Archives of Gynecology and Obstetrics (2019) 299:1233–1242
https://doi.org/10.1007/s00404-019-05103-1

REVIEW

Endometrial hyperplasia and progression to cancer: which classification system stratifies the risk better? A systematic review and meta-analysis

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Received: 10 September 2018 / Accepted: 22 February 2019 / Published online: 27 February 2019

Abstract

Purpose Benign and precancerous endometrial hyperplasias (EH) are differentiated thorough two possible histomorphologic classifications: WHO (adopting the subjective evaluation of cytologic atypia) and EIN (adopting several histomorphologic parameters, evaluable subjectively, or objectively with a computerized analysis calculating a prognostic score, the *D* score). ACOG recommends the use of EIN system although no distinction was made between objective assessment (not widely available), and subjective assessment (more applicable in the common practice). Moreover, it is still unclear if subjective EIN system is actually preferable to WHO classification. We aimed to assess the reliability of WHO system, *D* score and subjective EIN system in stratifying the risk of progression to cancer in EH.

Methods MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, Cochrane Library and Google Scholar were searched for relevant articles from the inception to August 2018. All studies assessing the rates of progression of EH to cancer were included.

Results Twelve cohort studies and one case–control study, assessing 3629 EH, were included. Relative risk (RR) for cancer progression was calculated with 95% confidence interval (CI), and results were compared using Chi-square test (significant p value < 0.05). WHO system showed a RR of 8.74 (95% CI 6.66–11.47). Objective *D* score showed a RR of 29.22 (95% CI 13.24–64.51), significantly higher than WHO ($p = 0.005$). Subjective EIN system showed a RR of 19.37 (95% CI 5.86–64.01), intermediate between WHO and *D* score, without significant differences ($p = 0.20$ and $p = 0.57$, respectively).

Conclusion Objective EIN criteria with *D* score are significantly more reliable than WHO criteria in stratifying the risk of progression of EH to cancer. Subjective EIN criteria did not show significant superiority over WHO instead. Further studies are necessary to determine if subjective EIN system should replace WHO system in the routine diagnosis of EH.

Keywords World Health Organization · Endometrial intraepithelial neoplasia · Endometroid adenocarcinoma · Endometrial precancer · Prognosis · Concurrent cancer

Introduction

Endometrial hyperplasia (EH) is an irregular proliferation of endometrial glands, which can progress to endometrial cancer (EC) [1, 2]. The risk of progression of EH to EC depends on the nature of the lesion, which can be a benign reaction to an unopposed action of estrogens, or a neoplastic premalignant process [2, 3]. These two conditions require two different therapeutic approaches: benign EH may be managed with observation alone, with progestin reserved to symptomatic cases [4]. On the other hand, premalignant EH should be treated with hysterectomy, although a conservative treatment can be

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chosen in selected cases (strong wish to preserve fertility or contraindication for surgery) [3, 4].

The diagnosis of benignity or premalignancy of EH is usually made at histologic examination [2]. The most used classification system for differentiating premalignant EH is the one proposed by the World Health Organization (WHO) and repeatedly revised [2, 5, 6]. WHO system identifies cytologic atypia as the crucial criterion of premalignancy, indicating atypical EH as premalignant and non-atypical EH as benign [1, 2].

"Endometrial intraepithelial neoplasia" (EIN) is an alternative system which was proposed to overcome several problems risen for WHO criteria, such as low reproducibility and lack of a pathogenetic and molecular basis [2, 3, 6]. EIN system is based on nuclear and architectural features of EH, which can be objectively assessed through a computerized morphometric analysis calculating a prognostic score, the *D* score [3, 6]. *D* score takes into account volume percentage stroma, variability of nuclear axis and outer glandular perimeter, and classifies EH as "benign" if *D* score ≥ 1, and "EIN" if *D* score < 1 [2, 6]. Nonetheless, *D* score is not widespread, because of the costs of a morphometry workstation [6]. A subjectively assessable surrogate of EIN system was developed to allow a simpler and wider applicability of such system [3]. Subjective EIN criteria of precancer include increased gland to stroma ratio, distinct cytology compared to the adjacent endometrium, lesion size > 1 mm, exclusion of benign mimics and cancer [3].

The Royal College of Obstetricians and Gynaecologists (RCOG) recommends the use of WHO system to diagnose premalignant EH [4].

In contrast, the American College of Obstetricians and Gynecologists (ACOG) recommends the use of EIN system [7] since several studies support its better reproducibility and accuracy compared to WHO system [8–11]. However, ACOG makes no differentiations between objective *D* score and subjective EIN criteria [7]. Most of these studies referred to objective *D* score, while other studies showed for WHO and subjective EIN system similar accuracy [12, 13] and reproducibility [14].

It is still unclear which classification system of EH should be globally used to direct the management of the patients. In this respect, it should be determined which system better predicts the risk of progression to cancer, to identify patients who actually need treatment.

The aim of our study was to assess the reliability of WHO system, *D* score and subjective EIN system in stratifying the risk of progression to cancer in EH.

Materials and methods

Study protocol

This study was designed according to a protocol for systematic review and meta-analysis. Methods for collection, extraction and analysis of data were designed a priori. All review stages were conducted independently by two reviewers (AT, AR). Disagreements were resolved by discussion with a third reviewer (GS).

The study was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [15].

Search strategy

MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, Cochrane Library and Google Scholar were searched for relevant articles from the inception of each database to August 2018. Several researches were made using a combination of the following text words found on Medical SubHeading (MeSH) vocabulary: "endometr*"; "hyperplasia"; "intraepithelial neoplasia"; "EIN"; "WHO"; "cancer"; "adenocarcinoma"; "precancer"; "premalignant"; "precursor"; "predict*"; "prognos*"; "progression"; "development"; "risk"; "hysterectomy". References from relevant articles were also reviewed.

Study selection

We included all peer-reviewed, retrospective or prospective studies assessing the rates of progression of EH to cancer.

Exclusion criteria were

1. Assessment of only those EH undergone hysterectomy as primary treatment.
2. Inclusion of only benign or only premalignant EH.
3. EH not classified.
4. Classification system other than WHO or EIN.
5. Reviews.
6. Same cohort of patients as a study already included.

Risk of bias assessment

The risk of bias was assessed following the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [16]. Four domains related to risk of bias were assessed in each study: (1) patient selection (if consecutive patients were included); (2) index diagnosis (if endometrial sampling was performed with the same method for all patients), (3) reference diagnosis (if the progression to cancer was confirmed

on a subsequent hysterectomy), (4) flow and timing (if all patients were followed for at least 1 year since earlier cancers should be considered as already present at the time of first biopsy [9, 12]). Authors' judgment was "low risk", "high risk" or "unclear risk of bias" for each domain.

Data extraction

Data were extracted without modifications and reported in 2×2 contingency tables for each study. Within tables, two dichotomous qualitative variables were reported:

- EH category ("benign" or "premalignant");
- Progression to cancer ("no cancer" or "cancer").

For the studies adopting WHO criteria, EH without atypia (simple or complex) was considered as "benign", while atypical EH (simple or complex) as "premalignant".

For the studies adopting objective EIN criteria based on D score, $D \geq 1$ was considered as "benign", and $D < 1$ as "premalignant".

For the studies adopting subjective EIN criteria, benign EH was considered as "benign" and EIN as "premalignant".

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

Data analysis

The reliability of classification systems was assessed by calculating relative risk (RR) for progression to cancer. Values were reported for each study and as pooled estimate on forest plots, with 95% confidence interval (CI). A p value < 0.05 was considered significant.

Statistical heterogeneity among studies was assessed using the inconsistency index I^2: heterogeneity was considered insignificant for $I^2 < 25\%$, low for $I^2 < 50\%$, moderate for $I^2 < 75\%$ and high for $I^2 \geq 75\%$. The random effect model of DerSimonian and Laird was used only if $I^2 > 50\%$; otherwise, a fixed-effect model was adopted.

Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) was used for the analysis.

Results

Selection and characteristics of the studies

Thirteen retrospective studies with a total of 3629 EH were included [9–12, 17–25]. For classification of EH, WHO criteria were used in 11 studies (reporting also complexity of glandular architecture in 8), D score in 8, and subjective EIN criteria in 3. The process of study selection is reported in Fig. 1.

One study adopted a case–control design [12]; the others followed a retrospective cohort design. Sample size ranged from 39 to 1443. Sampling methods for index test included curettage in 11 studies, Pipelle biopsy in 2, hysteroscopic biopsy in 2, vacuum aspiration in 1.

Characteristics of the included studies are detailed in Table 1.

Risk of bias assessment

Results of risk of bias assessment are shown in Fig. 2.

For the "patient selection" domain, the risk of bias was high for one study, because its design (case–control with oversampling of atypical AH [12]) makes it unsuitable for comparison with other studies. Three studied were considered at unclear risk since they selected only EH with complex glandular architecture.

For the "index diagnosis" domain, five studies were considered at unclear risk since they did not report the index sampling methods, or because they used different ones.

For the "reference diagnosis" domain, nine studies were considered at unclear risk, because they did not

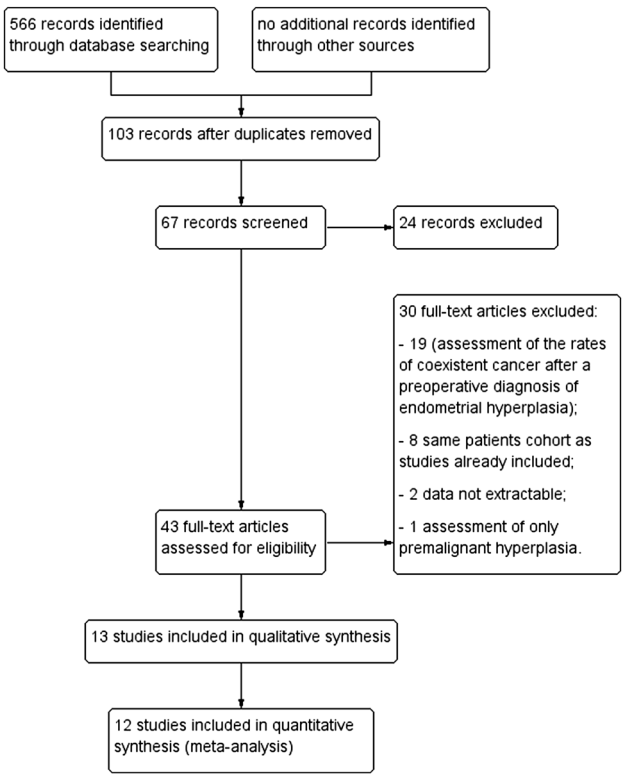

Fig. 1 Flow diagram of studies identified in the systematic review [Prisma template (Preferred Reporting Item for Systematic Reviews and Meta-analyses)]

Table 1 Characteristics of the included studies

Study	Country	Institute	Design	Period of enrollment	Sample size	Patients age (mean)	Sample type	Parameters assessed	Follow-up (mean)	Progression diagnosis	Conservative treatment
1985 Kurman	USA	Armed Forces Institute of Pathology	Retrospective cohort	1940–1970	170	17–71	Curettage	Complexity, atypia	1–27 years (13)	Variable	Discontinued estrogens, progesterone, none
1988 Baak	Netherlands	Pathological Institute and Department of Medical Statistics, Free University Hospital, De Boelelaan	Retrospective cohort	? < 1985	39	(53)^{C} (40)^{N}	Curettage	*D* score	6–52 months (17)^{C} (32 months)^{N}	Hysterectomy	n.r.
1992 Baak	Netherlands	University Hospital, De Boelelaan	Retrospective cohort	? < 1985	39	(53)^{C} (40)^{N}	Curettage	Complexity, atypia, *D* score	6–52 months (17)^{C} (32 months)^{N}	Hysterectomy	n.r.
1997 Ho	Singapore	Kandang Kerdau Hospital	Retrospective cohort	1991–1994	116	n.r.	Pipelle, curettage, hysteroscopy	Atypia	1 week-24 months	Variable	Progesterone
2000 Orbo	Norway	University Hospital of Tromsø	Retrospective cohort	1980–1991	68	28–77 (48)	Curettage	Complexity, atypia, *D* score	3–39 months (7)^{C} 2–21 years^{N}	Hysterectomy	In general none
2001 Baak	Netherlands, Norway	Free University Medical Center; Medical Center Alkmaar; Gemini Ziekenhuis; University Hospital of Tromsø	Retrospective cohort	1988–1998	132	34–77 (58)^{C} 20–93 (50)^{N}	Curettage	Complexity, atypia, *D* score	1–10 years (not excluding earlier cancers)	n.r.	Progesterone

Table 1 (continued)

Study	Country	Institute	Design	Period of enrollment	Sample size	Patients age (mean)	Sample type	Parameters assessed	Follow-up (mean)	Progression diagnosis	Conservative treatment
2004 Horn	Germany	Gyn-Path Laboratory at the Department of Obstetrics and Gynecology, University of Leipzig	Retrospective cohort	n.r.	502	n.r.	Curettage	Atypia	Partially reported	Variable	Oral progestin
2005 Baak	Europe, America	Multicentre	Retrospective cohort	22 years period (unspecified)	674	n.r.	Curettage, aspiration, Pipelle	Complexity, atypia, *D* score	13–120 months (48)[C] 13–216 months (68)[N]	n.r.	n.r.
2005 Baak	Norway	Stavanger University Hospital	Retrospective cohort	n.r.	103	29–71 (50)	Curettage	*D* score	12–154 months (50) (not excluding earlier cancers)	n.r.	In general none
2005 Hecht	Israel	Beth Israel Hospital	Retrospective cohort	1998–2000	97	n.r.	Biopsies, curettages	Complexity, atypia, subjective EIN, *D* score	At least 1 year (not excluding earlier cancers)	Variable	n.r.
2008 Lacey	USA	Kaiser Permanente Northwest Department of Pathology	Case–control	1970–2002	379	n.r.	n.r.	Complexity, atypia, subjective EIN	At least 1 year (68 days) hysterectomized (3 years) others	n.r.	None or oral progestin
2010 Reed	USA	Group Health, Washington State	Retrospective cohort	1985–2005	1443	18–88	n.r.	Atypia	8 weeks-21 years (5 years)	Hysterectomy	None or oral progestin
2011 Steinbakk	Norway	Stavanger University Hospital	Retrospective cohort	1980–2004	152	21–88 (53)	Curettage	Complexity, atypia, subjective EIN, *D* score	12–238 months (57)	n.r.	n.r.

[C]Cancer group; [N]no cancer group

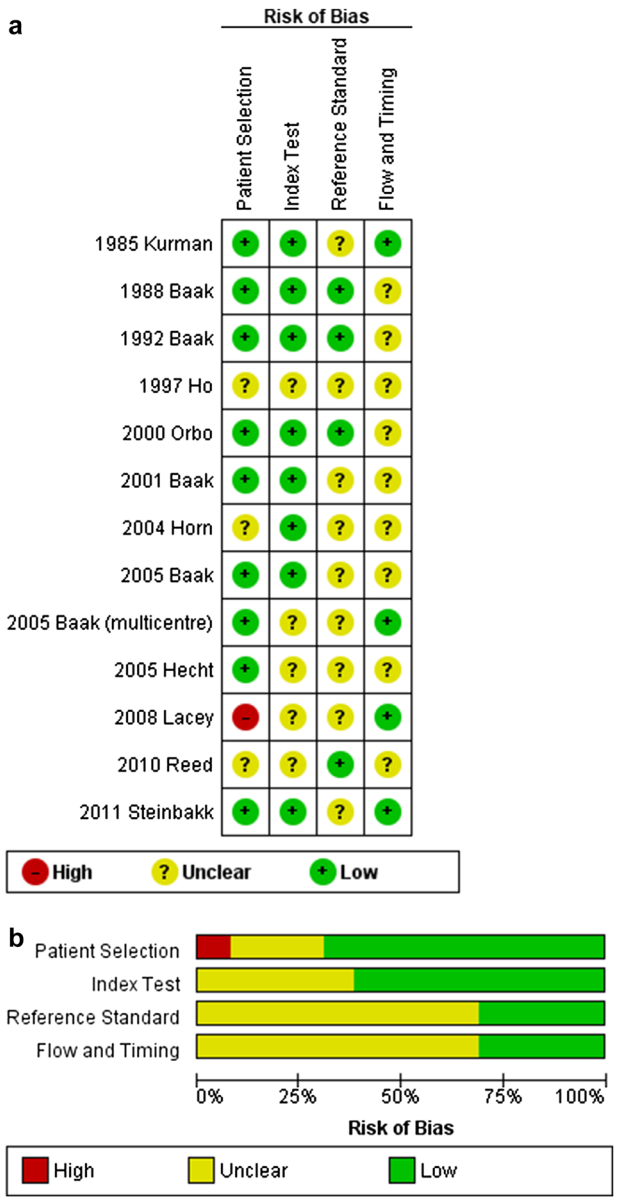

Fig. 2 **a** Assessment of risk of bias. Summary of risk of bias for each study; plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. **b** Risk of bias graph about each risk of bias item presented as percentages across all included studies

specify if all cancer diagnoses were confirmed on hysterectomy specimens.

For the "flow and timing" domain, eight studies were considered at unclear risk since they also included some patients with a follow-up < 1 year.

All remaining judgments for each domain were "low risk of bias".

Meta-analysis

Twelve studies were included in the meta-analysis since the only study at high risk of bias was excluded.

The group of EH classified according to WHO system consisted of 3384 EH from ten studies; heterogeneity among studies was low ($I^2 = 45\%$). Pooled RR for progression to cancer was 8.74 (95% CI 6.66–11.47).

The group of EH classified according subjective EIN criteria consisted of 236 EH from 2 studies, with no heterogeneity among studies ($I^2 = 0\%$). Pooled RR was 19.37 (95% CI 5.86–64.01), not significantly higher than WHO subgroup ($\chi^2 = 1.62$; $p = 0.20$).

The group of EH classified using *D* score consisted of 1106 EH from 6 studies; heterogeneity was insignificant ($I^2 = 5\%$). Pooled RR was 29.22 (95% CI 13.24–64.51), significantly higher than WHO subgroup ($\chi^2 = 7.99$; $p = 0.005$), but not than subjective EIN subgroup ($\chi^2 = 0.32$; $p = 0.57$).

Results are reported graphically in Fig. 3.

Discussion

Main findings and interpretations

Our study showed that objective EIN system based on *D* score better predicted the risk of cancer than WHO system. On the other hand, subjective EIN criteria showed intermediate reliability between WHO and objective EIN, without significant difference.

Classification of EH is a long-standing issue. Before 1994, EH had been classified as "mild", "moderate" and "severe", or alternatively as "cystic glandular", "adenomatous" and "atypical adenomatous" [26]. The 1994 WHO classification system had categorized EH according to two parameters: glandular complexity and cytologic atypia. Therefore, four categories of EH were proposed: "simple non-atypical", "complex non-atypical", "simple atypical" and "complex atypical" [2, 5, 6]. Cytologic atypia was already considered as the main factor associated with risk of progression to cancer [17]. However, these categories did not reflect the dichotomous nature of EH, which can be a polyclonal proliferation caused by the action of estrogens or a neoplastic process [3]. EIN system was developed to resolve this issue, distinguishing "benign EH" and "EIN" based on the pathogenetic mechanism underlying EH [2, 3, 6]. As already discussed, EIN system was first based on a computerized analysis calculating the prognostic "*D* score", developed by Baak et al. [2, 18]. Subsequently, a subjective assessment of EIN criteria was proposed to ensure a wide applicability of such system in the routine histologic examination [6]. On the other hand, the WHO revised its classification in 2003, proposing three EH categories:

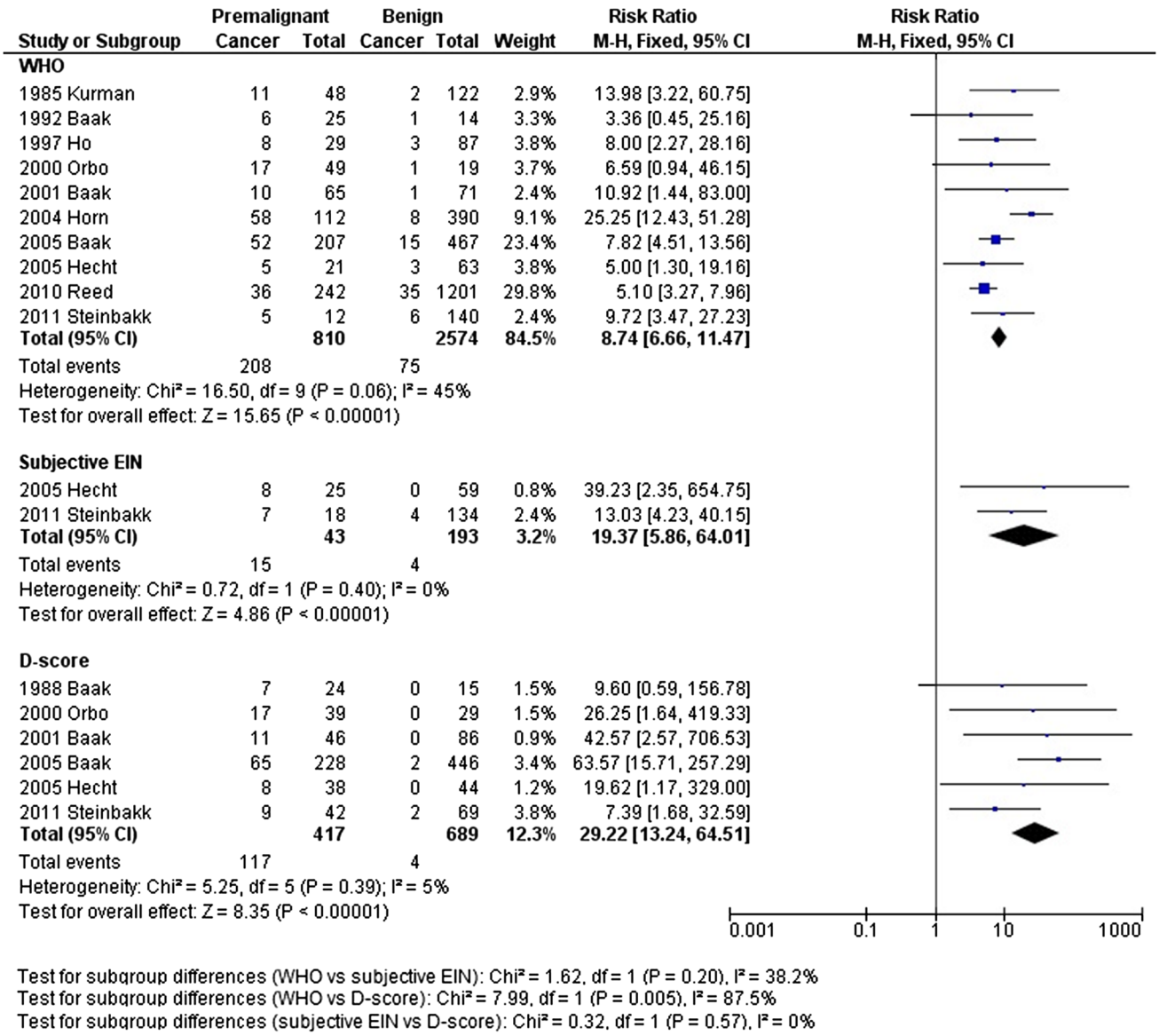

Fig. 3 Forest plot of individual studies and pooled relative risk for progression to cancer for WHO system, subjective EIN system and objective EIN system (*D* score) for classification of endometrial hyperplasia

"simple", "complex" and "atypical" [5, 14]; such system was quite superimposable to those used before 1994 and mentioned above. Finally, in 2014, the WHO proposed a dichotomous classification of EH into "non-atypical" and "atypical", reporting "EIN" as a synonym of the latter one [1, 2]. Therefore, WHO adopted the same conceptual basis as EIN system for EH categorization.

For WHO criteria, based on cytologic atypia, we found a RR for progression to cancer of 8.74. Objective EIN system based on *D* score showed a RR of 29.22, significantly higher than WHO ($p = 0.005$). Regarding subjective EIN system, we found a RR of 19.37, intermediate between WHO criteria and *D* score. However, the difference was not significant compared to both WHO ($p = 0.20$) and *D* score ($p = 0.57$). In fact, results from the literature are conflicting in this field. In our previous studies, we found that loss of expression of Bcl-2 and PAX2 was more strongly associated with subjective EIN criteria of premalignancy than WHO ones [27, 28], while loss of PTEN was not [29]. In predicting progression to cancer, Hecht et al. [23] reported a clear superiority of subjective EIN system over WHO, while a large study by Lacey et al. [12] showed similar accuracy between the two systems. For stratifying the risk of coexistent cancer, Yang et al. [30] showed higher accuracy of subjective EIN system, while Salman et al. [13] reported no difference with WHO; in our previous meta-analysis, the accuracy was similar in

the two systems, but they showed different values of sensitivity and specificity [31]. Regarding the reproducibility of the two systems, a study by Ordi et al. [14] found no significant differences between the two.

Based on these results, we support that a difference should always be made between the objective and subjective EIN systems. The first showed indeed clearly higher reliability than WHO system, but is not widely applicable in the routine practice. Regarding the second, the overall evidence of its superiority over WHO is not robust enough.

In this regard, it should be remarked that our previous meta-analysis showed that the subjective EIN system was more sensitive, but less specific than WHO system in stratifying the risk of coexistent cancer in EH. This finding may indicate that subjective EIN criteria identify precancerous lesions in an earlier phase compared to WHO criteria [31]. If this supposition is true, subjective EIN system might actually reveal higher accuracy than WHO for the risk of cancer on the long term. However, the currently available data are insufficient to draw such a conclusion, and further studies are needed before recommending a change in the diagnostic approach to EH.

Anyway, when a possible replacement of WHO system by EIN system is discussed, confusion between objective and subjective assessments should be avoided.

Strengths and limitations

To the best of our knowledge, this is the first meta-analysis evaluating the reliability of WHO system, *D* score and subjective EIN system in stratifying the risk of progression to cancer in EH.

However, several factors may affect our results, especially regarding the poor uniformity of methods among studies.

The different duration of follow-up might be the main limitation for our study since the cumulative risk of progression might be increasing over time [32]. However, such limitation may be tempered with the fact that most progressions occur early. In this regard, Horn et al. [21] pointed out that the rates of progression reported by the several studies in the literature tend to be constant, regardless of the follow-up duration.

Some studies also included some patients with a follow-up < 1 year. Such duration may be inadequate for assessing progression since endometrial cancer has a low growth rhythm and the progression rates may be underestimated. Furthermore, cancers occurred within 1 year from EH biopsy are usually considered as "coexistent" rather than "subsequent" [9, 12].

Progression rates might also be influenced by differences in the patient management (e.g., type of progestin administered or combination with hysteroscopic resection) [33–36]; unfortunately, patient management in the included studies was not detailed enough to allow a subgroup analysis.

In the large multicentre study by Baak et al. [9], a minor part of patient data overlapped with some previous studies; unfortunately, such data are not separable from the total. While in some studies the data overlap was clear, and consequently they were excluded from the analysis [37–40], overlap risk was not assessable for other studies [10, 25].

Finally, the low number of studies that used subjective EIN criteria was a major limitation to our results.

Conclusion

Among the classification systems of EH, objective EIN criteria with *D* score calculation are significantly more reliable than WHO criteria in stratifying the risk of progression of EH to cancer. Subjective EIN criteria, which are more applicable in the common practice than *D* score, did not show significant superiority over WHO instead. Further studies are necessary to determine if subjective EIN system should replace WHO system in the routine diagnosis of EH.

Author's contribution AR, AT: protocol/project development, data collection, data analysis, and manuscript writing/editing. GS: data analysis and manuscript writing/editing. AM: protocol/project development and study supervision. LI: manuscript writing/editing and study supervision. FZ: protocol/project development, manuscript writing/editing and study supervision. GDP: protocol/project development and study supervision.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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