCs classified as test negatives)	7	1264
3 Exfoliative cytology - BCC (pigmented lesion population)	1	185
4 Dermoscopy - BCC (pigmented lesion population)	1	200
5 Exfoliative Cytology - BCC (Mixed population, Munchener diagnostic criteria)	1	206
6 Exfoliative Cytology - cSCC (suspected BCC population)	1	141
7 Exfoliative Cytology - cSCC (Mixed population, Munchener diagnostic criteria)	1	206
8 Exfolative cytology - melanoma (pigmented lesion population)	1	185
9 Dermoscopy - melanoma (pigmented lesion population)	1	200
10 Exfoliative Cytology - any skin cancer (suspected BCC population, possible BCCs classified as test positives)	4	573
11 Exfoliative Cytology - any skin cancer (suspected BCC population, possible BCCs classified as test negatives)	4	573
12 Exfoliative Cytology - any skin cancer (pigmented lesion population)	1	185
13 Dermoscopy - any skin cancer (pigmented lesion population)	1	200
14 Exfoliative Cytology - any skin cancer (Mixed population, Munchener diagnostic criteria)	1	206
15 Exfolative Cytology (Papanicolaou + MGG stain) - BCC (stain comparison)	1	76
16 Exfolative Cytology (MGG stain) - BCC (stain comparison)	1	73
17 Exfolative Cytology (Papanicolaou stain) - BCC (stain comparison)	1	77

Figures

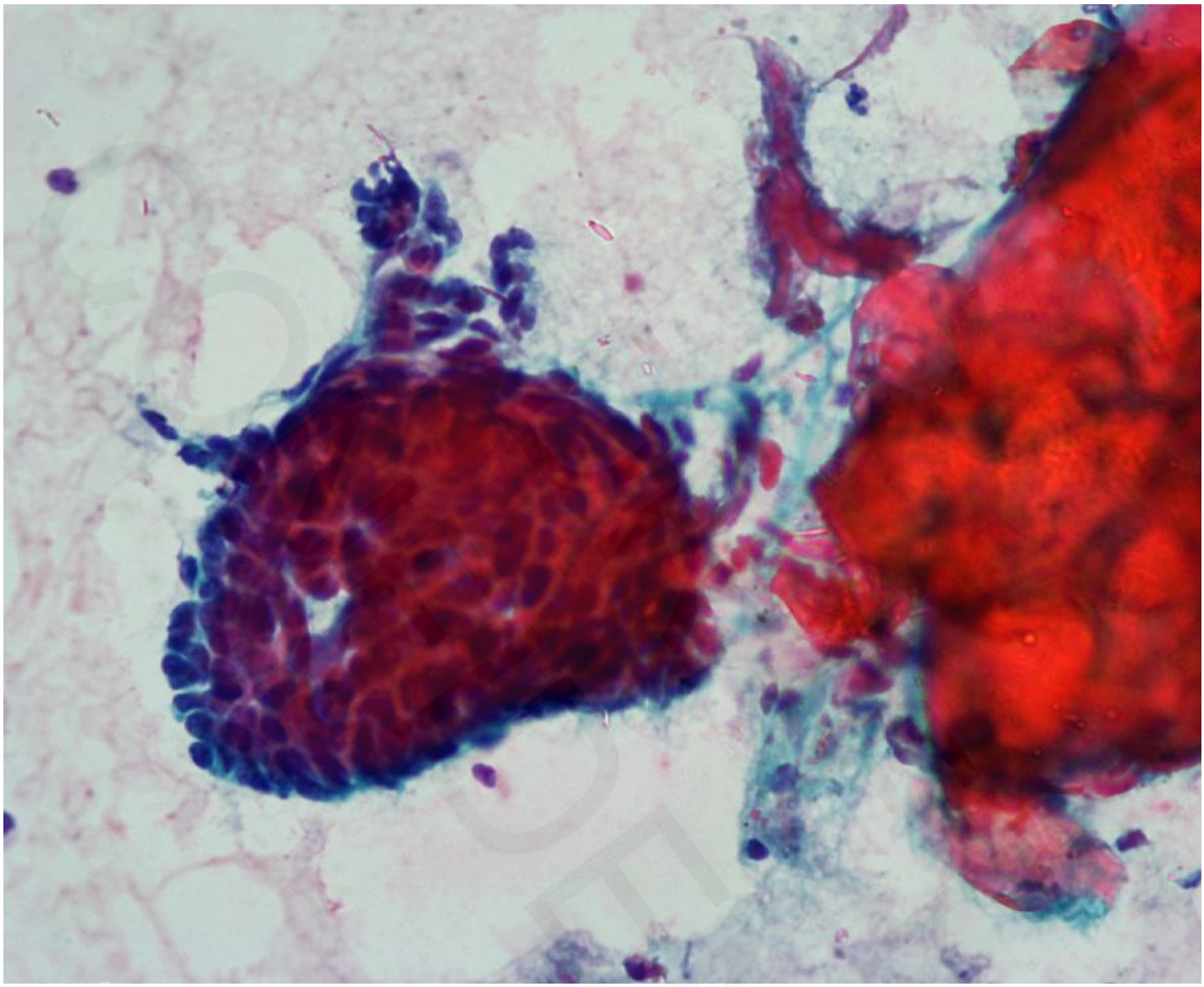
Figure 1



Caption

Sample photographs of BCC (left) and cSCC (right)

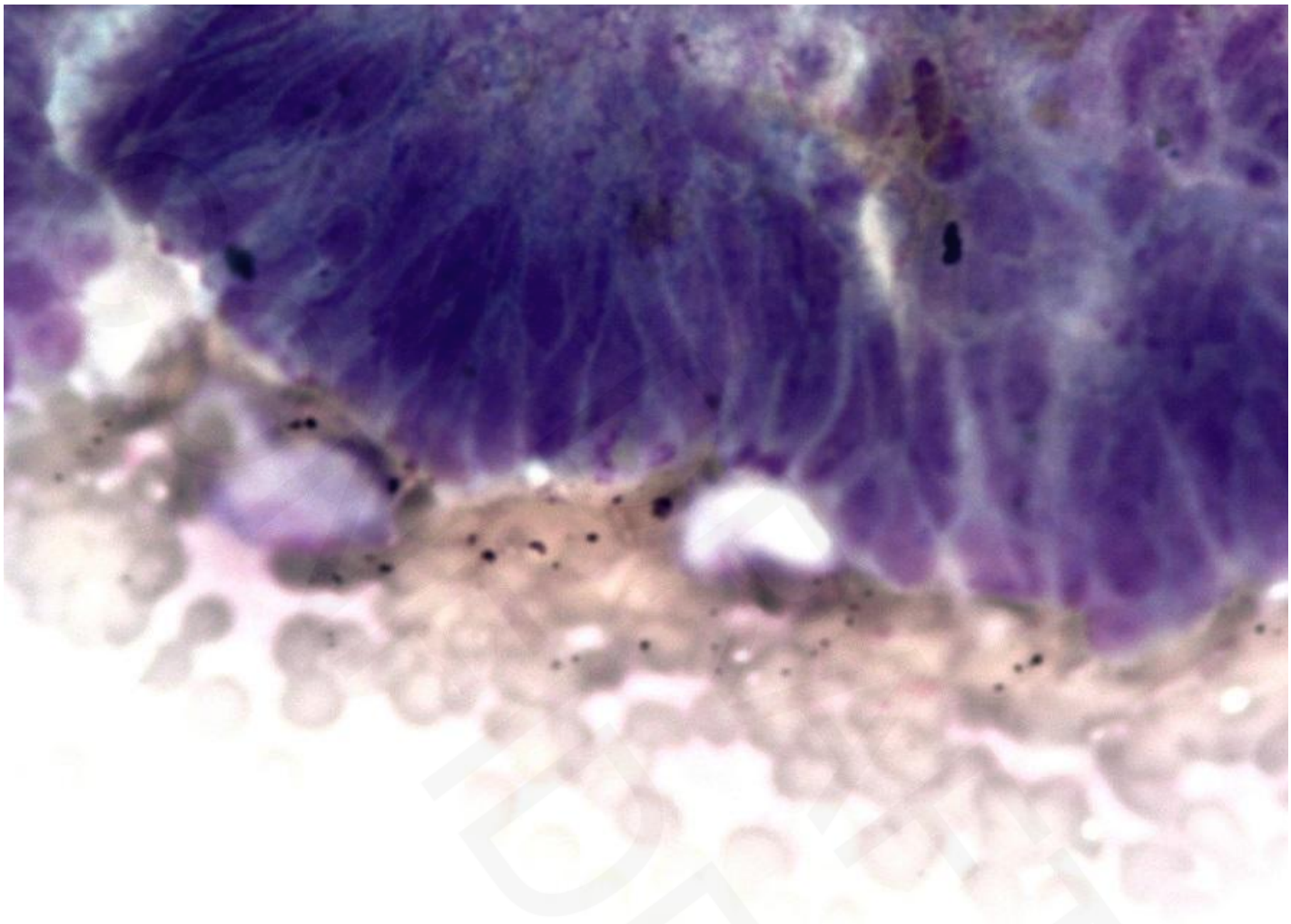
Figure 2



Caption

Cytological image of BCC using Papanicoloau stain showing a tissue fragment of BCC on the left and anucleate squamous cells from the epidermis on the right. Copyright © [2018] [Derek Roskell]: reproduced with permission.

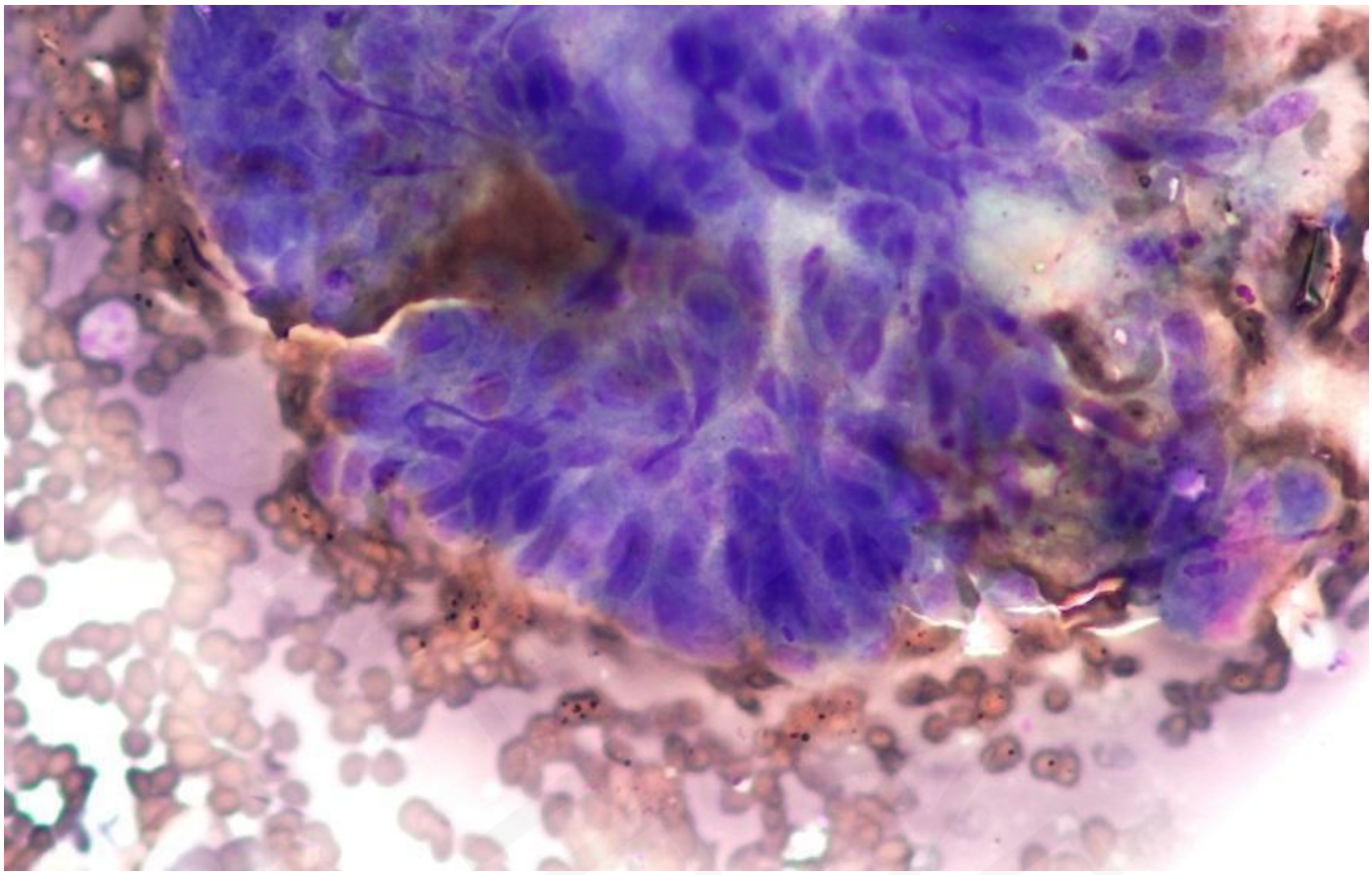
Figure 3



Caption

Cytological image of a BCC using Giemsa stain. Focally the nuclei are aligned perpendicular to the basement edge of the cluster (peripheral palisading), a feature characteristic of BCC.

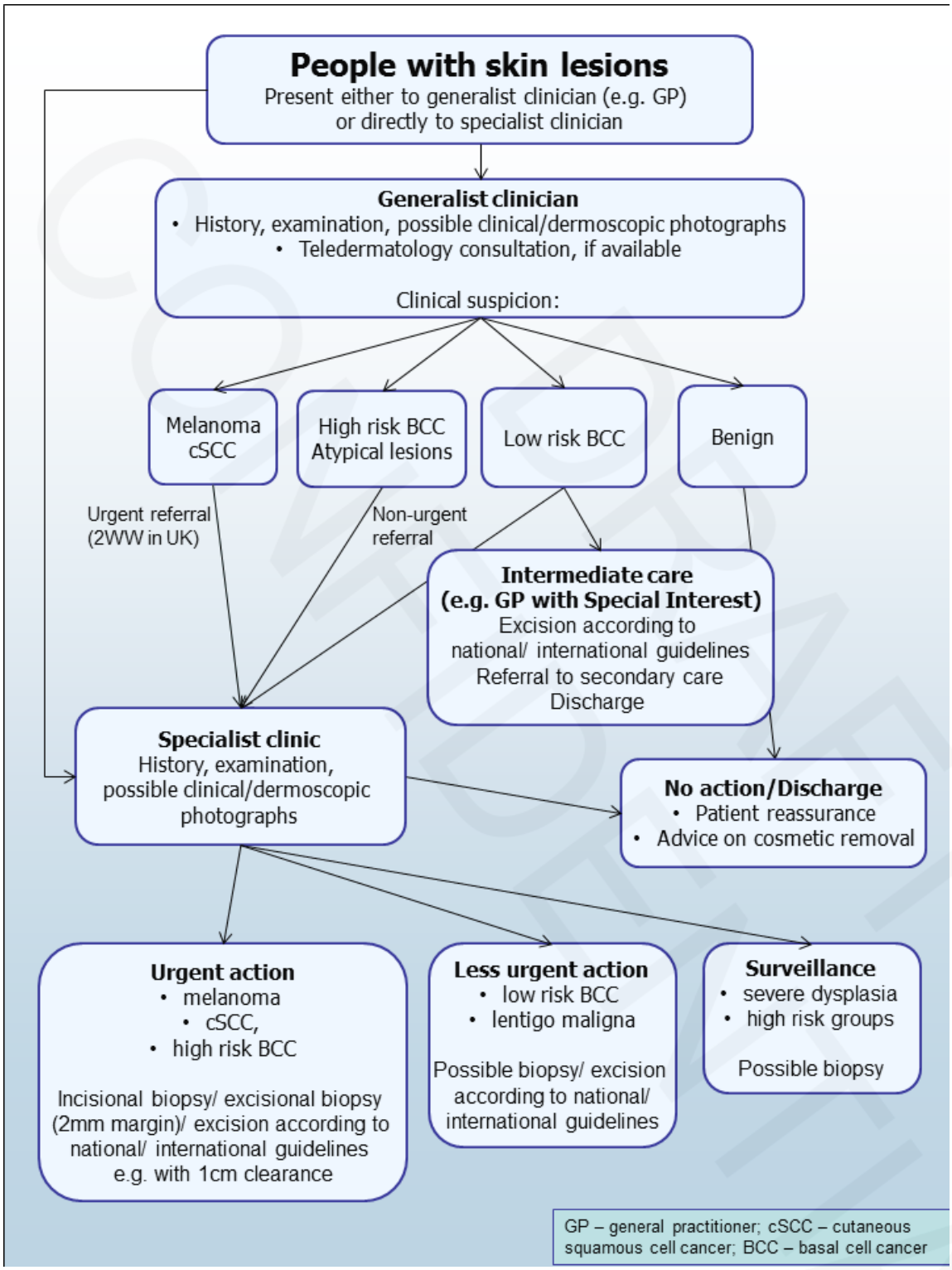
Figure 4



Caption

Cytological image of a BCC using Giemsa stain. The BCC cells are tightly cohesive in a cluster with a distinct edge to the group.

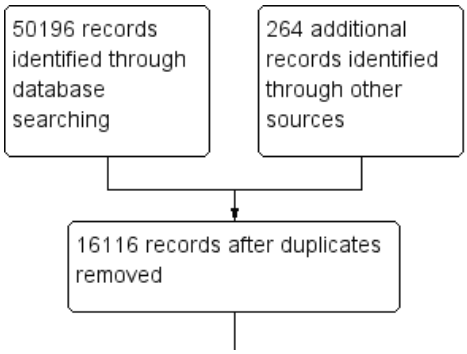
Figure 5

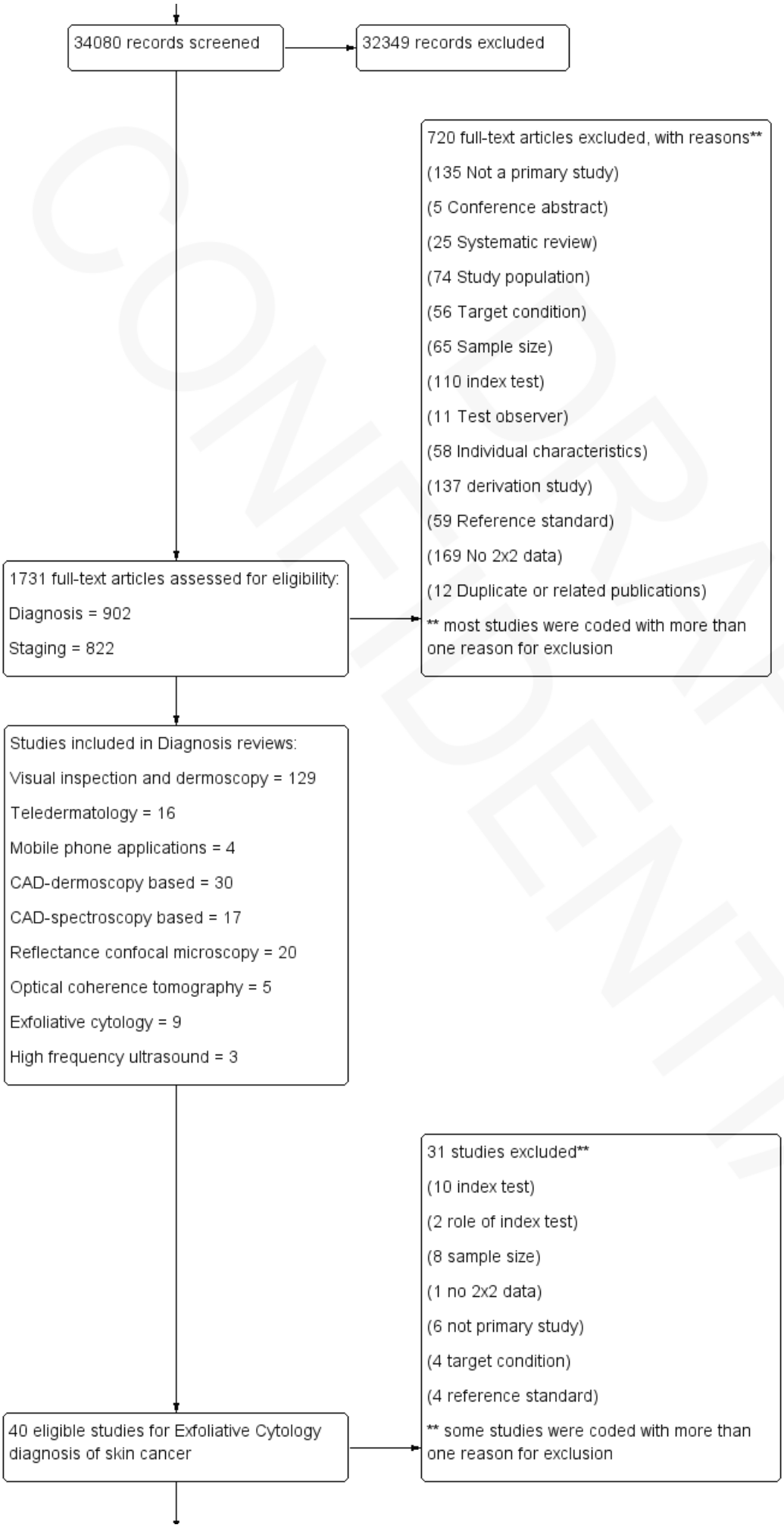


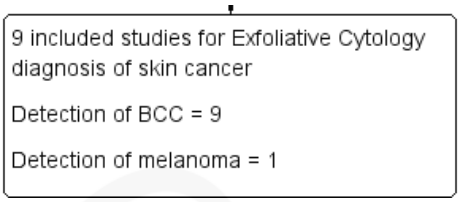
Caption

Current clinical pathway for people with skin lesions

Figure 6



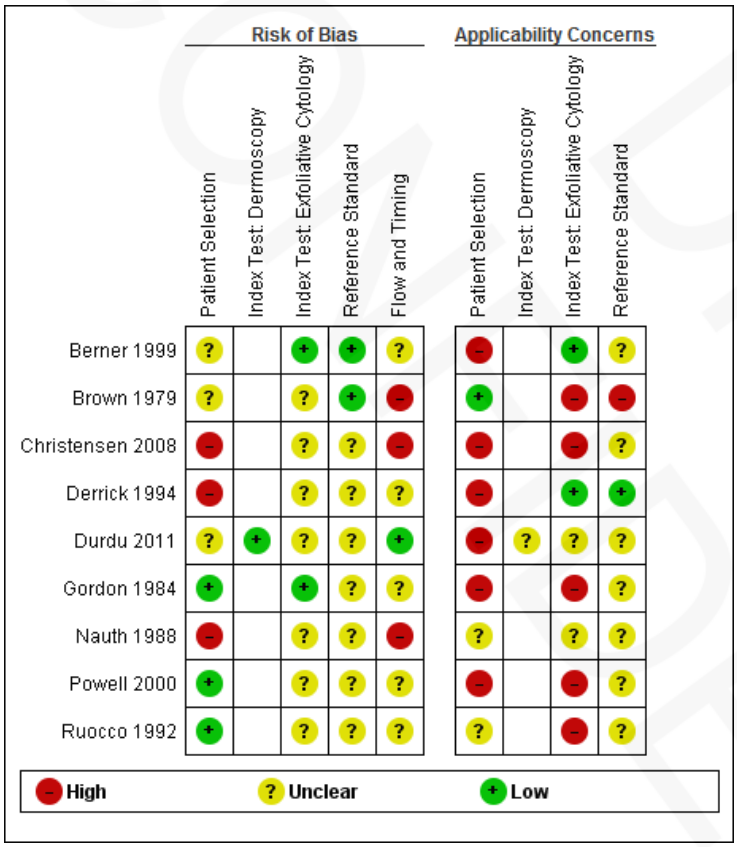




Caption

PRISMA flow diagram.

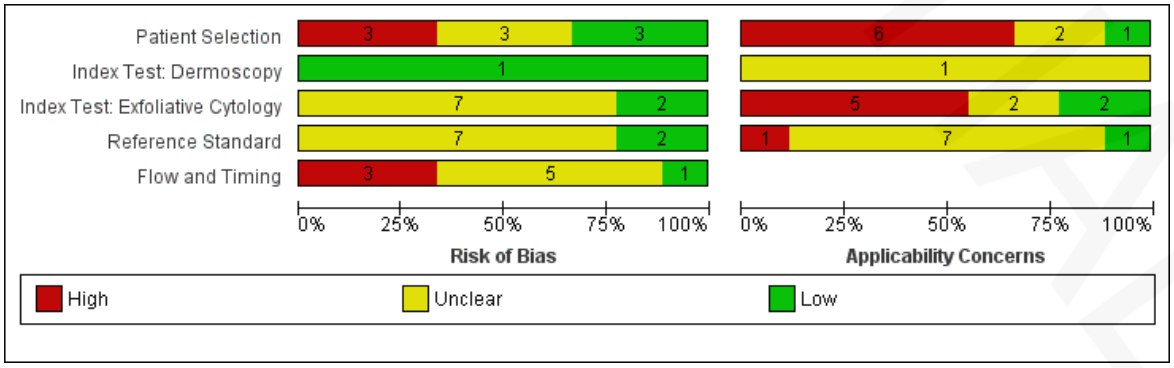
Figure 7



Caption

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study. One study (Durdu 2011) was assessed in the comparative domain as 'Unclear' for both risk of bias and applicability concerns.

Figure 8



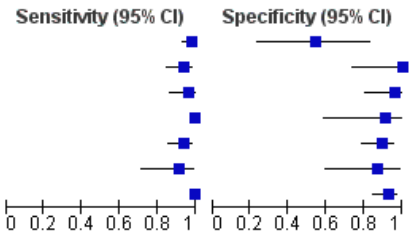
Caption

Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies. One study (Durdu 2011) was assessed in the comparative domain as 'Unclear' for both risk of bias and applicability concerns.

Figure 9 (Analysis 10)

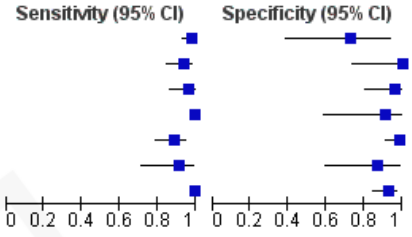
Exfoliative Cytology - BCC (possible BCCs classified as test positives)

Study	TP	FP	FN	TN	Stain	Sensitivity (95% CI)	Specificity (95% CI)
Berner 1999	94	5	2	6	Diff-Quick	0.98 [0.93, 1.00]	0.55 [0.23, 0.83]
Brown 1979	68	0	5	12	Mix	0.93 [0.85, 0.98]	1.00 [0.74, 1.00]
Christensen 2008	48	1	2	25	MGG & Pap	0.96 [0.86, 1.00]	0.96 [0.80, 1.00]
Derrick 1994	228	1	1	10	MGG	1.00 [0.98, 1.00]	0.91 [0.59, 1.00]
Gordon 1984	72	7	5	57	Pap	0.94 [0.85, 0.98]	0.89 [0.79, 0.95]
Powell 2000	20	2	2	13	NR	0.91 [0.71, 0.99]	0.87 [0.60, 0.98]
Ruocco 1992	494	6	4	74	Mix	0.99 [0.98, 1.00]	0.93 [0.84, 0.97]



Exfoliative Cytology - BCC (possible BCCs classified as test negatives)

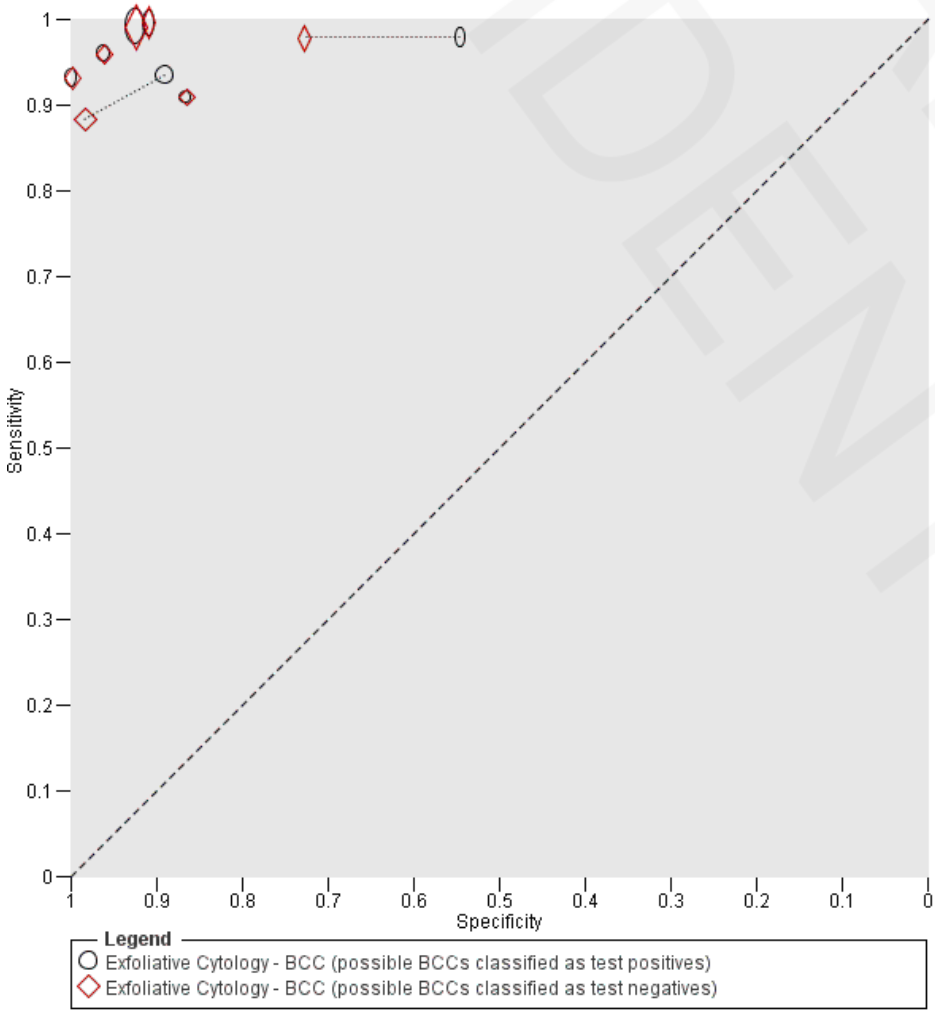
Study	TP	FP	FN	TN	Stain	Sensitivity (95% CI)	Specificity (95% CI)
Berner 1999	94	3	2	8	Diff-Quick	0.98 [0.93, 1.00]	0.73 [0.39, 0.94]
Brown 1979	68	0	5	12	Mix	0.93 [0.85, 0.98]	1.00 [0.74, 1.00]
Christensen 2008	48	1	2	25	MGG & Pap	0.96 [0.86, 1.00]	0.96 [0.80, 1.00]
Derrick 1994	228	1	1	10	MGG	1.00 [0.98, 1.00]	0.91 [0.59, 1.00]
Gordon 1984	68	1	9	63	Pap	0.88 [0.79, 0.95]	0.98 [0.92, 1.00]
Powell 2000	20	2	2	13	NR	0.91 [0.71, 0.99]	0.87 [0.60, 0.98]
Ruocco 1992	494	6	4	74	Mix	0.99 [0.98, 1.00]	0.93 [0.84, 0.97]



Caption

Forest plot of exfoliative cytology to detect BCC in patients with suspected BCCs, showing classificaton of 'possible BCCs' as test positives or as test negatives.

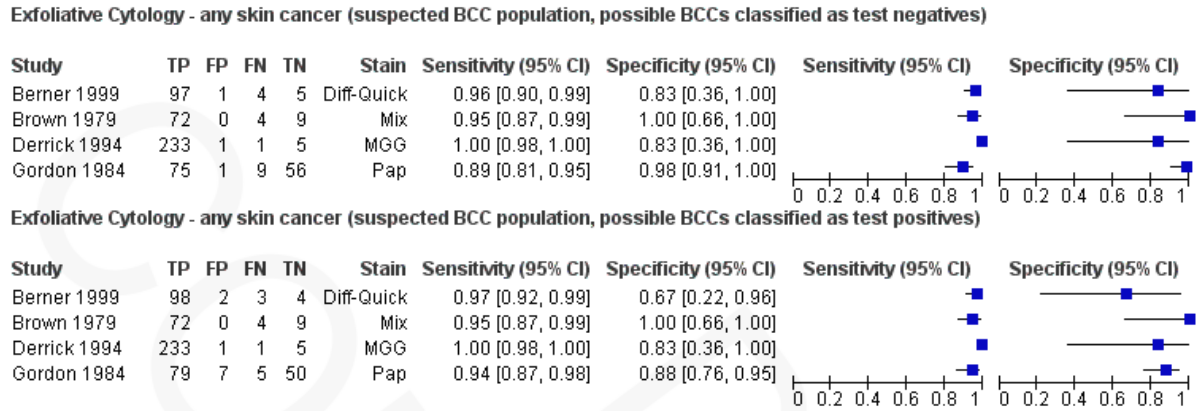
Figure 10 (Analysis 10)



Caption

Summary ROC Plot of exfoliative cytology to detect BCC in patients with suspected BCCs, showing classification of 'possible BCCs' as test positives or as test negatives.

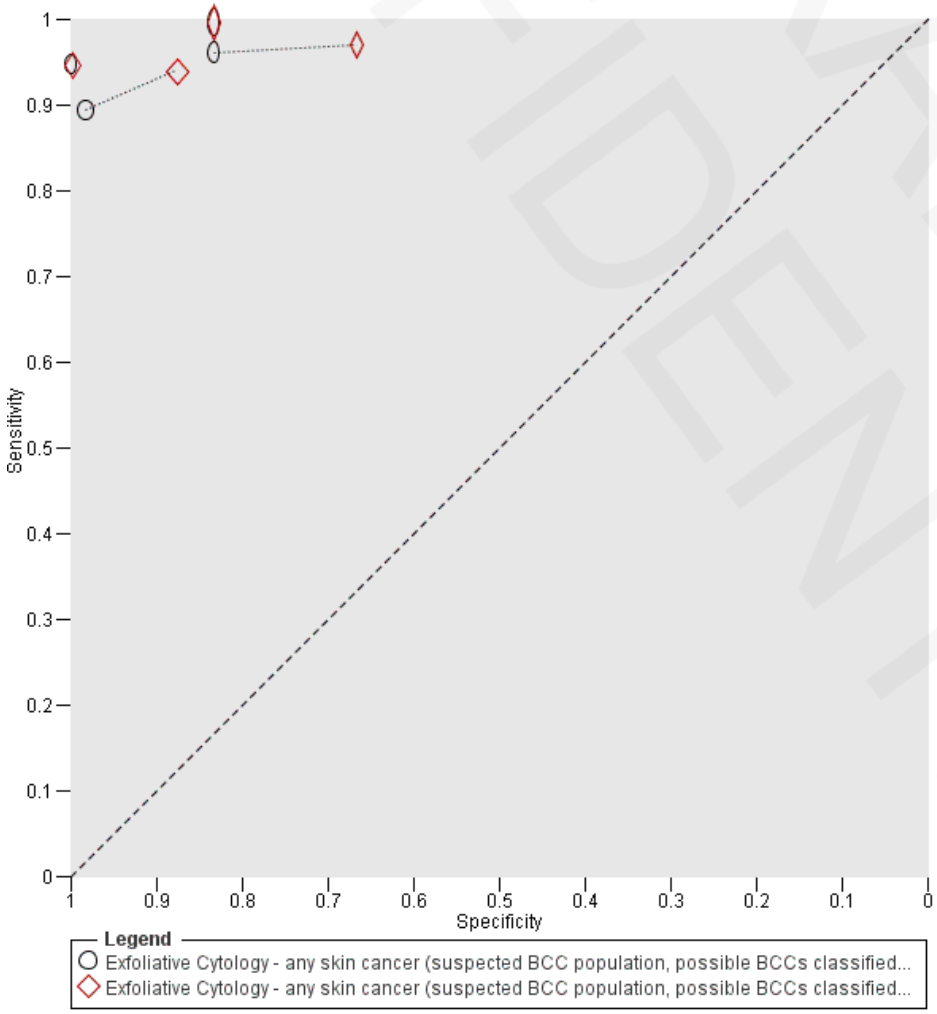
Figure 11 (Analysis 11)



Caption

Forest plot of studies pooled for accuracy of exfoliative cytology to detect any skin cancer in patients with suspected BCCs, comparing: 1) classificaton of 'possible BCCs' as test positives, with 2) classification of 'possible BCCs' as test negatives.

Figure 12 (Analysis 11)



Caption

Summary ROC plot of pooled studies for accuracy of exfoliative cytology to detect any skin cancer in patients with suspected BCCs, comparing: 1) classificaton of 'possible BCCs' as test positives, with 2) classification of 'possible BCCs' as test negatives.

Sources of support

Internal sources

- No sources of support provided

External sources

- The National Institute for Health Research (NIHR), UK
  The NIHR, UK, is the largest single funder of the Cochrane Skin Group
- NIHR Systematic Review Programme, UK

Feedback

Appendices

1 Current content and structure of the Programme Grant

List of reviews	Estimated number of studies
Diagnosis of melanoma	
1. Visual inspection versus visual inspection plus dermoscopy	120
2. Teledermatology	12
3. Mobile phone applications	2
4. Computer-aided diagnosis: dermoscopy based and spectroscopy based techniques	37
5. Reflectance confocal microscopy	19
6. High frequency ultrasound	3
7. Overview: comparing the accuracy of tests for which sufficient evidence was identified either alone or in combination	–
Diagnosis of keratinocyte skin cancer (basal cell carcinoma and cutaneous squamous cell carcinoma)	
8. Visual inspection ± dermoscopy	22
9. Computer aided diagnosis: dermoscopy based and spectroscopy based techniques	3
10. Optical coherence tomography	6
11. Reflectance confocal microscopy	9
12. High frequency ultrasound	1
13. Exfoliative cytology	5
14. Overview: comparing the accuracy of tests for which sufficient evidence was identified either alone or in combination	–
Staging of melanoma	
15. Ultrasound	25 to 30
16. Computer tomography	5 to 10
17. Positron emission tomography or positron emission tomography-computer tomography	20 to 25
18. Magnetic resonance imaging	5
19. Sentinel lymph node biopsy ± high frequency ultrasound	70
20. Overview: comparing the accuracy of tests for which sufficient evidence was identified either alone or in combination	–
Staging of cutaneous squamous cell carcinoma	
21. Imaging tests review	10 to 15
22. Sentinel lymph node biopsy ± high frequency ultrasound	15 to 20

2 Treatments for skin cancer - further details

People with locally advanced and metastatic BCC can now be treated with the hedgehog pathway inhibitor vismodegib (Lear 2012; Sekulic 2012; Von Hoff 2009). It has demonstrated response rates of 30% to 43% in those with metastatic or advanced BCC (Sekulic 2012) and a reduction in the rate of new surgically eligible basal cell carcinomas per year in those with Gorlin syndrome, compared with placebo (Tang 2012), although adverse event rates are high.

For primary melanoma, local or regional intervention beyond wide local excision consists of completion

lymphadenectomy (removal of all regional lymph nodes) which is undertaken for those with clinically palpable lymph nodes. It may also be considered if micrometastatic disease is identified on sentinel lymph node biopsy (NICE 2015a) although no survival benefit has been shown to date for those undergoing sentinel node staging (Kyrgidis 2015; Morton 2014; van Akkooi 2014). Elective lymph node dissection (Eggermont 2007), adjuvant radiotherapy or adjuvant systemic treatments are not recommended for routine use in stage I, II or III disease in the UK (NICE 2015a), and in many parts of Europe (Garbe 2016), other than interferon-alpha (licensed by FDA and EMEA) (Garbe 2016), which has been shown to be effective for the treatment of high risk

groups in terms of both disease-free and overall survival in a Cochrane review found evidence for its effectiveness for disease-free survival but not for overall survival (Mocellin 2013).

For stage IV melanoma, two distinct therapeutic approaches suggesting survival benefits in metastatic melanoma are available: targeting mutated signal transduction in the RAS-RAF signalling pathway, e.g. BRAF-inhibitors (Chapman 2012; Villanueva 2010) and MEK inhibitors (Larkin 2014; Dummer 2014), and immunomodulation (Chapman 2011; Hamid 2013; Hodi 2010). Molecular targeted therapies recommended in the UK for unresectable or metastatic BRAF V600 mutation-positive melanoma (around 45% of patients (Garbe 2016)) include BRAF-inhibitors dabrafenib (NICE 2014), vemurafenib (NICE 2012) or trametinib (MEK inhibitor) in combination with dabrafenib (NICE 2016a). European guidelines recommend combinations of BRAF- and MEK-inhibitors as standard treatment where indicated (Garbe 2016). Immunotherapy-based approaches including ipilimumab (CTLA-4 inhibitor) and PD-1 inhibitors (nivolumab and pembrolizumab) have been approved in the US and Europe (Hodi 2010) and by NICE in the UK both as single agents (NICE 2012; NICE 2014; NICE 2015c; NICE 2015d) and in combination (NICE 2016b; NICE 2016ab). These have shown high response rates, and demonstrate the potential for a durable clinical response for the first time in the treatment of melanoma (Chapman 2011; Hamid 2013; Hodi 2010; Hodi 2016; Larkin 2015; Maio 2015; Sznol 2013)

An update of a Cochrane review comparing the efficacy of available systemic therapies for stage IIIc and stage IV melanoma is currently underway (Pasquali 2014), as are a number of further NICE appraisals of new therapeutic agents including binimetinib, talimogene laherparepvec (TVEC) and temozolomide (https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/skin-cancer).

3 Proposed sources of heterogeneity

i. Population characteristics

- general versus higher risk populations
- patient population: primary /secondary / specialist unit
- degree of prior clinical suspicion (highly suspicious vs. challenging/equivocal lesions)
- disease prevalence (high vs low)
- inclusion of multiple lesions per participant
- ethnicity

ii. Index test characteristics

- the nature of and definition of criteria for test positivity
- observer experience with the index test

iii. Reference standard characteristics

- whether histology-reporting meets pathology-reporting guidelines
- use of excisional versus diagnostic biopsy
- whether two independent dermatopathologists reviewed histological diagnosis

iv. Study quality

- consecutive or random sample of participants recruited
- index test interpreted blinded to the reference standard result
- index test interpreted blinded to the result of any other index test
- use of an adequate reference standard
- overall risk of bias

4 Final search strategies

Melanoma search strategies to August 2016

Database: Ovid MEDLINE(R) 1946 to August week 3 2016

Search strategy:

1 exp melanoma/

2 exp skin cancer/

3 exp basal cell carcinoma/

4 basalioma$1.ti,ab.

5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or lesion$1 or malignan$ or nodule$1)).ti,ab.

6 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.

7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.

8 nmsc.ti,ab.

9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.

10 (BCC or CSCC or NMSC).ti,ab.

11 keratinocy$.ti,ab.

12 Keratinocytes/

13 or/1-12

14 dermoscop$.ti,ab.

15 dermatoscop$.ti,ab.

16 photomicrograph$.ti,ab.

17 exp epiluminescence microscopy/

18 (epiluminescence adj2 microscop$).ti,ab.

19 (confocal adj2 microscop$).ti,ab.

20 (incident light adj2 microscop$).ti,ab.

21 (surface adj2 microscop$).ti,ab.

22 (visual adj (inspect$ or examin$)).ti,ab.

23 ((clinical or physical) adj examin$).ti,ab.

24 3 point.ti,ab.

25 three point.ti,ab.

26 pattern analys$.ti,ab.

27 ABCD$.ti,ab.

28 menzies.ti,ab.

29 7 point.ti,ab.

30 seven point.ti,ab.

31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.

32 artificial intelligence.ti,ab.

33 AI.ti,ab.

34 computer assisted.ti,ab.

35 computer aided.ti,ab.

36 neural network$.ti,ab.

37 exp diagnosis, computer-assisted/

38 MoleMax.ti,ab.

39 image process$.ti,ab.

40 automatic classif$.ti,ab.

41 image analysis.ti,ab.

42 SIAscop$.ti,ab.

43 Aura.ti,ab.

44 (optical adj2 scan$).ti,ab.

45 MelaFind.ti,ab.

46 SIMSYS.ti,ab.

47 MoleMate.ti,ab.

48 SolarScan.ti,ab.

49 VivaScope.ti,ab.

50 (high adj3 ultraso$).ti,ab.

51 (canine adj2 detect$).ti,ab.

52 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.

53 smartphone$.ti,ab.

54 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.

55 Mole Detective.ti,ab.

56 Spot Check.ti,ab.

57 (mole$1 adj2 map$).ti,ab.

58 (total adj2 body).ti,ab.

59 exfoliative cytolog$.ti,ab.

60 digital analys$.ti,ab.

61 (image$1 adj3 software).ti,ab.

62 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.

63 (optical coherence adj (technolog$ or tomog$)).ti,ab.

64 (computer adj2 diagnos$).ti,ab.

65 exp sentinel lymph node biopsy/

66 (sentinel adj2 node).ti,ab.

67 nevisense.mp. or HFUS.ti,ab.

68 electrical impedance spectroscopy.ti,ab.

69 history taking.ti,ab.

70 patient history.ti,ab.

71 (naked eye adj (exam$ or assess$)).ti,ab.

72 (skin adj exam$).ti,ab.

73 physical examination/

74 ugly duckling.mp. or UD.ti,ab.

75 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.

76 ABCDE.mp. or VOC.ti,ab.

77 clinical accuracy.ti,ab.

78 Family Practice/ or Physicians, Family/ or clinical competence/

79 (confocal adj2 microscop$).ti,ab.

80 diagnostic algorithm$1.ti,ab.

81 checklist$.ti,ab.

82 virtual imag$1.ti,ab.

83 volatile organic compound$1.ti,ab.

84 dog$1.ti,ab.

85 gene expression analy$.ti,ab.

86 reflex transmission imag$.ti,ab.

87 thermal imaging.ti,ab.

88 elastography.ti,ab.

89 or/14-88

90 (CT or PET).ti,ab.

91 PET-CT.ti,ab.

92 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.

93 exp Deoxyglucose/

94 deoxy-glucose.ti,ab.

95 deoxyglucose.ti,ab.

96 CATSCAN.ti,ab.

97 exp Tomography, Emission-Computed/

98 exp Tomography, X-ray computed/

99 positron emission tomograph$.ti,ab.

100 exp magnetic resonance imaging/

101 (MRI or fMRI or NMRI or scintigraph$).ti,ab.

102 exp echography/

103 Doppler echography.ti,ab.

104 sonograph$.ti,ab.

105 ultraso$.ti,ab.

106 doppler.ti,ab.

107 magnetic resonance imag$.ti,ab.

108 or/90-107

109 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.

110 "Sensitivity and Specificity"/

111 exp cancer staging/

112 or/109-111

113 108 and 112

114 89 or 113

115 13 and 114

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 29 August 2016

Search strategy:

1 basalioma$1.ti,ab.

2 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or lesion$1 or malignan$ or nodule$1)).ti,ab.

3 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.

4 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.

5 nmsc.ti,ab.

6 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.

7 (BCC or CSCC or NMSC).ti,ab.

8 keratinocy$.ti,ab.

9 or/1-8

10 dermoscop$.ti,ab.

11 dermatoscop$.ti,ab.

12 photomicrograph$.ti,ab.

13 (epiluminescence adj2 microscop$).ti,ab.

14 (confocal adj2 microscop$).ti,ab.

15 (incident light adj2 microscop$).ti,ab.

16 (surface adj2 microscop$).ti,ab.

17 (visual adj (inspect$ or examin$)).ti,ab.

18 ((clinical or physical) adj examin$).ti,ab.

19 3 point.ti,ab.

20 three point.ti,ab.

21 pattern analys$.ti,ab.

22 ABCD$.ti,ab.

23 menzies.ti,ab.

24 7 point.ti,ab.

25 seven point.ti,ab.

26 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.

27 artificial intelligence.ti,ab.

28 AI.ti,ab.

29 computer assisted.ti,ab.

30 computer aided.ti,ab.

31 neural network$.ti,ab.

32 MoleMax.ti,ab.

33 image process$.ti,ab.

34 automatic classif$.ti,ab.

35 image analysis.ti,ab.

36 SIAscop$.ti,ab.

37 Aura.ti,ab.

38 (optical adj2 scan$).ti,ab.

39 MelaFind.ti,ab.

40 SIMSYS.ti,ab.

41 MoleMate.ti,ab.

42 SolarScan.ti,ab.

43 VivaScope.ti,ab.

44 (high adj3 ultraso$).ti,ab.

45 (canine adj2 detect$).ti,ab.

46 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.

47 smartphone$.ti,ab.

48 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.

49 Mole Detective.ti,ab.

50 Spot Check.ti,ab.

51 (mole$1 adj2 map$).ti,ab.

52 (total adj2 body).ti,ab.

53 exfoliative cytolog$.ti,ab.

54 digital analys$.ti,ab.

55 (image$1 adj3 software).ti,ab.

56 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.

57 (optical coherence adj (technolog$ or tomog$)).ti,ab.

58 (computer adj2 diagnos$).ti,ab.

59 (sentinel adj2 node).ti,ab.

60 nevisense.mp. or HFUS.ti,ab.

61 electrical impedance spectroscopy.ti,ab.

62 history taking.ti,ab.

63 patient history.ti,ab.

64 (naked eye adj (exam$ or assess$)).ti,ab.

65 (skin adj exam$).ti,ab.

66 ugly duckling.mp. or UD.ti,ab.

67 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.

68 ABCDE.mp. or VOC.ti,ab.

69 clinical accuracy.ti,ab.

70 (Family adj (Practice or Physicians)).ti,ab.

71 (confocal adj2 microscop$).ti,ab.

72 clinical competence.ti,ab.

73 diagnostic algorithm$1.ti,ab.

74 checklist$.ti,ab.

75 virtual imag$1.ti,ab.

76 volatile organic compound$1.ti,ab.

77 dog$1.ti,ab.

78 gene expression analy$.ti,ab.

79 reflex transmission imag$.ti,ab.

80 thermal imaging.ti,ab.

81 elastography.ti,ab.

82 or/10-81

83 (CT or PET).ti,ab.

84 PET-CT.ti,ab.

85 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.

86 deoxy-glucose.ti,ab.

87 deoxyglucose.ti,ab.

88 CATSCAN.ti,ab.

89 positron emission tomograph$.ti,ab.

90 (MRI or fMRI or NMRI or scintigraph$).ti,ab.

91 Doppler echography.ti,ab.

92 sonograph$.ti,ab.

93 ultraso$.ti,ab.

94 doppler.ti,ab.

95 magnetic resonance imag$.ti,ab.

96 or/83-95

97 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.

98 96 and 97

99 82 or 98

100 9 and 99

Database: Embase 1974 to 29 August 2016

Search strategy:

1 *melanoma/

2 *skin cancer/

3 *basal cell carcinoma/

4 basalioma$.ti,ab.

5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$ or adenoma$ or epithelioma$ or lesion$ or malignan$ or nodule$)).ti,ab.

6 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.

7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.

8 nmsc.ti,ab.

9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.

10 (BCC or cscc).mp. or NMSC.ti,ab.

11 keratinocyte.ti,ab.

12 keratinocy$.ti,ab.

13 or/1-12

14 dermoscop$.ti,ab.
15 dermatoscop$.ti,ab.
16 photomicrograph$.ti,ab.
17 *epiluminescence microscopy/
18 (epiluminescence adj2 microscop$).ti,ab.
19 (confocal adj2 microscop$).ti,ab.
20 (incident light adj2 microscop$).ti,ab.
21 (surface adj2 microscop$).ti,ab.
22 (visual adj (inspect$ or examin$)).ti,ab.
23 ((clinical or physical) adj examin$).ti,ab.
24 3 point.ti,ab.
25 three point.ti,ab.
26 pattern analys$.ti,ab.
27 ABCD$.ti,ab.
28 menzies.ti,ab.
29 7 point.ti,ab.
30 seven point.ti,ab.
31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
32 artificial intelligence.ti,ab.
33 AI.ti,ab.
34 computer assisted.ti,ab.
35 computer aided.ti,ab.
36 neural network$.ti,ab.
37 MoleMax.ti,ab.
38 exp diagnosis, computer-assisted/
39 image process$.ti,ab.
40 automatic classif$.ti,ab.
41 image analysis.ti,ab.
42 SIAscop$.ti,ab.
43 (optical adj2 scan$).ti,ab.
44 Aura.ti,ab.
45 MelaFind.ti,ab.
46 SIMSYS.ti,ab.
47 MoleMate.ti,ab.
48 SolarScan.ti,ab.
49 VivaScope.ti,ab.
50 confocal microscop$.ti,ab.
51 (high adj3 ultraso$).ti,ab.
52 (canine adj2 detect$).ti,ab.
53 ((mobile or cell$ or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
54 smartphone$.ti,ab.
55 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
56 Spot Check.ti,ab.
57 Mole Detective.ti,ab.
58 (mole$1 adj2 map$).ti,ab.
59 (total adj2 body).ti,ab.

60 exfoliative cytolog$.ti,ab.

61 digital analys$.ti,ab.

62 (image$1 adj3 software).ti,ab.

63 (optical coherence adj (technolog$ or tomog$)).ti,ab.

64 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$).mp. or tele-dermatoscop$.ti,ab.

65 (computer adj2 diagnos$).ti,ab.

66 *sentinel lymph node biopsy/

67 (sentinel adj2 node).ti,ab.

68 nevisense.ti,ab.

69 HFUS.ti,ab.

70 electrical impedance spectroscopy.ti,ab.

71 history taking.ti,ab.

72 patient history.ti,ab.

73 (naked eye adj (exam$ or assess$)).ti,ab.

74 (skin adj exam$).ti,ab.

75 *physical examination/

76 ugly duckling.ti,ab.

77 UD sign$.ti,ab.

78 ((physician$ or clinical or physical) adj (exam$ or recog$ or triage)).ti,ab.

79 ABCDE.ti,ab.

80 clinical accuracy.ti,ab.

81 *general practice/

82 (confocal adj2 microscop$).ti,ab.

83 clinical competence/

84 diagnostic algorithm$.ti,ab.

85 checklist$1.ti,ab.

86 virtual image$1.ti,ab.

87 volatile organic compound$1.ti,ab.

88 VOC.ti,ab.

89 dog$1.ti,ab.

90 gene expression analys$.ti,ab.

91 reflex transmission imaging.ti,ab.

92 thermal imaging.ti,ab.

93 elastography.ti,ab.

94 dog$1.ti,ab.

95 gene expression analys$.ti,ab.

96 reflex transmission imaging.ti,ab.

97 thermal imaging.ti,ab.

98 elastography.ti,ab.

99 or/14-93

100 PET-CT.ti,ab.

101 (CT or PET).ti,ab.

102 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.

103 exp Deoxyglucose/

104 CATSCAN.ti,ab.

105 deoxyglucose.ti,ab.

106 deoxy-glucose.ti,ab.

107 *positron emission tomography/

108 *computer assisted tomography/

109 positron emission tomograph$.ti,ab.

110 *nuclear magnetic resonance imaging/

111 (MRI or fMRI or NMRI or scintigraph$).ti,ab.

112 *echography/

113 Doppler.ti,ab.

114 sonograph$.ti,ab.

115 ultraso$.ti,ab.

116 magnetic resonance imag$.ti,ab.

117 or/100-116

118 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.

119 "Sensitivity and Specificity"/

120 *cancer staging/

121 or/118-120

122 117 and 121

123 99 or 122

124 13 and 123

Database: Cochrane Library (Wiley) 2016 searched 30 August 2016 CDSR Issue 8 of 12 2016 CENTRAL Issue 7 of 12 2016 HTA Issue 3 of 4 July 2016 DARE Issue 3 of 4 2015

Search strategy:

#1 melanoma* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyte*

#2 MeSH descriptor: [Melanoma] explode all trees

#3 "skin cancer*"

#4 MeSH descriptor: [Skin Neoplasms] explode all trees

#5 skin near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)

#6 nmsc

#7 "squamous cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*) near/2 (skin or epiderm* or cutaneous)

#8 "basal cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)

#9 pigmented near/2 (lesion* or nevus or mole* or naevi or naevus or nevi or skin)

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#11 dermoscop*

#12 dermatoscop*

#13 Photomicrograph*

#14 MeSH descriptor: [Dermoscopy] explode all trees

#15 confocal near/2 microscop*

#16 epiluminescence near/2 microscop*

#17 incident next light near/2 microscop*

#18 surface near/2 microscop*

#19 "visual inspect*"

#20 "visual exam*"

#21 (clinical or physical) next (exam*)

#22 "3 point"

#23 "three point"

#24 "pattern analys*"
#25 ABDC
#26 menzies
#27 "7 point"
#28 "seven point"
#29 digital near/2 (dermoscop* or dermatoscop*)
#30 "artificial intelligence"
#31 "AI"
#32 "computer assisted"
#33 "computer aided"
#34 AI
#35 "neural network*"
#36 MoleMax
#37 "computer diagnosis"
#38 "image process*"
#39 "automatic classif*"
#40 SIAscope
#41 "image analysis"
#42 "optical near/2 scan*"
#43 Aura
#44 MelaFind
#45 SIMSYS
#46 MoleMate
#47 SolarScan
#48 Vivascope
#49 "confocal microscopy"
#50 high near/3 ultraso*
#51 canine near/2 detect*
#52 Mole* near/2 map*
#53 total near/2 body
#54 mobile* or smart near/2 phone*
#55 cell next phone*
#56 smartphone*
#57 "mitotic index"
#58 DermoScan or SkinVision or DermLink or SpotCheck
#59 "Mole Detective"
#60 "Spot Check"
#61 mole* near/2 map*
#62 total near/2 body
#63 "exfoliative cytolog*"
#64 "digital analys*"
#65 image near/3 software
#66 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatolog*
#67 "optical coherence" next (technolog* or tomog*)
#68 computer near/2 diagnos*
#69 sentinel near/2 node*

#70 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69

#71 ultraso*

#72 sonograph*

#73 MeSH descriptor: [Ultrasonography] explode all trees

#74 Doppler

#75 CT or PET or PET-CT

#76 "CAT SCAN" or "CATSCAN"

#77 MeSH descriptor: [Positron-Emission Tomography] explode all trees

#78 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees

#79 MRI

#80 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees

#81 MRI or fMRI or NMRI or scintigraph*

#82 "magnetic resonance imag*"

#83 MeSH descriptor: [Deoxyglucose] explode all trees

#84 deoxyglucose or deoxy-glucose

#85 "positron emission tomograph*"

#86 #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85

#87 stage* or staging or metasta* or recurrence or sensitivity or specificity or "false negative*" or thickness*

#88 MeSH descriptor: [Neoplasm Staging] explode all trees

#89 #87 or #88

#90 #89 and #86

#91 #70 or #90

#92 #10 and #91

#93 BCC or CSCC or NMCS

#94 keratinocy*

#95 #93 or #94

#96 #10 or #95

#97 nevisense

#98 HFUS

#99 "electrical impedance spectroscopy"

#100 "history taking"

#101 "patient history"

#102 naked next eye near/1 (exam* or assess*)

#103 skin next exam*

#104 "ugly duckling" or (UD sign*)

#105 MeSH descriptor: [Physical Examination] explode all trees

#106 (physician* or clinical or physical) near/1 (exam* or recog* or triage*)

#107 ABCDE

#108 "clinical accuracy"

#109 MeSH descriptor: [General Practice] explode all trees

#110 confocal near microscop*

#111 "diagnostic algorithm*"

#112 MeSH descriptor: [Clinical Competence] explode all trees

#113 checklist*

#114 "virtual image*"

#115 "volatile organic compound*"

#116 dog or dogs

#117 VOC

#118 "gene expression analys*"

#119 "reflex transmission imaging"

#120 "thermal imaging"

#121 elastography

#122 #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121

#123 #70 or #122

#124 #96 and #123

#125 #96 and #90

#126 #125 or #124

#127 #10 and #126

Database : CINAHL Plus (EBSCO) 1937 to 30 August 2016

Search strategy:

S1 (MH "Melanoma") OR (MH "Nevi and Melanomas+")

S2 (MH "Skin Neoplasms+")

S3 (MH "Carcinoma, Basal Cell+")

S4 basalioma*

S5 (basal cell) N2 (cancer* or carcinoma* or mass or masses or tumor* or tumour* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)

S6 (pigmented) N2 (lesion* or mole* or nevus or nevi or naevus or naevi or skin)

S7 melanom* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt*

S8 nmsc

S9 TX BCC or cscc or NMSC

S10 (MH "Keratinocytes")

S11 keratinocyt*

S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11

S13 dermoscop* or dermatoscop* or photomicrograph* or (3 point) or (three point) or ABCD* or menzies or (7 point) or (seven point) or AI or Molemax or SIASCOP* or Aura or MelaFind or SIMSYS or MoleMate or SolarScan or smartphone* or DermoScan or SkinVision or DermLink or SpotCheck

S14 (epiluminescence or confocal or incident or surface) N2 (microscop*)

S15 visual N1 (inspect* or examin*)

S16 (clinical or physical) N1 (examin*)

S17 pattern analys*

S18 (digital) N2 (dermoscop* or dermatoscop*)

S19 (artificial intelligence)

S20 (computer) N2 (assisted or aided)

S21 (neural network*)

S22 (MH "Diagnosis, Computer Assisted+")

S23 (image process*)

S24 (automatic classif*)

S25 (image analysis)

S26 SIAScop*

S27 (optical) N2 (scan*)

S28 (high) N3 (ultraso*)

S29 elastography

S30 (mobile or cell or cellular or smart) N2 (phone*) N2 (app or application*)

S31 (mole*) N2 (map*)

S32 total N2 body

S33 exfoliative cytolog*

S34 digital analys*

S35 image N3 software

S36 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatoscop* teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop*

S37 (optical coherence) N1 (technolog* or tomog*)

S38 computer N2 diagnos*

S39 sentinel N2 node

S40 (MH "Sentinel Lymph Node Biopsy")

S41 nevisense or HFUS or checklist* or VOC or dog*

S42 electrical impedance spectroscopy

S43 history taking

S44 "Patient history"

S45 naked eye

S46 skin exam*

S47 physical exam*

S48 ugly duckling

S49 UD sign*

S50 (physician* or clinical or physical) N1 (exam*)

S51 clinical accuracy

S52 general practice

S53 (physician* or clinical or physical) N1 (recog* or triage)

S54 confocal microscop*

S55 clinical competence

S56 diagnostic algorithm*

S57 checklist*

S58 virtual image*

S59 volatile organic compound*

S60 gene expression analys*

S61 reflex transmission imag*

S62 thermal imaging

S63 S13 or S14 or S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62

S64 CT or PET

S65 PET-CT

S66 FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical*

S67 (MH "Deoxyglucose+")

S68 deoxy-glucose or deoxyglucose

S69 CATSCAN

S70 CAT-SCAN

S71 (MH "Deoxyglucose+")

S72 (MH "Tomography, Emission-Computed+")

S73 (MH "Tomography, X-Ray Computed")

S74 positron emission tomograph*

S75 (MH "Magnetic Resonance Imaging+")

S76 MRI or fMRI or NMRI or scintigraph*

S77 echography

S78 doppler

S79 sonograph*

S80 ultraso*

S81 magnetic resonance imag*

S82 S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81

S83 stage* or staging or metasta* or recurrence or sensitivity or specificity or (false negative*) or thickness

S84 (MH "Neoplasm Staging")

S85 S83 OR S84

S86 S82 AND S85

S87 S63 OR S86

S88 S12 AND S87

Database: Science Citation Index SCI Expanded (Web of Science) 1900 to 30 August 2016

Conference Proceedings Citation Index (Web of Science) 1900 to 1 September 2016

Search strategy:

#1 (melanom* or nonmelanom* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyt*)

#2 (basalioma*)

#3 ((skin) near/2 (cancer* or carcinoma or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))

#4 ((basal) near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))

#5 ((pigmented) near/2 (lesion* or mole* or nevus or nevi or naevus or naevi or skin))

#6 (nmsc or BCC or NMSC or keratinocy*)

#7 ((squamous cell (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))

#8 (skin or epiderm* or cutaneous)

#9 #8 AND #7

#10 #9 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

#11 ((dermoscop* or dermatoscop* or photomicrograph* or epiluminescence or confocal or "incident light" or "surface microscop*" or "visual inspect*" or "physical exam*" or 3 point or three point or pattern analy* or ABCDE or menzies or 7 point or seven point or dermoscop* or dermatoscop* or AI or artificial or computer aided or computer assisted or neural network* or Molemax or image process* or automatic classif* or image analysis or siascope or optical scan* or Aura or melafind or simsys or molemate or solarscan or vivascope or confocal microscop* or high ultraso* or canine detect* or cellphone* or mobile* or phone* or smartphone or dermoscan or skinvision or dermlink or spotcheck or spot check or mole detective or mole map* or total body or exfoliative psychology or digital or image software or optical coherence or teledermatology or telederm* or teledermoscop* or teledermatoscop* or computer diagnos* or sentinel))

#12 ((nevisense or HFUS or impedance spectroscopy or history taking or patient history or naked eye or skin exam* or physical exam* or ugly duckling or UD sign* or physician* exam* or physical exam* or ABCDE or clinical accuracy or general practice or confocal microscop* or clinical competence or diagnostic algorithm* or checklist* or virtual image* or volatile organic or VOC or dog* or gene expression or reflex transmission or thermal imag* or elastography))

#13 #11 or #12

#14 ((PET or CT or FDG or deoxyglucose or deoxy-glucose or fluorodeoxy* or radiopharma* or CATSCAN or positron emission or computer assisted or nuclear magnetic or MRI or FMRI or NMRI or scintigraph* or echograph* or Doppler or sonograph* or ultraso* or magnetic reson*))

#15 ((stage* or staging or metast* or recurrence or sensitivity or specificity or false negative* or thickness*))

#16 #14 AND #15

#17 #16 OR #13

#18 #10 AND #17

Refined by: DOCUMENT TYPES: (MEETING ABSTRACT OR PROCEEDINGS PAPER)

5 Full text inclusion criteria

The table below summarises the inclusion criteria applied to each study.

Criterion	Inclusion	Exclusion

Study design	For diagnostic and staging reviews
	• Any study for which a 2×2 contingency table can be extracted, e.g.
	  ◦ diagnostic case control studies
	  ◦ 'cross-sectional' test accuracy study with retrospective or prospective data collection
	  ◦ studies where estimation of test accuracy was not the primary objective but test results for both index and reference standard were available
	  ◦ RCTs of tests or testing strategies where participants were randomised between index tests and all undergo a reference standard (i.e. accuracy RCTs)
		• < 5 melanoma cases (diagnosis reviews)
		• < 10 participants (staging reviews)
		• Studies developing new criteria for diagnosis unless a separate 'test set' of images were used to evaluate the criteria (mainly digital dermoscopy)
		• Studies using 'normal' skin as controls
		• Letters, editorials, comment papers, narrative reviews
		• Insufficient data to construct a 2×2 table

Target condition	• Melanoma
	• Keratinocyte skin cancer (or non-melanoma skin cancer)
	  ◦ BCC or epithelioma
	  ◦ cSCC
		• Studies exclusively conducted in children
		• Studies of non-cutaneous melanoma or SCC

Population	For diagnostic reviews • Adults with a skin lesion suspicious for melanoma, BCC, or cSCC (other terms include pigmented skin lesion/nevi, melanocytic, keratinocyte, etc.) • Adults at high risk of developing melanoma skin cancer, BCC, or cSCC For staging reviews • Adults with a diagnosis of melanoma or cSCC undergoing tests for staging of lymph nodes or distant metastases or both	• People suspected of other forms of skin cancer • Studies conducted exclusively in children

Criterion	Inclusion	Exclusion
Index tests	**For diagnosis** • Visual inspection/clinical examination • Dermoscopy/dermatoscopy • Teledermoscpoy • Smartphone/mobile phone applications • Digital dermoscopy/artificial intelligence • Confocal microscopy • Ocular coherence tomography • Exfoliative cytology • High frequency ultrasound • Canine odour detection • DNA expression analysis/gene chip analysis • Other **For staging** • CT • PET • PET-CT • MRI • Ultrasound +/fine needle aspiration cytology FNAC • SLNB +/high frequency ultrasound • Other Any test combination and in any order Any test positivity threshold Any variation in testing procedure (e.g. radioisotope used)	• Sentinel lymph biopsy for therapeutic rather than staging purposes • Tests to determine melanoma thickness • Tests to determine surgical margins/lesion borders • Tests to improve histopathology diagnose • LND
Reference standard	**For diagnostic studies** • Histopathology of the excised lesion • Clinical follow-up of non-excised/benign appearing lesions with later histopathology if suspicious • Expert diagnosis (studies should not be included if expert diagnosis is the sole reference standard) **For studies of imaging tests for staging** • Histopathology (via LND or SLMB) • Clinical/radiological follow-up • A combination of the above **For studies of SLNB accuracy for staging** • LND of both SLN+ and SLn participants to identify all diseased nodes • LND of SLN+ participants and follow-up of SLN participants to identify a subsequent nodal recurrence in a *previously investigated* nodal basin	**For diagnostic studies** • Exclude if any disease positive participants have diagnosis unconfirmed by histology • Exclude if > 50% of disease negative participants have diagnosis confirmed by expert opinion with no histology or follow-up • Exclude studies of referral accuracy, i.e. comparing referral decision with expert diagnosis, unless evaluations of teledermatology or mobile phone applications

BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma; CT: computed tomography; FNAC: fine needle aspiration cytology; LND: lymph node dissection; MRI: magnetic resonance imaging; PET: positron emission tomography; PET-CT: positron emission tomography computed tomography; RCT: randomised controlled trial; SCC: squamous cell carcinoma; SLN+: positive sentinel lymph node; SLn: negative sentinel lymph node; SLNB: sentinel lymph node biopsy.

6 Quality assessment (based on QUADAS-2)

The QUADAS-2 checklist (Whiting 2011) was tailored to the review topic as follows below.

Patient selection domain (1)

Selective recruitment of study participants can be a key influence on test accuracy. In general terms, all participants eligible to undergo a test should be included in a study, allowing for the intended use of that test within the context of the study. We considered studies that separately sampled malignant and benign lesions to have used a case-control design; and those that supplemented a series of suspicious lesions with additional malignant or benign lesions to be at unclear risk of bias

In terms of exclusions, we considered studies that excluded particular lesion types, particular lesion sites, or that excluded lesions on the basis of image quality or lack of observer agreement (e.g. on histopathology) to be at high risk of bias.

In judging the applicability of patient populations to the review question, we considered restriction to particular lesion

populations, such as melanocytic, nodular, high risk or restrictions by size to be of high concern for applicability.

Given that diagnosis of skin cancer is primarily lesion-based, there is the potential for study participants with multiple lesions to contribute disproportionately to estimates of test accuracy, especially if they are at particular risk of having skin cancer. We considered studies that include a high number of lesions in relation to the number of study to be less representative than studies conducted in a more general population participants (i.e., if the difference between the number of included lesions and number of included participants is greater than 5%).

Index test domain (2)

Given the potential for subjective differences in test interpretation, the interpretation of the index test blinded to the result of the reference standard is a key means of reducing bias. For prospective studies and retrospective studies that used the original index test interpretation, the diagnosis will by nature be interpreted and recorded before the result of the reference standard is known; however, studies using previously acquired images could be particularly susceptible to information bias. For these studies to be at low risk of bias, we required a clear indication that observers were unaware of the reference standard diagnosis at time of test interpretation. An item was also added to assess the presence of blinding between interpretations of different algorithms, however this item was not included in the overall assessment of risk of bias.

Pre-specification of the index test threshold was considered present if the study clearly reported that the threshold used was not data driven, i.e., was not based on study results. Studies that did not clearly describe the threshold used but that required clinicians to record a diagnosis or management decision for a lesion were considered to be unclear on this criterion. Studies reporting accuracy for multiple numeric thresholds, where ROC analysis was used to select the threshold, or that reported accuracy for the presence of independently significant lesion characteristics with no separate test set of lesions were considered at high risk of bias.

In terms of applicability of the index test to the review question, we required exfoliative cytology to be applied and interpreted as it would be in a clinical practice setting:

- Sample obtained by dragging scalpel/curette across lesion, possibly after removal of crust.
- Material spread directly on to a slide and wet-fixed or air-dried.
- At least one slide stained with either Pap or MGG (Romanowsky) stain

Rapid staining methods were also acceptable, however studies were considered to be of high concern for clinical applicability if interpretation of cytology slides was made without access to the clinical referral information.

Despite the often subjective nature of test interpretation, it is also important for study authors to outline the particular lesion characteristics that were considered to be indicative for skin cancer, particularly where established algorithms or checklists were not used. Studies were considered of low concern if the threshold used was established in a prior study or sufficient threshold details were presented to allow replication.

The experience of the examiner will also impact on the applicability of study results. We required studies to describe the test interpreter as ‘experienced’ or ‘expert’ in exfoliative cytology to have low concern about applicability.

Reference standard domain (3)

In an ideal study, consecutively recruited participants should all undergo incisional or excisional biopsy of the skin lesion regardless of level of clinical suspicion. In reality, both partial and differential verification bias are likely. Partial verification bias may occur where histology is the only reference standard used, and only those participants with a certain degree of suspicion of malignancy based on the result of the index test undergo verification, the others either being excluded from the study or defined as being disease-negative without further assessment or follow-up, as discussed above.

Differential verification bias will be present where other reference standards are used in addition to histological verification of suspicious lesions. A typical example of verification bias in skin cancer occurs when investigators do not biopsy people with benign-appearing lesions but instead follow them up for a period of time to determine whether any malignancy subsequently develops (these would be false-negatives on the index test). We defined an 'adequate' reference standard as: all disease-positive individuals having a histological reference standard either at the time of application of the index test or after a period of clinical follow-up; and at least 80% of disease-negative participants have received a histological diagnosis, with up to 20% undergoing at least three months' follow-up of benign-appearing lesions.

A further challenge is the potential for incorporation bias, i.e., where the result of the index test is used to help determine the reference standard diagnosis. It is normal practice for the clinical diagnosis (usually by visual inspection or dermoscopy) to be included on pathology request forms and for the histopathologist to use this diagnosis to help with the pathology interpretation. Although inclusion of such clinical information on the histopathology request form is theoretically a form of incorporation bias, blinded interpretation of the histopathology reference standard is not normal practice, and enforcement of such conditions would significantly limit the generalisability of the study results. For studies evaluating exfoliative cytology, this item was divided into two questions, firstly whether the reference standard was blinded to the index test result (Exfoliative Cytology), and secondly whether it was blinded to the clinical diagnosis. Only the response to the first part (i.e. blinding to Exfoliative Cytology) was included in our overall assessment of risk of bias for the reference standard domain.

In judging the applicability of the reference standard to our review question, scored studies as high concern around applicability if they used expert diagnosis (with no follow-up) as a reference standard in any patient, or did not report histology interpretation by a dermatopathologist.

Flow and timing domain (4)

In the ideal study, the diagnosis based on the index test and reference standard should be made consecutively or as near to each other in time as possible to avoid changes in lesion over time. For lesions with a histological reference standard, we have defined a one-month period as an appropriate interval between application of the index test and the reference standard. For studies using clinical follow-up, a minimum three-month follow-up period has been defined as at low risk of bias for detecting false-negatives.

In assessing whether all patients were included in the analysis, we considered studies at high risk of bias if participants were excluded following recruitment for any reason other than due to inadequate collection of cellular material for cytological analysis ('test failures').

Comparative domain

A comparative domain was added to the QUADAS-2 checklist for studies comparing the accuracy of Exfoliative Cytology and dermoscopy. Items were included to assess the presence blinding of interpretation between tests, and to specify a maximum of one month interval between application of index tests, as intervals greater than these may be accompanied by changes in tumour characteristics. As it would not be normal practice for Exfoliative Cytology to be interpreted blinded to the clinical or dermoscopic diagnosis, the scoring of this item did not contribute to our overall assessment of risk of bias. We also considered whether both tests were applied and interpreted in a clinically applicable manner.

The following tables use text that was originally published in the QUADAS-2 tool by Whiting and colleagues (Whiting 2011 *).*

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
1) Was a consecutive or random sample of participants or images enrolled?	**Yes** – if paper states consecutive or random **No** – if paper describes other method of sampling **Unclear** – if participant sampling not described
2) Was a case-control design avoided?	**Yes** – if consecutive or random or case-control design clearly not used **No** – if study described as case-control or describes sampling specific numbers of participants with particular diagnoses **Unclear** – if not described
3) Did the study avoid inappropriate exclusions, e.g., • 'difficult to diagnose' lesions not excluded • lesions not excluded on basis of disagreement between evaluators	**Yes** if inappropriate exclusions were avoided **No** – if lesions were excluded that might affect test accuracy, e.g., 'difficult to diagnose' lesions, or where disagreement between evaluators was observed **Unclear** – if not clearly reported but there is suspicion that difficult to diagnose lesions may have been excluded
4) For between-person comparative studies only (i.e., allocating different tests to different study participants): • **A)** were the same participant selection criteria used for those allocated to each test? • **B)** was the potential for biased allocation between tests avoided through adequate generation of a randomised sequence? • **C)** was the potential for biased allocation between tests avoided through concealment of allocation prior to assignment?	**For A)** • **Yes** – if same selection criteria were used for each index test, **No** – if different selection criteria were used for each index test, **Unclear** – if selection criteria per test were not described, **N/A** – if only 1 index test was evaluated or all participants received all tests **For B)** • **Yes** – if adequate randomisation procedures are described, **No** – if inadequate randomisation procedures are described, **Unclear** – if the method of allocation to groups is not described (a description of 'random' or 'randomised' is insufficient), **N/A** – if only 1 index test was evaluated or all participants received all tests **For C)** • **Yes** – if appropriate methods of allocation concealment are described, **No** – if appropriate methods of allocation concealment are not described, **Unclear** – if the method of allocation concealment is not described (sufficient detail to allow a definite judgement is required), **N/A** – if only 1 index test was evaluated

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
Could the selection of participants have introduced bias? **For non-comparative and within person-comparative studies** 1. If answers to all of questions 1), 2), and 3) 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) 'No': 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear': **For between-person comparative studies** 1. If answers to all of questions 1), 2), 3), and 4) 'Yes': 2. If answers to any 1 of questions 1), 2), 3), or 4) 'No': 3. If answers to any 1 of questions 1), 2), 3), or 4) 'Unclear':	**For non-comparative and within person-comparative studies** 1. Risk is low 2. Risk is high 3. Risk unclear **For between-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk unclear
PARTICIPANT SELECTION (1) CONCERNS REGARDING APPLICABILITY	
1) Are the included participants and chosen study setting appropriate to answer the review question, i.e., are the study results generalisable? • This item is not asking whether exclusion of certain participant groups might bias the study's results (as in Risk of Bias above), but is asking whether the chosen study participants and setting are appropriate to answer our review question. Because we are looking to establish test accuracy in both primary presentation and referred participants, a study could be appropriate for 1 setting and not for the other, or it could be unclear as to whether the study can appropriately answer either question • For each study assessed, please consider whether it is more relevant for A) participants with a primary presentation of a skin lesion or B) referred participants, and respond to the questions in either A) or B) accordingly. If the study gives insufficient details, please respond **Unclear** to both parts of the question	**A) For studies that will contribute to the analysis of participants with a primary presentation of a skin lesion (i.e., test naive)** **Yes** – if participants included in the study appear to be generally representative of those who might present in a usual practice setting **No** – if study participants appear to be unrepresentative of usual practice, e.g., in terms of severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols **Unclear –** if insufficient details are provided to determine the generalisability of study participants **B) For studies that will contribute to the analysis of referred participants (i.e., who have already undergone some form of testing)** **Yes** – if study participants appear to be representative of those who might be referred for further investigation. If the study focuses only on those with equivocal lesions, for example, we would suggest that this is not representative of the wider referred population **No** – if study participants appear to be unrepresentative of usual practice, e.g., if a particularly high proportion of participants have been self-referred or referred for cosmetic reasons. Other factors to consider include severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols **Unclear –** if insufficient details are provided to determine the generalisability of study participants
2) Did the study **avoid including** participants with multiple lesions?	**Yes** – if the difference between the number of included lesions and number of included participants is less than 5% **No** – if the difference between the number of included lesions and number of included participants is greater than 5% **Unclear –** if it is not possible to assess
Is there concern that the included participants do not match the review question? 1. If the answer to question 1) or 2) 'Yes': 2. If the answer to question 1) or 2) 'No': 3. If the answer to question 1) or 2) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
INDEX TEST (2) RISK OF BIAS (to be completed per test evaluated)	
1) Was the index test or testing strategy result interpreted without knowledge of the results of the reference standard?	**Yes** – if index test described as interpreted without knowledge of reference standard result or, for prospective studies, if index test is always conducted and interpreted prior to the reference standard **No** – if index test described as interpreted in knowledge of reference standard result **Unclear** – if index test blinding is not described
2) Was the diagnostic threshold at which the test was considered positive prespecified?	**Yes** – if threshold was prespecified (i.e., prior to analysing study results) **No** – if threshold was not prespecified **Unclear** – if not possible to tell whether or not diagnostic threshold was prespecified
3) For within-person comparisons of index tests or testing strategies (i.e., > 1 index test applied per participant): was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	**Yes** – if all index tests were described as interpreted without knowledge of the results of the others **No** – if the index tests were described as interpreted in the knowledge of the results of the others **Unclear** – if it is not possible to tell whether knowledge of other index tests could have influenced test interpretation **N/A** – if only 1 index test was evaluated
Could the conduct or interpretation of the index test have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1) and 2) 'Yes': 2. If answers to either questions 1) or 2) 'No': 3. If answers to either questions 1) or 2) 'Unclear': **For within-person comparative studies** 1. If answers to all questions 1), 2), for any index test and 3) 'Yes': 2. If answers to any 1 of questions 1) or 2) for any index test or 3) 'No': 3. If answers to any 1 of questions 1) or 2) for any index test or 3) 'Unclear':	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
INDEX TEST (2) CONCERN ABOUT APPLICABILITY	
1) Was the test applied and interpreted in a clinically applicable manner?	**Yes** – sample of cells was obtained by dragging a scalpel/curette across the lesion, after removal of any crust, material was spread directly onto a slide and wet-fixed or air-dried, at least one slide was stained using either Pap or MGG technique, or a rapid staining method. **No** – not all of the above were carried out OR interpretation was blinded to clinical diagnosis. **Unclear** – if insufficient information was reported
2) Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication? Study results can only be reproduced if the diagnostic threshold is described in sufficient detail. This item applies equally to studies using pattern recognition and those using checklists or algorithms to aid test interpretation	**Yes** – If the criteria for diagnosis were reported in sufficient detail to allow replication **No** – if the criteria for diagnosis were not reported in sufficient detail to allow replication **Unclear** – If some but not sufficient information on criteria for diagnosis to allow replication were provided

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
3) Was the test interpretation carried out by an experienced examiner?	**Yes** – if the test was interpreted by 1 or more speciality-accredited dermatologists, or by examiners of any clinical background with special interest in dermatology and with any formal training in the use of the test **No** – if the test was not interpreted by an experienced examiner (see above) **Unclear** – if the experience of the examiner(s) was not reported in sufficient detail to judge or if examiners were described as 'Expert' with no further detail given **N/A** – if system-based diagnosis, i.e., no observer interpretation
Is there concern that the index test, its conduct, or interpretation differ from the review question? 1. If answers to questions 1), 2), and 3) 'Yes': 2. If answers to questions 1), 2), or 3) 'No': 3. If answers to questions 1), 2), or 3) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear
REFERENCE STANDARD (3) RISK OF BIAS	
1) Is the reference standard likely to correctly classify the target condition? A) Disease-positive – 1 or more of the following: • histological confirmation of malignancy following biopsy or lesion excision • clinical follow-up of benign-appearing lesions for at least 3 months following the application of the index test, leading to a histological diagnosis of skin cancer B) Disease-negative – 1 or more of the following: • histological confirmation of absence of malignancy following biopsy or lesion excision in at least 80% of disease-negative participants • clinical follow-up of benign-appearing lesions for a minimum of 3 months following the index test in up to 20% of disease-negative participants	A) Disease-positive **Yes** – if all participants with a final diagnosis of malignancy underwent 1 of the listed reference standards **No** – If a final diagnosis of malignancy for any participant was reached without histopathology **Unclear** – if the method of final diagnosis was not reported for any participant with a final diagnosis of malignancy or if the length of clinical follow-up used was not clear or if a clinical follow-up reference standard was reported in combination with a participant-based analysis and it was not possible to determine whether the detection of a malignant lesion during follow-up is the same lesion that originally tested negative on the index test B) Disease-negative **Yes** – If at least 80% of benign diagnoses were reached by histology and up to 20% were reached by clinical follow-up for a minimum of 3 months following the index test **No** – if more than 20% of benign diagnoses were reached by clinical follow-up for a minimum of 3 months following the index test or if clinical follow-up period was less than 3 months **Unclear** – if the method of final diagnosis was not reported for any participant with benign or non-melanoma diagnosis
2) Were the reference standard results interpreted without knowledge of the results of the index test? Please score this item for all studies even though histopathology interpretation is usually conducted with knowledge of the clinical diagnosis (from visual inspection or dermoscopy or both). We will deal with this by not including the response to this item in the 'Risk of bias' assessment for these tests. For reviews of all other tests, this item will be retained	**Yes** – if the reference standard diagnosis was reached blinded to the index test result **No** – if the reference standard diagnosis was reached with knowledge of the index test result **Unclear** – if blinded reference test interpretation was not clearly reported

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
Could the reference standard, its conduct, or its interpretation have introduced bias? **For visual inspection/dermoscopy evaluations** 1. If answer to question 1) 'Yes': 2. If answer to question 1) 'No': 3. If answer to question 1) 'Unclear': **For all other tests** 1. If answers to questions 1) and 2) 'Yes': 2. If answers to questions 1) or 2) 'No': 3. If answers to questions 1) or 2) 'Unclear':	**For visual inspection/dermoscopy evaluations** 1. Risk is low 2. Risk is high 3. Risk is unclear **For all other tests** 1. Risk is low 2. Risk is high 3. Risk is unclear
REFERENCE STANDARD (3) CONCERN ABOUT APPLICABILITY	
1) Expert opinion (with no histological confirmation) was not used as a reference standard 'Expert opinion' means diagnosis based on the standard clinical examination, with no histology or lesion follow-up	**Yes** – if expert opinion was not used as a reference standard for any participant **No** – if expert opinion was used as a reference standard for any participant **Unclear** – if not clearly reported
2) Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	**Yes –** if histology interpretation was reported to be carried out by an experienced histopathologist or dermatopathologist **No –** if histology interpretation was reported to be carried out by a less experienced histopathologist **Unclear** – if the experience/qualifications of the pathologist were not reported
Is there concern that the target condition as defined by the reference standard does not match the review question? 1. If answers to both questions 1), 2), 'Yes': 2. If answers to any 1 of questions 1), 2), 'No': 3. If answers to any 1 of questions 1), 2), 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear
FLOW AND TIMING (4): RISK OF BIAS	
1) Was there an appropriate interval between index test and reference standard? **A)** For histopathological reference standard, was the interval between index test and reference standard ≤ 1 month? **B)** If the reference standard includes clinical follow-up of borderline/benign-appearing lesions, was there at least 3 months' follow-up following application of index test(s)?	**A)** **Yes** – if study reports ≤ 1 month between index and reference standard **No** – if study reports > 1 month between index and reference standard **Unclear** – if study does not report interval between index and reference standard **B)** **Yes** – if study reports ≥ 3 months' follow-up **No** – if study reports < 3 months' follow-up **Unclear** – if study does not report the length of clinical follow-up
2) Did all participants receive the same reference standard?	**Yes** – if all participants underwent the same reference standard **No** – if more than 1 reference standard was used **Unclear** – if not clearly reported

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
3) Were all participants included in the analysis?	**Yes** – if all participants were included in the analysis **No** – if some participants were excluded from the analysis **Unclear**– if not clearly reported
4) **For within-person comparisons of index tests** Was the interval between application of index tests ≤ 1 month?	**Yes** – if study reports ≤ 1 month between index tests **No** – if study reports > 1 month between index tests **Unclear** – if study does not report the interval between index tests
Could the participant flow have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1), 2), and 3) 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) 'No': 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear': **For within-person comparative studies** 1. If answers to all questions 1), 2), 3), and 4) 'Yes': 2. If answers to any 1 of questions 1), 2), 3), or 4) 'No': 3. If answers to any 1 of questions 1), 2), 3), or 4) 'Unclear':	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma.	

7 Summary of studies

Study author Outcomes reported	Study type	Inclusion criteria Exclusions	No. patients / lesions	Lesion_site	Stain technique	Cytopathological criteria	Uncertain cytological diagnoses	Observer qualifications (n) Test experience	Test failures	R F
Berner (1999) BCC Any	NC P-CS Norway	Lesions clinically suspected of being nodular BBCs, located on the head, thorax or abdomen Excluded: Thickness < 2mm, inadequate cellular material for cytological or histological evaluation.	90 / 112	Head, Face, Thorax, Abdomen (%s NR)	Diff–Quick	Presence of small dissociated hyperchromatic cells in cohesive sheets. The cells have scanty cytoplasm, indistinct cell borders and the cohesive sheets often demonstrate palisading.	2 ?BCC	Cytopathologist (n=3) NR	Excluded at study entry	H (s B cS C A

Study author Outcomes reported	Study type	Inclusion criteria Exclusions	No. patients / lesions	Lesion_site	Stain technique	Cytopathological criteria	Uncertain cytological diagnoses	Observer qualifications (n) Test experience	Test failures	R F
Brown (1979) BCC Any	NC NR-CS UK	Localised lesions for which a histological diagnosis was required to confirm clinical diagnosis of BCC, or in a minority to exclude BCC Exclusions not reported	81 / 85	NR	MGG or rapid stain with aqueous toluidine blue	BCC: tumour cells occur dispersed and in small clusters and large clusters with a lobulated outline; mostly of uniform size and shape, having very little cytoplasm, an oval nucleus with a smooth outline, and evenly dispersed, finely dotted chromatin, sometimes with one or two small distinct nucleoli; The squamous tumour cells are similar in size to prickle layer cells and typically are uniform in size and occur as irregular clusters or as small nests distinct fiom the squamous cells of the epidermis; most tumours were uniform in size and cytological detail with only occasional very large or very small forms. cSCC: cells are larger though more varied in size and outline; nuclear chromatin shows irregular clumping, nucleoli are often very conspicuous, while some heavily keratinised cells retain a densely staining, pyknotic nucleus.	0	NR (n=NR) NR	0	H pl s o B c 5

Study author Outcomes reported	Study type	Inclusion criteria Exclusions	No. patients / lesions	Lesion_site	Stain technique	Cytopathological criteria	Uncertain cytological diagnoses	Observer qualifications (n) Test experience	Test failures	R F
Christensen (2008) BCC	NC CCS Norway	Histologically confirmed BCC or AK lesions Excluded: other diagnoses	64 / 78	H/N (56, 72%), trunk (15, 19%), extremities (7, 9%)	3 slides per lesion: Pap MGG Touch Imprint (not eval)	Fragments of closely packed cells presenting in monolayers or a club-like formations, demonstrating smooth external contours and peripheral palisading of nuclei. Little dissociation of cells. Malignant basal cells have small, oval, hyperchromatic nuclei. Extermely high nucleus to cytoplasmic ratio. AK lesions - greater cellular dissociation, individual and clumps of dysplastic keratinocytes, often with ragged edges. Polyhedral or spindle-shaped configuration. Moderately high nucleus to cytoplasmic ratio.		Pathologist (n=2) "Extensive experience in cytology, but no specific training in skin scrape cytology"	Pap – 1 MGG – 3	H bi B A
Derrick (1994) BCC	NC NR–CS UK	Lesion on the head or neck clinically suspected of being BCC Excluded: lesions on the trunk or extremities	240 / 240	H/N (%s NR)	MGG	Presence of tight groups of uniform small cells; pink amorphous material in MGG-stained preparations. Squamous cell lesions showed less cellular adhesion, much more nuclear pleomorphism and no pink material.		Consultant pathologist (NR) NR	0	H bi w hi di B c B T N

Study author Outcomes reported	Study type	Inclusion criteria Exclusions	No. patients / lesions	Lesion_site	Stain technique	Cytopathological criteria	Uncertain cytological diagnoses	Observer qualifications (n) Test experience	Test failures	R F
Gordon (1984) BCC cSCC Any	NC P–CS Australia	Cutaneous neoplasm requiring diagnostic biopsy or definitive excision at a routine clinic. Exclusions: suspected malignant melanomas or lesions that were 'too small' to allow both cytologic and histopathologic assessment	112 / 150	NR	Pap	BCC characteristics: cohesive epithelial fragments composed of tightly packed small cells with uniform, oval, dark nuclei. The nuclear chromatin is dense, but granular and evenly distributed; nucleoli are small and indistinct. Cytoplasm is scanty and cyanophilic. Usually, some fragments show the marginal palisading arrangement of tumor cells familiar to the histopathologist (Figs. I and 2). Squamous differentiation may be present within BCC (keratotic BCC and metatypical epithelioma). When this is prominent and associated with nuclear enlargement and pleomorphism, the cytologic differentiation between cSCC and pleomorphic BCC is difficult or impossible. Strong cohesiveness, uniformly high nuclear/cytoplasmic ratio, and evenly distributed nuclear chromatin favor a diagnosis of pleomorphic BCC (Fig. 3).	10 4 BCC 4 m-atypia 2 SK	Cytologist (1) NR	9 1 BCC 1 cSCC 7 benign	H e B c s A

Study author Outcomes reported	Study type	Inclusion criteria Exclusions	No. patients / lesions	Lesion_site	Stain technique	Cytopathological criteria	Uncertain cytological diagnoses	Observer qualifications (n) Test experience	Test failures	R F
Powell (2000) BCC	NC R–CS UK	All cytology smears taken over a 9–month period Excluded: no histological specimen available	30 / 37	NR	NR	Not described	0	NR (NR) NR	0	H
Ruocco	NC R–CS Italy	Patients with a suspected clinical diagnosis of BCC, for whom cytology and histology test results available. Exclusions: insufficient material for histology or cytology diagnosis, patient undergoing treatment (diathermal coagulation, cryotherapy, radiotherapy, local chemotherapy with 5–fluorouracile or interferon a–2b) or treated elsewhere.	NR / 578	NR	MGG and Pap or pure Giemsa	Characteristics suggestive of BCC: basaloid cells arranged in groups, clumped in the centre and at times arranged as 'fences/palisades' around the periphery (as found in histological specimens), slightly increased compared to normal epidermal basal keratinocytes, but in a single dimension, with an elongated shape, oval nucleus, intensely basophilic, occupying 4/5 of the entire cell with weak/thin cytoplasm, sometimes containing coarse melanin granules.	0	NR (NR) NR	Excluded at study entry	H o B c 5 C m vi 2 C B 1 T S p 8 h B k m c p p s s a c p n

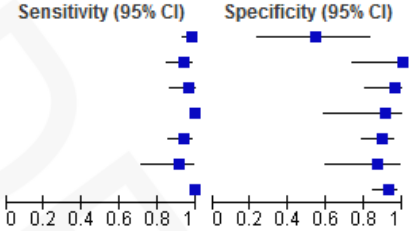
Study author Outcomes reported	Study type	Inclusion criteria Exclusions	No. patients / lesions	Lesion_site	Stain technique	Cytopathological criteria	Uncertain cytological diagnoses	Observer qualifications (n) Test experience	Test failures	R F
Durdu (2013) BCC MM alone Any	WPC P–CS Turkey	Pigmented skin lesions that could not be diagnosed with only dermatologic physical examination No exclusions reported	176 / 200	NR	MGG	Cytologic diagnoses were made according to findings reported previously: pigmented BCC: Clusters of basaloid cells containing pigment granules. Melanoma – Epithelioid or spindle-type atypical nevoid cells; pigmented mammary Paget's disease - Clusters of round to ovoid Paget cells; metastatic carcinoma - atypical (nonkeratinocytic and nonnevoid) cells; melanocytiv nevi - Epidermal and dermal-type nevoid cells; seborrhoeic keratosis - Horny cysts, pigmented keratinocytes; warts - Koilocytes; dermtofibroma - Spindle-shaped fibroblasts with collagenized stroma.	0	Dermatologist (n=1) single observer	15	H (e p B M 2 p m d p m c b n b n le

Footnotes: AC - Apocrine carcinoma; AK - actinic keratosis; BCC - basal cell carcinoma; ?BCC - possible basal cell carcinoma; BD - Bowens disease; CCS - case-control study; cSCC - cutnaeous squamous cell carcinoma; H/N - Head and neck; LED - disease type, acronym not provided by study; m-atypia - marked squamour atypia; MGG - May-Grünwald Giemsa stain technique; MM - invasive melanoma and atypical intraepidermal melanocytic variants; NC - non-comparative study design; NR - not reported; NR-CS - case series data collection method not reported; NS - not specified; Pap - Papanicolaou stain technique; P-CS - prospective case series; R-CS - restrospective case series; SK - seborrhoeic keratosis; WPC - within-person comparison study design.

Graphs

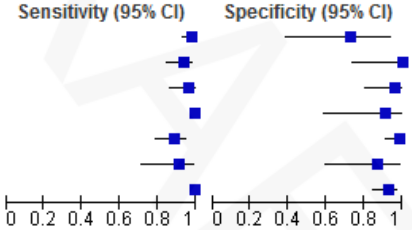
Exfoliative Cytology - BCC (possible BCCs classified as test positives)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berner 1999	94	5	2	6	0.98 [0.93, 1.00]	0.55 [0.23, 0.83]
Brown 1979	68	0	5	12	0.93 [0.85, 0.98]	1.00 [0.74, 1.00]
Christensen 2008	48	1	2	25	0.96 [0.86, 1.00]	0.96 [0.80, 1.00]
Derrick 1994	228	1	1	10	1.00 [0.98, 1.00]	0.91 [0.59, 1.00]
Gordon 1984	72	7	5	57	0.94 [0.85, 0.98]	0.89 [0.79, 0.95]
Powell 2000	20	2	2	13	0.91 [0.71, 0.99]	0.87 [0.60, 0.98]
Ruocco 1992	494	6	4	74	0.99 [0.98, 1.00]	0.93 [0.84, 0.97]



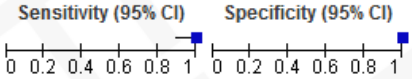
Exfoliative Cytology - BCC (possible BCCs classified as test negatives)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berner 1999	94	3	2	8	0.98 [0.93, 1.00]	0.73 [0.39, 0.94]
Brown 1979	68	0	5	12	0.93 [0.85, 0.98]	1.00 [0.74, 1.00]
Christensen 2008	48	1	2	25	0.96 [0.86, 1.00]	0.96 [0.80, 1.00]
Derrick 1994	228	1	1	10	1.00 [0.98, 1.00]	0.91 [0.59, 1.00]
Gordon 1984	68	1	9	63	0.88 [0.79, 0.95]	0.98 [0.92, 1.00]
Powell 2000	20	2	2	13	0.91 [0.71, 0.99]	0.87 [0.60, 0.98]
Ruocco 1992	494	6	4	74	0.99 [0.98, 1.00]	0.93 [0.84, 0.97]



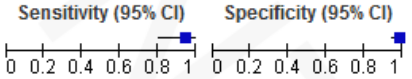
Exfoliative cytology - BCC (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Durdu 2011	34	0	0	151	1.00 [0.90, 1.00]	1.00 [0.98, 1.00]



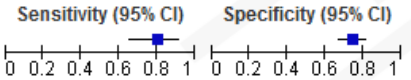
Dermoscopy - BCC (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Durdu 2011	32	3	2	163	0.94 [0.80, 0.99]	0.98 [0.95, 1.00]



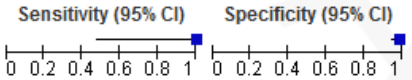
Exfoliative Cytology - BCC (Mixed population, Munchener diagnostic criteria)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nauth 1988	33	42	8	123	0.80 [0.65, 0.91]	0.75 [0.67, 0.81]



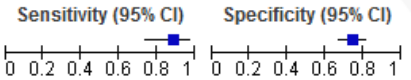
Exfoliative Cytology - cSCC (suspected BCC population)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gordon 1984	5	2	0	134	1.00 [0.48, 1.00]	0.99 [0.95, 1.00]



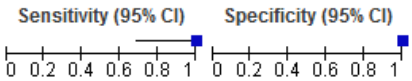
Exfoliative Cytology - cSCC (Mixed population, Munchener diagnostic criteria)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nauth 1988	32	43	4	127	0.89 [0.74, 0.97]	0.75 [0.67, 0.81]



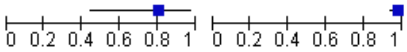
Exfolative cytology - melanoma (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Durdu 2011	10	0	0	175	1.00 [0.69, 1.00]	1.00 [0.98, 1.00]



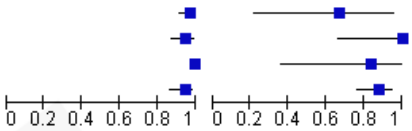
Dermoscopy - melanoma (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Durdu 2011	8	5	2	185	0.80 [0.44, 0.97]	0.97 [0.94, 0.99]		



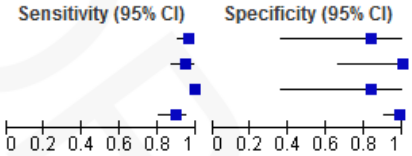
Exfoliative Cytology - any skin cancer (suspected BCC population, possible BCCs classified as test positives)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berner 1999	98	2	3	4	0.97 [0.92, 0.99]	0.67 [0.22, 0.96]		
Brown 1979	72	0	4	9	0.95 [0.87, 0.99]	1.00 [0.66, 1.00]		
Derrick 1994	233	1	1	5	1.00 [0.98, 1.00]	0.83 [0.36, 1.00]		
Gordon 1984	79	7	5	50	0.94 [0.87, 0.98]	0.88 [0.76, 0.95]		



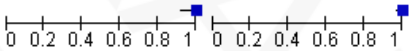
Exfoliative Cytology - any skin cancer (suspected BCC population, possible BCCs classified as test negatives)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berner 1999	97	1	4	5	0.96 [0.90, 0.99]	0.83 [0.36, 1.00]		
Brown 1979	72	0	4	9	0.95 [0.87, 0.99]	1.00 [0.66, 1.00]		
Derrick 1994	233	1	1	5	1.00 [0.98, 1.00]	0.83 [0.36, 1.00]		
Gordon 1984	75	1	9	56	0.89 [0.81, 0.95]	0.98 [0.91, 1.00]		



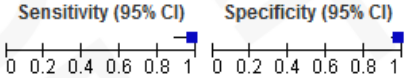
Exfoliative Cytology - any skin cancer (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Durdu 2011	46	0	0	139	1.00 [0.92, 1.00]	1.00 [0.97, 1.00]		



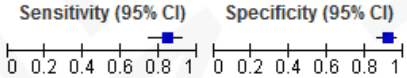
Dermoscopy - any skin cancer (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Durdu 2011	45	3	1	151	0.98 [0.88, 1.00]	0.98 [0.94, 1.00]		



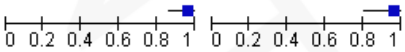
Exfoliative Cytology - any skin cancer (Mixed population, Munchener diagnostic criteria)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Nauth 1988	65	10	12	119	0.84 [0.74, 0.92]	0.92 [0.86, 0.96]		



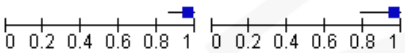
Exfolative Cytology (Papanicolaou + MGG stain) - BCC (stain comparison)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Christensen 2008	48	1	2	25	0.96 [0.86, 1.00]	0.96 [0.80, 1.00]		



Exfolative Cytology (MGG stain) - BCC (stain comparison)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Christensen 2008	47	1	2	23	0.96 [0.86, 1.00]	0.96 [0.79, 1.00]		



Exfolative Cytology (Papanicolaou stain) - BCC (stain comparison)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Christensen 2008	48	1	2	26	0.96 [0.86, 1.00]	0.96 [0.81, 1.00]