Endometrial Cancer Prevention, Early Diagnosis and Treatment

Subjects: Obstetrics & Gynaecology

Contributor: Holly Baker-Rand , Sarah J. Kitson

Endometrial cancer is the fourth most common female malignancy in high socioeconomic index nations and the sixth most common cancer in women worldwide. The disease incidence has increased globally by 132% in the last 30 years, and this trend is set to continue in light of an ageing population and increasing levels of obesity and diabetes. Although more women than ever before are dying of endometrial cancer, the mortality rates are falling due to recent advances in early diagnosis and treatment. Our understanding of the molecular drivers of endometrial cancer has increased substantially, and doctors are now, for the first time, starting to translate this knowledge into the true personalisation of care.

endometrial cancer prevention diagnosis treatment advances

1. Advances in Endometrial Cancer Prevention

Given the strong association with modifiable risk factors, endometrial cancer appears eminently suited to primary disease prevention, with modelling suggesting that up to 60% of endometrial cancer cases could be potentially prevented [1][2][3]. An increased understanding of the mechanisms driving endometrial carcinogenesis, namely unopposed oestrogen, insulin resistance and chronic inflammation, has led to the proposal of a number of interventions designed to reduce endometrial cancer incidence, albeit with data on their efficacy largely limited to retrospective observational studies [4][5].

1.1. Weight Management

Obesity has the strongest link with endometrial cancer of the twenty most common tumour types and is plausibly implicated in 34% of diagnoses [1]. Conversely, weight loss, by reducing adiposity and the aromatase-induced conversion of androgens into oestrogen, improving insulin sensitivity and lowering the levels of inflammation, is associated with a reduction in the endometrial cancer risk [5]. Observational data from the Women's Health Initiative suggests that intentional weight loss of as little as 5% bodyweight over a three year period is associated with a 39% (95%CI 12–58%) reduction in endometrial cancer incidence [6]. Interestingly, whilst women with obesity had the greatest benefit (HR 0.44, 95%CI 0.25–0.78), weight loss was also beneficial for women with a BMI within the normal range (HR 0.61, 95%CI 0.27–1.38). Achieving weight loss through lifestyle modification is feasible, but challenging to maintain and risks weight cycling, which appears to be more detrimental to endometrial cancer risk than a stable higher weight [7]. Certainly, the seven hours of jogging a week required to reduce endometrial cancer risk by 10% is not likely to be achievable for the majority of women [8].

The focus has, therefore, shifted to the new anti-obesity medications (AOMs) that have been developed in recent years and which appear to lead to more significant and sustained weight loss in comparison with lifestyle interventions and older AOMs such as orlistat [9][10]. Glucagon-like peptide 1 (GLP-1) agonists, such as semaglutide and liraglutide, improve insulin sensitivity, delay gastric emptying and decrease a person's appetite [11]. The mean weight change at two years was −15.2% with weekly semaglutide compared with −2.6% with a placebo in a STEP 5 randomised controlled trial (RCT), when used in combination with a behavioural intervention ($p < 0.0001$) [12]. Liraglutide appears to be similarly efficacious, with 51.8% of participants achieving ≥5% bodyweight loss compared with 24% of those treated with a placebo in an SCALE RCT ($p < 0.0001$) [13]. The side effects include gastrointestinal disruption, skin reactions, atrioventricular blockage, and rarely, pancreatitis, and long-term tolerance and safety have yet to be established. Whether the effects of GLP-1 agonists on bodyweight and insulin sensitivity can also translate into a reduction in endometrial cancer risk remains to be seen and should be included as a secondary outcome measure in long-term cohort studies.

Bariatric surgery alters the anatomy of the digestive system to restrict the capacity of the stomach, reduce nutrient absorption and induce early satiety [14]. It is the most effective intervention for obesity identified to date, leading to the long-term weight loss of up to 29 kg depending upon the exact procedure performed [15]. Wilson et al. demonstrated in their meta-analysis that bariatric surgery is effective in reducing the risk of subsequent endometrial cancer by 62% (pooled relative risk 0.38, 95%CI 0.26–0.55) [16]. Despite this, endometrial cancer prevention is not currently an indication for bariatric surgery, potentially because of the risk of long-term complications, including malabsorption, nutritional deficiencies, small bowel obstruction, dumping syndrome and gastric or stomal stenosis and resource issues limiting its availability [17].

1.2. Hormonal Chemoprevention

The beneficial effects of oral contraceptives on endometrial cancer risk have been known for the last 20 years, with every five years of use associated with a 24% reduction in the disease risk [18]. Importantly, this effect appears to persist for up to 30 years after the discontinuation of use. Whilst oestrogen-containing preparations are not advisable for women with a BMI > 35 kg/m^2 due to an elevated risk of arterial and venous thrombotic events, the combined oral contraceptive pill is recommended by the international consensus group for women with Lynch syndrome requiring contraception due to its beneficial effects on both the endometrial and ovarian cancer risks [19][20]. Progestin-only contraception is also likely to be beneficial, although the discontinuation rates are often higher due to irregular bleeding [21]. The levonorgestrel-releasing intra-uterine system (LNG-IUS) may well be the most effective endometrial cancer prevention measure, with large-scale observational studies describing up to a 78% reduction in endometrial cancer risk among the users, particularly if used long-term [22][23]. It certainly appears to reduce endometrial proliferation, even in women with a BMI ≥ 40 kg/m^2, with modelling suggesting that it could be a cost-effective approach for primary disease prevention in high-risk women [24][25]. Reassuringly, the previously raised concerns about an increased risk of postmenopausal breast cancer with LNG-IUS use were not confirmed in a recent meta-analysis [26]. Adequately powered clinical trials are now required to determine whether the LNG-IUS is both effective at reducing the incidence of endometrial cancer and is sufficiently acceptable to women for it to be used in routine practice.

1.3. Aspirin

Aspirin, a cycloxyengase-2 inhibitor, has anti-inflammatory effects and acts to reduce the aromatase and oestrogen levels and increase apoptosis [27][28]. Whilst women within the general population may benefit from only a small reduction in endometrial cancer risk from long-term aspirin use (8–11%), this may prove to be a more effective strategy in women with obesity (relative risk reduction 20–44%) [29]. The CAPP2 study demonstrated a clear reduction in the colorectal cancer risk with regular aspirin use in individuals with Lynch syndrome, but this RCT was insufficiently powered to assess the benefit to women with regard to the endometrial cancer risk [30]. The results were, however, encouraging (hazard ratio 0.50, 95%CI 0.22–1.11) and should be investigated further.

1.4. Metformin

Much interest has been expressed in the re-purposing of metformin, an oral biguanide and insulin-sensitiser, in the management of endometrial cancer. Despite early promising results in single-arm studies, metformin did not appear to reduce endometrial proliferation when evaluated within a more methodologically robust RCT [31]. These findings have been confirmed in a Cochrane review, in which it was noted that there was insufficient evidence to support the use of metformin either alone or in combination with progestin therapy for the management of endometrial hyperplasia [32]. The authors did note, however, that only two trials totally 59 patients were eligible for inclusion in their review, making it difficult to draw generalisable conclusions. A meta-analysis of six studies also found that metformin use was not associated with a reduction in the endometrial cancer risk (odds ratio 1.05, 95%CI 0.82–1.35), even when adjusting for the confounding variable of diabetes [33]. A recently published feMMe trial again demonstrated the limited cytostatic effect of metformin on the endometrium, with no increase in the effectiveness of the LNG-IUS for the management of early-stage endometrial cancer with the addition of metformin [34]. Together, these results should dissuade researchers from pursuing metformin for the chemoprevention or treatment of endometrial cancer.

1.5. Identifying High-Risk Women

Identifying high-risk individuals for targeted endometrial cancer prevention is imperative in order to maximise the benefits and minimise the risk of harm from long-term intervention. Women with Lynch syndrome represent the highest-risk group, with a 40–60% lifetime risk of endometrial cancer depending upon the underlying genetic variant [35]. The widespread adoption of reflex immunohistochemistry for mismatch repair genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*) on endometrial cancers prompts the identification of affected individuals, who will, themselves, benefit from surveillance for colorectal malignancies and whose affected female relatives should be offered a risk-reducing hysterectomy from the age of 40 years [20].

Only 3% of endometrial cancers are, however, related to Lynch syndrome, with a much greater number of women within the general population at moderate–high risk of the disease secondary to polygenic and environmental factors. Offering an intervention to this group has the potential to dramatically reduce the endometrial cancer incidence. To date, four risk prediction models have been developed with the aim of stratifying the endometrial cancer risk within the general population, of which three models have been externally validated [36][37][38][39]. All are

based on similar epidemiological risk factors, with or without the addition of serum biomarkers, with the E2C2 and PRECISION models demonstrating the highest discrimination (0.64–0.69) and best calibration (E/0 1.03–1.09) via external validation [38][39]. The advantage of the PRECISION model is its generalisability to non-White ethnic groups and suitability for use in both pre- and postmenopausal women, although, currently, it has only been validated within a UK population. In this setting, it outperformed the other published models in decision curve analysis and was associated with a greater net benefit than offering endometrial cancer prevention to all the women. An endometrial cancer risk assessment appeals to women who are keen to know their own individualised risk, in theory, and are willing to make lifestyle changes or have an LNG-IUS inserted if it will be of benefit [40]. The uptake of interventions to reduce the endometrial cancer risk need, therefore, to be urgently assessed within the context of a clinical trial.

2. Advances in Early Diagnosis

The majority of cases of endometrial cancer are diagnosed among postmenopausal women who frequently present with postmenopausal bleeding [4]. Transvaginal ultrasound in combination with endometrial sampling enables the histological diagnosis of endometrial cancer and can accurately exclude the presence of disease. Endometrial biopsies are, however, invasive and have a failure rate of around 11% due to inadequate samples and cervical stenosis [41]. Innovations in diagnostic tests are underway to identify alternative methods of identifying high-risk women for further testing and which can be used to reassure those at low risk of the disease. Peripheral blood, cervicovaginal fluid and urine offer potential sources of DNA or protein biomarkers and cells for cytological assessment.

2.1. Peripheral Blood

Human epididymis protein 4 (HE4) has emerged as the most promising of a number of serum diagnostic endometrial cancer biomarkers examined to date. Two meta-analyses have demonstrated a relatively modest pooled sensitivity of 65%, but with a higher specificity at 91%, albeit with marked inter-study heterogeneity [42][43]. The addition of further biomarkers, including cancer antigen 125 (CA125), and anthropometric data, such as BMI, has not been shown to improve the test performance [44]. These results suggest that the HE4 levels alone are unlikely to be sufficiently informative for them to be used in a diagnostic test, but that they may have a role as a triage tool for high-risk populations.

There has been increasing interest in the role of plasma cell free DNA (cfDNA), circulating tumour DNA (ctDNA) and circulating microRNA (miRNA) for the detection of endometrial cancer. The next-generation sequencing of cfDNA using a targeted four-gene panel (CTNNB1, K-ras, PTEN and PIK3CA) identified mutations within the plasma that matched those within the corresponding endometrial tumour in 33% of women, although this could only detect 18% of mutations in women with early-stage disease [45]. A recent study using ctDNA detected the hypermethylation of *zinc finger and SCAN domain containing 12* (*ZSCAN12*) and/or *oxytocin* (*OXT*) in 9/11 and 5/20 women with advanced and non-advanced endometrial cancer, respectively, giving a sensitivity of 98%, specificity of 97% and an area under the curve (AUC) of 0.99 [46]. Fan et al. assessed the miRNA signatures in 92

endometrial cancer subjects and 102 control subjects and externally validated the identified signatures in three large datasets. Six miRNAs (miR-143-3p, miR-195-5p, miR-20b-5p, miR-204-5p, miR-423-3p and miR-484) were overexpressed in endometrial cancer, with an AUC via external validation of 0.97 [47]. The observed discrepancy in test performance based on the stage of disease is not surprising given that localised disease is unlikely to shed sufficient ctDNA into the blood for it to be reliably detected. These biomarkers may, therefore, be better suited to identifying aggressive and potentially recurrent endometrial cancer rather than being used for the early diagnosis of disease.

Advances in the use of high-throughput technology have led to a rapid increase in the number of registered studies aiming to identify novel genomic, transcriptomic, proteomic and metabolomic blood biomarkers to be used in the early diagnosis of endometrial cancer. Single biomarkers may not be sufficiently informative to be used in clinical practice, and many of the ‘omic signatures’ identified have yet to be externally validated. This remains, however, an active area of research.

2.2. Uterine and Cervicovaginal Fluid

Uterine lavage fluid has been shown to have good sensitivity and specificity for endometrial cancer detection; however, it needs to be collected via hysteroscopy and is associated with significant discomfort for women [48]. Cervicovaginal samples are easier to obtain and can be as informative for the detection of an endometrial cancer as uterine lavage due to the shedding of malignant cells into the lower genital tract. The PapSEEK test, which incorporates assays for mutations in 18 genes as well as aneuploidy, has been shown to identify 81% of endometrial cancers when conducted during a routine Pap test, including 78% with early-stage disease [49]. The sensitivity increased to 93%, with a specificity of 100% when a Tao brush was used to obtain the samples. The Tao brush needs to be inserted up to the uterine fundus though and is associated with discomfort and a high failure rate. Alternatively, vaginal tampons can be used to collect cervicovaginal fluid, representing an inexpensive, easy-to-use self-collection system that is more likely to appeal to women. The samples can be analysed by next-generation sequencing to identify somatic mutations [50] or, of notable promise, undergo methylation testing [51]. The WID-qEC test, a three-marker test that appraises DNA methylation in the gene regions of GYPC and ZSCAN12 has been shown to outperform the transvaginal ultrasound measurement of endometrial thickness in the diagnosis of endometrial cancer (AUC WID-qEC 0.94 vs. ET measurement 0.87) among women with abnormal uterine bleeding [51]. The high negative predictive value of the test means that it could be used to reduce the number of women requiring invasive histological assessments.

2.3. Urine and Vaginal Cytology

Intact cells shed from the upper genital tract can also be detected in the vaginal fluid and, interestingly, within urine. This is thought to be related to the contamination of voided urine samples during self-collection, with higher cellular loads potentially more likely to be found in the samples collected from women with concurrent abnormal uterine or postmenopausal bleeding [52]. Cytological assessment is labour-intense and requires specialist interpretation, but has been shown within a diagnostic accuracy study to have a combined sensitivity of 91.7% (95%CI 85.0–96.1%)

and specificity of 88.8% (95%CI 81.2–94.1%) for the detection of gynaecological malignancies, the majority of which were endometrial cancers [52]. The high negative predictive value (91.4%, 95%CI 84.9–95.2%) of urine and vaginal cytology may mean that it can be used to identify women for future investigations, reducing the number of women with abnormal uterine bleeding who require an invasive endometrial biopsy. There is clear potential for the analysis of these samples to extend to adjunct immunocytochemistry and genomic analysis, with the role of artificial intelligence to support this currently under investigation.

All of these novel diagnostic techniques have the potential to change the landscape of endometrial cancer diagnosis. Minimally invasive tests are likely to reduce pain and distress for women and could be used to reassure women at low risk of the disease, meaning that only those most likely to have an underlying endometrial cancer are required to undergo endometrial biopsy. These tests could also be used repeatedly to screen for endometrial cancer in women at high risk of the disease. At present, however, these early diagnostic techniques are only being used within the context of research studies, with evidence of their clinical utility available from a limited number of small cohorts of women who have already been diagnosed with endometrial cancer or presenting with postmenopausal bleeding.

References

1. Brown, K.F.; Rumgay, H.; Dunlop, C.; Ryan, M.; Quartly, F.; Cox, A.; Deas, A.; Elliss-Brookes, L.; Gavin, A.; Hounsome, L.; et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br. J. Cancer 2018, 118, 1130–1141.
2. Fortner, R.T.; Hüsing, A.; Dossus, L.; Tjønneland, A.; Overvad, K.; Dahm, C.C.; Arveux, P.; Fournier, A.; Kvaskoff, M.; Schulze, M.B.; et al. Theoretical potential for endometrial cancer prevention through primary risk factor modification: Estimates from the EPIC cohort. Int. J. Cancer 2020, 147, 1325–1333.
3. Kohler, L.N.; Garcia, D.O.; Harris, R.B.; Oren, E.; Roe, D.J.; Jacobs, E.T. Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review. Cancer Epidemiol. Biomark. Prev. 2016, 25, 1018–1028.
4. Crosbie, E.J.; Kitson, S.J.; McAlpine, J.N.; Mukhopadhyay, A.; Powell, M.E.; Singh, N. Endometrial cancer. Lancet 2022, 399, 1412–1428.
5. Kitson, S.J.; Evans, D.G.; Crosbie, E.J. Identifying High-Risk Women for Endometrial Cancer Prevention Strategies: Proposal of an Endometrial Cancer Risk Prediction Model. Cancer Prev. Res. 2017, 10, 1–13.
6. Luo, J.; Chlebowski, R.T.; Hendryx, M.; Rohan, T.; Wactawski-Wende, J.; Thomson, C.A.; Felix, A.S.; Chen, C.; Barrington, W.; Coday, M.; et al. Intentional Weight Loss and Endometrial Cancer

Risk. J. Clin. Oncol. 2017, 35, 1189–1193.

7. Zhang, X.; Rhoades, J.; Caan, B.J.; Cohn, D.E.; Salani, R.; Noria, S.; Suarez, A.A.; Paskett, E.D.; Felix, A.S. Intentional weight loss, weight cycling, and endometrial cancer risk: A systematic review and meta-analysis. Int. J. Gynecol. Cancer 2019, 29, 1361–1371.
8. Kitson, S.J.; Aurangzeb, O.; Parvaiz, J.; Lophatananon, A.; Muir, K.R.; Crosbie, E.J. Quantifying the Effect of Physical Activity on Endometrial Cancer Risk. Cancer Prev. Res. 2022, 15, 605–621.
9. Rubino, D.; Abrahamsson, N.; Davies, M.; Hesse, D.; Greenway, F.L.; Jensen, C.; Lingvay, I.; Mosenzon, O.; Rosenstock, J.; Rubio, M.A.; et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA 2021, 325, 1414–1425.
10. Valladales-Restrepo, L.F.; Sánchez-Ramírez, N.; Usma-Valencia, A.F.; Gaviria-Mendoza, A.; Machado-Duque, M.E.; Machado-Alba, J.E. Effectiveness, persistence of use, and safety of orlistat and liraglutide in a group of patients with obesity. Expert. Opin. Pharmacother. 2023, 24, 535–543.
11. Melson, E.; Ashraf, U.; Papamargaritis, D.; Davies, M.J. What is the pipeline for future medications for obesity? Int. J. Obes. 2024. ahead of print.
12. Garvey, W.T.; Batterham, R.L.; Bhatta, M.; Buscemi, S.; Christensen, L.N.; Frias, J.P.; Jódar, E.; Kandler, K.; Rigas, G.; Wadden, T.A.; et al. Two-year effects of semaglutide in adults with overweight or obesity: The STEP 5 trial. Nat. Med. 2022, 28, 2083–2091.
13. Wadden, T.A.; Tronieri, J.S.; Sugimoto, D.; Lund, M.T.; Auerbach, P.; Jensen, C.; Rubino, D. Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for Obesity in Primary Care: The SCALE IBT Randomized Controlled Trial. Obesity 2020, 28, 529–536.
14. Pucci, A.; Batterham, R.L. Mechanisms underlying the weight loss effects of RYGB and SG: Similar, yet different. J. Endocrinol. Investig. 2019, 42, 117–128.
15. Haghighat, N.; Kazemi, A.; Asbaghi, O.; Jafarian, F.; Moeinvaziri, N.; Hosseini, B.; Amini, M. Long-term effect of bariatric surgery on body composition in patients with morbid obesity: A systematic review and meta-analysis. Clin. Nutr. 2021, 40, 1755–1766.
16. Wilson, R.B.; Lathigara, D.; Kaushal, D. Systematic Review and Meta-Analysis of the Impact of Bariatric Surgery on Future Cancer Risk. Int. J. Mol. Sci. 2023, 24, 6192.
17. Holmberg, D.; Lagergren, J. What do we know about long-term effects of bariatric surgery? Br. J. Surg. 2022, 110, 1–2.
18. Allen, N.; Yang, T.O.; Olsson, H. Endometrial cancer and oral contraceptives: An individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 2015, 16, 1061–1070.

19. Faculty of Sexual and Reproductive Healthcare. Overweight, Obesity and Contraception; FSRH: London, UK, 2019.
20. Crosbie, E.J.; Ryan, N.A.J.; Arends, M.J.; Bosse, T.; Burn, J.; Cornes, J.M.; Crawford, R.; Eccles, D.; Frayling, I.M.; Ghaem-Maghami, S.; et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet. Med. 2019, 21, 2390–2400.
21. Iversen, L.; Fielding, S.; Lidegaard, Ø.; Hannaford, P.C. Contemporary hormonal contraception and risk of endometrial cancer in women younger than age 50: A retrospective cohort study of Danish women. Contraception 2020, 102, 152–158.
22. Soini, T.; Hurskainen, R.; Grenman, S.; Maenpaa, J.; Paavonen, J.; Pukkala, E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet. Gynecol. 2014, 124, 292–299.
23. Jareid, M.; Thalabard, J.C.; Aarflot, M.; Bøvelstad, H.M.; Lund, E.; Braaten, T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study. Gynecol. Oncol. 2018, 149, 127–132.
24. Derbyshire, A.E.; Allen, J.L.; Gittins, M.; Lakhiani, B.; Bolton, J.; Shaw, J.; Pemberton, P.W.; Needham, M.; MacKintosh, M.L.; Edmondson, R.J.; et al. PROgesterone Therapy for Endometrial Cancer Prevention in Obese Women (PROTEC) Trial: A Feasibility Study. Cancer Prev. Res. 2021, 14, 263–274.
25. Bernard, L.; Kwon, J.S.; Simpson, A.N.; Ferguson, S.E.; Sinasac, S.; Pina, A.; Reade, C.J. The levonorgestrel intrauterine system for prevention of endometrial cancer in women with obesity: A cost-effectiveness study. Gynecol. Oncol. 2021, 161, 367–373.
26. Silva, F.R.; Grande, A.J.; Lacerda Macedo, A.C.; Colonetti, T.; Rocha, M.C.; Rodrigues Uggioni, M.L.; Silva, B.R.; da Rosa, M.I. Meta-Analysis of Breast Cancer Risk in Levonorgestrel-Releasing Intrauterine System Users. Clin. Breast Cancer 2021, 21, 497–508.
27. Dossus, L.; Rinaldi, S.; Becker, S.; Lukanova, A.; Tjonneland, A.; Olsen, A.; Stegger, J.; Overvad, K.; Chabbert-Buffet, N.; Jimenez-Corona, A.; et al. Obesity, inflammatory markers, and endometrial cancer risk: A prospective case-control study. Endocr. Relat. Cancer 2010, 17, 1007–1019.
28. Modugno, F.; Ness, R.B.; Chen, C.; Weiss, N.S. Inflammation and endometrial cancer: A hypothesis. Cancer Epidemiol. Biomark. Prev. 2005, 14, 2840–2847.
29. Verdoodt, F.; Friis, S.; Dehlendorff, C.; Albieri, V.; Kjaer, S.K. Non-steroidal anti-inflammatory drug use and risk of endometrial cancer: A systematic review and meta-analysis of observational studies. Gynecol. Oncol. 2016, 140, 352–358.

30. Burn, J.; Sheth, H.; Elliott, F.; Reed, L.; Macrae, F.; Mecklin, J.P.; Möslein, G.; McRonald, F.E.; Bertario, L.; Evans, D.G.; et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: A double-blind, randomised, placebo-controlled trial. Lancet 2020, 395, 1855–1863.
31. Kitson, S.; Maskell, Z.; Sivalingam, V.N.; Allen, J.L.; Ali, S.; Burns, S.; Gilmour, K.; Latheef, R.; Slade, R.J.; Pemberton, P.; et al. PRE-surgical Metformin in Uterine Malignancy (PREMIUM): A multi-center, randomized double-blind, placebo-controlled phase 3 trial. Clin. Cancer Res. 2019, 25, 2424–2432.
32. Clement, N.S.; Oliver, T.R.; Shiwani, H.; Sanner, J.R.; Mulvaney, C.A.; Atiomo, W. Metformin for endometrial hyperplasia. Cochrane Database Syst. Rev. 2017, 10, CD012214.
33. Chu, D.; Wu, J.; Wang, K.; Zhao, M.; Wang, C.; Li, L.; Guo, R. Effect of metformin use on the risk and prognosis of endometrial cancer: A systematic review and meta-analysis. BMC Cancer 2018, 18, 438.
34. Janda, M.; Robledo, K.P.; Gebski, V.; Armes, J.E.; Alizart, M.; Cummings, M.; Chen, C.; Leung, Y.; Sykes, P.; McNally, O.; et al. Complete pathological response following levonorgestrel intrauterine device in clinically stage 1 endometrial adenocarcinoma: Results of a randomized clinical trial. Gynecol. Oncol. 2021, 161, 143–151.
35. Moller, P.; Seppala, T.; Bernstein, I.; Holinski-Feder, E.; Sala, P.; Evans, D.G.; Lindblom, A.; Macrae, F.; Blanco, I.; Sijmons, R.; et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: First report from the prospective Lynch syndrome database. Gut 2017, 66, 464–472.
36. Pfeiffer, R.M.; Park, Y.; Kreimer, A.R.; Lacey, J.V., Jr.; Pee, D.; Greenlee, R.T.; Buys, S.S.; Hollenbeck, A.; Rosner, B.; Gail, M.H.; et al. Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: Derivation and validation from population-based cohort studies. PLoS Med. 2013, 10, e1001492.
37. Husing, A.; Dossus, L.; Ferrari, P.; Tjonneland, A.; Hansen, L.; Fagherazzi, G.; Baglietto, L.; Schock, H.; Chang-Claude, J.; Boeing, H.; et al. An epidemiological model for prediction of endometrial cancer risk in Europe. Eur. J. Epidemiol. 2016, 31, 51–60.
38. Shi, J.; Kraft, P.; Rosner, B.; Benavente, Y.; Black, A.; Brinton, L.A.; Chen, C.; Clarke, M.A.; Cook, L.S.; Costas, L.; et al. Risk prediction models for endometrial cancer: Development and validation in an international consortium. J. Natl. Cancer Inst. 2023, 115, 552–559.
39. Kitson, S.J.; Crosbie, E.J.; Evans, D.G.; Lophatananon, A.; Muir, K.R.; Ashcroft, D.; Kontopantelis, E.; Martin, G.P. Predicting risk of endometrial cancer in asymptomatic women (PRECISION): Model development and external validation. BJOG 2023. early view.

40. Kitson, S.J.; Khan, U.; Crosbie, E.J. Lay and general practitioner attitudes towards endometrial cancer prevention: A cross-sectional study. Fam. Pract. 2023, 2023, cmad076.
41. van Hanegem, N.; Prins, M.M.; Bongers, M.Y.; Opmeer, B.C.; Sahota, D.S.; Mol, B.W.; Timmermans, A. The accuracy of endometrial sampling in women with postmenopausal bleeding: A systematic review and meta-analysis. Eur. J. Obstet. Gynecol. Reprod. Biol. 2016, 197, 147–155.
42. Liu, J.; Han, L.; Sun, Q.; Li, Y.; Niyazi, M. Meta-analysis of the diagnostic accuracy of HE4 for endometrial carcinoma. Eur. J. Obstet. Gynecol. Reprod. Biol. 2020, 252, 404–411.
43. Li, L.M.; Zhu, Y.X.; Zhong, Y.; Su, T.; Fan, X.M.; Xi, Q.; Li, M.Y.; Fu, J.; Tan, H.; Liu, S. Human epididymis protein 4 in endometrial cancer: A meta-analysis. Clin. Chim. Acta 2018, 482, 215–223.
44. Knific, T.; Osredkar, J.; Smrkolj, Š.; Tonin, I.; Vouk, K.; Blejec, A.; Frković Grazio, S.; Rižner, T.L. Novel algorithm including CA-125, HE4 and body mass index in the diagnosis of endometrial cancer. Gynecol. Oncol. 2017, 147, 126–132.
45. Bolivar, A.M.; Luthra, R.; Mehrotra, M.; Chen, W.; Barkoh, B.A.; Hu, P.; Zhang, W.; Broaddus, R.R. Targeted next-generation sequencing of endometrial cancer and matched circulating tumor DNA: Identification of plasma-based, tumor-associated mutations in early stage patients. Mod. Pathol. 2019, 32, 405–414.
46. Beinse, G.; Borghese, B.; Métairie, M.; Just, P.A.; Poulet, G.; Garinet, S.; Parfait, B.; Didelot, A.; Bourreau, C.; Agueeff, N.; et al. Highly Specific Droplet-Digital PCR Detection of Universally Methylated Circulating Tumor DNA in Endometrial Carcinoma. Clin. Chem. 2022, 68, 782–793.
47. Fan, X.; Zou, X.; Liu, C.; Cheng, W.; Zhang, S.; Geng, X.; Zhu, W. MicroRNA expression profile in serum reveals novel diagnostic biomarkers for endometrial cancer. Biosci. Rep. 2021, 41, BSR20210111.
48. Nair, N.; Camacho-Vanegas, O.; Rykunov, D.; Dashkoff, M.; Camacho, S.C.; Schumacher, C.A.; Irish, J.C.; Harkins, T.T.; Freeman, E.; Garcia, I.; et al. Genomic Analysis of Uterine Lavage Fluid Detects Early Endometrial Cancers and Reveals a Prevalent Landscape of Driver Mutations in Women without Histopathologic Evidence of Cancer: A Prospective Cross-Sectional Study. PLoS Med. 2016, 13, e1002206.
49. Wang, Y.; Li, L.; Douville, C.; Cohen, J.D.; Yen, T.T.; Kinde, I.; Sundfelt, K.; Kjær, S.K.; Hruban, R.H.; Shih, I.M.; et al. Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers. Sci. Transl. Med. 2018, 10, eaap8793.
50. Pelegrina, B.; Paytubi, S.; Marin, F.; Martínez, J.M.; Carmona, Á.; Frias-Gomez, J.; Peremiquel-Trillas, P.; Dorca, E.; Zanca, A.; López-Querol, M.; et al. Evaluation of somatic mutations in

cervicovaginal samples as a non-invasive method for the detection and molecular classification of endometrial cancer. EBioMedicine 2023, 94, 104716.

51. Evans, I.; Reisel, D.; Jones, A.; Bajrami, A.; Nijjar, S.; Solangon, S.A.; Arora, R.; Redl, E.; Schreiberhuber, L.; Ishaq-Parveen, I.; et al. Performance of the WID-qEC test versus sonography to detect uterine cancers in women with abnormal uterine bleeding (EPI-SURE): A prospective, consecutive observational cohort study in the UK. Lancet Oncol. 2023, 24, 1375–1386.
52. O'Flynn, H.; Ryan, N.A.J.; Narine, N.; Shelton, D.; Rana, D.; Crosbie, E.J. Diagnostic accuracy of cytology for the detection of endometrial cancer in urine and vaginal samples. Nat. Commun. 2021, 12, 952.