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REVIEW

Endometrial hyperplasia and the risk of coexistent cancer: WHO versus EIN criteria

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Endometrial hyperplasia and the risk of coexistent cancer: WHO versus EIN criteria

Endometrial hyperplasia (EH) is classified into benign and precancerous according to two different histomorphological systems: the World Health Organisation (WHO) system (based on the subjective evaluation of cytological atypia) and the endometrial intraepithelial neoplasia (EIN) system (based on a combination of several parameters that are assessable subjectively, or objectively through computerised analysis). The American College of Obstetricians and Gynecologists recommends use of the EIN system. Nonetheless, a higher prognostic value for EIN criteria was demonstrated only with the objective assessment, which is not routinely applicable. The aim of this study was to evaluate which of the subjective classifications of EH (WHO or EIN) has better prognostic value, by assessing the risk of coexistent cancer. Electronic databases were searched for relevant articles from the inception of the databases to July 2018. All studies assessing the presence of cancer on hysterectomy specimens after a preoperative histological diagnosis of EH were included. Odds ratios (ORs), sensitivity and specificity were calculated with 95% confidence intervals (CIs). Sixteen cohort studies and three case–control studies, assessing 2582 EHs, were included. The WHO criteria showed an OR of 11.15 (95% CI 7.65–16.24), a sensitivity of 0.86 (95% CI 0.82–0.90) and a specificity of 0.67 (95% CI 0.64–0.70) for coexistent cancer. The subjective EIN system showed a similar OR (11.85, 95% CI 4.91–28.62; $P = 0.90$), higher sensitivity (0.98, 95% CI 0.94–0.99), and lower specificity (0.29, 95% CI 0.24–0.34). The WHO system and the subjective EIN system have similar prognostic values. However, the EIN criteria appear to be more sensitive and thus more suitable for selecting women who need to be treated, whereas the WHO criteria, based on cytological atypia, seem to be more specific for lesions at higher risk of cancer. Therefore, integration of the EIN system with cytological atypia should be considered.

Keywords: concurrent cancer, endometrial intraepithelial neoplasia, endometrial precancer, endometrioid adenocarcinoma, prognosis, World Health Organization

Introduction

Endometrial hyperplasia (EH) is a hyperproliferative condition characterised by an increased gland to stroma ratio as compared with proliferative endometrium.[1,2] EH includes polyclonal proliferations

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caused by the unopposed action of oestrogens, and neoplastic lesions that can progress to endometrioid adenocarcinoma.[2,3] Differentiating between these two possibilities is crucial in order to choose an adequate treatment. In fact, women diagnosed with premalignant EH should undergo hysterectomy, whereas a conservative progestin-based treatment can be considered in selected cases (a strong wish to preserve fertility; contraindications to surgery). On the other hand, benign EH can be managed by observation alone or with progestins when symptomatic.[3,4]

The differential diagnosis is made by histological examination, although no consensus has been achieved in the literature on the criteria for defining premalignancy.[2,5]

The most widely used classification system is the one proposed by the World Health Organisation (WHO) in 1994 and revised in 2014, which differentiates between premalignant and benign EH on the basis of the presence of cytological atypia.[1,2] The WHO system has been criticised because of its low reproducibility and the lack of a pathogenic and molecular basis.[3,5,6] For this reason, an alternative system [the endometrial intraepithelial neoplasia (EIN system] has been proposed to improve the differential diagnosis.[2,3,5–8]

The EIN system separates EH into benign EH and EIN, according to a combination of morphological parameters that are assessable objectively or subjectively. The objective EIN criteria are based on a computerised morphometric analysis of gland to stroma ratio, glandular perimeter, and nuclear diameter, allowing the calculation of a prognostic score (D-score).[6–8] The subjective EIN criteria include gland to stroma ratio, cytological differences from the adjacent endometrium, lesion dimensions, exclusion of mimics, and cancer.[3,5]

The Royal College of Obstetricians and Gynaecologists (RCOG) recommends use of the WHO system for diagnosing premalignant EH,[4] whereas the American College of Obstetricians and Gynecologists (ACOG) recommends use of the EIN system,[9] because several studies have shown that it predicts the risk of progression to cancer better than the WHO system.[6–8] However, in most cases these results referred to the objective D-score calculation, which is not widely available in common practice. For the routinely applicable subjective EIN criteria, evidence of superiority over the WHO system is lacking. Thus, it is unclear whether the ACOG recommendation may actually improve the diagnosis of EH.

Unfortunately, it is difficult to draw conclusions from the literature regarding the prognostic value of the two systems, as the rates of progression to cancer reported in the several studies are strongly influenced by the duration of follow-up.[6,10]

Several authors have assessed the prognostic value of one or both classification systems by considering the rate of coexistent cancer on hysterectomy specimens after a preoperative diagnosis of EH.[11–29] This allows data from different studies to be compared, eliminating the confounding due to the varying durations of follow-up.

Thus, the main aim of our study was to determine which subjective classification system for EH (WHO or EIN) has a better prognostic value, based on the rate of coexistent cancers.

Materials and Methods

STUDY PROTOCOL

This study followed a recommended protocol for systematic review and meta-analysis. Methods for collection, extraction and analysis of data were designed a *priori*. All review stages, including risk of bias assessment, were conducted independently by two reviewers (A.T. and A.R.). Disagreements were resolved by discussion with a third reviewer (G.S.).

The study was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[30]

SEARCH STRATEGY

MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, the Cochrane Library and Google Scholar were searched for relevant articles from the inception of these databases to July 2018, by use of a combination of the following text words found in Medical Subject Headings (MeSH): 'endometr*'; 'hyperplasia'; 'intraepithelial neoplasia'; 'EIN'; 'WHO'; 'cancer'; 'adenocarcinoma'; 'precancer'; 'premalignant'; 'precursor'; 'concurren*'; 'coexisten*'; 'predict*'; 'prognos*'; 'progression'; 'development'; 'risk'; and 'hysterectomy'. References from relevant articles were also reviewed.

STUDY SELECTION

We included all peer-reviewed, retrospective or prospective studies assessing the presence of occult endometrial cancer in patients preoperatively diagnosed with EH and who underwent hysterectomy. Exclusion criteria were: (i) latency time from EH diagnosis to hysterectomy of >1 year; (ii) presence of cancer assessed by endometrial sampling and not by hysterectomy; (iii) inclusion of only benign or only

premalignant EH; (iv) classification system other than the WHO system or the EIN system; (v) EIN criteria assessed solely through morphometric analysis; (vi) total sample size of <20 EHs or sample size of <10 in each EH category; (vii) reviews; and (viii) overlapping patient data with those of a study already included. Reasons for exclusion are detailed in Data S1A. No language restrictions were applied.

RISK OF BIAS ASSESSMENT

The risk of bias was assessed according to the revised Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2).[31] In each study, four domains related to risk of bias were assessed, and, for each domain, the authors' judgement was 'low risk', 'high risk' or 'unclear risk' of bias: (i) patient selection (low risk if consecutive patients were included, a case–control design was avoided, and inappropriate exclusions were avoided); (ii) index test (low risk if EH categorisation was made blinded to the results of hysterectomy examination); (iii) reference standard (low risk if the presence of cancer on hysterectomy specimen was assessed blinded to the EH category); and (iv) flow and timing (low risk if all patients underwent hysterectomy within 1 year from the index test). For each domain, high risk of bias was assigned if any criterion was not met. If study data did not allow assessment of the risk of bias, unclear risk of bias was assigned. Concerns about applicability of domains 1, 2 and 3 were also assessed (i.e. if study methods did not suit the objective of our review, regardless of their correctness) and categorised as 'low', 'unclear' and 'high' concerns about applicability.

DATA EXTRACTION

Data were extracted from each included study without modifications. Two-by-two contingency tables were prepared for each study, reporting two dichotomous qualitative variables: (i) EH category at histological examination of preoperative biopsy ('benign' or 'premalignant'); and (ii) presence of occult cancer on hysterectomy specimen ('no cancer' or 'cancer').

For the studies using the WHO criteria, EH without atypia (simple or complex) was considered to be 'benign', whereas atypical EH (simple or complex) was considered to be 'premalignant'.

For the studies using the EIN criteria, benign EH was considered to be 'benign', whereas EIN was considered to be 'premalignant'.

In two studies,[16,19] some specimens categorised as EH according to the WHO criteria were reclassified as cancer according to the EIN criteria. These EHs were still included as 'premalignant', because their exclusion would have created a bias, as explained in detail in Data S1B.

If discrepancies between values reported in the text and the tables were found, values from the tables were used for the analysis.

In the analysis of sensitivity and specificity, the EH category on preoperative biopsy was considered to be the index test, whereas the presence of cancer at hysterectomy was considered to be the reference test. The combination of 'premalignant' with 'cancer' was considered to be true positive, the combination of 'benign' with 'no cancer' was considered to be true negative, the combination of 'benign' with 'cancer' was considered to be false negative, and the combination of 'premalignant' with 'no cancer' was considered to be false positive.

DATA ANALYSIS

The prognostic value of the classification system was assessed by calculating the odds ratio (OR), sensitivity and specificity for each study and as a pooled estimate, with a 95% confidence interval (CI). ORs for the two systems were compared by use of the chi-square test, with a significant $P < 0.05$. Results were reported graphically in forest plots.

Statistical heterogeneity among studies was assessed by use of the inconsistency index I^2: heterogeneity was considered to be insignificant for $I^2 < 25\%$, low for $I^2 < 50\%$, moderate for $I^2 < 75\%$, and high for $I^2 \geq 75\%$. In the case of $I^2 < 50\%$, a fixed-effect model was used; otherwise, the random effect model of DerSimonian and Laird was adopted.

Since the introduction of the EIN system, pathologists have been influenced in their histological diagnosis of EH, regardless of the classification system adopted. Among the included studies, the first study using the EIN system was published in 2008. Therefore, we excluded from the meta-analysis the studies using the WHO system and published before 2008, to obtain a balanced time frame.

REVIEW MANAGER 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark) and META-DISC version 1.4 (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain) were used for the analysis.

Results

SELECTION AND CHARACTERISTICS OF THE STUDIES

Eighteen studies with a total of 2527 EHs were included in the systematic review.[11–29] Fourteen studies used the WHO criteria, two used the EIN criteria,

and two used both systems. The process of study selection is shown schematically in Figure 1.

All studies were retrospective, although one assessed a series from a previous prospective trial. Three studies used a case–control design, whereas the others were designed as retrospective series. The sample size ranged from 39 to 386. Sampling methods for the index test included hysteroscopic biopsy, curettage, pipelle biopsy, and vacuum aspiration.

The characteristics of the included studies are shown in Table 1.

RISK OF BIAS ASSESSMENT

The results of risk of bias assessment are shown in Figure 2.

For the 'patient selection' domain, the risk of bias was high for one study (case–control design[28]) and unclear for two studies (selection criteria not specified); the remaining studies were considered to be at low risk. Concerns about applicability were high for four studies (study population composed of women with EH at higher risk of progression[12,16,19,20]). The reasons underlying the authors' judgements are explained in Data S1C.

For the 'index test' domain, one study was considered to be at high risk (simple EH without atypia grouped together with simple atypical EH[28]), four studies were considered to be at low risk (blinding to reference standard), and the remaining studies were considered to be at unclear risk (blinding not reported).

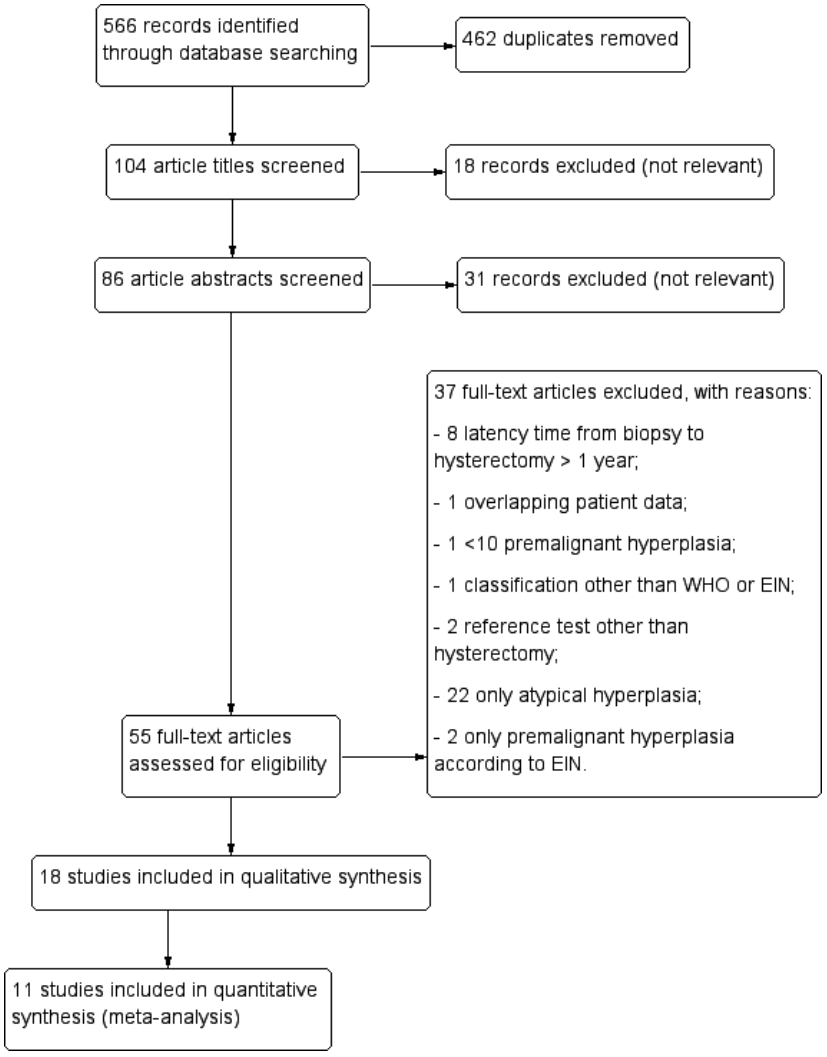

Figure 1. Flow diagram of studies identified in the systematic review [Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) template].

Table 1. Characteristics of the included studies

Study	Country	Setting	Study design	Period of enrolment	Sample size	Age (years), range (mean)	BMI, range (mean)	Parity, range (mean)	Sampling method	Latency time	Classification criteria
Hunter *et al.* (1994)[11]	USA	University of Kentucky Medical Center	Retrospective series	1970–1992	136	21–84 (52)* 31–83 (53)†	Reported height and weight	NR	Biopsy (unspecified), curettage	Preoperative (unspecified)	Cytological atypia, glandular complexity
Lambert *et al.* (1994)[12]	Canada	Hotel-Dieu Hospital, University of Montreal	Retrospective series	1980–1991	66	31–79 (56.8)* 37–75 (56.4)†	30–33 (27.7)* 24–45 (28.1)†	0–15 (3.2)* 0–5 (2)†	Curettage	Preoperative (unspecified)	Cytological atypia
Dunton *et al.* (1996)[13]	USA	Thomas Jefferson University Hospital	Retrospective series	1988–1993	45	34–81 (55.7)	NR	NR	Hysteroscopy, curettage, biopsy (unspecified)	Preoperative (mean 2.4 months)	Cytological atypia, glandular complexity
Xie *et al.* (2002)[14]	China	Women's Hospital, Zhejiang University	Retrospective series	1992–2000	150	31–76 (48.5)	NR	NR	Curettage	4–90 days	Cytological atypia, glandular complexity
Karamursel *et al.* (2005)[15]	Turkey	SSK Ankara Maternity and Women's Health Teaching Hospital; Hacettepe University	Retrospective series	1990–2003	204	28–87 (57.41)	NR	0–11 (3.28)	Curettage	≤1 month	Cytological atypia
Mutter *et al.* (2008)[16]	Europe, America	Multicentre	Retrospective analysis of a prospective series	1998–2003	189	NR	NR	NR	Curettage, pipelle, vacuum aspiration	≤3 months	Subjective EIN, computerised examination
Chen *et al.* (2009)[18]	Taiwan	National Taiwan University Hospital	Case–control	1996–2006	77	(48.7)* (52.2)†	(24)* (30)†	(2.5)* (2.6)†	Curettage	Preoperative (unspecified)	Cytological atypia
Ørbo *et al.* (2010)[19]	Norway	University of Tromso; Health Region of Northern Norway	Retrospective series	1999–2004	39	27–69 (50)* 44–79 (59)†	20–50 (29)* 22–29 (25)†	0–6 (2)* 0–3 (2)†	Biopsy (unspecified)	≤3 months	Subjective EIN, computerised examination
Pavlakis *et al.* (2010)[20]	Greece	IASO Women's Hospital, Athens	Retrospective series	NR	83	35–67	NR	NR	Curettage	≤12 weeks	Cytological atypia
Salman *et al.* (2010)[21]	Turkey	Hacettepe University	Retrospective series	2007–2009	49	36–79 (51.5)	NR	NR	Vacuum aspiration, curettage	≤2 weeks	Cytological atypia, glandular complexity, subjective EIN

Table 1. *(Continued)*

Study	Country	Setting	Study design	Period of enrolment	Sample size	Age (years), range (mean)	BMI, range (mean)	Parity, range (mean)	Sampling method	Latency time	Classification criteria
Daud *et al.* (2011)[22]	UK	Ipswich Hospital NHS Trust	Retrospective series	1998–2009	280	(55.7)	NR	0–7 (2)	Pipelle, curettage	2 weeks to 3 years (2 months)	Cytological atypia, glandular complexity
Yang *et al.* (2012)[23]	China	Shilong People's Hospital and The People's Hospital of Jieyang City	Retrospective series	2000–2011	139	37–69	NR	NR	Biopsy (unspecified)	≤1 year	Cytological atypia, glandular complexity, subjective EIN
Chen *et al.* (2013)[24]	Taiwan	Multicentre	Case–control	1991–2009	386	(50.4)* (48.3)†	Reported in ranges	Reported in ranges	Curettage, pipelle, hysteroscopy	Preoperative (unspecified)	Cytological atypia
Sirimusika *et al.* (2014)[25]	Thailand	Songklanagarind Hospital	Retrospective series	2000–2012	44	27–86 (47)	(26.8)	0–8 (2)	Curettage, hysteroscopy, biopsy (uspecified)	≤1 year	Cytological atypia, glandular complexity
Dolanbay *et al.* (2015)[26]	Turkey	Erciyes University	Retrospective series	2009–2013	82	(54.6)	(29.27)	(2.7)	Pipelle, biopsy (unspecified)	<6 weeks	Cytological atypia, glandular complexity
Kadirogullari *et al.* (2015)[27]	Turkey	Istanbul Kanuni Sultan Suleyman Research and Education Hospital	Retrospective series	2006–2012	158	(49.58)* (58.27)†	(30.2)* (31.7)†	(3.11)* (1.93)†	Biopsy (unspecified)	Preoperative (unspecified)	Cytological atypia, glandular complexity
Matsuo *et al.* (2015)[28]	USA	University of Southern California	Case–control	2003–2014	211	(45.2)	(35.6)	NR	Pipelle, vacuum aspiration, curettage	Median 105 days	Cytological atypia, glandular complexity
Boyraz *et al.* (2016)[29]	Turkey	Hacettepe University	Retrospective series	2007–2014	189	34–82 (50.4)	NR	NR	Biopsy (unspecified)	Preoperative (unspecified)	Cytological atypia, glandular complexity

BMI, Body mass index; EIN, Endometrial intraepithelial neoplasia; NR, Not reported.
*Women with benign hyperplasia or with no coexistent cancer.
†Women with premalignant hyperplasia or with coexistent cancer.

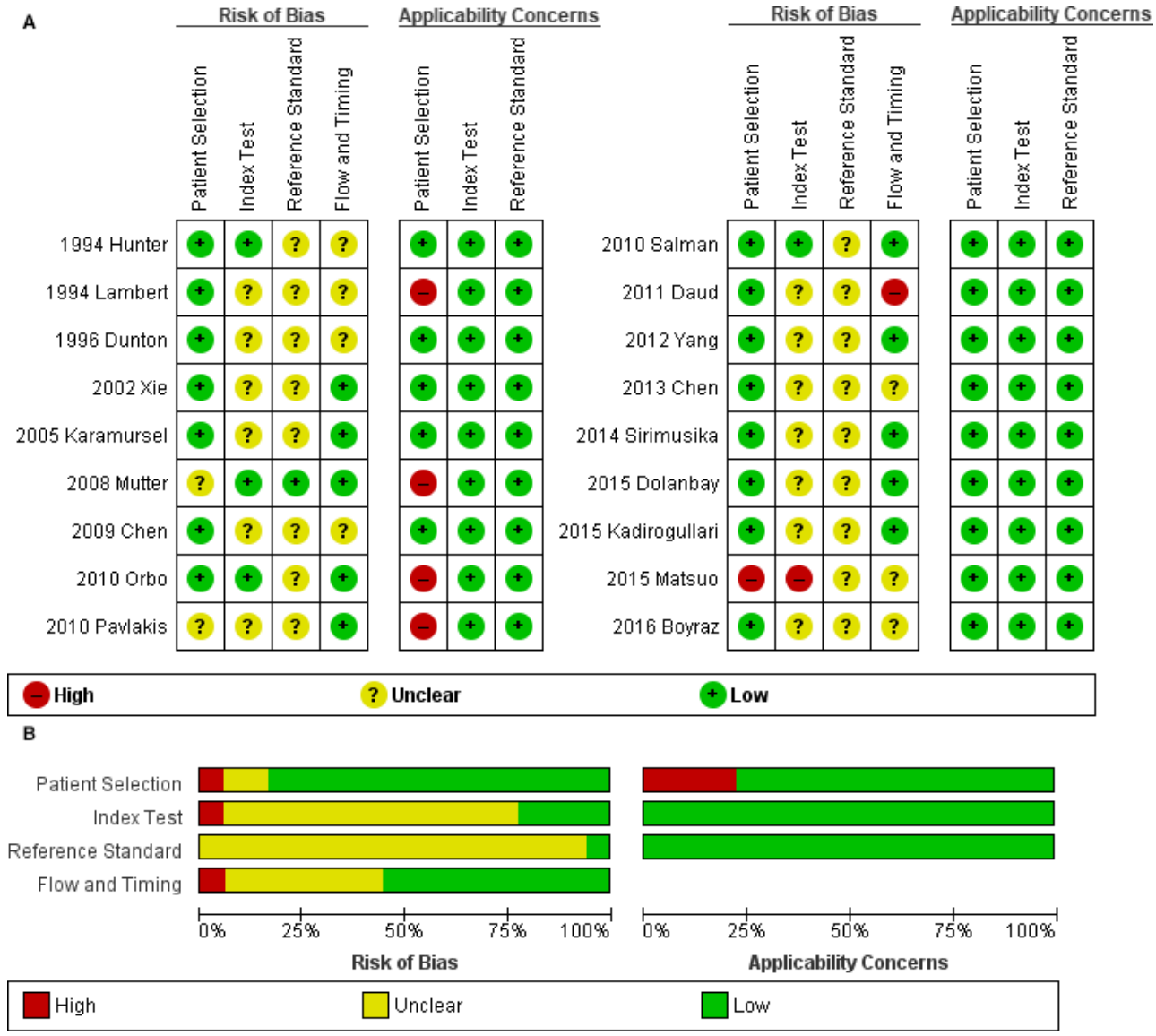

Figure 2. **A**, Assessment of risk of bias: summary of risk of bias for each study. Plus sign: low risk of bias. Minus sign: high risk of bias. Question mark: unclear risk of bias. **B**, Risk of bias graph for each risk of bias item presented as percentages across all included studies.

For the 'reference test' domain, one study was at low risk (blinding to index test) and the remaining studies were at unclear risk (blinding not reported).

For the 'flow and timing' domain, one study was considered to be at high risk (some patients underwent hysterectomy within 3 years from the EH biopsy[22]), seven studies were considered to be at unclear risk (latency time between EH biopsy and hysterectomy not clearly reported, although it was stated that EH biopsies were performed in the preoperative phase, implying a short latency time), and the remaining studies were considered to be at low risk (latency time of <1 year).

No further concerns about applicability were found.

RESULTS OF META-ANALYSIS

Eleven studies were included in the meta-analysis, owing to the exclusion of the two studies considered to be at high risk of bias and the five studies published before 2008.

Among nine studies assessing 1187 EHs according to the WHO criteria (cytological atypia), the pooled OR of coexistent cancer for premalignant EH versus benign EH was 11.15 (95% CI 7.65–16.24), with low heterogeneity among studies (I^2 = 32%) (Figure 3).

Among four studies assessing 507 EHs according to the EIN criteria, the pooled OR was 11.85 (95% CI

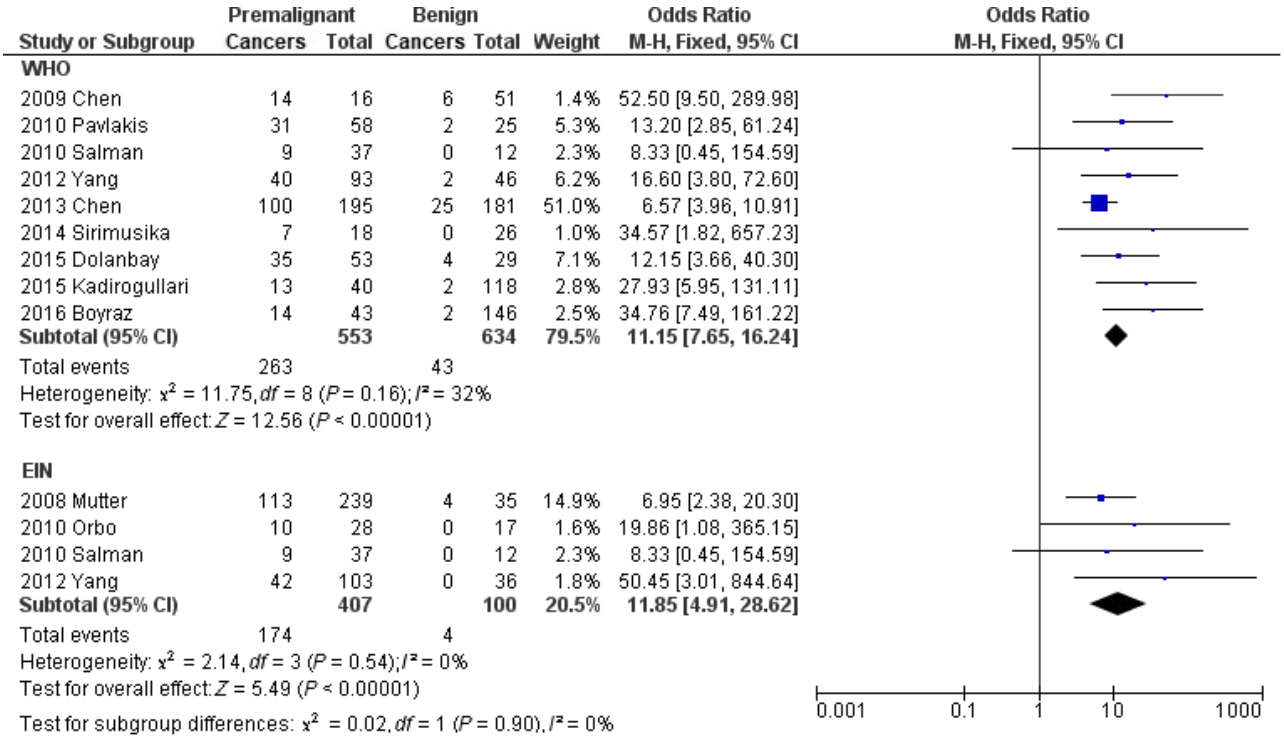

Figure 3. Forest plot of individual studies and pooled odds ratio for coexistent cancer with the World Health Organisation (WHO) and endometrial intraepithelial neoplasia (EIN) classification criteria for endometrial hyperplasia.

4.91–28.62), with no heterogeneity among studies (I^2 = 0%) (Figure 3).

There was no statistical difference between the two ORs (χ^2 = 0.02; P = 0.90) (Figure 3).

For the WHO criteria for premalignancy, the sensitivity in predicting a concurrent cancer was 0.86 (95% CI 0.82–0.90), with moderate heterogeneity (I^2 = 55.8%), whereas the specificity was 0.67 (95% CI 0.64–0.70), with high heterogeneity (I^2 = 91.6%) (Figure 4).

For the EIN criteria for premalignancy, sensitivity was 0.98 (95% CI 0.94–0.99), with insignificant heterogeneity (I^2 = 11.9%), whereas the specificity was 0.29 (95% CI 0.24–0.34), with high heterogeneity (I^2 = 81.2%) (Figure 4).

Discussion

O R

Our study showed that the WHO and EIN systems have similar prognostic value for the risk of cancer. To the best of our knowledge, this is the first meta-analysis comparing the WHO criteria and the subjective EIN criteria for risk stratification in EH. Our study attempted to address a long-standing issue.

The first problem with the former (1994) WHO system was that EH had been separated into four categories on the basis of both cytological atypia and glandular complexity.[2,5] This classification did not address the main question in EH diagnosis: how to differentiate neoplastic lesions from reactive proliferations. The EIN system was proposed as a possible solution to this problem, offering a dichotomous differential diagnosis between benign EH and EIN.[2,3,5,6] The 2014 WHO revision proposed a similar classification into EH without atypia and atypical EH/endometrioid intraepithelial neoplasia, overcoming this major conceptual problem with EH diagnosis. This revised classification reports 'EIN' as a synonym of atypical EH.[1] However, the WHO 2014 terminology might be confounding, because the acronym 'EIN' is used for 'endometrioid intraepithelial neoplasia'. Therefore, it is unclear whether it actually refers to the EIN (endometrial intraepithelial neoplasia) system. In fact, the WHO 2014 classification is not well integrated with the EIN criteria, and appears to be based too much on cytological atypia.

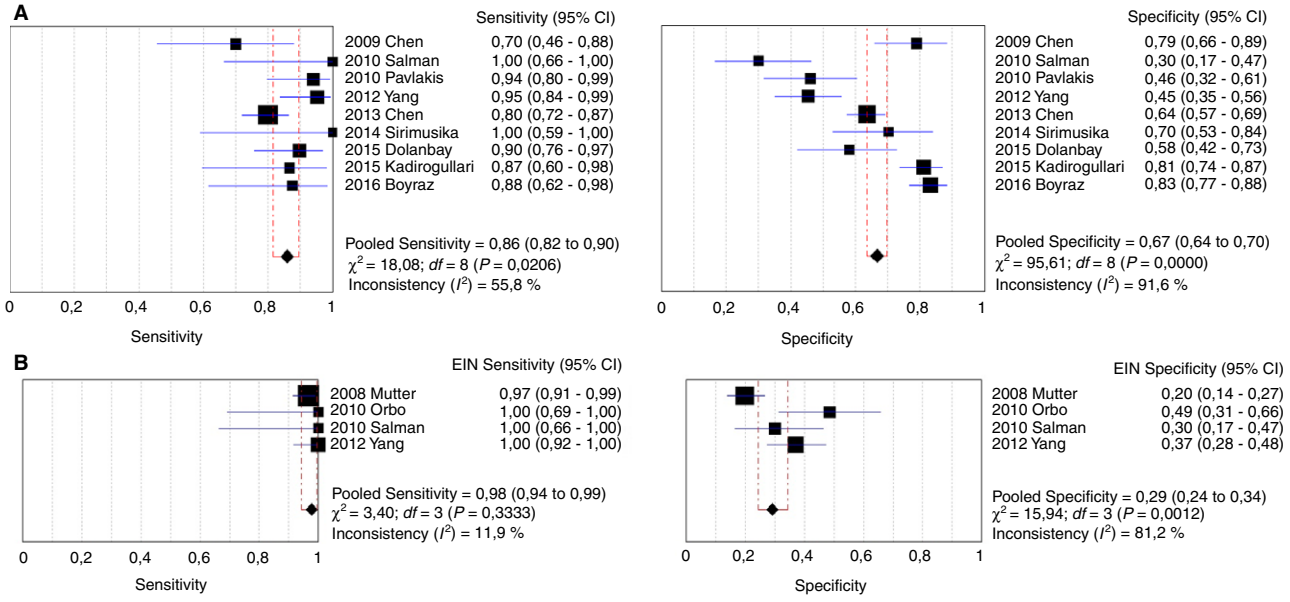

Figure 4. Forest plots of individual studies and pooled sensitivity and specificity for the World Health Organisation (WHO) (**A**) and endometrial intraepithelial neoplasia (EIN) (**B**) criteria for premalignancy in predicting a coexistent cancer in patients with endometrial hyperplasia. [Colour figure can be viewed at wileyonlinelibrary.com].

Regarding the prognostic value of premalignancy criteria, several studies showed that the objective EIN system with computerised calculation of the morphometric D-score had a higher prognostic value than the WHO system.[6–8] However, use of the D-score is not widespread, owing to the additional cost of a morphometry workstation.[5] Thus, it appears to be more important to assess the prognostic value of the subjective EIN system, which may be easily introduced into the routine histomorphological examination. In this regard, evidence is lacking. In our meta-analysis, we found that the ORs for a coexistent cancer were similar between the WHO system and the subjective EIN system (11.15 and 11.85, respectively; $P = 0.90$). In agreement with our results, a large study by Lacey *et al.* published in 2008 showed that a collapsed WHO system (based on cytological atypia alone, anticipating the 2014 WHO revision) and the subjective EIN system had similar accuracy in predicting the risk of cancer even in the long term (>1 year).[32] These findings suggest that the superiority of the EIN system over the WHO system is lost when the criteria for premalignancy are assessed subjectively.

Another major problem with the WHO system has been the low reproducibility of the diagnosis of cytological atypia.[33,34] Although this problem can be eliminated by the use of objective computerised morphometry, it remains when subjective criteria are used. In fact, Ordi *et al.* showed that diagnosis made with the subjective EIN system was also poorly reproducible, with no significant difference from the WHO system in interobserver agreement.[35]

Therefore, in the absence of further comparative studies, it appears that there is no evidence to support the superior reliability of the subjective EIN criteria over the WHO criteria for risk stratification in EH.

SENSITIVITY AND SPECIFICITY

Unlike the OR analysis, the analysis of sensitivity and specificity showed significant heterogeneity among studies. Such a finding is expected in meta-analyses of diagnostic accuracy.[36]

Despite having similar overall reliability, the WHO system and the EIN system showed different sensitivity and specificity. The excellent sensitivity of the EIN system (0.98) indicates that it correctly classified almost all EHs with coexistent cancer. The sensitivity of the WHO system appeared to be lower (0.86), implying that >10% of premalignant EHs were missed. 'Complex' EH without atypia might account for this discrepancy. 'Complex' refers to the complexity of glandular architecture, which was a parameter considered in the former WHO classification.[2,37] Many complex non-atypical EHs did indeed meet the EIN criteria for premalignancy.[6,32,37]

According to the RCOG guidelines, non-atypical EHs may be treated by observation alone, progestins being reserved for symptomatic cases. Furthermore, the follow-up recommended for non-atypical EH is

less close than that recommended for atypical EH.[4] This might imply that >10% of precancerous EHs are undertreated, increasing the risk of progression to cancer. The conservative treatment of premalignant EH has shown excellent outcomes, particularly with hysteroscopic resection and/or medicated intrauterine devices.[38–40] Therefore, a highly sensitive diagnostic method, such as the EIN system, may be more appropriate than the WHO system for the initial identification of women who need to be treated.

On the other hand, the WHO system showed higher specificity than the EIN system in predicting the risk of coexistent cancer. This implies that, among EHs without coexistent cancer, only a minority had cytological atypia, but most met the EIN criteria for premalignancy. In this regard, cytological atypia seems to characterise neoplastic EH in a more advanced phase of carcinogenesis, resulting in it being more specific for the risk of coexistent cancer. Thus, a diagnosis of atypical EH might have a stronger impact on prognosis than a diagnosis of EIN, because of the risk of there being an already present cancer rather than its neoplastic nature. In fact, the percentages of occult cancer in atypical EH are often >40%, with no significant difference if curettage is chosen over hysteroscopic biopsy.[41] For this reason, the presence of cytological atypia might indicate the need for closer and more careful follow-up in women who are eligible for conservative treatment (e.g. 3-monthly instead of 6-monthly), or a higher surgical priority for women eligible for hysterectomy. A more stratified diagnosis of premalignant EH may be crucial in the assessment of eligibility for conservative treatment in borderline cases, e.g. age Σ40 years, pluriparity, no wish to become pregnant in the short term, and low couple fertility potential. In these cases, the absence of cytological atypia might favour the choice of a conservative treatment, owing to the lower risk of cancer in the short term.

Besides these considerations, several other results in the literature suggest that the EIN criteria and cytological atypia have independent prognostic value. In fact, Pavlakis *et al.* showed that the presence of cytological atypia in EIN increases the risk of coexistent cancer.[20] On the other hand, Mutter *et al.* observed that atypical EH was at higher risk of having coexistent cancer when subjective EIN criteria were met.[16] Thus, each system might have its own role and significance in the diagnostic process. The possibility of integrating cytological atypia into the EIN system as an independent parameter should be considered. Basically, we would suggest classifying EH according to the EIN criteria, and substratifying the EIN diagnosis on the basis of the presence of overt cytological atypia. In this way, three EH categories would be identified: benign EH (polyclonal); EIN without overt atypia (monoclonal, but with a lower risk of coexistent cancer); and EIN with overt atypia (monoclonal, with a higher risk of coexistent cancer). A preliminary proposal for the clinical use of the two systems integrated is shown as a flowchart in Figure 5. Further studies are necessary to confirm and validate this diagnostic approach in the clinical setting.

LIMITATIONS

Our results may be limited by factors inherent to the methodology of the included studies and factors inherent to the topic assessed. In particular, the methodology of most included studies might be biased by the lack of blinding. Blinding in the index test was reported in only four studies, and blinding in the reference standard in only one. Unclear risk of bias was, indeed, assigned to most included studies with regard to the index test and reference standard domains. Regarding the topic assessed, a major limiting factor might be the loss of patients with EH who did not undergo hysterectomy. Such patients constitute the majority of benign EH patients, who are usually treated conservatively. This also resulted in a disproportion between benign and premalignant EH in our study population. The low reproducibility of EH

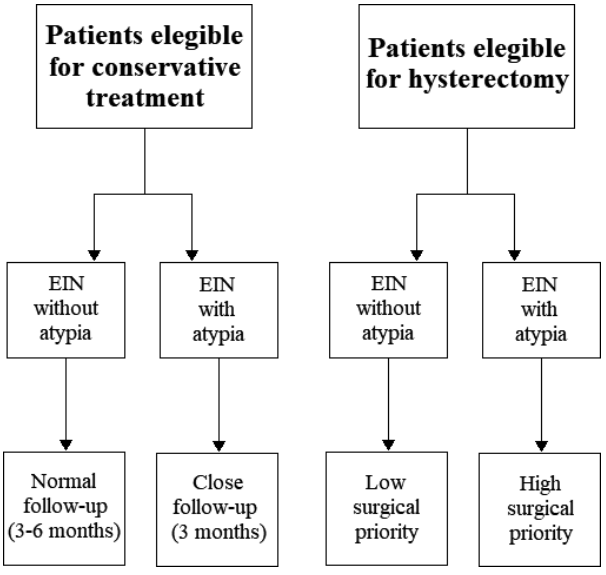

Figure 5. Flowchart showing the possible clinical use of cytological atypia integrated into the endometrial intraepithelial neoplasia (EIN) system.

diagnosis, as discussed above, might be another intrinsic limiting factor. Furthermore, the handling of hysterectomy specimens is also affected by the index diagnosis. In fact, if premalignant EH is the indication for hysterectomy, the endometrial cavity may undergo more extensive and accurate gross sampling. However, as these limitations to be appear intrinsic to the topic assessed, we did not consider them in the risk of bias assessment.

Conclusion

Despite the reported superiority of the objective EIN system based on computerised morphometry, the subjective EIN criteria have reliability similar to that of the WHO criteria in predicting the risk of coexistent cancer in EH. However, whereas the EIN criteria appear to be more sensitive in identifying neoplastic EH even in an earlier phase, the WHO criterion of cytological atypia seems to be more specific for high-risk lesions. Therefore, integration of the EIN criteria with cytological atypia may be considered, the first being more appropriate for the initial selection of patients for treatment (conservative or hysterectomy, according to the age and desire for pregnancy), and the second being more suitable for highlighting the need for closer follow-up or higher surgical priority. Further studies are necessary to confirm the clinical applicability of this approach.

Author contributions

A. Raffone and A. Travaglino independently assessed the electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction, and data analysis. Disagreements were resolved by discussion with G. Saccone. A. Mollo, A. Raffone and A. Travaglino conceived the study. F. Zullo, G. De Placido and L. Insabato worked on the design of the study. A. Raffone, A. Travaglino and G. Saccone worked on manuscript preparation. A. Mollo, F. Zullo, L. Insabato and G. De Placido supervised the whole study. All authors have read and approved the final manuscript.

References

1. Kurman R, Carcangiu M, Herrington C, Young R eds. *World Health Organization classification of tumors of female reproductive organs*. 4th ed. Lyon: IARC Press, 2014.
2. Sanderson PA, Critchley HOD, Williams ARW, Arends MJ, Saunders PTK. New concepts for an old problem: the diagnosis of endometrial hyperplasia. *Hum. Reprod. Update* 2017; **23**; 232–254.
3. Mutter GL. Endometrial intraepithelial neoplasia (EIN): will it bring order to chaos? The Endometrial Collaborative Group *Gynecol. Oncol.* 2000; **76**; 287–290.
4. International Society guidelines. Management of Endometrial Hyperplasia Green-top Guideline No. 67 RCOG/BSGE Joint Guideline, February 2016.
5. Baak JP, Mutter GL. EIN and WHO94. *J. Clin. Pathol.* 2005; **58**; 1–6.
6. Baak JP, Mutter GL, Robboy S *et al.* The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. *Cancer* 2005; **103**; 2304–2312.
7. Baak JP, Ørbo A, van Diest PJ *et al.* Prospective multicenter evaluation of the morphometric D-score for prediction of the outcome of endometrial hyperplasias. *Am. J. Surg. Pathol.* 2001; **25**; 930–935.
8. Orbo A, Baak JP, Kleivan I *et al.* Computerised morphometrical analysis in endometrial hyperplasia for the prediction of cancer development. A long-term retrospective study from northern Norway. *J. Clin. Pathol.* 2000; **53**; 697–703.
9. Lacey JV Jr, Sherman ME, Rush BB *et al.* Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J. Clin. Oncol.* 2010; **28**; 788–792.
10. Committee on Gynecologic Practice, Society of Gynecologic Oncology. The American College of Obstetricians and Gynecologists Committee Opinion no. 631. Endometrial intraepithelial neoplasia. *Obstet Gynecol.* 2015; **125**; 1272–1278.
11. Hunter JE, Tritz DE, Howell MG *et al.* The prognostic and therapeutic implications of cytologic atypia in patients with endometrial hyperplasia. *Gynecol. Oncol.* 1994; **55**; 66–71.
12. Lambert B, Muteganya D, Lepage Y, Boivin Y. Complex hyperplasia of the endometrium. Predictive value of curettage vs. hysterectomy specimens. *J. Reprod. Med.* 1994; **39**; 639–642.
13. Dunton CJ, Baak JP, Palazzo JP, van Diest PJ, McHugh M, Widra EA. Use of computerized morphometric analyses of endometrial hyperplasias in the prediction of coexistent cancer. *Am. J. Obstet. Gynecol.* 1996; **174**; 1518–1521.
14. Xie X, Lu WG, Ye DF, Chen HZ, Fu YF. The value of curettage in diagnosis of endometrial hyperplasia. *Gynecol. Oncol.* 2002; **84**; 135–139.
15. Karamursel BS, Guven S, Tulunay G, Kucukali T, Ayhan A. Which surgical procedure for patients with atypical endometrial hyperplasia? *Int. J. Gynecol. Cancer* 2005; **15**; 127–131.
16. Mutter GL, Kauderer J, Baak JP, Alberts D; Gynecologic Oncology Group. Biopsy histomorphometry predicts uterine myoinvasion by endometrial carcinoma: a Gynecologic Oncology Group study. *Hum. Pathol.* 2008; **39**; 866–874.
17. Chen YL, Cheng WF, Lin MC, Huang CY, Hsieh CY, Chen CA. Concurrent endometrial carcinoma in patients with a curettage diagnosis of endometrial hyperplasia. *J. Formos. Med. Assoc.* 2009; **108**; 502–507.
18. Ørbo A, Moe BT, Arnes M *et al.* Prognostic markers for detection of coexistent carcinoma in high-risk endometrial hyperplasia. *Anticancer Res.* 2010; **30**; 4649–4655.
19. Pavlakis K, Messini I, Vrekoussis T *et al.* PTEN-loss and nuclear atypia of EIN in endometrial biopsies can predict the existence of a concurrent endometrial carcinoma. *Gynecol. Oncol.* 2010; **119**; 516–519.

20. Salman MC, Usubutun A, Boynukalin K, Yuce K. Comparison of WHO and endometrial intraepithelial neoplasia classifications in predicting the presence of coexistent malignancy in endometrial hyperplasia. *J. Gynecol. Oncol.* 2010; **21**; 97–101.
21. Daud S, Jalil SS, Griffin M, Ewies AA. Endometrial hyperplasia—the dilemma of management remains: a retrospective observational study of 280 women. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 2011; **159**; 172–175.
22. Yang YF, Liao YY, Peng NF, Li LQ, Xie SR, Wang RB. Prediction of coexistent carcinomas risks by subjective EIN diagnosis and comparison with WHO classification in endometrial hyperplasias. *Pathol. Res. Pract.* 2012; **208**; 708–712.
23. Chen YL, Wang KL, Chen MY *et al.* Risk factor analysis of coexisting endometrial carcinoma in patients with endometrial hyperplasia: a retrospective observational study of Taiwanese Gynecologic Oncology Group. *J. Gynecol. Oncol.* 2013; **24**; 14–20.
24. Sirimusika N, Peeyananjarassri K, Suphasynth Y, Wootipoom V, Kanjanapradit K, Geater A. Management and clinical outcomes of endometrial hyperplasia during a 13-year period in Songklanagarind Hospital. *J. Med. Assoc. Thai.* 2014; **97**; 260–266.
25. Dolanbay M, Kutuk MS, Uludag S *et al.* Concurrent endometrial carcinoma in hysterectomy specimens in patients with histopathological diagnosis of endometrial hyperplasia in curettage specimens. *Ginekol. Pol.* 2015; **86**; 753–758.
26. Kadirogullari P, Atalay CR, Ozdemir O, Sari ME. Prevalence of co-existing endometrial carcinoma in patients with preoperative diagnosis of endometrial hyperplasia. *J. Clin. Diagn. Res.* 2015; **9**; QC10–QC14.
27. Matsuo K, Ramzan AA, Gualtieri MR *et al.* Prediction of concurrent endometrial carcinoma in women with endometrial hyperplasia. *Gynecol. Oncol.* 2015; **139**; 261–267.
28. Boyraz G, Başaran D, Salman MC, Özgül N, Yüce K. Does preoperative diagnosis of endometrial hyperplasia necessitate intraoperative frozen section consultation? *Balkan Med. J.* 2016; **33**; 657–661.
29. Moher D, Shamseer L, Clarke M *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* 2015; **4**; 1.
30. Whiting PF, Rutjes AW, Westwood ME *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann. Intern. Med.* 2011; **155**; 529–536.
31. Lacey JV Jr, Mutter GL, Nucci MR *et al.* Risk of subsequent endometrial carcinoma associated with endometrial intraepithelial neoplasia classification of endometrial biopsies. *Cancer* 2008; **113**; 2073–2081.
32. Zaino RJ, Kauderer J, Trimble CL *et al.* Reproducibility of the diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer* 2006; **106**; 804–811.
33. Allison KH, Reed SD, Voigt LF, Jordan CD, Newton KM, Garcia RL. Diagnosing endometrial hyperplasia: why is it so difficult to agree? *Am. J. Surg. Pathol.* 2008; **32**; 691–698.
34. Ordi J, Bergeron C, Hardisson D *et al.* Reproducibility of current classifications of endometrial endometrioid glandular proliferations: further evidence supporting a simplified classification. *Histopathology* 2014; **64**; 284–292.
35. Sotiriadis A, Papatheodorou SI, Martins WP. Synthesizing evidence from diagnostic accuracy tests: the SEDATE guideline. *Ultrasound Obstet. Gynecol.* 2016; **47**; 386–395.
36. Travaglino A, Raffone A, Saccone G *et al.* Loss of Bcl-2 immunohistochemical expression in endometrial hyperplasia: a specific marker of precancer and novel indication for treatment. A systematic review and meta-analysis. *Acta Obstet. Gynecol. Scand.* 2018; **97**; 1415–1426.
37. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis. *Am. J. Obstet. Gynecol.* 2010; **203**; 547.e1–547.e10.
38. Zhang Q, Qi G, Kanis MJ *et al.* Comparison among fertility-sparing therapies for well differentiated early-stage endometrial carcinoma and complex atypical hyperplasia. *Oncotarget* 2017; **8**; 57642–57653.
39. Giampaolino P, Di Spiezio Sardo A, Mollo A *et al.* Hysteroscopic endometrial focal resection followed by levonorgestrel intrauterine device insertion as a fertility-sparing treatment of atypical endometrial hyperplasia and early endometrial cancer: a retrospective study. *J. Minim. Invasive Gynecol.* 2018; **pii**: S1553-4650(18)30347-9; https://doi.org/10.1016/j.jmig.2018.07.001; [Epub ahead of print].
40. Bourdel N, Chauvet P, Tognazza E, Pereira B, Botchorishvili R, Canis M. Sampling in atypical endometrial hyperplasia: which method results in the lowest underestimation of endometrial cancer? A systematic review and meta-analysis. *J. Minim. Invasive Gynecol.* 2016; **23**; 692–701.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplementary material.

