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Current and future approaches to screening for endometrial cancer

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A B S T R A C T

Due largely to the rise in obesity and prolonged life expectancy, endometrial cancer (EC) rates have increased by 56% since the early 90s. Women at high risk (Lynch Syndrome) have a 12–47% lifetime risk of developing EC and professional societies recommend annual surveillance using transvaginal ultrasound (TVS) and endometrial biopsy (outpatients hysteroscopy) from the age of 30–35 years with hysterectomy from the age of 40 years. In women at low risk, screening is not currently advocated. The emerging data from Genome Wide Association studies (GWAS) in combination with epidemiological data may refine risk stratification in the future. In addition to screening, preventative approaches such as intrauterine progesterone may help reduce disease burden in those identified at 'higher risk'.

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Background

Endometrial cancer (EC) is the most common gynaecological cancer in high-income countries, and the fourth most common cancer in women. Worldwide there are over 320,000 cases of EC each year [1]. It is estimated that 3% of women will develop EC in their lifetime. There has been a sharp rise in incidence with a 56% increase since the early 90s (1993–2015) [2]. During the last decade alone, the rates of uterine cancer have increased by 21% [2]. This increase in incidence between the early 1990s and 2010s has largely been attributable to increased rates of obesity, with longer life expectancy also playing a role. US projections for the coming decades predict a 40–50% rise in incidence to 2030 [3,4].

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UK data suggests an overall increase in incidence from 21 to 33 ASR (age standardised rate), although this is projected to fall by 2035 [5]. Although typically a disease of high-income countries, increase in incidence has more recently been observed in low-middle income countries such as South Africa, Thailand and Brazil [1,6]. In parallel to this, over the past two decades mortality has also increased, with rates now similar to what they were in the early 80s (age standardised mortality rates decreasing to 5.0 in 1999 and rising to 7.1 in 2016) [2]. There is evidence that this increase is mainly in women over 70 years, pertinent to the aging population [7].

EC is overwhelmingly a disease of postmenopausal women, with over 90% occurring in women over 50 [8]; however, increasing rates of obesity may lead to a rise in the proportion of premenopausal cases [9].

As with ovarian cancer, EC has been dichotomously split into Type I and Type II tumours. Type I are almost exclusively endometrioid tumours, which are associated with oestrogen exposure. They account for 80–90% of cases, but only 40% of the mortality [10]. Type II tumours mostly include serous and clear cell cancers, which have a high fatality ratio. To have a bigger impact on mortality, preventative and early detection strategies should focus on detecting Type II cancers in parallel with efforts in detecting those that are fatal, whether Type I or Type II. More recent data suggest that 4 distinct molecular subtypes of EC exist, mismatch repair (MMR) deficient (MMR-D, deficient for MSH6 and PMS2), POLE exonuclease domain mutated (POLE EDM), p53 wild-type and p53 abnormal (null or missense mutations in p53) [11].

Three quarters of cases are diagnosed at an early stage (I/II), in which 5- and 10-year survival rates are 95% and 77%, respectively [12], the highest of all gynaecological cancers. When diagnosed at a late stage (IV), the survival is poor with only 14% of women surviving for 5 years [12]. The high proportion of ECs diagnosed at an early stage is largely due to abnormal vaginal bleeding being present in 94% of the cases [13]. In postmenopausal women, the presence of abnormal bleeding (postmenopausal bleeding, (PMB)) equates to a risk of EC in 9% of the cases. In contrast, the risk of EC in premenopausal women with abnormal bleeding is only 0.33% (95% CI, 0.23–0.48%) [13]. An EC study comparing 190 symptomatic with 123 asymptomatic women found that asymptomatic women were on average younger, less overweight, more likely to be hypertensive [14] and were less likely to be diagnosed with late stage disease. Asymptomatic women were found to have no prognostic advantage over the symptomatic women, as long as the bleeding had occurred for fewer than 8 weeks [14].

The precursor lesion for Type I EC, atypical endometrial hyperplasia (AEH) (referred to in the US as Endometrial Intraepithelial Neoplasia) also most commonly presents with abnormal vaginal bleeding, and shares the same oestrogen exposure-related risk factors as EC. Around a third of those with biopsy-diagnosed AEH have concurrent EC at hysterectomy, and around 40% of women with AEH will progress to EC [15]. It is, therefore, important that any screening strategy for EC includes AEH as a screen-positive result.

The identification of risk factors and biomarkers, which could be used for risk stratification and early detection strategies in the future, is of particular significance in view of the rise in EC incidence and mortality. The epidemiological, reproductive and genetic factors, and the current screening strategies for EC are discussed below.

Modifiable risk factors and potential for intervention

The lifetime risk of developing EC is 3%, or 1 in 36 [16]. As with most cancers, older age is the main risk factor for EC. The most significant risk factor is exposure to endogenous and exogenous unopposed oestrogens, which cause proliferative changes in the endometrium [17]. The hormonal exposure during a woman's life provided by excess adipose tissue is the most relevant source in today's society; however, reproductive choices also play a key role.

Epidemiological and lifestyle factors

Obesity

Thirty to forty per cent of EC cases are attributable to obesity, making it the biggest risk factor for the disease [18]. This is due to the oestrogenic effects of adipose tissue, which in turn causes proliferation of

the endometrium. There is some evidence to suggest that obesity is more strongly associated with Type I cancers, which would correlate with the oestrogenic aetiology of these tumours [10]. There is evidence of a dose-response relationship between obesity and EC, with reports of an 81% increase in risk per 5-unit increase of BMI during adulthood [19]. When compared to those with 'normal' BMI (18.5–24.9 kg/m^2), those who are 'overweight' (25.0–29.9 kg/m^2) are at a 1.43 (95% CI, 1.30–1.56) times increased risk of EC, which rises to 3.33 for those categorised as 'obese' (>30 kg/m^2) [20].

Women who were previously obese and have lost weight have been shown to experience a risk reduction of EC, making obesity a potentially modifiable risk factor [21]. In comparison to controls, obese women who underwent bariatric surgery and were followed up for 24 years had a 78% reduction in cancer risk [22]. A 2015 systematic review based on 890,110 women demonstrated a risk reduction in EC of 60% [23]. In a more recent study of 72 women who underwent bariatric surgery and achieved weight loss at 12 months, 5 of 6 women with AEH appeared to undergo regression (3 with surgery alone, 2 with intrauterine progestin) [24]. More data are needed to confirm these findings.

Endogenous hormones

Whilst younger age at menarche (RR = 0.68, 95% CI, 0.58–0.81 oldest versus youngest) [25], nulliparity (HR = 1.42, 95% CI, 1.26–1.60) [26], older age at last birth (0.87; 95% CI, 0.85–0.90; per 5-year increase at last birth) [27] and earlier-onset of menopause (HR = 1.89, 95% CI, 1.58–2.26) [28] all increase the risk of EC, breast feeding (HR = 0.89, 95%CI 0.81–0.98) [29], and the use of the combined oral contraceptives (RR = 0.76, 95% CI, 0.73–0.78) [30] decrease risk (Table 1). These risk factors have also been studied in combination with one another, for example nulliparity in combination with menarche at ≥13 years has a null effect (1.06; 95% CI, 0.86–1.32) [26].

All of these factors point to the role of the length of time of endogenous oestrogen exposure on EC risk. This notion is, however, not recent and likely a result of our evolution as elegantly presented by Eaton et al. in 1994 in a study of hunter-gatherer societies (data including 19th century Western nations, Japanese and rural Chinese in the 1940s) and contemporary American women to suggest that as women became better fed, their age of menarche decreased. In addition to this earlier menarche, having fewer children and later in life, shorter duration of breastfeeding and later menopause have all impacted on modern women's risk of female cancers including EC [31].

Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is a common endocrine and metabolic disorder that results in hyperandrogenism, oligo/amenstruation and hirsutism. It is commonly associated with obesity and Type II diabetes. Although many studies have reported that PCOS increases EC risk, most of these did not adjust for BMI [32]. Based on two case-control studies, even when controlling for BMI, there is still an increase in risk (2.79; 95%CI 1.31–5.96), which is higher in premenopausal women (4.05; 95%CI 2.42–6.76) [33].

The global prevalence of PCOS is 5–10% [34], although the challenging diagnostic criteria means that these figures are likely higher. Therefore, a large proportion of the population could potentially benefit from PCOS being included in risk-stratified EC screening strategies.

Exogenous hormones

In the 1970s, data became available that women with an intact uterus taking unopposed (oestrogen only) Hormone Replacement Therapy (HRT) were at a 2.3-fold increased risk of EC, rising to 9.5 if taken for >10 years. This risk persisted several years after discontinuation [35]. Combined HRT includes progestogens ('opposed' HRT) and attenuates the proliferating effects of oestrogen on the endometrium, and therefore, women with an intact uterus are prescribed combination therapy. A 2009 systematic review of 45 studies demonstrated that the risk of EC in women taking combined HRT is not increased [36], with a 29% reduction in EC risk reported for those using continuous combined preparations [37]. However, it must be noted that the risk varies based on the type of combined HRT, with a decrease in risk with continuous preparations (HR = 0.78, 95% CI, 0.72–0.86), increase in risk with sequential HRT with progestins given for <10 days each month (HR = 1.76, 95% CI, 1.51–2.05), but null effect with sequential HRT when progestins given >10 days a month (HR = 1.07, 95% CI, 0.92–1.04) [38].

Table 1
Epidemiological, reproductive and genetic risk factors for endometrial cancer.

Risk Factor	Effect on EC risk	Study design	OR/RR	95% CI	Details of comparisons	Author, Journal, Year
Lifestyle factors						
BMI	Higher BMI increases risk	Meta-analysis	1.34	1.20–1.48	Normal vs overweight - cohort	Jenabi & Poorolajal, Public Health, 2015 [20]
			1.43	1.30–1.56	Normal vs overweight - case-control	
			2.54	2.27–2.81	Normal vs obese - cohort	
			3.33	2.87–3.79	Normal vs obese - case-control	
	Higher BMI increases risk	Meta-analysis	1.60	1.52–1.68	Per 5 kg/m^2 increase	Crosbie et al., Cancer Epidemiol Biomarkers Prev, 2010 [136]
Coffee consumption	Decreases risk	Meta-analysis	0.80	0.72–0.89	Dose response relationship, 4+ cups per day. More strongly associated with obesity and postmenopausal women	Lafranconi et al., Nutrients, 2017 [50]
Physical activity	Decreases risk	Meta-analysis	0.80	0.75–0.85	High vs low physical activity	Schmid et al., Eur J Epidemiol, 2015 [47]
Reproductive factors						
Age at menarche	Increased age decreases risk	Meta-analysis	0.68	0.58–0.81	Oldest vs youngest age at menopause	Gong et al., Sci Rep, 2015 [25]
			0.96	0.94–0.98	Per 2 year delay in menarchal age	
Age at menopause	Increased age increases risk	Meta-analysis	1.89	1.58–2.26	Oldest vs youngest age at menopause	Wu et al., Biomed Res Int, 2019 [28]
Nulliparity	Increases risk	Pooled analysis	1.42	1.26–1.60	Parous vs nulliparous	Schonfeld et al., Cancer, 2013 [26]
Parous, age at menarche $\geq$ 13	Decreases risk	Pooled analysis	0.89	0.79–0.99	Compared with parous menarche <13	
Nulliparous, age at menarche $\geq$13	Null result		1.06	0.86–1.32	Compared with nulliparous menarche <13	
Breast feeding	Decreases risk	Meta-analysis	0.89	0.81–0.98	Ever breastfeeding vs none. Longer duration associated with lower risk, but levels off beyond 6–9 months. No difference seen by breastfeeding.	Jordan et al., Obstet Gynecol, 2017 [29]
Age at last birth	Younger age increases risk		0.87	0.85–0.90	Per 5 year increase at last birth	Setiawan et al., Am J Epidemiol, 2012 [27]
Endogenous oestrogen level						
oestrone	High level = higher risk	Prospective case-control study of 247 Ecs and 481 controls	2.66	1.50–4.72	Lowest tertile vs highest tertile	Allen et al., Endocr Relat Cancer, 2008 [17]
Estradiol			2.07	1.20–3.60		
Free estradiol			1.66	0.98–2.82		
Exogenous hormones						
OCP use (combined)	Decreases risk	Meta-analysis	0.76	0.73–0.78	Per every 5 years of use	Collaborative Group on Epidemiological Studies of Endometrial Cancer, Lancet, 2008 [30]
HRT use						
Oestrogen only	Increases risk	Meta-analysis	2.3	2.1–2.5	Users vs nonusers	Grady et al., Obstet Gynecol, 1995 [35]
			9.5		Used for 10 years or more	

Table 1 (*continued*)

Risk Factor	Effect on EC risk	Study design	OR/RR	95% CI	Details of comparisons	Author, Journal, Year
Oestrogen/ progesterone continuous	Decreases risk	Meta-analysis	0.78	0.72–0.86	Ever use vs never use	Brinton and Felix, J Steroid Biochem Mol Biol, 2014 [38]
Sequential HRT < 10 days per month	Increases risk	Meta-analysis	1.76	1.51–2.05	Ever use vs never use	
Sequential HRT ≥ 10 days per month	Neutral	Meta-analysis	1.07	0.92–1.04	Ever use vs never use	
Medicines						
Aspirin	Decreases risk	Case-control study of 1398 cases, 740 controls	0.54	0.38–0.78	At least 2 aspirins per week	Neil et al., Int J Cancer, 2013 [137]
			0.87	0.79–0.96	Ever vs never use	
Tamoxifen use	Increases risk	Prevention trial	2.53	1.35–4.97	In women at increased risk of breast cancer	Fisher et al., J Natl Cancer Inst, 1998 [44]
Gynaecological conditions						
Polycystic ovary syndrome	Increases risk	Systematic review and meta-analysis	2.79	1.31–5.96	Women of all ages. OR even higher when restricting to premenopausal women	Barry et al., Hum Reprod Update, 2014 [33]
Genetic predisposition						
Women at high risk						
Lynch syndrome						
MLH1	Increases risk	Prospective cohort study of 6350 carriers (3480 LS women)	35.2	28.8–43.4	Cumulative risk by age 70	Dominquez-Valentin et al., Genetics in Medicine, 2019 [54]
MSH2			46.5	38.3–56.3		
MSH6			41.1	28.6–61.5		
PMS2			12.8	5.2–49.5		
BRCA1/2	Increases risk	369 BRCA1/2 carriers (1779 woman-years follow up)	32.2	11.5–116	Serous subtype	Saule et al., J Natl Cancer Inst, 2018 [58]
Women at general population risk						
SNP	Locus				Mechanism/location	
rs11841589	13q22.1	Increases risk	1.15	1.11–1.21	Region of active chromatin that interacts with the KLF5 promoter region	Cheng et al., Nat Genet, 2016 [138]
rs13328298	6q22.31	Increases risk	1.13	1.09–1.18	Upstream of HEY2 and NCOA7	
rs4733613	8q24.21	Decreases risk	0.84	0.80.0.89	Telomeric to MYC	
rs937213	15q15.1	Decreases risk	0.90	0.86–0.93	EIF2AK4, and near BMF	
rs2498796	14q32.33	Decreases risk	0.89	0.85–0.93	AKT1	
rs11263763	17q12	Increases risk	1.20	1.15–1.25	HNF1B	
rs2414098	15q21	Increases risk	1.17	1.13–1.23	CYP19A1	
rs1202524	1q42.2	Increases risk	1.09	1.03–1.16	Downstream ofCAPN9	Long et al., Cancer Epidemiol Biomarkers Prev, 2012 [139]
rs4430796	17q12	Decreases risk	0.84	0.79–0.89	HNF1B	Spurdle et al., Nat Genet, 2011 [140]
rs4239217		Decreases risk	0.84	0.80–0.90	HNF1B	
rs7501939		Decreases risk	0.86	0.82–0.91	HNF1B	
rs9459805	chr 6	Increases risk	1.19	1.10–1.29	RNASET locus	De Vivo et al., Hum Genet, 2014 [141]
rs3184504	12q24	Increases risk	1.1	1.07–1.13	Missense variant in the SH2B3 gene	Cheng et al., Sci Rep, 2015 [142]
rs12970291			1.24	1.11–1/38	Near the TSHZ1 gene	
rs727479	chr 15	Increased risk, most strongly associated with circulating E2	1.15	1.11–1.21	CYP19A1	Thompson et al., Endocr Relat Cancer, 2016 [143]

BMI = Body Mass Index; OCP = Oral Contraceptive Pill; HRT = Hormone Replacement Therapy.

Diabetes and cardiovascular disease

Diabetes and hypertension have been long-established as risk factors for EC. The risk of EC is 40–81% higher in women with diabetes with overweight/obesity in diabetics possibly explaining some of this association [39,40]. Hypertension increases EC risk independently of BMI [41] along with other cardiovascular risk factors (incident hyperglycaemia, total: HDL cholesterol) more recently shown to contribute to this increase in risk [42].

Tamoxifen

Tamoxifen is used in both the treatment and prevention of breast cancer. Tamoxifen increases EC risk 2–3 fold, with the increase with longer duration, particularly after 5 years [43]. Data from the National Surgical Adjuvant Breast and Bowel Project P-1 trial reported a doubling in EC risk in women at high risk who were taking tamoxifen as chemoprevention compared with women receiving placebo, with the increased risk primarily in postmenopausal women [44]. Of note, the cancers that occur in tamoxifen-treated women have similar characteristics (stage, grade and histology) to those in the general population and have a good prognosis [45].

Other lifestyle factors (physical activity and coffee consumption)

The Women's Health Initiative observational study reported that more time spent sitting was associated with higher levels of unconjugated oestrone, independent of BMI [46]. Despite the obvious link between the two, weight loss and physical activity may independently affect EC, and so may be potentially two separate risk-reducing strategies [47]. However, such interventions are challenging and difficult to implement. Most recently, a Phase II randomised controlled trial (RCT) of personalised diet and exercise behaviour change in EC patients (Diet and Exercise in Uterine Cancer Survivors, DEUS) [48] demonstrated that a programme of diet and exercise change in EC patients (up to 3 years post diagnosis) was feasible, with 77% adherence (20/29). Of the women who declined study participation, convenience was cited as the most common reason [49]. This pilot paves the way for similar interventions in women who would benefit from the risk reduction associated with weight loss and/or increased physical activity.

There is now strong evidence of a dose-response relationship between coffee consumption ($\geq$4 cups a day) and a decrease in EC risk. A proposed mechanism is that coffee increases levels of sex hormone-binding globulin, lowering circulating oestrogen levels. The association appears to be particularly strong in obese, postmenopausal women [50,51].

Genetic and epigenetic risk factors

Women at high risk: Women with Lynch Syndrome (LS), previously referred to as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), are at markedly increased risk of EC compared with women in the general population [52]. LS is defined as per the Amsterdam II criteria, used to identify women for genetic testing [53]. LS is caused by a mutation in one of the MMR genes MSH2, MLH1, PMS1, PMS2 or MSH6. The cumulative incidence of EC by the age of 70 years (based on a study of 6350 carriers of pathogenic LS mutations of whom 3480 were female subjects) ranges from 12 to 47%, with MSH2 and MSH6 carriers being at the greatest risk (46.5%; 95% CI, 38.3–56.3% and 41.1%; 95% CI, 28.6–57.9%, respectively) and MLH1 and PMS2 mutation carriers at lower risk (35.2%; 95% CI, 28.8–43.4% and 12.8%; 95% CI, 5.2–49.5%, respectively), but still substantially higher than the population-level risk [54]. This risk appears to be directly related to age, with EC usually occurring 15 years earlier than in the low-risk population, with the highest risk between the ages of 55 and 65 years. The risk is substantially lower at the age of 40 (1.9–2.3% in MLH1, MSH6 and MSH2 carriers) with highest risk (48.9%) at the age of 75 in MSH2 carriers [54].

LS-associated ECs have a favourable outcome with Møller et al. more recently reporting a 10-year crude survival following endometrial, colon or ovarian cancer diagnosis in 80% of women [55]. Although most other reports support the encouraging survival [56], there is, however, some data to suggest that the LS ECs may differ from the sporadic cancers by more likely being poorly differentiated, with lymphatic/vascular invasion and diagnosed at advanced stage [57].

Recent data suggest that BRCA1 mutation carriers may also be at an increased risk of serous EC. In a series of 369 BRCA1/2 carriers (1779 woman-years follow up) who underwent risk-reducing salpingo-oophorectomy, Saule et al. reported a diagnosis of serous EC in two women (SIR 32.2, 95% CI, 11.5 to 116.4, $p < 0.001$) [58]. One potential implication of these preliminary data may be that offering women genetic testing for BRCA1/2, especially those diagnosed with breast cancer in the past may help detect their predisposition to serous EC, which has a high fatality rate. However, it must be noted that the risk of EC in a BRCA1 carrier is around 3% [58], and preventative strategies are not warranted.

These and other advances in the knowledge of genetic risk factors have been incorporated into commercial diagnostic panels, to be used by those with a family history of EC who 'may benefit from increased surveillance'. These panels test for mutations in a number of genes (including MLH1, MSH2, MSH6, PMS2, PTEN and TP53) but also include those associated with an increased risk of other cancers such as EPCAM, POLD1 and BRCA1/2 [59].

Low-risk women from the general population: Emerging data from GWAS are paving the way in our understanding of the genetic component of sporadic EC cases. To date, 20 single nucleotide polymorphisms (SNPs)/low-risk loci (16 directly genotyped SNPs, 11 of the 20 and 6 substitutes) associated with an increased risk of EC (Table 1) have been described [60]. When taken together, the loci identified to date probably account for ~5% of EC risk [61].

Epigenetic profiling: HAND2 methylation has been shown to be a common and crucial molecular alteration in EC with a potential to be used as a biomarker for early detection [62]. Moreover, the ease of collection of material such as that taken using tampons where epigenetic changes have been detected, given further studies, could be an avenue for a non-invasive screening method. In a study of 146 women with Type I EC sought to detect methylated genes in cervical scrapings, methylation of any two of a panel of 14 genes had a sensitivity of 91.8% and specificity of 95.5%. The same markers were also used in a smaller group of women with Type II EC, detecting 13/14 patients [63]. The carcinogenesis mechanism in EC is complex, with a suggestion that the familial predisposition may be mediated through epigenetic changes of MMR genes inherited over generations, whilst oestrogen exerts its effect both on cell proliferation and MMR activity [64].

Further efforts investigating whether epigenetic signature in cervical material could detect four types of women's cancers (ovarian, breast, endometrial and cervical) are underway [65].

Population-level genetic testing for cancer risk is increasingly more widely acceptable and available [61]. It is able to identify those at risk much more efficiently, with fewer resources and increase pick up rate by 50% compared to family history/clinical criteria alone [66]. Population-based genetic testing for multiple cancer susceptibility genes will likely lead to implementation studies, where the full benefit of such a strategy could be evaluated. As information about EC aetiology accumulates, it may be possible to identify screening and prevention interventions that are beneficial to categories of women with specific risk profiles, with risk-stratified screening [67] avenues akin to the efforts in breast and colorectal cancer.

Risk prediction models

In EC, efforts have focused on building risk prediction models incorporating epidemiological, reproductive and genetic factors, with serum biomarkers, ultrasound features and symptoms included in some. The current advances in these models are discussed below.

Epidemiological factors alone: Several EC risk prediction models have been developed using lifestyle, anthropometric and reproductive factors from large, prospective cohorts. The EPIC (European Prospective Investigation into Cancer and Nutrition) group reported that a risk prediction model, which included BMI, reproductive factors (menopausal status, age at menarche, parity, age at first full-term pregnancy and menopause, oral contraceptive use and duration), duration of HRT and smoking status had a discriminative capacity of 77% (C-statistic) improving on that based on age alone (71%), which was significantly better (IDI Index of 0.18) discrimination for predicting 5-year EC risk [68].

Despite the efforts exploring whether risk factor profile varies between Type I and II EC, data from 14,069 cases and 35,312 controls from the Epidemiology of Endometrial Cancer Consortium suggest that both types share many risk factors [10], with a greater effect of BMI on Type I when compared with

Type II ECs. Of note, similar pattern of risk was reported for high-grade endometrioid and Type II cancers.

Epidemiological factors and ultrasound features: A 2018 systematic review of EC risk prediction and diagnostic models in the general population reported that models including age, reproductive factors, hormone use, BMI, smoking history, comorbidities and endometrial features had a discriminative ability ranging from 0.68 to 0.77 [69], similar to the models based on the EPIC data [68].

Epidemiological factors and serum biomarkers: On the basis of a systematic review of EC risk factors, Kitson et al. have proposed a risk prediction model to incorporate measures of obesity, insulin resistance, unopposed oestrogen exposure and family history, with the latter being based on both epidemiological and biomarker data [70]. The model would stratify the general population of women into low, medium and high-risk categories, and offer prophylactic treatments to reduce EC risk, e.g. metformin recommended in those with a high insulin resistance score [70].

Predictive power may be improved by incorporating other biomarkers in the models. Data from EPIC suggest that the best performing markers (adiponectin, oestrone, interleukin-1 receptor antagonist, tumour necrosis factor-alpha and triglycerides) improved slightly on the discrimination capacity of epi-factor alone model by 1.7% [71]. Although modest improvements were noted, genetic factors may further improve on the performance of these models.

Epidemiological factors and symptoms: Available since 2012, QCancer uses primary care data to calculate the individual risk of any undiagnosed cancer and 11 specific tumour sites (for females), based on epidemiological risk factors and symptoms [72,73]. Although primarily intended for professional use, it also invites patients to use the tool and discuss the results with their doctor. For uterine cancer, the receiver operator characteristic curve of the model was high at 0.91, but this was largely attributable to the inclusion of PMB and BMI [74] in the tool.

Epidemiological and genetic factors: Efforts to combine genetic data with epidemiological factors to predict cancer risk continue. However, the value of risk-stratified screening for EC will depend on the performance of these models and whether low-risk loci provide further discriminatory power. The 2016 Chief Medical Officer's 'Generation Genome' report outlines current risk-stratified approaches in breast, colorectal and prostate cancer [67] but does not include EC. The latter may have been overlooked because of its known risk factors of obesity and PMB; however, in view of longer life expectancy and recently observed increases in fatal EC, there is an impetus to further explore screening/risk-stratified approaches.

Screening strategies

Screening for EC and impact on mortality

The main goal of screening is reduction in EC mortality. However, in view of the symptomatic presentation of EC usually detected at an early stage, an impetus to evaluate the impact of screening on EC mortality has been lacking.

Ultrasound

General population: Transvaginal ultrasound (TVS) is commonly used in the differential diagnosis/investigation of symptomatic women. The thickest antero-posterior diameter of the endometrium (endometrial thickness, ET) is used as an indication of risk of EC and to determine whether further and more invasive investigations such as endometrial biopsy are required.

Although TVS may be seen as an intrusive test, data from the ovarian cancer screening trial where women underwent 7–11 annual screens suggest that TVS-based screening in a postmenopausal woman causes very little discomfort (72.7% reported 'no discomfort') or pain (3.5% reported 'moderate/severe pain') [75].

As already discussed, 90% of women who are diagnosed with EC are symptomatic. In these women, an ET cut-off of 4 mm has a sensitivity of 98%, with a specificity ranging from 36% to 68% [76]. A thickened endometrium is more indicative of Type I EC risk, whereas Type II ECs are more often

associated with an atrophied endometrium [77]. Although it is generally accepted that a normal endometrium is less than 4-mm thick [78], cut-offs vary depending on menopausal status (premenopausal cut-off dependent on stage in cycle, up to 16 mm; postmenopausal ~4–5 mm) [79,80] and whether the woman has presented with abnormal bleeding (4–5 mm cut-off if symptomatic, ~10 mm if asymptomatic) [79,80]. The American College of Obstetricians and Gynecologists recommends endometrial biopsy in all postmenopausal women with persistent PMB, even where ET is $\leq$ 3 mm [79]. Although Smith-Bindman et al. report that in symptomatic postmenopausal women, a risk of EC of ~4.6% in those with ET $\geq$ 5 mm, similar as in asymptomatic women with ET $\geq$ 10 mm [81], other studies report the risk to be higher especially in women above 55 years of age. Based on the General Practice Research Database, data including 2732 women with uterine cancer (aged $\geq$40, diagnosed between 2000 and 2009) and 9537 matched controls (matched on age, sex and practice), Walker et al. report positive predictive value (PPV) of 4%, which increases to 9.6% (95% CI, 6.2–17.8) in those aged above 55 years [82]. In premenopausal women in the general population, screening using TVS is not recommended because of cyclical fluctuations in ET. Similarly, an ET cut-off in HRT users may be higher than 5 mm, some proposing a cut-off of 8 mm to result in fewer false positives. However, a cautionary note should be made as this would lead to miss detecting true positives in the 5–8 mm range [83]. There is a paucity of data regarding ET cut-offs and HRT type (sequential versus combined). Initial data on performance of ET as a screening tool for EC at a population level was first reported in a 1999 study of 1074 postmenopausal women aged 57–61 years undergoing conventional and Doppler TVS using a 4 mm cut-off [84]. Over a quarter (27%, n = 291) of the women underwent endometrial biopsy resulting in 3 cases of EC and 6 cases of AEH being detected. A larger study of 1926 women was undertaken, which was nested within an osteoporosis prevention trial where women underwent TVS at trial entry. Using a 6-mm cut-off, 42 women underwent endometrial biopsy, with EC diagnosed in 1 woman, and AEH in 4 women [85]. A major limitation of this study was that women with an ET of >6 mm were excluded from the study, leading to a sampling rate of women with a thickened endometrium of only 45% (42/92). In 2011, a study based on the data from the ultrasound arm of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) where 50,639 of the 202,638 postmenopausal women aged 50–74 years were randomised to annual screening using TVS reported the performance of ET as a screening test for EC. Based on 37,038 women with an intact uterus, an ET cut-off of $\geq$5 mm had a sensitivity of 80.5% and specificity of 86% for EC and AEH with 58 investigations per case detected [75]. The sensitivity was lower (54%) if a 10 mm cut-off was chosen (specificity of 95%) with 17 investigations per case detected. The optimum ET cut-off in this population was 5.15 mm, with a sensitivity of 80.5% (95% CI, 72.7–86.8) and specificity of 86.2% (95% CI, 85.8–86.6). Using a logistic regression based on the established epidemiological and reproductive EC risk factors (oral contraceptive pill (OCP) use, age at menarche, pregnancies longer than 6 months, weight, increasing age, personal history of breast and other cancers), women were stratified into quartiles of risk with the highest quartile containing 39.5% of the women with EC or AEH in the cohort. In the latter group, a 6.75 mm ET cut-off achieved a higher sensitivity (84.3%, 95% CI, 71.4–93.0) and specificity (89.9%, 95% CI, 89.3–90.5) with 22 investigations per case detected [75].

A 1998 study of 448 healthy postmenopausal, low-risk women included screening using both TVS and a concurrent endometrial biopsy. Using a 5-mm threshold, the sensitivity was 90%, specificity was 48% and the negative predictive value (NPV) was 99%. For detecting any abnormality, the PPV was 9%. Based on these values, over half of the women would require investigation, with a low yield (4%) of endometrial carcinomas [86]. Inclusion of endometrial abnormality detected on TVS has been explored in both UKCTOCS [75] and a cohort of 9888 pre- and perimenopausal women [87] with some suggestions of the value of including, in addition to ET, any abnormalities noted in the endometrial cavity.

There is currently insufficient evidence to support introducing routine TVS examination to screen asymptomatic low-risk women for EC [88].

Women at high risk: With a lifetime risk of developing EC by the age of 80 of up to 43%, various screening strategies have been investigated in women with LS. The main challenge in using ET as a screening tool in these women is due to a large proportion of women being premenopausal, where ET varies through the menstrual cycle. In a series of 269 LS women undergoing TVS (825.7 women-years of screening), only 2 cases of EC occurred, but neither of the two were detected through screening [89]. In a separate series evaluating annual TVS, of the 41 women in the study (totalling 197 women-years) 3

cases of AEH were detected with one EC missed as the woman presented with symptoms [90]. This suggests that annual screening using TVS alone does not have a role in screening high-risk women.

Endometrial biopsy

Endometrial sampling in the general population

Tissue sampling and subsequent histological examination of the endometrium provides the most accurate diagnosis; however, it has not been proven to impact on early detection or EC mortality [91]. Dilatation and curettage (D&C) and Pipelle biopsy are most commonly used, but other commercial samplers are available [92]. These are most commonly used in symptomatic women but have also been explored in high-risk women in a screening context as they are simple, easy to implement in an office-based setting and have good performance characteristics (sensitivity 73.5% and specificity 99.4%) [93]. Limitations across all outpatient endometrial sampling techniques are patient acceptability due to pain and discomfort, and difficulty of access due to the presence of cervical stenosis and atrophy, none of which are uncommon or insignificant. The procedure may also result in bleeding, with additional risk of infection, and rarely, uterine perforation. Finally, there is also a recognised sampling error as even with hysteroscopy and endometrial curettage, only 65% of the endometrial cavity is sampled. Concordance between all histological findings (benign and malignant) from endometrial biopsy compared with hysterectomy is between 60 and 70% [94].

Introduced to the market in 1984, Pipelle is by far the most studied and commonly used sampling device. Overall, Pipelle sampling causes significantly less pain than D&C, is less time-consuming and cheaper [95]. It has a higher sampling success rate than other aspiration devices such as Vabra (98.7% vs 88.7%) [96]. However, there are challenges in using each, with the Pipelle still having a 10% failure rate. Brush cytology methods (similar to cervical brushing/Pap smear) provide an opportunity to sample a greater surface area than the Pipelle or that of outpatient hysteroscopy with endometrial sampling (OHES), therefore reducing inadequate sampling by 25% [97]. A number of brushes are available, such as the Tao brush, SAP-1 device (adequate sample retrieved in 96.3%, 73% sensitivity, 95.8% PPV and 95.3% NPV), and the more recently described Li brush, which has both high sensitivity (92.7%) and specificity (98.2%) [98]. Despite the encouraging sensitivity and specificity of Tao Brush, it has a failure rate of 8% in parous women and 20% in nulliparous women, and is also considerably more and possibly prohibitively expensive in comparison with Pipelle [99]. The same study of 439 women of whom 270 provided data on acceptability, however, reported that the Tao brush was preferred to Pipelle [99].

There have been no RCTs exploring the impact of a sampling-based screening program on mortality from the disease. A study nested within the postmenopausal oestrogen/Progestin Interventions Trial including 448 postmenopausal women on oestrogen, combined HRT or placebo explored concurrent TVS and sampling. In this study, 1 EC, 2 AEHs and 8 cases of complex hyperplasia were detected. An ET cut-off of 5 mm had a sensitivity of 90%, specificity of 48%, PPV of 9% and NPV of 99%, therefore, suggesting that asymptomatic postmenopausal women, TVS with endometrial biopsy has a poor PPV but a high NPV for detecting endometrial disease [100].

Endometrial sampling in women at high risk

In view of the poor performance of annual TVS alone in LS women, endometrial sampling had been explored. In a Finnish Study of 175 women (759 screen years) undergoing TVS and intrauterine biopsy, EC was diagnosed in 14 women, 11 of whom were detected by screening (8 by sampling, 4 by TVS, 2 cases were detected by both TVS and sampling). Furthermore, the intrauterine biopsy detected 14 cases of AEH [101]. A second study of 62 women detected 3 ECs, all of which were in women with PMB. The failure rate for the procedure was 8% [102]. A 2011 systematic review suggested that in surveillance of asymptomatic LS women, endometrial sampling should be added to TVS [103]. The performance of OHES versus TVS was reported in a series of 41 LS women who had undergone both tests annually. Although both tests had a similar specificity (89.8%), the positive likelihood ratio was higher in OHES (9.8, 95%CI 4.6, 21) with a negative likelihood ratio of 0 suggesting that OHES had a higher diagnostic accuracy for EC and AEH [104]. Women preferences/acceptability have to also be taken into account. A small study of LS women ($n = 25$) reported that TVS causes less discomfort than OHES and that majority would choose TVS over OHES if a single test was required. They, however, reported similar pain

scores for hysteroscopy and Pipelle biopsy [105]. A larger study (n = 370) has also shown no statistically significant difference between the two in terms of discomfort and acceptability [106]. For LS women who are at risk of both colon cancer and EC, if the colonoscopy and hysteroscopy (under conscious sedation) are done at the same time, lower pain scores than outpatient hysteroscopy are reported [107].

A further consideration is cost. In a decision model comparing annual gynaecological examinations versus annual screening (TVS, endometrial biopsy, CA125) versus hysterectomy with bilateral salpingo-oophorectomy at the age of 30 in LS women, 48.7%, 18.4% and 0.0060% were diagnosed with EC, respectively. Surgery led to slightly longer life expectancy (80.0 years) compared to the other two strategies (79.3 years for screening and 77.4 for annual gynaecological examinations) [108]. To prevent EC, 6 prophylactic surgeries need to be performed suggesting risk-reducing hysterectomy may, therefore, be considered in this group of women. However, in women undergoing surgery, the issue of premature menopause needs to be discussed on an individual basis [109].

Guidance from the professional societies

The US [110] and European [111] professional societies and the Manchester International Consensus Group on Lynch Syndrome Management [56] have different recommendations as to the best approach to screening/surveillance (Table 2).

The American Cancer Society, unlike most other societies, stratifies the women into average, increased and very high risk of EC (LS women). The recommendation for both average (population risk) and intermediate-risk (defined as those have had increased exposure to unopposed oestrogens, but not those with LS or family history) is for the women to be counselled regarding symptoms and the risk of EC at the time of menopause.

Table 2
Professional societies screening guidelines.

Risk	Definition	Mode of screening/prevention				Society
		No screening (Advise to visit GP/family physician if experience PMB, advise of increased risk after menopause)	Annual endometrial biopsy from age 35	Annual TVS from age 35	Hysterectomy (*with salpingo-oophorectomy*[a]) from age 40	
Average risk	Population level, 3%	✓				ACS [105] BGCS [82] ESMO-ESGO-ESTRO [144]
Intermediate risk[b]	↑ unopposed oestrogens, no family history (<10% risk)	✓				ACS [105] BGCS [82] ESMO-ESGO-ESTRO [144]
High risk	Lynch Syndrome (LS) or family history (>10% risk)		✓ ✓ ✓	 ✓ ✓	 ✓	ACS [105] BGCS [82] ESMO-ESGO-ESTRO [144]

TVS = transvaginal ultrasound; PMB = postmenopausal bleeding; ACS = American Cancer Society; BGCS = British Gynaecological Cancer Society; ESGO = European Society of Gynaecological Oncology; ESMO = European Society of Medical Oncology; ESTRO = European SocieTy for Radiotherapy & Oncology.

[a] To reduce ovarian cancer risk.

[b] (As per ACS criteria): history of unopposed oestrogen therapy, late menopause, tamoxifen therapy, nulliparity, infertility or failure to ovulate, obesity, diabetes or hypertension.

Low risk: None of the societies advocate screening in low-risk (general population) women.

Intermediate risk: There are cogent reasons to consider screening in the latter group (increased risk but no known LS or other mutation) as women on tamoxifen therapy have a 2–3 fold increase in EC risk. It is worth noting that ET measurement in tamoxifen users presents a challenge because of the tamoxifen-induced sub-epithelial stromal hypertrophy (>40% of women taking tamoxifen will have an ET of more than 5 mm). In addition, several studies have reported a high false-positive rate (even when using a 10 mm ET cut-off). In a study of 247 women taking tamoxifen matched to 98 controls, Gerber et al. identified 52 asymptomatic patients with endometrial thickening who underwent curettage with only one EC diagnosed in this group, but 4 uterine perforations reported. Of the 20 symptomatic women, 2 ECs were diagnosed [112].

High risk: By current international standards, women defined as being 'high risk' are those who have either LS or a strong family history of EC. Screening guidelines for these women differ slightly between various professional bodies and societies (Table 2).

The American Cancer Society categorises these women as 'very high risk' and recommends an annual endometrial biopsy from the age of 35 years [110]. This is similar to the screening recommendations from the Royal College of Obstetricians and Gynaecologists. The American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) guidelines both advise annual TVS and aspiration biopsy screening from the age of 35 with prophylactic surgery as an option once childbearing is complete [111,144]. In 2003, the Royal Australian College of Obstetricians and Gynaecologists published a consensus statement suggesting screening is not required, but counselling regarding the risk and prompt investigation of any bleeding is strongly recommended in this group of women [113].

The timing of both screening and prophylactic approaches for the reduction of risk of EC have been refined in the American College of Gastroenterology guidelines, which suggest surveillance from the age of 30–35 and surgery at the age of 40–45 years [114]. Risk-reducing surgery is the most effective approach in reducing both EC and ovarian cancer risk in women at high risk, and is recommended by all professional societies/Manchester International Consensus Group as the primary option to be discussed with the patient. In view of the ovarian cancer risk in these women, the recommended approach is risk-reducing hysterectomy with bilateral salpingo-oophorectomy. There are encouraging data that compared with screening, such an approach is the most cost-effective and provides greatest gain in quality-adjusted life years [115].

Asymptomatic women with a family history of LS, or colorectal or endometrial cancer but not as part of Lynch, are advised to undergo genetic counselling and testing for MMR gene mutations [116].

Whilst the focus of this review is screening of asymptomatic women, other recent developments in EC are related to universal screening for LS mutations in all patients with EC at the point of diagnosis, which is gaining wide support. In unselected EC patients, a 2018 study of 484 patients suggested that universal screening identified 50% more patients with LS [117] who have been missed by current risk assessment tools.

Limitations of screening

In view of the low specificity and low PPV in the general population, screening is not currently advocated. A major concern in EC screening is false-positives, which lead to further unnecessary investigations (with estimates of 50 or 100 investigations per case detected) and the additional anxiety in women. As with any screening strategy, one pertinent issue is that of false negatives.

Novel screening tests

The utility of cervical smear samples as a screening tool for EC has been explored as far back as 1981 [118]. In 1280 asymptomatic women >45 years old, cervical cytology was able to detect 8 cases of EC and a further 25 cases of AEH or other atypia. In 2012, Kinde et al. detected genetic mutations commonly associated with EC in the Pap smear samples of all women with EC (24/24) [119]. Therefore, there appears to be an opportunity for Pap smear to be used as a method of detecting occult

endometrial carcinomas. A PCR-based test (PapSEEK), designed to detect mutations in 18 genes in Pap smear samples detected 81% of cases from standard Pap smear brush samples and 93% in Tao brush samples in 382 EC patients. Over three-quarters of the Pap smear cases were early stage [120]. About 87.5% and 37.8% of women with serous or endometrioid EC, respectively, will have cytologically abnormal endometrial cells present at Pap smear [121]. Although not having the necessary performance for use as a screening test at present, it holds promise for detection of the aggressive cancers accounting for the highest proportion of EC deaths. However, as cervical smear samples are increasingly being triaged based on being HPV positive, this resource will be lost in all but those who have simultaneous HPV infection.

Targeted screening

Defining an 'at risk' population based on epidemiological and low to moderate risk genetic factors is likely to be the basis for an EC screening programme if one were to be implemented. In ovarian cancer, based on a combination of epidemiological factors and low risk loci, the risk in the women unselected for family history ranges from 0.35% to 8.78% [122].

Risk stratified screening would, therefore, allow the classification of women at (1) low risk who would not need screening, (2) intermediate risk who would be offered screening or risk-reducing strategies such as intrauterine device with progestogen (e.g. Mirena), which decreases EC risk by 19% [123], or (3) high risk (LS ~12–47% lifetime risk) who would be recommended to undergo annual hysteroscopy (and TVS), with hysterectomy advised in those who have completed their families. In addition, women at high risk may be advised to take aspirin as chemoprevention, as it has been shown to reduce colorectal cancer risk (CaPP2 trial) [124]. The effect of different doses (100 mg, 300 mg or 600 mg daily) in the prevention of a number of cancers including EC is currently being explored in the CaPP3 trial, due to report in 2024 [125].

There has also been some encouraging preliminary data on metformin, which is thought to reduce cellular proliferation in women with EC [126], as a potential chemopreventative agent.

Some of these approaches are dependent on the EC risk based on BMI. In morbidly obese women, in selected women who opt for bariatric surgery for weight loss, the additional advantage of undergoing the procedure is reduction in EC risk.

Progestin-based devices (intrauterine devices such as the Mirena coil) have long been established to have an effect on abrogating endometrial proliferation. In LS women, a trial was planned where women would be randomised to Mirena coil versus control, but unfortunately the trial failed to recruit [127]. To ensure adequate protection, biomarkers predicting response to progestin in this context are required.

Serum-based screening as a first line test has not been explored. There is, however, data based on Markov modelling of serum screening using a biomarker panel versus no screening, annual endometrial biopsy or annual TVS, which in low-risk women aged 50 years is not cost effective unless applied to obese women aged 45–80 years [128]. The impetus in screening is to identify non-invasive strategies for screening using biomarkers/panels of promising markers. Sex steroid hormones, L1CAM [145] and adiponectin [146] may hold promise, but the data on latter are based on clinical case series and prognostic studies. Recently, a pan-cancer panel (CancerSEEK) [129] has been described but its value in EC screening is as yet not clear.

Further studies will help shed light on both the potential benefits and also longer term harms associated with any of these approaches. Currently encouraging data are only based on small short-term studies.

EC patient engagement is essential in identifying areas to focus on. A 2016 survey of 211 EC patients and their carers highlighted public awareness and the development of personalised risk prediction as being two of the most important issues to be addressed [130]. This shows that patients are interested in understanding their own risk, and believe that awareness is not adequate at present.

Awareness of presentation and risk factors

Awareness of EC in the population is low [131]. Increasing awareness of the risk associated with symptomatic presentation and obesity would likely contribute to earlier detection. A systematic review

of symptoms reported that up to 90% of ECs could be diagnosed at an early stage, if women experiencing PMB sought medical attention promptly [13]. The NHS health check [132] is offered to those aged between 40 and 74 every 5 years through primary care. Assessments take place with a nurse or healthcare assistant and patients are asked questions about their lifestyle and family history, and have height, weight and blood pressure measured. The aim of this is to be able to offer personalised advice to reduce the risk of stroke, heart disease and diabetes. For postmenopausal women, this could be an ideal opportunity to advise women on PMB and EC risk more generally, especially because obesity, hypertension and diabetes are already included in the health check.

The recent Cancer Research UK (CRUK) public awareness campaign includes obesity as one of the major risk factors for cancer. As globally 12% of the population is obese [133], expanding on these to highlight the magnitude of EC risk related to obesity may further help raise awareness. As EC arises after menopause, education on the need to promptly present for investigation in case of any bleeding, however slight, is essential. Although an early symptom, PMB is not always assessed as being important by the patient.

Furthermore, although incidence of EC is lower in black than white women, the proportion diagnosed with advanced disease is 20% higher [134]. It is, therefore, important that any awareness campaigns should incorporate ways to target this group to improve early diagnosis.

Summary

Current evidence does not support routine EC screening in the general population. The greatest impact may be achieved through education of patients regarding the significance of PMB. Further efforts are needed to focus on detecting the fatal cancers, whether Type I or II.

As most patients with EC present early, it is unlikely, based on the current technology, that a population-based screening program would be instigated. However, in view of the rise in obesity and aging population, risk stratified approaches based on epidemiological and genetic factors may be of value. This is in line with a 2014 Cochrane review suggesting that in view of the emerging epidemic of EC, it is now time to take action with risk stratification and prevention opportunities fitting well within some of these action plans that merit further exploration [135].

As globally mortality rates are projected to rise in the next 2 decades, there is impetus to better define risk factors and identify biomarkers that could be used for risk stratification so that preventative strategies such as progestin-based hormonal treatments or screening could be offered.

In high-risk (LS) women, annual screening with endometrial biopsy and/or TVS is advocated by most societies along with further recommendation for prophylactic surgery on the completion of child bearing.

Over the next few years, major efforts are needed to be directed towards raising awareness of the disease and exploring risk-stratified screening. The lack of evidence base of impact on mortality also needs addressing in the future.

Declaration of Competing Interest

The authors have no conflicts of interest.

Practice points

- EC is the most common gynaecological cancer in high-income countries. It has increased in incidence and mortality over the past two decades.
- Screening in the general population is currently not advocated, although ET as a screening tool has been explored in large cohorts.
- In high-risk (LS) women, screening using endometrial biopsy and TVS from the age of 30–35 years and prophylactic surgery from the age of 40 years is advocated by most professional societies.

Research agenda

- Women lack awareness that obesity is a risk factor for EC. In conjunction with not seeking physician referral if abnormal bleeding persists, both factors likely contribute to the increase in rates and deaths from the disease.
- In women at perceived low risk, risk stratified approaches based on epidemiological, reproductive and genetic factors may have a role in population screening approaches in the future.

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