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5

Endometrial cancer prevention in high-risk women

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A B S T R A C T

Endometrial cancer (EC) is the most common gynaecological malignancy, and its incidence is rising alongside the growing prevalence of obesity. Effective risk-reducing interventions hijacking the key mechanisms driving endometrial carcinogenesis may affect EC diagnoses if aimed at those at greatest risk. An understanding of the key risk factors and their role in tumourigenesis is critical in developing such prevention strategies. In this review, we summarise the major risk factors for EC and the evidence for available risk-reducing interventions in high-risk women. We suggest potential prevention strategies and make a case for the need for risk prediction models that identify specific groups of women at a particularly high risk of EC for whom risk-reducing interventions are likely to have a significant impact.

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Introduction

Endometrial cancer (EC) is the sixth most frequently diagnosed cancer and the 14th leading cause of cancer mortality in women globally, with over 380,000 new cases and 89,000 deaths in 2018 [1]. In the United States (US), there are over 60,000 incident cases and 10,000 deaths from EC each year. By 2030, its incidence is expected to double to over 120,000 cases, with EC becoming the third most common cancer affecting women in the US after lung and colorectal cancers (CRC) [2]. As a direct consequence, the number of women dying from EC is also rising, despite improvements in overall survival [3].

EC has traditionally been classified into two histological categories that differ in incidence, oestrogen responsiveness and prognosis (Bokhmans dichotomous model) [4]. Type I tumours have a recognised precursor lesion, atypical hyperplasia (AH), and are by far the most common. They are low-grade, low-stage, oestrogen-driven tumours that are associated with obesity and a favourable outcome. By contrast, type II tumours are relatively rare, high-grade, clinically aggressive tumours that are more common in non-obese women and act independently of oestrogen [4,5]. Recent epidemiological studies however indicate a complexity in EC risk factors with obesity playing an important role in both types [5,6]. The more recent classification by the Cancer Genome Atlas Research Network based on a comprehensive genomic and transcriptomic analysis classifies EC into four molecular categories based on mutation spectra, microsatellite instability and copy number aberrations: polymerase-epsilon (*POLE)* ultramutated, microsatellite instable, copy number low and copy number high [7]. This classification has been validated in subsequent studies and shown to have prognostic and therapeutic implications [8,9].

EC usually presents at an early stage following the onset of postmenopausal bleeding, reflected in excellent overall 5-year survival rates [10]. Treatment is primarily surgery with or without adjuvant therapy but is not without considerable morbidity, especially in an increasingly ageing population [10]. For young women, hysterectomy has devastating consequences for fertility, but alternative non-surgical treatments are less effective and risk progressive diseases [11]. Women with advanced or recurrent EC have limited evidence-based treatment options and face a dismal prognosis [12,13]. There is currently insufficient evidence to support screening in either the general population or high-risk women for the detection and treatment of premalignant disease. Prevention strategies are therefore urgently needed, particularly in the wake of the emerging epidemic of EC predicted by the explosion in obesity rates worldwide alongside changing patterns of hysterectomy [14].

Defining high-risk women

Identifying women at high risk of EC and the likely carcinogenic mechanisms involved is important to 1) select women most likely to derive clinical benefits; 2) choose the most appropriate risk-reducing measure; and 3) avoid the side effects and costs of unnecessary interventions for those at lowest risk. Only a proportion of women deemed at high risk through genetic predisposition, increased body mass index (BMI), lifestyle or reproductive risk factors will ever develop EC; thus, it is important to develop robust, accurate and clinically implementable risk prediction tools to quantify risk.

As an example, obesity (BMI $\geq$ 30 kg/m^2) is the strongest risk factor for EC. For every 5 kg/m^2 increase in BMI, there is a 60% increased risk of EC, with a BMI above 25 kg/m^2 doubling the risk and a BMI above 30 kg/m^2 tripling the risk [15,16]. The lifetime risk of EC is calculated at 2–3% and 9–10% in normal weight and obese women respectively [15], and it has been estimated that 35% of all EC are directly attributable to obesity [17,18]. However, not every obese woman will develop EC. Type 2 diabetes mellitus is also a strong risk factor for EC [19], with large epidemiological studies adjusting for BMI, concluding that type 2 diabetes confers a 62% increased risk of EC, independent of obesity [20]. Yet, insulin resistance and obesity act synergistically to increase EC risk [21]. Other high-risk groups include women with polycystic ovary syndrome (PCOS), who have a 9% lifetime risk of EC [22]; nulliparous women, particularly those with early menarche and late menopause [23]; and those who take tamoxifen for the prevention or adjuvant treatment of breast cancer, which increases the risk of EC by two-to three-fold [10,24].

Genetic risk factors for EC include Lynch syndrome (LS) and Cowden syndrome. LS is an autosomal dominant inherited disorder that results from a germline pathogenic variant in one of the DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6* and *PMS2*. Women with LS have a 27–57% lifetime risk of developing EC [25,26]. They are also more likely to develop the disease at a young age and are prone to other malignancies including colorectal and ovarian cancers [27]. Ryan and colleagues, in a meta-analysis of data from 53 studies involving over 12,000 EC patients, report the prevalence of LS in EC to be 3%, similar to the prevalence of LS in CRC [28]. Cowden syndrome (CS), however, an often overlooked and underdiagnosed cancer predisposition syndrome, is a rare autosomal dominant disorder resulting most commonly from germline mutations in the phosphatase and tensin homolog *(PTEN)* gene located on chromosome 10q.23.21 [29]. Other genes implicated in CS include PIK3CA and AKT1 [30]. Women with CS have a 5–28% lifetime risk of EC and are also prone to breast, thyroid and renal cancers as well as hamartomatous growths in many body areas [29]. Pre implantation genetic diagnosis in conjunction with in vitro fertilisation can enable women with hereditary cancer syndromes such as LS reduce the chances of their children inheriting the responsible pathogenic variant [31]. Whether EC risk is increased in female carriers of *BRCA1 and BRCA2* pathogenic variants is unclear. While multiple studies [32–34] report an increased risk in women with a BRCA + status, others suggest a risk mostly limited to tamoxifen users [35,36]. Several other studies [37,38] have suggested an increased risk of the more aggressive serous and serous-like EC, especially in women with BRCA1+ status, but this has not been confirmed in others [39–41]. Thus, more studies are needed to clarify the association between EC risk and germline BRCA status.

Few studies have sought to develop risk prediction models to inform women and their doctors of their risk status, or define eligibility for EC prevention strategies. Alblas et al. carried out a systematic review of 14 relevant studies and identified two EC risk prediction models for use in the general population based on serum biomarkers and epidemiological variables, specifically BMI and reproductive history [42]. Neither model has been externally validated. Our group has recently proposed a comprehensive model incorporating clinical measures of obesity, insulin resistance, reproductive hormones and family history for the identification of high-risk women [10], with ongoing plans to test its performance in prospective cohorts. Future work will incorporate genetic markers into our EC risk prediction model.

Understanding endometrial carcinogenesis

Women with familial risk carry a pathogenic variant in a key gene implicated in endometrial carcinogenesis. MMR deficiency, for example, results in an inability to correct base substitution errors that occur during DNA replication, thus predisposing to tumour formation in individuals with LS [43]. Three biological pathways are strongly implicated in obesity-driven endometrial carcinogenesis, specifically hormonal imbalance, insulin resistance and systemic inflammation. Of these three, hormonal imbalance, especially adipose-derived unopposed oestrogen in obese postmenopausal women, is the most established [15,18]. Oestrogen, by binding to endometrial cell DNA, not only activates the proliferative PI3K/AKT/mTOR signalling pathway but also positively modulates the expression of genes linked to endometrial proliferation including cMyc and cyclin A, leading to uncontrolled cellular proliferation and the accumulation of replication errors predisposing to malignancy [21,44,45]. Unopposed oestrogen *per se* is not the whole story, however, as there is mounting evidence for cross-talk with other hormones such as insulin, and for the direct pro-proliferative and anti-apoptotic effect of insulin and IGF-1 on EC cells [10,46] (Fig. 1). Chronic inflammation, a common feature of obesity, results in DNA damage through free radical formation and defective immunosurveillance, facilitating tumourigenesis [10]. Understanding the pathogenesis of obesity-driven EC is fundamental to the design of effective risk-reducing strategies (Fig. 1).

EC prevention interventions

Weight loss and physical activity

Maintaining a healthy BMI reduces EC risk [21,44]. The cohort study by Schouten et al. showed that women with a significantly lower BMI at an older age compared to their BMI at age 20 were 50% less

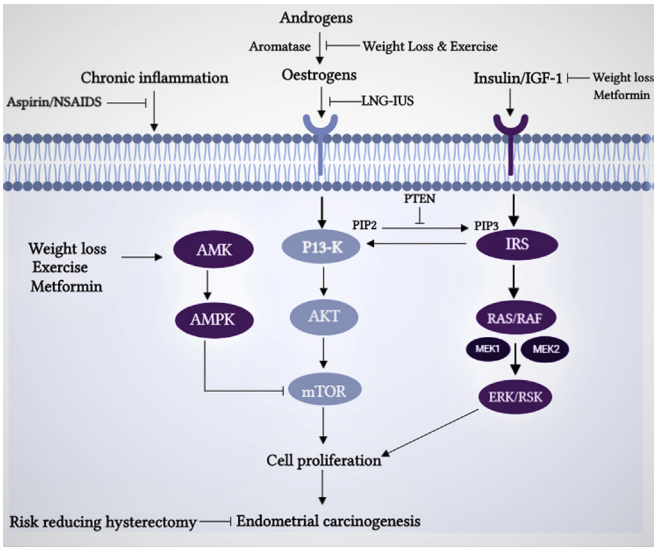

Fig. 1. Knowledge of obesity-driven endometrial carcinogenesis can facilitate the design of risk-reducing intervention strategies. This figure shows how known prevention interventions may impact pro-oncogenic signalling pathways. Key: LNG-IUS, levonorgestrel-releasing intrauterine system; NSAIDS, non-steroidal anti-inflammatory drugs.

likely to develop EC than those with a stable BMI [47]. Trentham et al., in a population-based case–control study found that obese women who maintained weight loss for at least five years had a 25% reduced risk of EC compared to those whose weight remained stable [48].

Lifestyle modification and anti-obesity medications can result in 4–6% and 7–10% loss of excess body weight respectively; however, this is difficult to sustain [49,50]. Bariatric surgery, however, by either gastric bypass, sleeve or banding, restricts the amount of food the stomach can hold and results in sustained loss of as much as 15% of a woman's excess body weight by two months, and continuing weight loss to one year post surgery, albeit at an ever decreasing rate [21,49,50].

There is good evidence that obese women who achieve and maintain bariatric surgery-induced weight loss have a significantly lower risk of EC than those who remain obese [51]. Ward and colleagues, in a retrospective cohort study of over 100,000 bariatric surgery patients in the US, reported a 77–81% decrease in the risk of EC after bariatric surgery [52]. In a prospective study of morbidly obese Swedish patients who underwent bariatric surgery or had medical weight loss management, there was a 38% reduction in all cancer incidence in women who sustained a weight loss of at least 20 kg for at least 10 years and a 34% reduction in the risk of EC [53]. The meta-analysis by Upala and colleagues involving over 800,000 participants confirmed a 60% reduction in the risk of EC following bariatric surgery [51]. However, most of the evidence comes from observational studies because randomised controlled trials are challenging in this area.

Studies have been consistent in showing that higher levels of physical activity reduce the risk of EC [13,54,55]. A recent meta-analysis of over 19,000 EC cases found a 20% lower risk of EC in women with high physical activity levels compared to those with sedentary lifestyles [54]. Studies involving physical activity are complicated by overreliance on self-reported activity levels that are challenging to quantify accurately. Possible biological mechanisms linking weight loss and physical activity with altered EC risk include reduced obesity and adiposity, changes in endogenous hormone levels, metabolism and growth factors, as well as alterations in immune function [15,21,44]. A recent study by our group looked at the impact of obesity and bariatric surgery on circulating and tissue biomarkers of EC risk and found a reversal of EC precursor lesions and down regulation of the P13–AKT–mTOR signalling pathway with weight loss [56].

Arthur and colleagues, in the study of cancer risk and the Healthy Lifestyle Index (HLI), a model of lifestyle factors including physical activity and obesity, report a 5% decrease in EC risk for every unit increase in HLI [57]. Based on existing evidence, several health organisations including the World Cancer Research Fund now recommend a minimum of 30 min of moderate-to vigorous-intensity physical activity for at least 5 days a week for cancer prevention [58].

Reversing insulin resistance

Insulin resistance and compensatory hyperinsulinism are cardinal features of PCOS [59] and acting via signal transduction pathways play an important role in carcinogenesis [60]. Lifestyle changes incorporating exercise and weight loss are first-line recommendations for managing the menstrual and subfertility manifestations of PCOS. Weight loss also reduces circulating insulin levels and improves insulin sensitivity, which may be mechanistically important in reducing EC risk [44], although this has not been convincingly shown in PCOS [61]. The insulin sensitising drug metformin is used to manage subfertility and oligomenorrhoea in women with PCOS, based on the assumption that insulin resistance is the major player in its pathogenesis [62]. There is however no RCT evidence to support its use for EC prevention in women with PCOS.

There is lack of robust evidence to support the use of metformin alone or in combination with progestins for the treatment of AH, and hence EC prevention. In a small, nonrandomised study, Mitsuashi and colleagues investigated the efficacy of metformin in combination with medroxyprogesterone acetate (MPA) in 17 women with AH and 19 with EC, and reported a 81% complete pathological response rate and 89% 3-year relapse-free rate [63]. None of the women with AH who achieved a complete response relapsed during the median follow period of 38 months (range, 9–66 months) [63]. As this was a phase II trial, there was no comparator (MPA only) group. Caution must be entertained when comparing the study findings with those from MPA only studies, where a 75–93% response rate has been reported [64,65], due to the substantial heterogeneity in the studied population and MPA doses used. A Cochrane review found insufficient evidence to support or refute the use of metformin with or without progestin in treating women with AH although this was based on two RCTs involving just 59 women, and more studies are needed [66]. The feMME trial, a phase II RCT is currently investigating the levonorgestrel-releasing intra-uterine system (LNG-IUS) alone or in combination with metformin or weight loss for the treatment of low-grade early stage EC [67]. These results are eagerly awaited although biomarker studies have so far failed to demonstrate convincing evidence for a cytostatic effect of 2–16 weeks of metformin therapy in women with EC [19,68].

A meta-analysis by Chu and colleagues reports that metformin prolongs overall survival and reduces the risk of EC recurrence, but has no beneficial effect on EC risk in women with type 2 diabetes mellitus [69]. While metformin certainly reduces the risk of type 2 diabetes in obese women with non-diabetic hyperglycaemia [70], it is unclear whether, in so doing, it also reduces EC risk, although this is a tantalising concept that our group seeks to explore further [71].

Exogenous hormones

Tamoxifen

Tamoxifen, a selective oestrogen receptor modulator, is used for the prevention and adjuvant treatment of breast cancer but results in a two-to three-fold increased risk of EC due to its agonistic effect on the endometrium [24]. Recent changes to NICE guidance may see more women exposed to tamoxifen for primary breast cancer prevention in genetically predisposed women [72]. The EC risk, largely restricted to postmenopausal women, is both dose and duration-of-exposure dependent [10]. In the meta-analysis of four RCTs by Fleming and colleagues, the incidence of EC increased two-fold with extended tamoxifen use compared to the standard five years of tamoxifen [24]. There is currently no endometrial surveillance programme in place for tamoxifen users despite increased risks of endometrial polyps, hyperplasia and cancer [73]. Neither the Royal College of Obstetricians and Gynaecologists (RCOG) nor the American College of Obstetricians and Gynaecologists (ACOG) guidelines recommend routine endometrial surveillance in asymptomatic women taking tamoxifen [74]. Wong and colleagues, in an RCT, report that concurrent use of LNG-IUS reduced the risk of endometrial polyps

in tamoxifen users [75]. A convincing reduction in EC risk with concurrent LNG-IUS therapy is, however, yet to be demonstrated.

Hormone replacement therapy

Studies have been consistent in showing an increased incidence of EC according to dose and duration of oestrogen-only hormone replacement therapy (HRT) use with relative risks ranging from 1.1 to 15 [15,76]. Unopposed oestrogens are no longer recommended for the treatment of postmenopausal symptoms in women who have not had a hysterectomy. However, safer oestrogen-based, progestin-free oral menopausal HRT has now been developed as a hormone replacement option for women with an intact uterus [21]. The combination of conjugated oestrogens with the SERM bazedoxifene (CE/BZA) minimises the agonistic effect of oestrogen on the endometrium while treating menopausal symptoms and protecting against osteoporosis. RCTs have been consistent in showing no increase in endometrial hyperplasia with CE/BZA [77]. It may thus be an option for women who are unable to tolerate progestin due to side effects.

Progestins

Combined oestrogen-progestin therapy (combined oral contraceptive, COC and combined HRT) has a protective effect on EC risk [21]. The benefit of COC and combined HRT relates to the progestin component, which suppresses endometrial proliferation [78]. A meta-analysis of over 27,000 women with EC showed a 24% reduction in EC risk for every 5 years of COC use, with the benefit persisting for more than 30 years after discontinuation [79]. The Royal College of Physicians General Practitioners Oral Contraception study, the largest and longest-duration study of COC use, showed that ever users of COC had a 34% decreased risk of EC [80]. The UK Faculty of Sexual and Reproductive Health however advises that the risks of COC are likely to outweigh the benefits at BMI >35 kg/m^2, thus precluding its use in most obese women [81].

Effective treatment of endometrial hyperplasia, especially those with atypia, is crucial in preventing their progression to EC. Studies have been consistent in showing regression of AH with continuous oral and intrauterine progestins. The Cochrane systematic review by Luo et al. involving 153 women, 19 of whom had AH, assessed the efficacy of LNG-IUS vs oral progestins for the treatment of AH and reported a 100% regression in the former vs 77% in the latter group [82]. There was insufficient evidence to draw definite conclusions regarding the relative efficacy of the route of administration due to small numbers. Orbo and colleagues, in a multicentre RCT, investigated the effectiveness of LNG-IUS vs oral MPA in treating low- and medium-risk endometrial hyperplasia (*D*-score >0) and reported 100% response rate at 6 months in the LNG-IUS group (53/53, 95% CI 0.93–1.0), 96% in the continuous oral MPA group (46/48, 95% CI 0.86–0.99) and 69% in the cyclic oral MPA group (36/52, 95% CI 0.55–0.8) [83]. Given the higher regression rate and favourable side effect profile, the RCOG recommends LNG-IUS as first-line treatment for endometrial hyperplasia without atypia, while continuous progestogens (MPA 10–20 mg/day or norethisterone 10–15 mg/day) can be offered to women who decline LNG-IUS [13,84]. Cyclical progestogens are less effective and not recommended. Women with *atypical* hyperplasia, however, are best managed by hysterectomy (see section Risk-reducing hysterectomy). For those not fit for surgery or wishing to preserve their fertility, LNG-IUS or continuous high-dose oral progestogens (MPA 400–600 mg/day or megestrol 160–320 mg/day) are recommended by expert groups [84]. Women will however need to be carefully counselled about the risks involved with this option, including but not limited to progression to EC. In a meta-analysis of 34 observational studies evaluating regression and relapse rates of AH and early-stage EC in women treated conservatively for fertility-sparing reasons, Gallos and colleagues report a pooled regression rate of 85.6% and relapse rate of 26% in women with AH [64]. This should however be interpreted with caution, given the substantial heterogeneity in the studied populations, types and doses of treatment options used.

There is good evidence to suggest a reduction in EC risk with progestin-only contraceptives in the general population. The Finnish study of over 90,000 women using the LNG-IUS showed a decreased incidence of EC (observed to expected ratio of 0.50) among LNG-IUS users [85]. The NOWAC study, a population-based prospective cohort study of Norwegian women, reported a reduced risk of EC among ever users of LNG-IUS (RR 0.22, 95% CI 0.13–0.40) compared to never users [86]. It is unclear whether progestin-based therapy is as effective in high-risk women, e.g. those with LS as they are in the general

population. The POET trial, a phase III RCT, was designed to investigate the efficacy of LNG-IUS in LS-associated EC prevention but failed to recruit and was discontinued [87]. Lu and colleagues, in a prospective randomised biomarker study, compared COC vs depo-provera for the prevention of EC in women with LS and reported a dramatic decrease in endometrial proliferation with both [88]. Ongoing work in our group is looking at the feasibility, acceptability and compliance of LNG-IUS for the primary prevention of EC in obese women with BMI >40 kg/m^2 (PROTEC 1 study) [89].

Withdrawal bleeds, pregnancy and breast feeding

The anovulation that characterises PCOS exposes the endometrium to prolonged oestrogenic stimulation and oligo- or amenorrhoea. Induction of regular withdrawal bleeds in women with PCOS using progestogens allows for regular endometrial shedding and is crucial in reducing the risk of developing AH and carcinoma [21,90]. Progestogens also have a direct pro-apoptotic and anti-mitotic effect on endometrial cells [91,92] and can be potent EC prevention agents in these women.

Breast feeding protects against EC [93,94]. In a meta-analysis of 17 studies in the Epidemiology of Endometrial Cancer Consortium, ever breast feeding was associated with an 11% decrease in the risk of EC [93]. In another meta-analysis by Zhan et al., a decrease in EC risk of 1.2% was observed for every month of breastfeeding [94]. Continued efforts at promoting breastfeeding at a population level may therefore help reduce the risk of EC.

Childbearing at an older age has been shown to be independently associated with a reduced risk of EC. In a large pooled analysis of studies in the Epidemiology of Endometrial Cancer Consortium, a 13% decrease in EC risk per 5-year delay in last child birth was found. Women whose age at last birth was at least 40 years had a 44% decreased EC risk compared to those who had their last birth at age 25 years [95]. A number of biological mechanisms have been suggested for this observation and include: 1) older women capable of being pregnant have a healthy endometrium and/or have experienced fewer anovulatory cycles [96]; 2) prolonged progesterone exposure during pregnancy may be more beneficial at older ages [96]; and 3) shedding of premalignant cells during childbirth [95]. The associated risks of child bearing at advanced age clearly outweigh any potential benefits for EC risk reduction; however, these observations provide unique insights into the mechanisms involved in endometrial carcinogenesis and clues for intervention.

Risk-reducing hysterectomy

Prophylactic hysterectomy and bilateral salpingo-oophorectomy when fertility is no longer required is effective in preventing EC and ovarian cancer in women with LS and is recommended by expert groups [13,97]. A case–control study comparing women with documented LS who had prophylactic hysterectomy versus those who did not, showed absence of EC in the former group vs 33% risk of EC over a limited follow-up period in the latter, suggesting a 100% prevented fraction [98]. Risk-reducing hysterectomy is also recommended in women with AH, which has progression rates in the order of 8–25% [84]. There is, however, insufficient evidence to justify its use in *BRCA1* and *BRCA2* pathogenic variant carriers or tamoxifen users to prevent EC. Given that surgery is not without risks, especially in obese women, with intra-operative and post-operative morbidity affecting a significant minority, there is a need for alternative non-surgical prevention interventions in those at highest risk [13,97].

Non-steroidal anti-inflammatory drugs and aspirin

Burn et al., in a primary prevention trial (CaPP2) evaluating the long-term effect of aspirin on cancer risk in LS, reported a non-statistically significant reduction in the risk of EC with a once daily aspirin regimen of 600 mg for up to four years [99]. This study was powered for CRC prevention and had insufficient numbers to conclude that aspirin is effective for EC prevention; however, the data are encouraging. The precise mechanism by which aspirin prevents EC in women with LS remains unclear. Reduced microsatellite instability and increased apoptosis in MMR-deficient cells have been suggested [100]. The ongoing CaPP3 trial will identify the most appropriate dose for cancer prevention in this

Table 1
Summary of endometrial cancer prevention strategies and recommendations.

A. Avoid risk factors
A1. Attain and maintain a healthy BMI (<25 kg/m^2).
A2. Exercise for 30 min a day, five days a week (moderate/vigorous intensity).
A3. Attend regular health checkups (e.g. Well Woman Check) for early detection and management of overweight/obesity and PCOS.
A4. Recommend bariatric surgery when BMI> 40 kg/m^2 or if BMI >35 kg/m^2 in presence of other comorbidities.
A5. Do not use oestrogen-only hormone replacement therapy in women with an intact uterus.
B. Engage in risk reduction
B1. Encourage weight loss in overweight and obese women.
B2. Consider use of the combined oral contraceptive, where not contraindicated, if contraception is required.
B3. Use oral or intrauterine progestins, where not contra-indicated.
B4. Induce regular withdrawal bleeds with cyclical hormones in women with PCOS.
B5: Encourage breast feeding.
B6. Drink coffee, in moderation.
C. Prevention in high-risk women
C1. Genetic testing for those with a family history of LS.
C2. Risk-reducing hysterectomy after completion of childbearing.
D. Potential prevention strategies (Further research needed)
D1. Use of aspirin in those with LS
D2. Use of LNG-IUS in obese women and those with LS
D2. Bisphosphonates
D3. Metformin

group [101]. A 2016 meta-analysis of observational studies by Verdoodt and colleagues suggested a marginally reduced risk of EC with aspirin and regular NSAIDS and a larger risk reduction with a high frequency of NSAID usage in obese women [102]. These findings should be interpreted with caution given the wide variability in the dose and duration of aspirin use between studies. A more recent meta-analysis by Qiao and Yang et al. is also in keeping with an inverse association between aspirin use and EC risk [103]. There was however substantial heterogeneity across included studies, and it was unclear what dose of aspirin women were taking.

Bisphosphonates

Bisphosphonates have been shown to have anti-tumour properties in both pre-clinical and animal model studies, through induction of apoptosis, reduced tumour proliferation, antiangiogenic and immune modulatory mechanisms [104]. A meta-analysis including over 6000 EC cases reported a 56% reduction in the risk of EC with 3 years or more usage of bisphosphonates [105]. This meta-analysis is however limited by the observational nature of included studies, all of which were from anonymised prescription databases and hence may not reflect the true adherence of users to their prescribed medications.

Dietary interventions

Soy, coffee and tea have all been associated with reduced EC risk. The meta-analysis by Zhong and colleagues involving 13 epidemiological studies demonstrated an inverse relationship between dietary isoflavones and EC risk [106]. Zhou et al., in a meta-analysis of over 1.5 million subjects and 10,100 EC cases, reported a dose-dependent decrease in EC risk with coffee intake, greater with but not limited to caffeinated coffee [107]. There was a 7% reduction in risk per cup of caffeinated coffee per day in comparison to a 4% risk reduction per cup of decaffeinated coffee per day. Tang and colleagues in another meta-analysis demonstrated that an increase in tea intake of 2 cups per day was associated with a 25% reduction in EC risk [108]. While isoflavones from soy products reduce EC risk by interfering with the synthesis, metabolism and signal transduction of oestrogen hormones [106], polyphenols and caffeine in tea and coffee act by scavenging free radicals, improving insulin sensitivity, inhibiting inflammation and reducing levels of free oestradiol [109]. Most of the studies linking soy, coffee and tea

Table 2
Major gaps in our knowledge of endometrial cancer risk assessment and prevention.

A. Gaps in risk estimation
A1. Identification of women at high risk of EC who will benefit from prevention strategies.
A2.The optimal prediction model to estimate risk in the general population and in high-risk populations.
A3. Whether genetic and epigenetic markers improve the performance of proposed risk prediction models?
B. Gaps in risk-reducing interventions
B1. Evidence for aspirin, metformin and bisphosphonates for chemoprevention in high-risk women.
B2. Robust evidence for the use of LNG-IUS in high-risk women such as those with LS, obese women and tamoxifen users.
B3. Novel therapies for women who do not benefit from current prevention strategies.
B4: Clarity on whether hormonal contraceptives are as effective for chemoprevention in LS as they are in the general population.
C. Gaps in understanding the biology of EC risk
C1. An understanding of the biological mechanisms driving EC
D. Gaps in implementing known prevention measures
D1. The role of screening for EC in women with LS
D2. How to effectively engage women and families in EC prevention throughout the life course.
D3. How to make current prevention therapies, including bariatric surgery, available to those who will benefit from it.

to EC have been observational in nature and limited by recall and selection bias. Larger prospective studies are needed to provide better quality evidence.

Cigarette smoking has been found to be protective against EC, especially in postmenopausal women, but is not recommended for EC prevention [110]. In the meta-analysis of prospective studies by Zhou et al., women with a smoking history had a 29% reduction in EC risk compared to non-smokers [110]. Possible underpinning mechanisms include altered oestrogen production and metabolism [110,111] and direct ovarian toxicity leading to early menopause [112]. However, the health risks associated with smoking far outweigh the benefit.

Conclusion

Risk-reducing hysterectomy (LS, AH), bariatric surgery (obesity), induction of withdrawal bleeds with cyclical hormones (PCOS) and use of LNG-IUS/high-dose progestogens (as fertility-sparing treatment of AH) are proven methods of EC prevention in high-risk women, while nonsurgical weight loss and modulation of insulin resistance are potential methods of prevention that require further evidence to support their use (Table 1). While findings from the CaPP2 trial provide a basis for recommending aspirin chemoprophylaxis in women with LS, the CaPP3 trial is investigating the optimal dose and duration of aspirin treatment for cancer prevention. Risk prediction models capable of predicting women at the highest risk of developing EC will help maximise the benefits from targeted prevention strategies. Future research incorporating genetic markers into epidemiology-based prediction studies are likely to yield clinically relevant risk prediction tools that can be validated and translated into the clinic.

Practice points

- Obesity is the strongest modifiable risk factor for EC.
- Bariatric surgery is effective in reducing EC risk in obese women by up to 80%.
- Risk-reducing hysterectomy and bilateral salpingo-oophorectomy is a proven method of EC and ovarian cancer prevention in women with LS.
- COC is an effective and durable prevention strategy with risks outweighing benefit at BMI >35 kg/m^2.
- Induction of regular withdrawal bleeds using cyclical hormones is effective in reducing the risk of EC in women with PCOS.
- LNG-IUS and high-dose oral progestogens are fertility-sparing treatment options for EC prevention in women with AH.

Research agenda

- Good-quality studies are needed to provide robust evidence for the efficacy and safety of aspirin, metformin and bisphosphonates as prevention therapies in high-risk women.
- Future research should aim to identify specific patient groups who are at a particularly high risk of developing EC and in whom risk-reducing interventions are more likely to have significant impact (Table 2).
- Existing EC risk prediction models may be improved by the incorporation of genetic markers, and further research is needed.

Declaration of Competing Interest

We have no conflicts of interest to disclose.

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