Systematic Review

Screening Strategies for Endometrial Cancer: A Systematic Review of Current Practices and Perspectives

Chia-Chen Liu[1,2], Ann-Chi Shyur[2,3], Chih-Chien Cheng[2,4,5,]*, Ching-Hsuan Chen[6], Shih-Chi Lin[7], Chen-Li Lin[7]

[1]Department of Obstetrics & Gynecology, National Taiwan University Hospital, 115006 Taipei, Taiwan
[2]School of Medicine, College of Medicine, Fu Jen Catholic University, 242062 New Taipei, Taiwan
[3]Department of Obstetrics & Gynecology, Fu Jen Catholic University Hospital, 242352 New Taipei, Taiwan
[4]Department of Health and Welfare, University of Taipei, 100234 Taipei, Taiwan
[5]Department of Obstetrics & Gynecology, Taipei City Hospital, Zhongxiao Branch, 241008 Taipei, Taiwan
[6]Department of Obstetrics & Gynecology, Taipei City Hospital, Heping Branch, 100065 Taipei, Taiwan
[7]Department of Obstetrics & Gynecology, Taipei City Hospital, Fuyou Branch, 100027 Taipei, Taiwan
*Correspondence: DXO90@tpech.gov.tw; freddycccheng@hotmail.com (Chih-Chien Cheng)
Academic Editor: Michael H. Dahan
Submitted: 30 November 2024 Revised: 27 March 2025 Accepted: 5 June 2025 Published: 25 September 2025

Abstract

Background: Endometrial cancer (EC) is the most common gynecological malignancy, and its incidence has recently increased. Several screening tools have been developed, including the Papanicolaou (Pap) smear, cervical methylation test, traditional transvaginal ultrasound (TVU), three-dimensional TVU (3D-TVU), circulating tumor DNA (ctDNA), and direct endometrial sampling. Each screening methods differ in characteristics, cost, and accuracy. **Methods**: A systematic review was conducted to assess publications offering different perspectives on screening methods for EC and to identifity viable methods in practice, using PubMed and Google Scholar for studies published between 1995 and 2024. In addition, different strategies were summarized, and their cost-effectiveness was evaluated. **Results**: Known detection methods include various screening tools. Herein, we provide a comparison of current early diagnostic and screening tools for EC and their accuracy, and review existing knowledge on screening methods while identifying viable methods for clinical practice. Currently, no optimal screening method exists for EC. **Conclusion**: With the increasing global incidence of EC, the demand for effective EC screening is more noteworthy. Concerning cost-effectiveness, convenience, and complications, it has been suggested that TVU or DNA methylation testing in cervical samples may be preferable options. Additionally, differential diagnosis of other etiologies and patient education regarding red-flag signs are also important.

Keywords: endometrial cancer; screening; Pap smear; DNA methylation; transvaginal ultrasound; accuracy

1. Introduction

Endometrial cancer (EC) is the sixth most common cancer in women, with 420,368 newly diagnosed cases worldwide in 2022, and the highest disease burden in North America and Western Europe [1,2]. The prevalence was higher in Caucasian areas, such as North America and Western Europe, while it was relatively low in Asia, Africa, and South America. Several risk factors are associated with EC. From the perspective of geographic, socioeconomic, and racial disparities, EC is more prevalent in high-income and developed countries than in low-income, middle-income, and developing countries, and access to high-quality healthcare and oncologist density may be attributed to this phenomenon [2–4]. African-American women are diagnosed with poorer prognostic histological subtypes and higher stages and grades of EC than European women [5]. Additionally, obesity was another risk factor, particularly for endometrioid EC, with approximate relative risks of 1.5 fold for those with overweight, 2.5 fold for those with class 1 obesity [body mass index (BMI), 30.0–34.9 kg/m^2], 4.5

for those with class 2 obesity (BMI, 35.0–39.9 kg/m^2) and 7.1 fold for class 3 obesity (those with BMI $\geq$40.0 kg/m^2) [2,6,7]. This mechanism is primarily due to increased estrogen production by adipocytes. Hyperglycemia and insulin resistance result in elevated insulin-like growth factor 1 (IGF-1) signaling and activation of the mammalian target of the rapamycin pathway, which in turn causes cellular proliferation [2]. A positive correlation between the risk of metabolic syndrome and EC has been established [8–10]. Furthermore, some germline mutations increase the risk of EC, with Lynch syndrome showing the strongest association [2].

Most clinical presentation was post-menopausal bleeding, which could be easily noted for patients [2]. In a systematic review and meta-analysis [3], the pooled prevalence of post-menopausal bleeding among women with EC was approximately 90%, irrespective of tumor stage, whereas overall percentage of EC in post-menopausal bleeding was approximately 9%; that is, 10% ECs may have delayed diagnosis and management. Thus, the
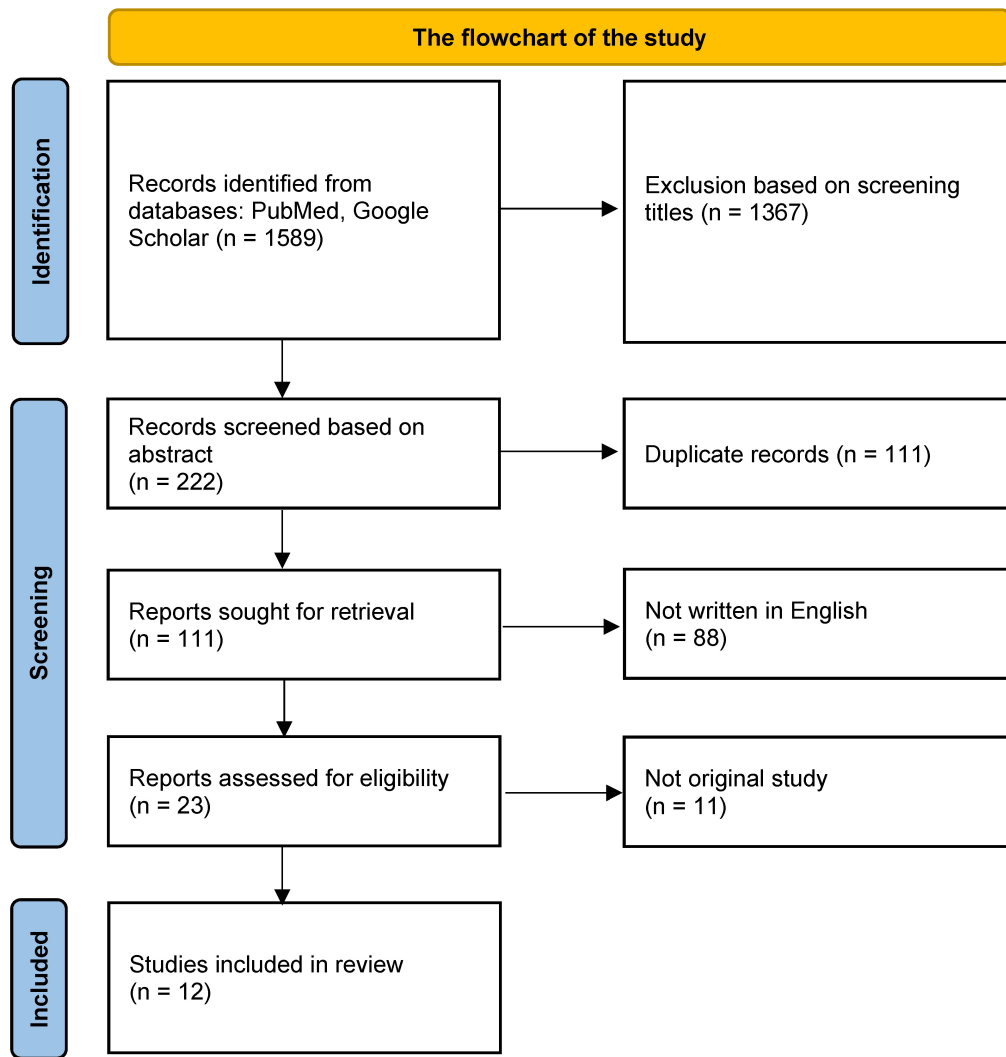
The flowchart of the study

Identification
- Records identified from databases: PubMed, Google Scholar (n = 1589) → Exclusion based on screening titles (n = 1367)

Screening
- Records screened based on abstract (n = 222) → Duplicate records (n = 111)
- Reports sought for retrieval (n = 111) → Not written in English (n = 88)
- Reports assessed for eligibility (n = 23) → Not original study (n = 11)

Included
- Studies included in review (n = 12)

Fig. 1. The flowchart of the study.

development of screening tests and guidelines of EC is crucial for early detection and treatment, which further improves the survival rate and prognosis in EC. Currently, some screening methods, such as the Papanicolaou (Pap) smear, cervical methylation test, two-dimensional (2D) or three-dimensional (3D) transvaginal ultrasound (TVU), circulating tumor cells, and direct endometrial biopsy, have been postulated. However, no detailed comparison and introduction of screening tests have been conducted. Therefore, in this study, we enumerated and compared different screening methods for EC.

2. Method

2.1 Study Design

A systematic review aimed at assessing and comparing the methods for screening EC was performed.

2.2 Search Strategies

This systematic review was undertaken and reported in adherence to the Preferred Reporting Items for System-atic Reviews and Meta-Analyses (PRISMA) [11] (Fig. 1). All relevant articles were searched for in the following databases: PubMed and Google Scholar with the keywords "endometrial cancer screening", "Pap smear", "DNA methylation", "transvaginal ultrasound", "3D ultrasound", "circulating tumor cells", and "endometrial biopsy" (**Supplementary Table 1**). All scientific publications between 1995–2024. The articles were limited to those written in English language. In this systemic review, all the inclusive characteristics were evaluated carefully, such as author and year, study type, location, study subjects, intervention measures, study results, etc. (**Supplementary Table 2**). In addition, the quality of each study was evaluated. The principle of Newcastle-Ottawa Scale (NOS) [12] was used to evaluate the quality of the study to assess the quality of non-randomized studies and a modifed version of NOS for cross-sectional studies [13].

Table 1. Sensitivity and specificity of different screening methods.

Screening method	Sensitivity	Specificity
Papanicolaou (Pap) smear	45%	Not assessed (NA)
DNA methylation in cervical sampling	83.7–96.0%	69–99%
Transvaginal ultrasound (TVU) -for post-menopausal female (cut-off 5 mm)	33–90%	48–85.7%
Three-dimensional (3D) ultrasound with power Doppler (without post-menopausal bleeding)	For endometrial volume: 74.2% For vascular index: 90.3%	For endometrial volume: 60.6% For vascular index: 81.8%
Endometrial sampling	75–95%	92–100%
Circulating tumor DNA (ctDNA)	10–22%	95%

3. Result

Currently, there is no optimal screening method for EC [2,14]. The known detection methods include various screening tools. Table 1 lists a comparison of current early diagnosis and screening tools for EC and their accuracy, including the Pap cervical smear, traditional 2D ultrasound, 3D ultrasound, DNA methylation in cervical sampling, and endometrial sampling by surgical procedures.

Table 2 compares the characteristics, advantages, and disadvantages of different methods. The details are discussed and compared below.

3.1 Pap Smear

In a systematic review and meta-analysis [14], the overall pooled sensitivity was 45% (95% confidence interval [CI], 40–50%). This percentage was significantly higher among those with non-endometrioid histology than that in those endometrioid subtypes (77% [95% CI, 66–87%] vs. 44% [95% CI, 34–53%], respectively). Additionally, some clinical factors influenced the results, with higher sensitivity in advanced stages, more myometrial invasion, positive abdominal cytology, lymph node metastasis, cervical involvement, and lympho-vascular invasion.

3.2 DNA Methylation in Cervical Sampling

Additional genetic detection in Pap smears could increase sensitivity. In a study analyzing two methylomic databases of endometrioid-type EC [15], 14 genes that were hypermethylated in EC were found with best performance with basic-helix-loop-helix E22 (*BHLHE22*), cysteine dioxygenase 1 (*CDO1*), and CUGBP Elav-like family member 4 (*CELF4*) (sensitivity of 83.7–96.0% and specificity of 78.7–96.0%). Additionally, a study [16] testing methylation status by quantitative methylation-specific polymerase chain reaction for 14 genes in DNA pools of endometrial and ovarian cancer tissues demonstrated that POU class 4 homeobox 3 (*POU4F3*) and Membrane associated guanylate kinase, WW and PDZ domain containing 2 (*MAGI2*) are valid with sensitivity of 83–90% and specificity 69–75% for detection of EC. In a retrospective study [17] using PapSEEK (assays for mutations in 18 genes as well as an assay for aneuploidy), 81% of the Pap brush samples from women with EC were positive, including 78% of patients with early-stage disease and 92% of those with late-stage disease. Only 1.4% of the Pap brush samples from 714 women without cancer were PapSEEK-positive, meaning specificity of approximately 99%.

3.3 TVU

In a case-control study of post-menopausal study [18], sensitivity and specificity at endometrial thickness 5 mm or greater cut-off were 80.5% and 85.7% for EC and atypical endometrial hyperplasia. For a cut-off of 10 mm or greater, sensitivity and specificity were 54.1% (45.3–62.8) and 97.2% (97.0–97.4). The optimal cut-off for endometrial thickness was 5.15 mm, with sensitivity of 80.5% and specificity of 86.2%. A comparison between TVU and endometrial aspiration was conducted among asymptomatic post-menopausal women potentially eligible for an osteoporosis prevention trial [19]. In this population, the estimated sensitivities for TVU with threshold values of 6 and 5 mm were 17% and 33%, respectively. In a study published in The New England Journal of Medicine [20], at a threshold value of 5 mm for endometrial thickness, TVU had a positive predictive value (PPV) of 9% for detecting any abnormality, with 90% sensitivity, 48% specificity, and a negative predictive value (NPV) of 99% for post-menopausal conditions.

In patients with breast cancer with tamoxifen, the sensitivity was 63.3% and specificity was 60.4% by setting the endometrial thickness cut-off at more than 9 mm to represent significant abnormality. Additionally, PPVs were 43.3% and NPV was 77.5% [21].

3.4 3D Ultrasound With Power Doppler

In a study conducted in Southern India [22], the sensitivity and specificity of endometrial volume were 74.2% and 60.6% with a cut-off of 4.52 mL. However, the optimal parameters for EC were vascularization index (sensitivity, 90.3%; specificity 78.8%; cut-off, 2.02) and vascularization flow index (sensitivity, 90.3%; specificity, 81.8%; cut-off, 0.76). In a systematic review [23], endometrial volume estimation was more specific than endometrial thickness measurement for predicting EC in post-menopausal bleeding

Table 2. Characteristics, advantages, and disadvantages of different screening methods for endometrial evaluation.

Screening method	Characteristics	Advantages	Disadvantage
Pap smear	With test stick to obtain a cervical specimen at transitional zone	- Also for cervical cancer screening - Low invasiveness and cost	- Possible discomfort during exam - No direct sampling of the endometrium in cavity
DNA methylation in cervical sampling	Abnormalities in methylation increase cancerous risk	- High accessibility - At the same time with Pap smear	- Corresponding genetic indicators needed according to different races - Expensiveness in comparison to Pap smear
TVU	First-line screening tool Detection EM blood flow, other EM lesions, and adnexa lesions	- Non-invasive method - Low discomfort sensation	- EM thickening not necessarily cancerous - Low specificity - Operator dependence - No consensus of definition on EM thickening pre-menopause
3D ultrasound with power Doppler (without PMB)	Identification three dimensions at the same time Two current mainstream modes: recombining 2D images, or obtaining images directly through a specialized 3D probe	More clear and precise image than traditional TVU	- Expensiveness - Not yet popularized - Artifacts may present, causing misreading
Endometrial sampling (brush, lavage, suction)	Sampling EM tissue with brush, lavage, suction, including Tao brush, EndPap, Endocyte	Direct acquirement of EM tissue	- Discomfort sensation Bleeding after examination - Local sampling, possibly missing lesions
CtDNA	Gain the genetic information of tumor cells in blood (recently, new methods with urine or vaginal tampon)	- Noninvasiveness - Convenience	- Risk for not acquirement of tumor DNA fragments - Expensiveness

Abbreviations: EM, endometrium; PMB, post-menopausal bleeding; 2D, two-dimensional.

(specificity, 12–88% vs. 36–99%). However, regarding the sensitivity of volume estimation and endometrial vascular assessment using 3D-power-Doppler, the results are controversial.

3.5 Endometrial Sampling

Currently, there are several methods for obtaining endometrial tissue, such as the classic dilatation and curettage (D&C), hysteroscopy, Pipelle sampling, and Tao Brush.

D&C, considered the 'gold standard' method for acquiring endometrial tissue and diagnosis, allows for the examination of 50–60% of the lining surface, while the percentage of non-diagnostic results reaches 3% [24,25]. With the use of Pipelle endometrial sampling [26], sensitivity and specificity were 75% and 100% for EC, respectively. However, sensitivity decreased to 12.5% for endometrial polyp. In a systematic review and meta-analysis [27], cytological examination using Tao brush for endometrial premalignancy and malignancy revealed pooled sensitivity of 95%, specificity of 92%, and diagnostic odds ratio of 184.84.

Furthermore, in a genetic analysis with Tao brush [17], 93% samples patients with EC contained genetic alterations detected by PapSEEK, most common with phosphatase and tensin homolog (PTEN) (63%), tumor protein p53 (TP53) (42%), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) (36%) mutations.

3.6 CtDNA

At the 2018 American Society of Clinical Oncology annual meeting, GRAIL Biotechnology reported that the sensitivity of ctDNA detection for uterine cancer was <10%, while its specificity was as high as 95% [28]. In a prospective study for sequencing circulating DNA in EC [29], mutations in cell-free DNA at baseline were detected preoperatively in 22% patients, all of whom were diagnosed with advanced-stage disease, high tumor volume, and/or aggressive histological type. Furthermore, the presence of ctDNAs at baseline or postoperatively was associated with a poorer prognosis.

IMR Press

4. Discussion

Generally, ultrasound examination is the first line choice for the evaluation of endometrial abnormalities in patients with symptoms, such as abnormal uterine bleeding, owing to its ability to evaluate endometrial thickness or morphology, and even blood flow of the endometrium. The generally accepted threshold (cut-off value) for postmenopausal women is 4–5 mm (sensitivity 98%; specificity 36–68%). In fact, sensitivity and specificity are significantly affected by the threshold. If the cut-off value increases, the specificity also significantly increases, thereby reducing unnecessary invasive examinations [30]. However, not all patients with EC exhibit significant endometrial thickening. Especially in patients with type II EC, the endometrium is relatively unaffected by estrogen stimulation, and sometimes it is difficult to identify and has a worse prognosis; therefore, raising the threshold will risk delaying the diagnosis. Furthermore, there is currently no consensus on the decision value for premenopausal women or for those using hormonal medications (such as tamoxifen).

Recently, 3D TVU has been developed to visualize the coronal plane, which is difficult to visualize using traditional ultrasound. The bilateral uterine horns, endometrium, and cervix can be identified from a single plane, providing clearer and more precise images than traditional TVU. The function of 3D ultrasound also includes the use of power Doppler imaging to measure vascular blood flow. Excessive blood flow may originate from angiogenic tumors, thereby helping physicians to determine whether there are abnormalities within the uterus.

3D ultrasound, compared with the diagnostic accuracy of 2D ultrasound, is similar [31]. Moreover, studies have shown that the specificity and sensitivity of 3D ultrasound and magnetic resonance imaging (MRI) are almost the same [32]. Although the time spent is less than that of MRI examination, 3D ultrasound has a high potential to become a good tool in screening and diagnosis.

The newly developed testing method, the cervical methylation test, can analyze methylated genes using cervical smear specimens to identify those who are truly at high risk, and then conduct invasive examinations to confirm the diagnosis, eliminating the need for additional procedures. However, validation is still needed because the technique is new and the price of screening is very high.

The development of ctDNA is currently not a good biomarker of EC. Ongoing studies have focused on tumor molecules in the blood, including ctDNA, circulating tumor cells, circulating microRNA (miRNA), etc. CtDNA has benefits in post-treatment tracking and early identification of cancer recurrence. For early diagnosis, a study has also used methylated DNA to successfully distinguish affected from unaffected individuals [33]. However, it is sometimes difficult to detect mutations in all tumor genes in blood samples. Furthermore, precision tests are expensive, and some patients may not be able to afford them.

Limited laboratories perform genetic testing, and they have not yet been widely used clinically. The sensitivity ranges from <10% to 22%, whereas the specificity can be as high as 95% [28,29]. Low sensitivity is mainly due to the selection of the tested gene, and it is expected that sensitivity can be greatly improved by increasing the number of tested genes. However, the detection of circulating fractional DNA (cfDNA) may indicate advanced stages and histology. Due to the convenience of the ctDNA, it still remains an option for EC screening and may be more precise in the future with the discovery of more target genes.

Finally, a direct endometrial biopsy is the gold standard for diagnosing EC. Diagnostic rates can be achieved at different levels, depending on how the specimen is obtained. In the early days, the Tao Brush and Pipelle tubes were the mainstream methods of aspiration. In recent years, endometrial D&C and hysteroscope-assisted slicing has been commonly used. Compared with the first two methods, hysteroscopy is the only method to observe the endometrial pattern with the naked eye, by which suspicious lesions can more accurately obtained, such as abnormal vessels, surface smoothness, papillary structures, and polypoid structures [34], thereby increasing the diagnostic rate and reducing false negatives. However, sampling is associated with surgical risks. In addition to postoperative pain and bleeding, it may cause uterine rupture, fluid overload, and anesthesia-related complications. A Study indicates that approximately 6% of patients suffer from cervical stenosis or intraoperative pain, which prevents the performing physician from completing the examination [35].

The incidence and prevalence of EC have increased in the past few years; thus, the demand for screening has come to the forefront [36]. According to a statistical study [37], the PPV and NPV are influenced by prevalence. As the prevalence increased, the PPV also increased, but the NPV decreased. Therefore, with an increasing number of cases, screening for EC is becoming more important. From a public health perspective, costs and benefits must be considered. We take the current situation in Taiwan as an example. The range of costs for Pap smear, DNA methylation in cervical sampling, TVU, 3D ultrasound with power Doppler, ctDNA, D&C, hysteroscopic examination, and even polypectomy varies widely (8 to 2667 US dollars) (Table 3). An optimal screening test must be inexpensive, accessible, and highly sensitive. Pap smear is the most inexpensive method, but it has very low sensitivity. For TVU, the cost is only 32 US dollars and the sensitivity can approach approximately 90%, ranging between 33–90%. The price of 3D ultrasound with power Doppler is 24 times higher than the price of TVU; however, studies revealed that its sensitivity is only approximately 74.2–90%. Methylation of DNA in cervical sampling is less expensive than 3D ultrasound with higher sensitivity than that of 3D ultrasound (83.7–96.0% vs. 74.2–90%). Endometrial sampling is relatively inexpensive and sensitive, with a cost of only

Table 3. Cost of different screening methods in Taiwan.

Screening method	Cost (US dollars)
Pap smear	8
DNA methylation in cervical sampling	500
TVU	32
3D ultrasound with power Doppler (without post-menopausal bleeding)	100
Endometrial sampling	39
Dilatation and curettage (not including anesthesia)	60
Hysteroscopic exam (not including anesthesia)	68
Hysteroscopic polypectomy (not including anesthesia)	336
CtDNA	2667

Abbreviation: US, United States; D&C, dilatation and curettage.

39 US dollars. However, bleeding and discomfort during the examination must be considered. D&C and hysteroscopic methods are the most precise; however, the demand for anesthesia, risk of bleeding, and perforation make them inconvenient; thus, they are not good screening methods. D&C and hysteroscopic procedures are important for diagnosis. CtDNA is the most expensive and has poor sensitivity; therefore, further investigation is required. Thus, it is postulated that in view of cost-effectiveness, public health, convenience, and complications, TVU and DNA methylation in cervical sampling are the most feasible methods for screening, and can be performed for those at risk, such as those with obesity, positive family history, poorly controlled metabolic syndrome, and previous history of polycystic ovary syndrome with the use of tamoxifen. Furthermore, patient education for red flag signs (abnormal bleeding, recent weight loss, abdominal or pelvic discomfort, lower urinary tract symptoms, and gastrointestinal symptoms) and differential diagnosis of other etiologies of bleeding are also important in clinical practice. Therefore, further studies and guidelines are recommended in the future.

Limitations

1. The articles were reviewed without using any statistical tools or methods.

2. We searchd articles in Pubmed and Google Scholar. However, not all studies worldwide were included.

3. We analyzed the cost-effectiveness only in Taiwanese situation rather globally and without any statistical evidence.

4. The range of sensitivity and specificity among different methods are wide, making it difficult to calculate the definite cost-effectiveness of screening tests.

5. This study is a literature systemic review rather than a meta-analysis, and thus heterogeneity analysis and integration or pooling among different studies were not performed.

5. Conclusion

With the increasing number of EC worldwide, the demand for EC screening is more noteworthy. Concerning cost-effectiveness, convenience, and complications , we postulated that TVU or DNA methylation in cervical sampling may be better options. Additionally, the differential diagnosis of other etiologies and patient education regarding red flag signs are also important.

Availability of Data and Materials

The data sets generated and analyzed during the current study are available in the web repository: PubMed and Google Scholar.

Author Contributions

CCL, ACS and CCC designed the research study and performed the research. CHC, SCL and CLL made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Funding

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG33417.

IMR Press

References

[1] Endometrial cancer statistics. World Cancer Research Fund International. 2024. Available at: https://www.wcrf.org/cancer-trends/endometrial-cancer-statistics/ (Accessed: 20 November 2024).

[2] Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, *et al*. Endometrial cancer. Nature Reviews. Disease Primers. 2021; 7: 88. https://doi.org/10.1038/s41572-021-00324-8.

[3] Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Internal Medicine. 2018; 178: 1210–1222. https://doi.org/10.1001/jamainternmed.2018.2820.

[4] Chatterjee S, Gupta D, Caputo TA, Holcomb K. Disparities in Gynecological Malignancies. Frontiers in Oncology. 2016; 6: 36. https://doi.org/10.3389/fonc.2016.00036.

[5] Felix AS, Weissfeld JL, Stone RA, Bowser R, Chivukula M, Edwards RP, *et al*. Factors associated with Type I and Type II endometrial cancer. Cancer Causes & Control: CCC. 2010; 21: 1851–1856. https://doi.org/10.1007/s10552-010-9612-8.

[6] Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, *et al*. Body Fatness and Cancer–Viewpoint of the IARC Working Group. The New England Journal of Medicine. 2016; 375: 794–798. https://doi.org/10.1056/NEJMsr1606602.

[7] Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, *et al*. Type I and II endometrial cancers: have they different risk factors? Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2013; 31: 2607–2618. https://doi.org/10.1200/JCO.2012.48.2596.

[8] Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Giugliano D. Metabolic syndrome and endometrial cancer: a meta-analysis. Endocrine. 2014; 45: 28–36. https://doi.org/10.1007/s12020-013-9973-3.

[9] Rosato V, Zucchetto A, Bosetti C, Dal Maso L, Montella M, Pelucchi C, *et al*. Metabolic syndrome and endometrial cancer risk. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2011; 22: 884–889. https://doi.org/10.1093/annonc/mdq464.

[10] Trabert B, Wentzensen N, Felix AS, Yang HP, Sherman ME, Brinton LA. Metabolic syndrome and risk of endometrial cancer in the united states: a study in the SEER-medicare linked database. Cancer Epidemiology, Biomarkers & Prevention: a Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology. 2015; 24: 261–267. https://doi.org/10.1158/1055-9965.EPI-14-0923.

[11] PRISMA. PRISMA flow diagram. Available at: https://www.prisma-statement.org/prisma-2020-flow-diagram (Accessed: 1 January 2025).

[12] Wells GASB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2016. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed 25 April 2016).

[13] Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, *et al*. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. PloS One. 2016; 11: e0147601. https://doi.org/10.1371/journal.pone.0147601.

[14] Frias-Gomez J, Benavente Y, Ponce J, Brunet J, Ibáñez R, Peremiquel-Trillas P, *et al*. Sensitivity of cervico-vaginal cytology in endometrial carcinoma: A systematic review and meta-analysis. Cancer Cytopathology. 2020; 128: 792–802. https://doi.org/10.1002/cncy.22266.

[15] Huang RL, Su PH, Liao YP, Wu TI, Hsu YT, Lin WY, et *al*. Integrated Epigenomics Analysis Reveals a DNA Methylation Panel for Endometrial Cancer Detection Using Cervical Scrapings. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2017; 23: 263–272. https://doi.org/10.1158/1078-0432.CCR-16-0863.

[16] Chang CC, Wang HC, Liao YP, Chen YC, Weng YC, Yu MH, *et al*. The feasibility of detecting endometrial and ovarian cancer using DNA methylation biomarkers in cervical scrapings. Journal of Gynecologic Oncology. 2018; 29: e17. https://doi.org/10.3802/jgo.2018.29.e17.

[17] Wang Y, Li L, Douville C, Cohen JD, Yen TT, Kinde I, *et al*. Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers. Science Translational Medicine. 2018; 10: eaap8793. https://doi.org/10.1126/scitranslmed.aap8793.

[18] Jacobs I, Gentry-Maharaj A, Burnell M, Manchanda R, Singh N, Sharma A, *et al*. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. The Lancet. Oncology. 2011; 12: 38–48. https://doi.org/10.1016/S1470-2045(10)70268-0.

[19] Fleischer AC, Wheeler JE, Lindsay I, Hendrix SL, Grabill S, Kravitz B, *et al*. An assessment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. American Journal of Obstetrics and Gynecology. 2001; 184: 70–75. https://doi.org/10.1067/mob.2001.111088.

[20] Langer RD, Pierce JJ, O'Hanlan KA, Johnson SR, Espeland MA, Trabal JF, *et al*. Transvaginal ultrasonography compared with endometrial biopsy for the detection of endometrial disease. Postmenopausal Estrogen/Progestin Interventions Trial. The New England Journal of Medicine. 1997; 337: 1792–1798. https://doi.org/10.1056/NEJM199712183372502.

[21] Fung MFK, Reid A, Faught W, Le T, Chenier C, Verma S, *et al*. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecologic Oncology. 2003; 91: 154–159. https://doi.org/10.1016/s0090-8258(03)00441-4.

[22] Pandey H, Guruvare S, Kadavigere R, Rao CR. Utility of three dimensional (3-D) ultrasound and power Doppler in identification of high risk endometrial cancer at a tertiary care hospital in southern India: A preliminary study. Taiwanese Journal of Obstetrics & Gynecology. 2018; 57: 522–527. https://doi.org/10.1016/j.tjog.2018.06.007.

[23] Alcázar JL, Jurado M. Three-dimensional ultrasound for assessing women with gynecological cancer: a systematic review. Gynecologic Oncology. 2011; 120: 340–346. https://doi.org/10.1016/j.ygyno.2010.10.023.

[24] Piatek S, Warzecha D, Kisielewski F, Szymusik I, Panek G, Wielgos M. Pipelle biopsy and dilatation and curettage in clinical practice: are factors affecting their effectiveness the same? The Journal of Obstetrics and Gynaecology Research. 2019; 45: 645–651. https://doi.org/10.1111/jog.13882.

[25] Dijkhuizen FP, Mol BW, Brölmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer. 2000; 89: 1765–1772.

[26] Terzic MM, Aimagambetova G, Terzic S, Norton M, Bapayeva G, Garzon S. Current role of Pipelle endometrial sampling in early diagnosis of endometrial cancer. Translational Cancer Research. 2020; 9: 7716–7724. https://doi.org/10.21037/tcr.2020.04.20.

[27] Raffone A, Raimondo D, Raspollini A, Oliviero A, Travaglino A, Santoro A, *et al*. Accuracy of cytological examination of Tao brush endometrial sampling in diagnosing endometrial premalignancy and malignancy. International Journal of Gynaecol-

ogy and Obstetrics: the Official Organ of the International Federation of Gynaecology and Obstetrics. 2022; 159: 615–621. https://doi.org/10.1002/ijgo.14204.

[28] Shen Y, Shi R, Zhao R, Wang H. Clinical application of liquid biopsy in endometrial carcinoma. Medical Oncology (Northwood, London, England). 2023; 40: 92. https://doi.org/10.1007/s12032-023-01956-4.

[29] Ashley CW, Selenica P, Patel J, Wu M, Nincevic J, Lakhman Y, et al. High-Sensitivity Mutation Analysis of Cell-Free DNA for Disease Monitoring in Endometrial Cancer. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2023; 29: 410–421. https://doi.org/10.1158/1078-0432.CCR-22-1134.

[30] Jones ER, O'Flynn H, Njoku K, Crosbie EJ. Detecting endometrial cancer. The Obstetrician & Gynecologist. 2021; 23: 103–112. https://doi.org/10.1111/tog.12722.

[31] Spagnol G, Noventa M, Bonaldo G, Marchetti M, Vitagliano A, Laganà AS, et al. Three-dimensional transvaginal ultrasound vs magnetic resonance imaging for preoperative staging of deep myometrial and cervical invasion in patients with endometrial cancer: systematic review and meta-analysis. Ultrasound in Obstetrics & Gynecology: the Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2022; 60: 604–611. https://doi.org/10.1002/uog.24967.

[32] Ziogas A, Xydias E, Kalantzi S, Papageorgouli D, Liasidi PN, Lamari I, et al. The diagnostic accuracy of 3D ultrasound com-

pared to 2D ultrasound and MRI in the assessment of deep myometrial invasion in endometrial cancer patients: A systematic review. Taiwanese Journal of Obstetrics & Gynecology. 2022; 61: 746–754. https://doi.org/10.1016/j.tjog.2022.06.002.

[33] Beinse G, Borghese B, Métairie M, Just PA, Poulet G, Garinet S, et al. Highly Specific Droplet-Digital PCR Detection of Universally Methylated Circulating Tumor DNA in Endometrial Carcinoma. Clinical Chemistry. 2022; 68: 782–793. https://doi.org/10.1093/clinchem/hvac020.

[34] Miyamoto T, Abiko K, Murakami R, Furutake Y, Baba T, Horie A, et al. Hysteroscopic morphological pattern reflects histological grade of endometrial cancer. The Journal of Obstetrics and Gynaecology Research. 2019; 45: 1479–1487. https://doi.org/10.1111/jog.13998.

[35] Bettocchi S, Bramante S, Bifulco G, Spinelli M, Ceci O, Fascilla FD, et al. Challenging the cervix: strategies to overcome the anatomic impediments to hysteroscopy: analysis of 31,052 office hysteroscopies. Fertility and Sterility. 2016; 105: e16–e17. https://doi.org/10.1016/j.fertnstert.2016.01.030.

[36] Lai JCY, Weng CS, Huang SM, Huang N, Chou YJ, Wang CC, et al. Incidence and lifetime risk of uterine corpus cancer in Taiwanese women from 1991 to 2010. Taiwanese Journal of Obstetrics & Gynecology. 2017; 56: 68–72. https://doi.org/10.1016/j.tjog.2015.09.010.

[37] Tenny S, Hoffman MR. Prevalence. StatPearls [Internet]. StatPearls Publishing: Treasure Island (FL). 2022.