Screening tests for endometrial cancer in the general population

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[Diagnostic Test Accuracy Protocol]

Screening tests for endometrial cancer in the general population

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (diagnostic). The objectives are as follows:

To assess the diagnostic accuracy of potential screening tests for the detection of atypical hyperplasia (pre-cancer) and endometrial cancer of all stages and grades in asymptomatic (healthy) women in the general population.

Secondary objectives

- To determine the optimal endometrial thickness cut-off value using transvaginal ultrasound scan for the screening of asymptomatic women for endometrial cancer and atypical hyperplasia.
- To investigate sources of heterogeneity in endometrial cancer screening studies, including:
 - * characteristics of the studied population including age, menopausal status (pre- and postmenopausal), country of study and risk status (body mass index (BMI) categories, diabetes mellitus, polycystic ovary syndrome (PCOS));
 - * characteristics of index test such as cytological classification used and sampling device;
 - * methodological quality (low risk of bias compared to high risk of bias);
 - * disease factors (endometrioid versus non-endometrioid, low grade versus high grade).

BACKGROUND

Target condition being diagnosed

Endometrial cancer, also known as uterine or womb cancer, is a type of cancer that originates in the inner lining of the womb (the endometrium) and is mostly a disease of postmenopausal women. Globally, there were an estimated 380,000 incident cases in 2018 and about 89,000 died from their disease, making endometrial cancer the sixth most common female cancer, and the 14th leading cause of death from cancer in women (Bray 2018; Lortet-Tieulent 2018). Its incidence is projected to rise in the coming years in parallel with the growing prevalence of obesity (Crosbie 2014). Declining rates of hysterectomy for benign womb conditions and an ageing population also contribute to the rising trends (Morice 2016; Temkin 2016).

Approximately two-thirds of women with endometrial cancer reside in the developed world, especially in countries with a high human development index (Lortet-Tieulent 2018). Most endometrial cancers are sporadic, with only about 5% occurring in the context of an inherited predisposing condition, such as Lynch syndrome (Ryan 2019; Sundar 2017). Diabetes mellitus, hypertension, polycystic ovary syndrome, use of tamoxifen and oestrogen-only hormone replacement therapy are other important risk factors (Njoku 2019).

There are various histological subtypes of endometrial cancer that differ in incidence, clinical presentations, prognoses and associated risk factors. These include endometrioid endometrial cancer, serous endometrial cancer, clear cell endometrial cancer and uterine carcinosarcoma (Colombo 2016). Whilst the majority of the endometrioid cancers are low grade, and in general have a good prognosis, a significant minority are high grade (aggressive-looking and faster-growing) and are associated with poorer outcomes (Brinton 2013). The non-endometrioid cancers, on the other hand, are mostly high grade and are often diagnosed at an advanced stage (Brooks 2019; Suarez 2017). There is emerging evidence to suggest that the growing incidence of endometrial cancer in several Western countries is due to an upward trend in the diagnosis of the clinically aggressive, non-endometrioid endometrial cancers (Clarke 2019; Faber 2017; Urick 2019). Screening tests that are able to detect all endometrial cancers at an early stage, especially the non-endometrioid tumours, are likely to improve survival outcomes.

The processes underlying endometrial cancer development are dependent on the histological subtype (Figure 1; Brinton 2013). Endometrioid tumours, for instance, result from the unopposed stimulation of the epithelial lining of the womb by the female sex hormone, oestrogen, which results in hyperplasia without atypia (i.e. individual cells still look relatively normal, although there is an overgrowth of cells), with the potential to evolve into atypical hyperplasia (where individual cells look more abnormal), an endometrial cancer precursor lesion, and ultimately endometrial cancer (Setiawan 2013). There is substantial histopathological overlap between severe atypical hyperplasia and low-grade endometrial cancer, making a diagnostic distinction between the two difficult and unnecessary in the context of screening. A particular gene fault, phosphatase and tensin homologue (PTEN) mutation, is the most frequent genetic abnormality in endometrioid endometrial cancer and occurs early in its development (Figure 1; Cancer Genome Atlas Research Network 2013; Levine 1998). It may thus be a potential target for endometrial cancer screening, although studies have shown that it is insufficient on its own to initiate tumour formation (Mutter 2000). Non-endometrioid endometrial cancers, on the other hand, are oestrogen-independent. Serous endometrial cancer, for instance, commonly develops on the surface of an endometrial polyp on a background of an atrophic endometrium (El-Sahwi 2012; Lax 2000). Although serous tumours are frequently diagnosed at an advanced stage, p53 gene faults have been suggested to occur early in serous tumour development (Figure 1). This raises the possibility that p53 gene faults may be targets for early detection of serous tumours (Sherman 1995). Uterine carcinosarcomas and clear cell endometrial cancers are other aggressive non-endometrioid types of endometrial cancer (Cherniack 2017; Le 2017). Whilst the underlying gene faults of carcinosarcoma closely resemble those of serous endometrial tumours, clear cell tumours share similar genetic abnormalities with endometrioid endometrial cancer (Cherniack 2017; Le 2017; Urick 2019). Recently, a classification by the Cancer Genome Atlas (TCGA) Research Network categorised endometrial cancer into four groups based on specific gene faults: polymerase epsilon (POLE) ultramutated, microsatellite instability (MSI) hypermutated, copy number low tumours and copy number high tumours (Cancer Genome Atlas Research Network 2013). This classification has been shown to predict outcomes for women with endometrial cancer (Stelloo 2015; Talhouk 2017).

Figure 1. Endometrial cancer development pathways and associated gene faults

Postmenopausal bleeding (PMB) is the most frequent symptom of endometrial cancer. It is, however, a non-specific marker of the disease. Although 90% of women with endometrial cancer initially present with PMB, only 5% to 10% of women with PMB are diagnosed with endometrial cancer (Clarke 2018; Gredmark 1995). Irregular or heavy pre- or perimenopausal bleeding, haematuria, abnormal vaginal discharge, abdominal distension, pelvic pain and weight loss are other important but less common symptoms (Braun 2016). It is not unusual for asymptomatic women to be diagnosed with endometrial cancer. As an example, endometrial

cancer may be diagnosed following presentation with abnormal findings on routine cervical screening (Wright 2007) or following evaluation for an incidental thickening of the womb lining found on ultrasound or magnetic resonance imaging (MRI) performed for other reasons (Arora 2012). Endometrial cancer may also be discovered incidentally following a hysterectomy performed for benign womb disease.

Treatment of endometrial cancer is usually surgical and involves the removal of the womb, cervix, both fallopian tubes and

ovaries. This may, in some women, be followed by chemotherapy, radiotherapy, or both, particularly in those who are deemed as high-risk for recurrence, based on the type and stage of their cancer (Colombo 2016). Hormonal treatments may be offered to young women with early stage disease (FIGO stages I and II) (Appendix 1), who wish to preserve their fertility, and to severely obese women, in whom surgery may be high risk. For those diagnosed with advanced disease (FIGO stages III and IV), there are no effective curative options and palliative chemotherapy is the mainstay of treatment. The use of chemotherapy, however, is not without considerable side effects, many of which impact quality of life (QoL). There is also the possibility of the cancer progressing, leading to poor survival outcomes (Sundar 2017). Women of child-bearing age with endometrial cancer face a dilemma when making treatment choices, as hysterectomy prevents future fertility, and alternative options, such as hormonal manipulations, are not as effective and risk cancer progression (Gallos 2012).

Survival from endometrial cancer depends on the stage at diagnosis, with age-adjusted five-year survival estimates averaging over 90% in early stage disease and less than 20% in advanced disease (CRUK 2019). By enabling the early detection of atypical hyperplasia (primary prevention) and early stage endometrial cancer (secondary prevention), an effective screening test will dramatically improve outcomes, as disease can be picked up at the earliest possible opportunity, when treatment is able to effect a cure. Early detection of the clinically aggressive non-endometrioid endometrial cancer will particularly improve outcomes for those diagnosed with this potentially fatal disease (Sundar 2017). There are, however, a number of harms that may result from screening for endometrial cancer that relate mostly to false positive and false negative results. False positive screening test results can lead to extreme anxiety and worry. In addition, women with these test results may be offered invasive diagnostic tests and treatments that are unnecessary, subjecting them to the associated risks of these procedures. False negative screening test results, on the other hand, will reassure women that they do not have endometrial cancer, when in fact they do. Such women may present much later, with more advanced disease, leading to a poorer survival outcome. There is also the concern of over diagnosis, where screening detects slow-growing 'harmless' cancers that would, under normal circumstances, pose little or no threat to a woman's health. The potential benefits of screening must therefore be weighed against the risks and harms that may result (Woolf 2012).

A glossary of commonly used terms is summarised in Appendix 2.

Index test(s)

An ideal endometrial cancer screening test should be easy to perform and interpret, reliable and accurate, with few false positives and false negatives. There are several potential screening tools (Table 1) that vary in the level of their supporting evidence in terms of accuracy, acceptability and test-related burden.

Transvaginal ultrasound

A transvaginal ultrasound scan (TVUSS) is presently the primary imaging test for the initial evaluation of symptomatic women. The diagnostic utility of TVUSS is based on the measurement of the endometrial thickness (ET), a known non-specific marker of endometrial cancer risk (Fleischer 2001; Sundar 2017). Measurement of ET is usually done by scanning the womb in

a sagittal (longitudinal) view and reported as a double-layer thickness, measured in an anteroposterior dimension from one basal layer (deeper layer of the womb lining) to the other with the exclusion of any fluid within the womb (Van den 2012). Measurement of ET using TVUSS is minimally invasive, precise and is useful when the womb lining is uniform. In the presence of localised growths within the womb, a biopsy is usually required (Timmermans 2010). Based on an ovarian cancer screening trial where postmenopausal women underwent between seven and 11 annual screens, there is evidence to suggest that TVUSS based screening causes little discomfort or pain, and is thus likely to be acceptable as a screening tool for endometrial cancer (Jacobs 2011). In some women, however, such as those with an atrophic vagina, vaginismus or a previous sexual assault, the procedure can be traumatic and painful. The use of ET measurement for screening has a number of limitations, the most important of which is its low specificity, as multiple benign conditions including polyps, blood clots or even artefacts can create the appearance of a thickened endometrium (Smith-Bindman 1998). Due to its suboptimal specificity, symptomatic women with thickened endometria are offered further invasive tests in order to establish a diagnosis. The British Gynaecological Cancer Society (BGCS) recommends that every ET measurement on TVUSS of 4 mm or more should be investigated further. In the absence of any irregularity with and an ET of less than 4 mm, no further investigations are necessary, except in cases of recurrent PMB (Sundar 2017). ET measurement is less useful for the detection of non-endometrioid endometrial cancer, as these are commonly associated with an atrophied endometrium (Gentry-Maharaj 2020). Sometimes, the endometrium may not be visualised due to distortion of the womb cavity, commonly caused by fibroids within the womb. In premenopausal women, the use of TVUSS for endometrial cancer detection is limited by the cyclical fluctuations in ET. Use of hormone replacement therapy (HRT) and tamoxifen can also influence the optimal ET cut-off value (Colombo 2016). Other factors that preclude the utility of ET measurement for endometrial cancer screening include previous uterine surgery, presence of a uterine mass and obesity (ACOG 2018).

Cervical cytology

There is interest in the potential of the cervical cytology (smear test), established as a screening test for cervical cancer, to also serve as a screening tool for endometrial cancer (Frias-Gomez 2020). Cytology involves looking at individual cells for evidence of a disease (cancer). As far back as 1981, studies have explored the potential of the smear test to detect endometrial cancer in an asymptomatic population (Koss 1981). A feasibility study of 1280 asymptomatic women aged 45 years and above, who were evaluated by several smear tests, detected eight cases of endometrial cancer and 25 cases of atypical hyperplasia (Koss 1981). The conventional smear test has been reported to have a sensitivity of 40% to 55% for endometrial cancer detection and 60% to 84%, if liquid-based preparations are used (Frias-Gomez 2020; Gu 2001; Guidos 2000; Kurokawa 2014; Schorge 2002). A few proof-of-concept studies have shown that the performance of cytology for endometrial cancer screening may be improved when combined with technologies that can identify specific gene faults (genomics or epi-genomic technologies). In the study by Kinde 2013, endometrial cancer-associated gene faults were detected in all smear samples of women with endometrial cancer. In another study where the Pap test (cervical smear) was used alongside PapSEEK, a new test that can identify gene faults in DNA obtained from body fluids, a

sensitivity of around 80% was reported (Wang 2018). The use of Pap smear for gynaecological screening is generally acceptable to women. In England and Wales, however, only seven in 10 women attend cervical screening, with barriers to attendance that include individual barriers (e.g. fear, embarrassment, lack of transport or childcare), cultural barriers (e.g. stigma associated with a disease related to sexual activity), and societal barriers (e.g. lack of access to healthcare providers and resources for screening) (Bennett 2018).

Endometrial cytology

Endometrial cytology is an endometrial cancer screening strategy in Japan that started in 1987 as a national health project (Fujiwara 2012). This 'selective screening' focuses on women aged 50 years and over, who are postmenopausal, and women with abnormal vaginal bleeding (Sato 1998). Several studies have explored the effectiveness of this approach for endometrial cancer detection (Bistoletti 1988; Byrne 1990; Fujiwara 2012; Fujiwara 2015; LaPolla 1990; Sato 1998; Yoshida 2001). In the study by Fujiwara and colleagues, endometrial cytology had a high sensitivity for detecting advanced stage and non-endometrioid endometrial cancer, but at the risk of potentially misdiagnosing early stage disease (Fujiwara 2012; Fujiwara 2015). In Japan, a higher five-year survival rate has been reported for women diagnosed through the screening pathway, compared to those diagnosed in the outpatient clinics via the usual clinical pathway (Nakagawa-Okamura 2002). Although endometrial cytology has been used in a wide variety of populations, from asymptomatic women to high-risk groups, its accuracy for endometrial cancer detection is still unclear, particularly when used for population-level screening (Tajima 1998).

Potential screening tests based on minimally invasive sampling

There is emerging evidence to suggest that endometrial cancer may be diagnosed from urogenital specimens obtained using minimally invasive sampling methodologies and that these may hold potential as screening tests for endometrial cancer. Uterine lavage, for example, may be an effective sampling method in which to detect genetic faults observed in endometrial cancer. A PTEN mutation was detected in the uterine lavage fluid of an asymptomatic postmenopausal woman with no clinical or pathologic evidence of endometrial cancer, 10 months prior to its clinical detection (Martignetti 2017). In the study by Nair 2016, there were endometrial cancer-associated gene faults in the lavage specimens of all women with cancer and in a significant proportion of women who did not have cancer, suggesting that they may represent signs of pre-cancer in those women (Nair 2016). This study was, however, based on a symptomatic population. Multiple studies have explored the potential of cervicovaginal secretions (Calis 2015; Finan 2012); endocervical swabs (Heng 2016; Lai 2016; Lim 2018); cervical scrapings, vaginal swabs/tampons (Bakkum-Gamez 2015; Fiegl 2004); blood-based markers such as proteins (Diefenbach 2007; Moore 2008; Njoku 2019a; Tarney 2019); and metabolites (Audet-Delage 2018; Ihata 2014; Knific 2018; Njoku 2020a), as well as urine tests for the detection of endometrial cancer in symptomatic women (Njoku 2020b; Shao 2016; Srivastava 2018). It remains unclear whether these approaches are effective for endometrial cancer detection in the general population.

Imaging tests

Imaging using computed tomography (CT) and MRI scans are other potential screening tests for endometrial cancer. Franconeri and colleagues assessed the utility of ET on sagittal post-contrast CT and report that an ET of 8 mm or greater in asymptomatic postmenopausal women had 86% sensitivity and 91% specificity for the opportunistic detection of endometrial cancer (Franconeri 2019). The use of CT scans for screening is, however, not without risks, including the risk of an increase in cancers caused by X-ray exposure. CT scan is also not sensitive enough to accurately measure ET or detect endometrial cancer. MRI scans, on the other hand, are able to differentiate between benign and malignant causes of post-menopausal bleeding in women, with a sensitivity of up to 96% (Takeuchi 2009). MRI scans are non-invasive and unlike CT scans, do not involve radiation. Their utility is, however, limited by high equipment and examination costs.

Hysteroscopy

Hysteroscopy (camera test) is another potential test, and it refers to the endoscopic examination of the womb cavity with a very fine telescope. By allowing for a direct visualization of the womb, hysteroscopy enables targeted biopsy or removal of abnormalities identified during the procedure (Tahir 1999). The increased training of physicians, availability of smaller diameter hysteroscopes and increased emphasis on vaginoscopic outpatient-based procedures have led to the widespread usage of this technology. This diagnostic modality offers the potential of combining investigation with treatment and also avoids the risk of missing a focal pathology, as may occur with the blind Pipelle biopsy. However, hysteroscopy is invasive and often plagued by several operative challenges. In the outpatient setting, severe pain, cervical stenosis and suboptimal visualization are the most frequent reasons for abandonment (Jansen 2000; Tahir 1999). In our scoping search, we did not identify any studies where hysteroscopy was used as a screening test for endometrial cancer in the general population.

Clinical pathway

There are currently no established programmes for population-level screening of endometrial cancer. Neither the American Cancer Society (ACS) nor the BGCS recommend routine screening of asymptomatic women who are at an average risk for endometrial cancer or are at increased risk due to a history of nulliparity, infertility, unopposed oestrogen replacement therapy, tamoxifen therapy or late menopause (Smith 2019; Smith 2005; Sundar 2017). Both societies recommend that such women should be counselled at menopause on the risks and symptoms of endometrial cancer, so that they can in turn alert their general practitioners, should symptoms occur. Although not evidence-based, screening is commonly offered to women at a significantly increased risk of endometrial cancer, such as those who harbour gene faults associated with Lynch syndrome, and those with a strong family history of endometrial cancer. Screening is also offered to those with a suspected autosomal predisposition to colon cancer in the absence of genetic testing (Crosbie 2019; Smith 2019; Sundar 2017).

The clinical pathway for symptomatic women is more defined and evidence-based, although there is currently no international consensus on the order of investigations. When symptomatic with PMB, women in the UK first undergo TVUSS. Depending on their endometrial thickness, a large proportion of women are offered

further invasive testing, with endometrial biopsy and/or outpatient hysteroscopy, for a definitive diagnosis ([Cooper 2014](#)).

Prior test(s)

Women may have had a clinical assessment (history and clinical examination) prior to testing with the index test. While those undergoing TVUSS may not have had any other prior test, those undergoing cervical or endometrial cytology may have had TVUSS prior to testing, depending on what point in the screening pathway the index test is being evaluated.

Role of index test(s)

The index tests to be investigated in this review will be used in clinical practice to triage asymptomatic women for further testing with a more definitive test.

Alternative test(s)

Given that this review is appraising all potential screening tests for endometrial cancer, there are no alternative tests to report.

Rationale

Early detection, through screening for pre-malignant and early stage endometrial cancer, is crucial for an improved disease-free survival (DFS) and overall survival (OS). It would enable conservative management options to be available to women still wishing to preserve their fertility and for morbidly obese women in whom surgery may be potentially hazardous. However, there is insufficient evidence at present to recommend screening in the general population, due to lack of robust and acceptable diagnostic accuracy estimates of the available potential screening tools. Among the most important research priorities identified by patients, the public and healthcare professionals for the UK-led James Lind Alliance Detecting Cancer Early Priority Setting Partnership (JLA-PSP), the question of developing screening tests for cancers not currently screened for was ranked within the top 10 ([Badrick 2019](#)). Findings from this review could therefore inform future research proposals.

This Cochrane Review will appraise all population-level screening tests for endometrial cancer in order to identify the most accurate test or tests available. Findings from this review will provide policymakers, clinicians and, importantly, women with the much-needed balanced and robust evidence to guide interpretation of potential endometrial cancer screening test results. It will also inform the decision to implement screening programmes for endometrial cancer at a population level. This review will be carried out with a global perspective as some screening tests have been mainly explored in certain regions of the world. High-risk groups, such as those with Lynch syndrome, will be excluded from this review, as the index tests and test thresholds for this group are different from those of the general population. For example, transvaginal ultrasound screening for endometrial cancer in Lynch syndrome is not useful, because screening is focused on premenopausal women, in whom cyclical fluctuation of endometrial thickness is normal and does not indicate pathology; whereas in postmenopausal women of the general population, transvaginal ultrasound scanning may accurately discriminate benign from malignant disease.

OBJECTIVES

To assess the diagnostic accuracy of potential screening tests for the detection of atypical hyperplasia (pre-cancer) and endometrial cancer of all stages and grades in asymptomatic (healthy) women in the general population.

Secondary objectives

- To determine the optimal endometrial thickness cut-off value using transvaginal ultrasound scan for the screening of asymptomatic women for endometrial cancer and atypical hyperplasia.
- To investigate sources of heterogeneity in endometrial cancer screening studies, including:
 - * characteristics of the studied population including age, menopausal status (pre- and postmenopausal), country of study and risk status (body mass index (BMI) categories, diabetes mellitus, polycystic ovary syndrome (PCOS));
 - * characteristics of index test such as cytological classification used and sampling device;
 - * methodological quality (low risk of bias compared to high risk of bias);
 - * disease factors (endometrioid versus non-endometrioid, low grade versus high grade).

METHODS

Criteria for considering studies for this review

Types of studies

We will include all cross-sectional and comparative diagnostic accuracy studies in which asymptomatic women received one or more of any of the index screening tests, in addition to the reference standard. We will exclude diagnostic case-control studies, as they are known to overestimate performance in diagnostic test accuracy reviews ([Deeks 2005](#)). However, there will be no limitation on the number of participants in the included studies. We will include studies published as full article papers, and where studies are available only in an abstract form, we will contact the authors for the full data. Where the authors are unable to provide full data needed for analysis, we will analyse the studies narratively but will exclude them from subsequent meta-analyses (see [Appendix 3](#)).

Participants

We will focus on studies carried out on an asymptomatic (healthy) population of women. There will be no restriction based on age or menopausal status. We will, however, collect data on menopausal status and the proportion of women aged 45 years or over in the studied populations. We will exclude studies focused on high-risk women such as those with Lynch syndrome or a family history of Lynch syndrome or endometrial cancer as well as studies done on a symptomatic population. We will also exclude studies where women have previously had surgery to remove their wombs (hysterectomy).

Index tests

The index tests include TVUSS, cervical and endometrial cytology and molecular and genetic tests using novel minimally invasive sampling methodologies as described above. For cervical and endometrial cytology, abnormal cells of uncertain significance or

worse will be used as diagnostic threshold as per the Bethesda system (Nayar 2014). Where a different cytological classification is used, such as the British Society for Clinical Cytology (BSCC) (Denton 2008) or the Munich Cytological classification (Griesser 2013), they will be re-classified using their equivalents in the Bethesda system (Nayar 2014) (see Appendix 4).

Target conditions

The target condition is endometrial cancer of all grades and stages and will be defined histologically by the invasion of malignant endometrial cells beyond the endometrium. The secondary target condition is atypical endometrial hyperplasia, an endometrioid endometrial cancer precursor lesion, defined by WHO recommendations 2014, as "hyperplasia with evidence of cytological atypia" (Emons 2015). We will assess whether these definitions were applied in each included study. Where a different definition such as the WHO 1994 classification is used, we will state explicitly which criteria were used.

Reference standards

The reference standard is histological confirmation of endometrial cancer based on either endometrial biopsy, hysterectomy or dilatation and curettage specimens. For studies where participants with a negative index test do not go on to have a tissue diagnosis, we will use follow-up information for at least one year as reference standard. The use of different reference standards, although likely to impact on the validity of study findings, is consistent with current clinical practice. We will, however, perform a sub-group analysis based on the reference standard used.

Search methods for identification of studies

We have developed a comprehensive search strategy in collaboration with the information specialist of the Gynaecological, Neuro-oncology and Orphan Cancers group (see Appendix 5). We will search the literature using key words from the study titles, abstracts, text words and indexing terms. There will be no search limitation based on language or date of publication. We will have articles written in languages other than English translated by native speakers.

Electronic searches

We will search the following electronic databases:

- MEDLINE via Ovid (1946 to current date) (Appendix 5);
- Embase via Ovid (1980 to current date);
- BIOSIS Citation Index (1996 to current date);

We will also conduct a PubMed search in order to identify recent trials not indexed by MEDLINE, and Web of Science for relevant conference abstracts.

We will search the following review databases in order to identify relevant systematic reviews based on the primary studies to be included in our review.

- PROSPERO
- ARIF
- HTA
- DARE

Databases of the following trial registers will be searched to identify on-going trials.

- ClinicalTrials.gov at the US National Institutes of Health (NIH)
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP)

Searching other resources

We will handsearch reference lists of all relevant publications for additional studies or trials and will also review the grey literature and conference proceedings. We will also check the lists of included studies of relevant systematic reviews identified. Where needed, we will contact the principal investigators of relevant studies, in order to clarify aspects of the methods or results that are unclear, or to ask for unpublished/missing data where indicated.

Data collection and analysis

Selection of studies

Four review authors (KN, HOF, EJ and NR) working independently and in duplicate will assess whether the titles and abstracts of the search results are eligible for further reading based on the review's inclusion criteria. We will obtain full-text publications of all potentially relevant references. Following this, studies meeting the inclusion criteria will be included in the review. We will resolve any disagreement between review authors by discussion in a consensus meeting, or, if required, we will consult a third review author (EJC). Where necessary, we will contact study authors to confirm inclusion eligibility, to provide data required for the development of 2 x 2 tables or to provide further information needed for risk of bias assessment. We will record all excluded studies in a 'Characteristics of excluded studies' table with reasons for exclusion clearly stated. Studies to be included in meta-analysis must have sufficient data to enable development of a 2 x 2 contingency table.

Data extraction and management

Four review authors (KN, HOF, EJ and NR) will independently and in duplicate extract relevant study characteristics onto a pre-piloted data collection form (Appendix 6). The data to be extracted for each index test include: true positives (TP) (i.e. the number of women with a positive index test and endometrial cancer detected using the reference standard); true negatives (TN) (i.e. the number of women with a negative index test result with no endometrial cancer based on the reference standard (biopsy or follow-up data)); false positives (FP) (i.e. the number of women with a positive index test result but no endometrial cancer detected with the reference standard); and false negatives (FN) (i.e. the number of women with a negative index test result but with endometrial cancer based on the reference standard). Where these data are not clearly stated in the articles, we will reconstruct them based on the frequencies reported in the articles. We will merge the extracted data into a 2 x 2 table that contains the TP, FP, FN, TN, enter these data into RevMan 5 (Review Manager 2020) and use them to calculate and meta-analyse the sensitivity and specificity measures. We will design a Microsoft Excel (Microsoft Excel 2018) data extraction form to aid extraction and will pilot-test it before finalising it for use..

Assessment of methodological quality

We developed a tailored Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool (Whiting 2011) and we summarise it in

Table 2. We will use this tool to assess the methodological quality of included studies and we will pilot-test it prior to use ([Appendix 7](#)).

Four review authors (KN, EJ, HOF and NR) working independently and in duplicate will assess included studies for methodological quality. We will resolve disagreements by consulting a third review author (EJC). We will assess each study for risk of bias and applicability based on the four domains of QUADAS-2 tool: participant selection, index tests, reference standard, and participant flow. We will present a summary of results of the QUADAS-2 assessments of all included studies and summarise the number of studies judged to have low, high or unclear risk of bias/concerns regarding applicability for each domain. However, we will not generate a summary quality score, because of the well-documented problems with this approach ([Deeks 2009](#)).

Statistical analysis and data synthesis

We will present an overview of all included studies in a 'Characteristics of included studies' table that includes study design, country of study, test characteristics and study findings. We will calculate estimates of diagnostic accuracy for each study and express the results as sensitivity and specificity with their 95% confidence intervals. We will display study-specific estimates as coupled forest plots and plot a receiver operating characteristic (ROC) curve per index test. We will use the hierarchical (mixed) models comprising both the bivariate model and the hierarchical summary ROC (HSROC) model for data synthesis ([Harbord 2007](#); [Reitsma 2005](#)). The HSROC analysis would be necessary where we have a diagnostic tool that provides a result on a continuous scale, where the cut-off point varies between studies. Otherwise, we would apply the bivariate model. For bivariate analysis, we would use the R package lme4 and for HSROC, the MetaDAS package in SAS. We will conduct a meta-analysis focused on the primary outcome measures of sensitivity and specificity where there are sufficient studies (two or more) with similar outcome measures per index test. Where there is a common threshold for a given index test across studies, we will present a summary operating point (using the bivariate model) with confidence and prediction regions on the ROC space and 95% confidence regions. On the other hand, where there are sufficient number of studies analysing different thresholds, as may be expected in the use of endometrial thickness, we will present a summary ROC curve, using the Rutter and Gatsonis HSROC model ([Rutter 2001](#)). Where there is heterogeneity in the couple forest plots and there are fewer than four studies, we will not pool data. Comparative accuracy analysis of similar index tests will be presented as a summary ROC curve (shape and relative position) and/or using summary estimates of sensitivity and specificity. We will undertake a separate analysis restricted to those studies that make direct comparisons between tests. Within-study (direct) comparisons will be annotated to distinguish them from between-study (indirect) comparisons. Where possible, we will aim to identify the optimal endometrial thickness threshold for screening by performing a separate meta-analysis of data at each threshold, or for groups with similar thresholds ([Jones 2019](#)). For cytology, a binary threshold (presence/absence) will be used, with disease presence defined by results of 'uncertain significance or severe' using the Bethesda classification system, or conversion to this classification. We will appraise the choice of the models once we have insight into the data from included studies.

Where there are missing data, we will in the first instance contact the study investigators to request the missing data. Where the data

are still missing, and if they are deemed to be missing at random, we will only analyse the available data (i.e. we will ignore the missing data). However, where data are not missing at random, we will impute the missing data, with predicted values from regression analyses. We will perform a sensitivity analysis to assess how sensitive our results are to the changes in assumptions made, while the potential impact of 'missingness on the study findings will be highlighted in the discussion section. We will use [Review Manager 2020](#), [R 2017](#), [SAS 2020](#) and [Stata 2019](#) for all analyses.

Investigations of heterogeneity

Where there are sufficient studies, we will formally assess heterogeneity by meta-regression analyses. Covariates will be tested by their inclusion as cofactors in the bivariate model, or their sequential addition to the HSROC model, in order to assess the degree of heterogeneity in test positivity (threshold), accuracy (position of the curve) and shape of the curve. We will use the likelihood ratio tests to assess the statistical significance of including variables in the models.

We will investigate the following sources of heterogeneity for each index test.

1. Population and study characteristics

- Age limits
- Menopausal status
- Ethnicity/country of study
- Risk status e.g. BMI categories, diabetic mellitus and PCOS where feasible
- Study date

2. Index characteristics

- Cytological classification system
- Urogenital sampling site (for novel molecular tests: uterine versus cervical versus vaginal)
- Sampling device (Pipelle, Tao brush, Endoflower device, SAP-1 brush, Utero brush etc.)

3. Disease characteristics

- Histological subtype/tumour grade
- FIGO stage

Where there is evidence of a substantial amount of heterogeneity, we will report this in the 'Summary of findings' tables.

Sensitivity analyses

Where there are sufficient number of studies investigating the same index test, we will conduct the following sensitivity analyses to assess the effect on summary estimates of restricting the analyses according to the following criteria.

- Studies where a low risk of bias exists for the index test
- Studies where a low risk of bias exists for the reference standard
- Studies classed as low risk on all four domains of the QUADAS-2 tool ([Whiting 2011](#))

We will also conduct a sensitivity analysis based on age (45 years or over), menopausal status (pre-menopausal versus post-menopausal), publication status of included studies, reference

standard used, and disease type (atypical hyperplasia versus endometrial cancer).

Assessment of reporting bias

We will not formally assess for publication bias due to the high possibility of misleading results (Deeks 2005). We will, however, try to minimise the risk of publication bias by using a robust and comprehensive search strategy, covering all possible sources, including searches of the grey literature and registries of published and unpublished studies.

Summary of findings for assessing the certainty of the evidence

We will develop a 'Summary of findings' table for each index test, in line with the GRADE methods (Appendix 8) (Schünemann 2013; Hsu 2011) and with the aid of the GRADEPro GDT online tool (GRADEproGDT 2020). We will present test accuracy results in natural frequencies indicating true and false positives and negatives. We will appraise the body of research evidence for screening based on an assessment of the overall risk of bias of included studies, level of consistency of study results, precision of estimates, presence of publication bias and level of directness of evidence. For each of the main accuracy measures, we will categorise the overall body of evidence as high-certainty evidence, moderate-certainty evidence, low-certainty evidence or very low-certainty evidence.

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ADDITIONAL TABLES

Table 1. Index tests for endometrial cancer screening in the general population

Tests	Characteristics	Use in current clinical pathway	Other information
Transvaginal ultrasound scan (TVUSS)	Insertion of a specially designed ultrasound probe into the vagina and subsequent measurement of the endometrial thickness (ET).	<p>Currently used as the initial diagnostic test in symptomatic women.</p> <p>It is used to triage women for definitive testing based on the ET.</p> <p>In the UK, women with an ET ≥ 4 mm are referred for further invasive testing.</p> <p>Potential to serve a similar role in the screening of the general population.</p>	<p>Advantages</p> <p>Minimally invasive</p> <p>Safe, causes little discomfort or pain</p> <p>Useful when the womb lining is uniform</p> <p>Real time diagnostic test</p> <p>Disadvantages</p> <p>Non-definitive</p> <p>A thick endometrium may not be endometrial cancer</p> <p>Sometimes, the endometrium cannot be visualised due to cavity distortion or a stretched uterine position</p> <p>Operator-dependent</p>
Cervical cytology (smear test)	Involves taking samples from the cervix with the aid of a brush or scraping device for cytological analysis.	<p>Historically used as a screening test for cervical cancer.</p> <p>The finding of atypical (abnormal) endometrial cells usually warrants further investigation for endometrial cancer.</p> <p>Has potential to serve as a screening test for endometrial cancer.</p>	<p>Advantages</p> <p>Widely acceptable to women</p> <p>Simple and minimally invasive</p> <p>Inexpensive</p> <p>Disadvantages</p> <p>Intimate procedure</p> <p>Discomfort from speculum examination</p> <p>Contact bleeding</p> <p>Does not involve direct sampling of the endometrium, hence may miss endometrial cancer</p> <p>Dependent on experience of the cytologist which may vary widely.</p>

Table 1. Index tests for endometrial cancer screening in the general population (Continued)

Endometrial cytology	Cytology of cells obtained from the womb lining using a brush, lavage or suction technique. Sampling devices may include EndPap, Endocyte, Endoflower device, Tao brush, Utero brush, SAP-1 brush etc.	Currently used in Japan to screen post-menopausal women aged 50 years and over, and women presenting with abnormal vaginal bleeding. Not in clinical use in most Western countries.	Advantages Involves a direct sampling of the endometrium Potential for targeted sampling when used alongside hysteroscopy. Potential for histological examination of obtained samples. Disadvantages Relatively invasive Pain and discomfort. May miss focal pathologies if done blindly. Risk of infection, bleeding and perforation. Less useful in women with cervical stenosis (due to high-risk of insertion failure)
Imaging	Use of imaging tests such as computed tomography (CT) or magnetic resonance imaging (MRI) scans to take pictures of the inside of the womb to detect endometrial cancer.	Not routinely used in the current endometrial cancer diagnostic pathway. MRI or CT scan of the abdomen and pelvis is often used to plan treatment. It is recommended that women with endometrial cancer that has potentially spread outside the womb should have CT of the chest, abdomen and pelvis to plan for surgery or prevent upfront surgery if evidence of spread is found.	Advantages CT and MRI are painless and non-invasive. MRI scans are safe and do not expose women to X-ray radiation. Disadvantages CT scans can induce cancer from X-ray exposure. MRI scans are expensive Women with metal fragments can not undergo an MRI scan.
Hysteroscopy (camera test)	Endoscopic examination of the womb cavity	Currently used in the diagnostic pathway of symptomatic women who are at a high-risk of endometrial cancer, especially those who present with an irregular endometrium. Hysteroscopy alongside biopsy is also used in cases of recurrent PMB	Advantages Allows for direct visualisation of the womb lining. Enables targeted biopsy of suspicious lesions Facilitates removal of suspicious lesions(therapeutic) Disadvantages Invasive Operative challenges are common May be abandoned due to severe pain, cervical stenosis or sub-optimal visualisation.
Potential tests based on minimally invasive sampling	A variety of index tests based on non- and minimally invasive sampling	Blood, urine and use of vaginal tampons/endocervical swabs may be used as screening tests based on their potential to enable the detection of endome-	Advantages Non and minimally invasive

Table 1. Index tests for endometrial cancer screening in the general population (Continued)

methodologies and include blood based markers, urine tests, use of vaginal tampons/endocervical swabs amongst others.	trial cancer related genetic faults, proteins and metabolites.	Likely to be acceptable to women and physicians. Urine and vaginal tampons can be self-collected Disadvantages Blood-based tests may be limited by the low amount of cancer related signals in the blood in early stage cancer. Vaginal tampons are unappealing to elderly women. Biomarkers may not be excreted in urine.
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CT: computed tomography; **ET:** endometrial thickness; **MRI:** magnetic resonance imaging; **PMB:** postmenopausal bleeding; **TVUSS:** transvaginal ultrasound scan

Table 2. Tailored QUADAS-2 tool for assessment of methodological quality of included studies

Item	Response
Participant selection: Risk of bias	
1) Was a consecutive or random sample of women enrolled?	<p>Yes if the study participants were randomly or consecutively selected.</p> <p>No if non-consecutive or convenience sampling was used.</p> <p>Unclear if the provided information is insufficient to enable an assessment of the sampling technique used.</p>
2) Was a case-control design avoided?	<p>Yes if all participants were recruited from the same population. Those diagnosed with endometrial cancer should not have been recruited from a separate population from those without endometrial cancer.</p> <p>No if women with endometrial cancer were recruited from a separate population from those without endometrial cancer.</p> <p>Unclear if the available information is insufficient to make a judgement on whether a case-control design was avoided.</p>
3) Did the study avoid inappropriate exclusions? Exclusion of symptomatic women and those at a high risk of EC such as women with LS are appropriate exclusions.	<p>Yes if inappropriate exclusions were avoided.</p> <p>No if a group of women were inappropriately excluded that may affect the study tests accuracy.</p> <p>Unclear if the provided information is unclear as to who was excluded and whether this was appropriate.</p>
Could the selection of participants have introduced bias?	
If answers to all of questions 1) and 2) and 3) was Yes	Risk is low
If answers to any of questions 1) and 2) and 3) was No	Risk is high

Table 2. Tailored QUADAS-2 tool for assessment of methodological quality of included studies (Continued)

If answers to any of questions 1) and 2) and 3) was Unclear		Risk is unclear
Participant selection: Concerns regarding applicability		
Is there concern that the included participants do not match the review question?		<p>Low concerns if the study participants are representative of the full spectrum of women likely to be eligible for a population-level EC screening programme.</p> <p>High concerns if study participants are not representative of the spectrum of women who will be eligible for a population-level EC screening programme.</p> <p>This may include studies done exclusively in: obese women, pre-menopausal women, narrow age distribution, narrow group of ethnicity that will impact on the applicability of the study findings to other group of asymptomatic women.</p> <p>Unclear concerns if the provided information is insufficient to enable an assessment of the applicability of the study.</p>
Index test: Risk of bias (to be completed per test evaluated)		
1) Were the index test results interpreted without knowledge of the results of the reference standard?		<p>Yes if the index test was performed and interpreted prior to the completion of the reference standard or if there was a clear statement that the interpretation of the index test result was done without knowledge of the reference standard.</p> <p>No if the index test was either conducted or interpreted following completion of the reference standard.</p> <p>Unclear if the provided information is unclear to enable a judgement of the blinding of the index test interpretation to the reference standard results.</p>
2) If an index test threshold was used, such as ET cut-off value for TVS, was this pre-specified?		<p>Yes if the threshold for a positive test discrimination was pre-specified.</p> <p>No if the threshold for a positive test discrimination was not pre-specified or if the threshold was defined based on the study data, e.g ROC-optimised.</p> <p>Unclear if the provided information is insufficient to make a judgement on whether the threshold was pre-specified.</p>
Could the conduct or interpretation of the index test have introduced bias?		
If answers to all of questions 1) and 2),		Risk is low
If answers to any of questions 1) and 2)		Risk is high
If answers to any of questions 1) and 2)		Risk is unclear
Index test: Concerns regarding applicability		
1) Was the interpretation of index test results such as ET or cytology performed by someone with expertise?		<p>Yes if interpretation of index test was performed by an expert</p> <p>No if interpretation of index test was not performed by an expert</p> <p>Unclear if insufficient information within study</p>

Table 2. Tailored QUADAS-2 tool for assessment of methodological quality of included studies (Continued)

2) Were thresholds or diagnostic criteria reported in enough detail to allow replication?	<p>Yes if the criteria used for the diagnosis of endometrial cancer based on the index test were reported in sufficient detail to enable replication or can be assumed based on international standards such as ET.</p> <p>No if the criteria used for the diagnosis of endometrial cancer were not reported in sufficient detail to enable replication.</p> <p>Unclear if the available information on the diagnostic criteria is insufficient to allow for replication.</p>
Are there concerns that the index test, its conduct, or interpretation may not be applicable in clinical practice?	
If the answer to question 1) and 2) was Yes	Low concern
If the answer to question 1) and 2) was No	High concerns
If the answer to question 1) and 2) was Unclear	Concern is unclear
Reference standard: Risk of bias	
1) Is the reference standard likely to correctly classify the target condition	<p>Yes if the final diagnosis was based on a histological assessment of endometrial tissue specimens (obtained by biopsy, dilation and curettage or following hysterectomy) or follow up information of at least a year for those with a negative index test.</p> <p>No if the final diagnosis was not based upon histological assessment of endometrial tissue specimens or follow up information of at least a year.</p> <p>Unclear if there was insufficient information to make a judgement.</p>
2) Were the reference standard results interpreted without knowledge of the results of the index test?	<p>Yes if the reference standard examiner was described as blinded to the index test result</p> <p>No if the reference standard examiner was described as having knowledge of the index test result</p> <p>Unclear if blinded reference standard interpretation was not clearly reported or where blinding cannot be assumed based on provided information.</p>
Could the reference standard, its conduct, or its interpretation have introduced bias?	
If answers to questions 1) and 2) was Yes	Risk is low
If the answer to question 1) and 2) was No	Risk is high
If the answer to question 1) and 2) was Unclear	Risk is unclear
Reference test: Concerns regarding applicability	
1) Does the study use the same definition of disease positive as that prescribed in the review question?	Low concerns if same definition of disease-positive was used, i.e histological diagnosis endometrial cancer or atypical hyperplasia.

Table 2. Tailored QUADAS-2 tool for assessment of methodological quality of included studies (Continued)

High concerns if an alternative definition of disease-positive was used.

Unclear if the definition of disease-positive was not clearly reported

Flow and timing: Risk of bias	
1) Was there an appropriate interval between index test and reference standard? Was the interval between the reference standard and the index test short enough to ensure that the target condition did not change between the two tests?	<p>Yes if the index test and reference standard were performed at a suitable interval.</p> <p>No if the index test and reference standard were not performed at a suitable interval.</p> <p>Unclear if the study does not report the interval between the index test and reference standard.</p>
2) Did all participants receive the same reference standard?	<p>Yes if all participants underwent histological sampling or follow up where clinically indicated as per the protocol.</p> <p>No if participants did not have histological sampling performed or were not followed up for at least a year where index test was negative as per protocol.</p> <p>Unclear if not clearly reported.</p>
3) Were all participants included in the analysis?	<p>Yes if all participants were included in the analysis.</p> <p>No if some participants were excluded from the analysis.</p> <p>Unclear if not clearly reported.</p>
If answers to all of questions 1) and 2) and 3) was Yes	Risk is low
If answers to any of questions 1) and 2) and 3) was No	Risk is high
If answers to any of questions 1) and 2) and 3) was Unclear	Risk is unclear

EC: endometrial cancer; **ET:** endometrial thickness; **LS:** Lynch syndrome; **ROC:** receiver operating characteristic

APPENDICES

Appendix 1. FIGO Staging of endometrial cancer

Tumour Stage	Description
I	Tumour confined to the uterus (womb)
I A	<50% invasion of the myometrium
I B	≥50% invasion of the myometrium
II	Tumour invades the cervical stroma but does not extend beyond the uterus.
III	Local or regional spread of tumour
III A	Serosal or adnexal invasion

(Continued)

III B	Vaginal or parametrial involvement
III C	Pelvic or paraaortic lymph node metastasis
III C1	Pelvic lymph node involvement
III C2	Paraaortic lymph node involvement (with or without pelvic nodes)
IV	Extension to the pelvic wall, one-third of the vagina, hydronephrosis or non-functioning kidney.
IV A	Invasion of bladder or bowel mucosa.
IV B	Distant metastasis including abdominal or inguinal lymph node involvement.

Appendix 2. Glossary of terms

Term	Definition
Advanced stage womb cancers	Cancers that have grown beyond the womb to nearby structures and distant organs. These are usually FIGO stages III and IV.
Anteroposterior	Front to back
Atrophic endometrium	Abnormal thinning of the lining of the womb
Atypical hyperplasia	Pre-cancer
Autosomal	Traits that can be passed down in families relating to chromosomes other than the X chromosome
Benign	Not harmful (non-cancer)
Cervical cytology	Pap smear test
Chemotherapy	Medications that can kill cancer cells or stop them from multiplying
Cytology	Examining cells for evidence of cancer
Early stage womb cancers	Small cancers that are localised to the womb. These are usually FIGO stages I and II.
Endometrial biopsy	Removal of a small piece of tissue from the lining of the womb
Endometrial polyp	Growths attached to the lining of the womb
Endometrial thickness	Amount of thickening of the inner lining of the womb
Endometrium	Inner lining of the womb
Gene	A hereditary unit transferred from parents to their off-springs
Grade	How abnormal and how fast-growing cells appear
Heterogeneity	Diversity

(Continued)

Histology	Microscopic study of tissue specimens for evidence of disease
Human Development Index	A measure of life expectancy, education and income that is used to rank countries.
Hyperplasia	Too many cells
Hypertension	Persistent elevation in blood pressure
Hysterectomy	Surgical removal of the womb and the cervix
Hysteroscopy	A camera test used to visualize and take samples from the womb
Incidence	Total number of new cases of a disease
Index tests	The screening tests or procedures to be evaluated in this review
Lynch syndrome	Inherited condition due to specific gene faults (MMR mutations) with increased predisposition to endometrial and colon cancers.
Late-menopause	Menopause occurring after the age of 55 years.
Molecular genetic tests	Tests that aim to identify underlying gene changes
Mutations	Gene faults
Non-specific marker	A test that is not diagnostic but may along with other tests aid diagnosis
Nulliparity	Never given birth before
Obesity	Excess body weight/fat based on a body mass index of more than 30kg/m ²
Polycystic ovarian syndrome	A medical condition in which women have a hormonal imbalance and metabolism problems leading to infertility and obesity
Polymerase epsilon	A gene that codes for an enzyme that plays a role in DNA repair and has been linked to cancer
Post-menopausal bleeding	Bleeding occurring at least 12 months after the end of menstruation in women not taking a hormone treatment.
Prevalence	Total number of people with a disease (both old and new cases)
Prognosis	Predicted outcome
PTEN	A gene (phosphatase and tensine homologue) that gives instructions for making a specific enzyme which regulates the rate at which cells grow and divide.
Radiotherapy	High energy X-rays used to treat cancer
Screening	Detecting a disease in healthy people before they develop symptoms
Sensitivity	The ability of a test to correctly identify those that have a disease
Specificity	The ability of a test to correctly identify those who do not have a disease
Sporadic	Occurring randomly in the population

(Continued)

Stage	How far the disease has spread
Tamoxifen	A medication used to treat and prevent breast cancer but which also increases risk of EC
Transvaginal ultrasound	A type of scan which uses a vaginal probe to examine the female reproductive organs
Tumour	Abnormal growth that may or may not be cancer
Uterine lavage	Washing the womb cavity with water
Uterus	Womb

Appendix 3. Review eligibility criteria

Study characteristics	Inclusion criteria	Exclusion criteria
Population	Asymptomatic(healthy) women in the general population. No restriction based on age or menopausal status.	Symptomatic women such as those with postmenopausal bleeding. Women at very high risk of endometrial cancer such as those with Lynch syndrome (not representative of the general population). Women who have had surgery to remove their wombs (hysterectomy).
Index tests	All potential screening tests including TVUSS, cervical cytology, endometrial cytology, molecular/genetic tests based on minimally invasive sampling techniques including uterine lavage, cervico-vaginal secretions and vaginal tampons.	No limitations provided test was carried out on the appropriate population
Reference standard	Histology of endometrial tissue based on biopsy, hysterectomy specimens or dilation and curettage specimens. Follow up information for at least 1 year for participants with a negative test who do not go on to have endometrial biopsy	Studies not meeting the inclusion criteria of a reference standard.
Outcomes	Any of: Sensitivity and specificity Positive predictive value and negative predictive value Positive likelihood ratio and negative likelihood ratio	Studies in which diagnostic performance of the index tests were not investigated.
Study designs	All cross sectional and comparative diagnostic test accuracy studies	Case control study designs

TVUSS: transvaginal ultrasound scan

Appendix 4. Cytology reclassification scheme

Bethesda classification	British Society for Clinical Cytology (BSCC)	Munich III
ASCUS	Borderline	Pap IIw
LSIL	Mild dyskaryosis Glandular cells	Pap IIID

ASCUS: Atypical squamous cells of undetermined significance. **LSIL:** Low-grade squamous intra-epithelial lesion

Appendix 5. MEDLINE search strategy

BB10: Screening tests for endometrial cancer in the general population

1. exp Endometrial Neoplasms/
2. (endom* adj5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or hyperplasia* or lesion* or abnormal* or disease*)) .ti,ab,kw.
3. ((uter* and lining) adj5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or lesion* or abnormal* or disease*)) .ti,ab,kw.
4. ((womb or corpus uter*) adj5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or lesion* or abnormal* or disease*)) .ti,ab,kw.
5. Endometrial Hyperplasia/
6. 1 or 2 or 3 or 4 or 5
7. ((cervi* or uter* or endometrial or endometrium or endocervical or endo-cervical or cervico-vaginal or vaginal* or urine or intrauterine) adj5 (sampl* or diagnos* or detect* or collect* or screen* or swab* or tampon* or marker* or device* or test* or analys* or patholog* or smear* or lavage* or scrap* or suction or vacuum* or tool or tools or aspirat* or biops* or brush* or technique* or tecnic or tecnicas or liquid*)) .ti,ab,kw.
8. cyto* .ti,ab,kw.
9. 7 and 8
10. (cervi* or uter* or endometrial or endometrium or endocervical or endo-cervical or cervico-vaginal or vaginal*) .ti,ab,kw.
11. cytodiagnosis/
12. 10 and 11
13. Tomography, X-Ray Computed/
14. (Computed tomography scan* or CT scan*) .ti,ab,kw.
15. Magnetic Resonance Imaging/
16. (magnetic resonance imag* or MRI) .ti,ab,kw.
17. (abdom* or pelvi*) .ti,ab,kw.
18. 13 or 14 or 15 or 16
19. 17 and 18
20. hysteroscopy/
21. hysteroscop* .ti,ab,kw.
22. (transvaginal ultraso* or trans-vaginal ultraso* or TVS or TVUSS or transvaginal scan* or trans-vaginal scan* or sonograph*) .ti,ab,kw.
23. (pap* adj3 (test or tests or testing or smear)) .ti,ab,kw.
24. Hematologic Tests/
25. 10 and 24
26. (CA-125 or HE4) .ti,ab,kw.
27. (blood* or serum* or plasma or protein* or peptide* or proteomic* or metabolite* or metabolomic*) .ti,ab,kw.
28. 7 and 27
29. ultrasonography/
30. 19 or 20 or 21 or 22 or 23 or 25 or 26 or 28 or 29
31. exp "sensitivity and specificity"/
32. "reproducibility of results"/
33. diagnos* .ti.
34. di.fs.
35. sensitivit* .ab.
36. specificit* .ab.
37. (ROC or "receiver operat*") .ab.
38. Area under curve/
39. ("Area under curve" or AUC) .ab.

40. sROC.ab.
41. accura*.ti,ab.
42. (likelihood adj3 (ratio* or function*)).ab.
43. ((true or false) adj3 (positive* or negative*)).ab.
44. ((positive* or negative* or false or true) adj3 rate*).ti,ab.
45. 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
46. Asymptomatic Diseases/
47. (subclinical* or sub-clinical*).ti,ab,kw.
48. asymptomatic.ti,ab,kw.
49. 46 or 47 or 48
50. 6 or 9 or 12
51. 45 and 50 and 30
52. 49 and 50 and 30
53. 51 or 52

Key:

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

Appendix 6. Data extraction form for study characteristics and diagnostic accuracy estimates
General Information

Reviewer: <i>(Initials)</i>
Unique review ID: <i>(All studies to be reviewed will be given a unique ID from 1 to n)</i>
Date of extraction: <i>(dd/mm/yyyy)</i>
Study ID: <i>(surname of first author and year of publication of first study report e.g. Jones 2020)</i>
Publication status: <i>(e.g. published full report, conference abstract, letter)</i>
Country of study:
Title of article:
Study author contact details:
Report ID of other reports of this study including errata or retractions
Notes :

Study eligibility

Study Characteristics	Eligibility criteria	Eligibility criteria met?	If eligibility not met, include de-	Location in text or source <i>(page number)</i>

(Continued)

		tails why			
		Yes	No	Un- clear	De- tails
Type of study	Prospective cross-sectional study				
	Prospective comparative study				
Participants	Asymptomatic (healthy) population of women Are not at very high risk of EC (LS or family history of LS/EC)				
Index test	TVUSS Cervical smear test Endometrial cytology Others				
Reference stan- dard	Histological diagnosis or follow up for at least one year				
Target condition	Endometrial cancer and/or atypical hyperplasia				
Study outcomes	Diagnostic accuracy reports(sensitivity, specificity etc)				
Include OR Exclude					
Reason for exclusion:					

ONLY PROCEED IF STUDY HAS BEEN INCLUDED FOR REVIEW

Characteristics of included studies

Methodology

	Study descriptions	Location in text or source (page number or table number)
Study aim		
Study setting	(Clinical or research setting, hospital or community-based)	
Start date		
End date		
Duration of follow-up (from recruitment to last follow-up)		
Funding		

(Continued)

Possible conflicts of interests

Study participants

	Description	Location in text (page number, figure/table/other)
Population description (from which study participants were drawn)		
Study specific inclusion criteria		
Study specific exclusion criteria		
Informed consent	Yes, No, Not reported	
Method of recruitment		
Total number of women consented at start of study		
Number analysed at the end		
Sample attrition or drop-outs		
Age distribution		
Race/ethnicity		
Menopausal status		
Obesity distribution		
Use of hormonal treatment		
Use of tamoxifen		
Other relevant sociodemographic information		

Description of index test

	Description as stated in report/paper	Location in text or source (page & figure/table/other)
Name of index test		
Was there a diagnostic threshold?	Yes, No, Unclear	
If Yes, was this pre-specified?	Yes, No, Unclear	

(Continued)

Description of index test *(include sufficient detail for replication)*

If cytology, what reporting system was used?

Timing *(e.g. when was test performed in relation to reference standard)*

Site of index test *(e.g. anatomical area)*

Test providers *(e.g. profession, training, calibration etc. if relevant)*

Assessors of test *(e.g. profession, training, blinded to reference test results)*

Number who received index test

Completion of test *(e.g. failure rate and reasons for failure)*

Inadequacy rate

Adverse effects reported

Additional notes:

Description of reference standard

	Description as stated in report/paper	Location in text or source <i>(page & figure/table/other)</i>
Name of reference standard		
Number who received reference standard		
Description <i>(include sufficient detail for replication)</i>		
Histology reporting system used		
Timing <i>(e.g. when was test performed in relation to index test)</i>		
Providers <i>(e.g. profession, training etc. if relevant)</i>		
Assessors of test <i>(e.g. profession, training, blinded to index test results)</i>		
Completion of test <i>(e.g. failure rate and reasons for failure)</i>		
Inadequacy rate		
Other reference standards used for participants		
Number who received 'other' reference standard		
Length of follow up of participants		

(Continued)

Additional notes:

Target condition

	Description as stated in report/paper	Location in text or source (page & figure/table/other)
Endometrial cancer only		
Atypical hyperplasia only		
Both endometrial cancer and AH		
Detailed information on grade and stage of cancer detected		
Other information		

Data and analysis .

	Description as stated in report/paper	Location in text or source (page & figure/ta- ble/other)
Power and sample size calculation	Yes, No, Not reported	
What power was achieved based on eventual sample size?		
How was missing data handled?	Imputation?	
What comparisons were made		
Results	Disease present	Disease absent
(Name of index test and standard)	Total	
Test positive		
Test negative		
Total		
Number of true positives		
Number of true negatives		

(Continued)

Number of false positives

Number of false negatives

Sensitivity (95% CI)

Specificity (95% CI)

AUC (95% CI)

Any other results reported (e.g. PPV, NPV, positive likelihood ratio, negative likelihood ratio, disease prevalence etc.)

No. of missing data

Reasons missing

Unit of analysis (by individuals, cluster/groups or samples)

Statistical methods used and appropriateness of these

Additional notes:

Other information

	Description as stated in report/paper	Location in text or source (page & figure/table/other)
Key conclusions of study authors		
Correspondence details for further study information		
Notes:		

AH: Atypical hyperplasia; **AUC:** Area under the curve; **CI:** confidence interval; **EC:** endometrial cancer; **LS:** Lynch syndrome; **NPV:** negative predictive value; **PPV:** positive predictive value; **TVUSS:** transvaginal ultrasound scan

Appendix 7. Data extraction form for methodological quality assessment

Data extraction form for methodological quality

Item	Authors judgement (using tailored QUADAS-2)	Description

(Continued)

Participant selection: Risk of bias

1) Were the study participants' representative of women likely to be eligible for a population level endometrial cancer screening programme?

2) Was a consecutive or random sample of patients enrolled?

3) Was a case-control design avoided?

4) Did the study avoid inappropriate exclusions? Exclusion of symptomatic women and those at a high risk of EC such as women with LS are appropriate exclusions.

Participant selection: Concerns regarding applicability

Is there concern that the included participants do not match the review question?

Index test: Risk of bias (to be completed per test evaluated)

1) Were the index test results interpreted without knowledge of the results of the reference standard?

2) If an index test threshold was used, such as ET cut-off value for TVS, was this pre-specified?

Index test: Concerns regarding applicability

1) Was the interpretation of index test results such as ET or cytology performed by someone with expertise?

2) Were thresholds or diagnostic criteria reported in enough detail to allow replication?

Are there concerns that the index test, its conduct, or interpretation differ from the review question or may not be applicable in clinical practice?
Reference standard - Risk of bias

1) Is the reference standard likely to correctly classify the target condition

2) Were the reference standard results interpreted without knowledge of the results of the index test?

Could the reference standard, its conduct, or its interpretation have introduced bias?
Reference test: Concerns regarding applicability

1) Does the study use the same definition of disease positive as that prescribed in the review question?

Flow and timing: Risk of bias

1) Was there an appropriate interval between index test and reference standard? Was the interval between the reference standard and the index test short enough to ensure that the target condition did not change between the two tests?

2) Did all participants receive the same reference standard?

(Continued)

3) Were all participants included in the analysis?

EC: endometrial cancer; **ET:** endometrial thickness; **LS:** Lynch syndrome; **QUADAS-2:** Quality Assessment of Diagnostic Accuracy Studies, version 2; **TVS:** transvaginal sonography

Appendix 8. Summary of findings template

Index tests	Study population & setting	Target condition	Reference standard	Types of studies included	Number of participants (studies)	Test threshold	Summary accuracy (95% CI)	Certainty of evidence	Implications for practice
TVUSS									
Cervical cytology									
Endometrial cytology									
Hysteroscopy (camera test)									
Imaging: CT Scan									
Imaging: MRI scan									
A specific blood-based test									
A specific urine-based test									
Vaginal tampon + genetic testing									
CI: confidence interval; CT: computed tomography; MRI: magnetic resonance imaging; TVUSS: transvaginal ultrasound scan									

HISTORY

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CONTRIBUTIONS OF AUTHORS

All authors contributed to the study design. Emma Crosbie is the principal investigator and study guarantor. Kelechi Njoku prepared the first draft of the protocol. Helena O'Flynn, Eleanor Jones, Richard Macey, Helen White and Emma Crosbie provided critical comment, edited the protocol draft, and approved its final version. Richard Macey provided expert methodological input. Data acquisition will be undertaken by Kelechi Njoku, Eleanor Jones, Helena O'Flynn and Neal Ramchander. Data analysis and interpretation will be undertaken by Kelechi Njoku, Helena O'Flynn, Eleanor Jones, Neal Ramchander, Richard Macey and Emma Crosbie. Helen White is a consumer co-author and will check that the review is relevant to consumers. Drafting of final review manuscript will be performed by Kelechi Njoku and Emma Crosbie and will be reviewed by all authors. The review update will be undertaken by Kelechi Njoku and Emma Crosbie.

DECLARATIONS OF INTEREST

Kelechi Njoku: None known
Helena O'Flynn: None known
Eleanor Jones: None known
Neal Ramchander: None known
Helen White: None known
Richard Macey: None known
Emma Crosbie: None known