

# Congruence Between 1994 WHO Classification of Endometrial Hyperplasia and Endometrial Intraepithelial Neoplasia System

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**Key Words:** World Health Organization; Endometrial intraepithelial neoplasia; Endometrioid adenocarcinoma; Endometrial precancer; Classification

*Am J Clin Pathol* January 2020;153:40-48

DOI: 10.1093/AJCP/AQZ132

## ABSTRACT

**Objectives:** To assess congruence between World Health Organization (WHO) 1994 and endometrial intraepithelial neoplasia (EIN) classification systems of endometrial hyperplasia.

**Methods:** Systematic review and meta-analysis were performed by searching electronic databases for studies that classified endometrial hyperplasia according to both WHO 1994 and EIN systems. Congruence was based on the rate of specimens classified as EIN in WHO categories, which should be virtually 0.000 in nonatypical hyperplasia (NAH) and 1.000 in atypical hyperplasia (AH). Subgroup analyses were performed based on architecture complexity.

**Results:** Eight studies with 1,352 hyperplasias were included. Congruence with EIN criteria was fair in NAH (0.241) and moderate in AH (0.815). Subgroup analyses of NAH showed high congruence in simple NAH (0.065), null in complex NAH (0.517), null in simple AH (0.148), and high in complex AH (0.901).

**Conclusions:** WHO 1994 system is not congruent with the EIN system and cannot be directly translated into a dual classification.

Endometrial hyperplasia is a pathologic proliferation of endometrial glands.<sup>1</sup> Its importance lies in the risk of progression to endometrial cancer.<sup>1,2</sup> In order to estimate such a risk, several histomorphologic features of endometrial hyperplasia have been studied.<sup>2-5</sup> Since 1994, the World Health Organization (WHO) classification had categorized endometrial hyperplasia based on the complexity of glandular architecture and the presence of cytologic atypia, identifying four categories: simple hyperplasia (SH), complex hyperplasia (CH), simple atypical hyperplasia (SAH), and complex atypical hyperplasia (CAH).<sup>2,3</sup> However, several studies demonstrated that endometrial hyperplasia has a dual nature, including benign proliferations reactive to unopposed action of estrogens, as well as precancerous lesions.<sup>1,2,6</sup> In order to distinguish between these two entities, an alternative classification system, the endometrial intraepithelial neoplasia (EIN) system, has been developed. The EIN system is based on three histomorphologic parameters (glandular crowding, lesion diameter >1 mm, and cytology different from adjacent endometrium) that allow differentiation between benign hyperplasia and EIN.<sup>2,3,6,7</sup> With the 2014 revision, the WHO system has conceptually accepted the EIN system, recognizing the presence of only two categories of endometrial hyperplasia: nonatypical (NAH, benign) or atypical (AH, premalignant).<sup>1,2</sup> Despite being equated to the EIN system, the 2014 WHO system does not extensively describe the changes in the criteria adopted to

define premalignancy. In fact, by using the terms “atypical” and “without atypia,” it might appear that SH and CH have been lumped together into NAH, and SAH and CAH into AH.<sup>1</sup> However, the 1994 WHO criteria for atypia were substantially different from EIN criteria of premalignancy; therefore, a “collapsed” 1994 WHO system might not meet the purpose of the 2014 revision.<sup>6</sup>

The objective of our study was to assess the rates of endometrial hyperplasia specimens meeting EIN criteria of premalignancy within the collapsed 1994 WHO categories of NAH and AH. We aimed to quantify the congruency between the 1994 WHO classification and the EIN system, defining whether the former WHO system can be directly translated into the current one.

## Materials and Methods

### Study Protocol

The study protocol, including methods for electronic search, study selection, risk of bias assessment, data extraction, and data analysis, was defined a priori. All review stages were performed independently by three authors (A.T., A.R., and M.M.). Disagreements were resolved by consensus with a fourth author (G.S.). This study was reported according to the PRISMA statement.<sup>8</sup>

### Electronic Search

MEDLINE, Scopus, Ovid, Web of Sciences, and Google scholar were searched from the inception of each database to March 2019, by using the following combination of the text words: (endometrial OR endometrioid OR endometrium) AND (hyperplasia OR intraepithelial neoplasia OR EIN OR precancer OR precursor OR classification). References from relevant studies were also checked.

### Study Selection

All studies assessing histologic specimens of endometrial hyperplasia according to both the 1994 WHO and the EIN system were included. Exclusion criteria, defined a priori, were the following: data overlap with an already included study; data not extractable; case reports and reviews; and use of morphometric analysis (D-score) to make diagnosis of EIN.<sup>3</sup> No language restrictions were planned.

### Data Extraction

No modification was made during the extraction of data from each included study. Data regarding

endometrial hyperplasia specimens were classified into NAH or AH. For this purpose, SH and CH were lumped together as NAH, while SAH and CAH were lumped together as AH. The rate of specimens reclassified as EIN according to the EIN system was extracted separately for NAH and AH.

### Risk of Bias Assessment

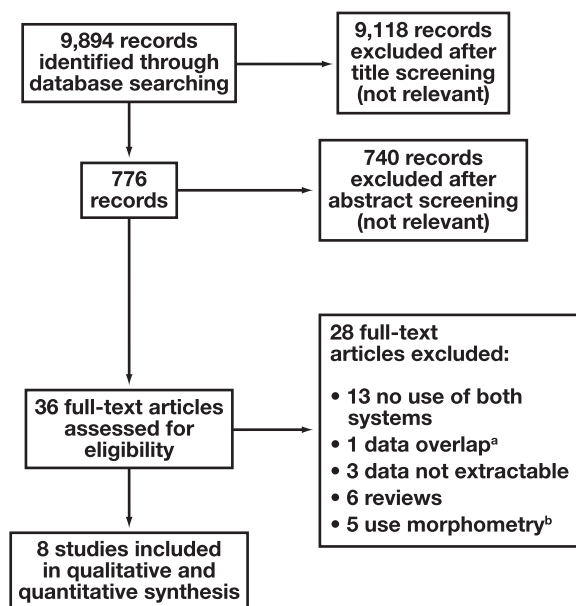
The risk of bias within studies was assessed according to the QUADAS-2.<sup>9</sup> Four domains were assessed: (1) patient selection (were patients selected consecutively?); (2) index test (were histologic slides revised to confirm WHO categories?); (3) reference standard (were EIN criteria applied blindly to the index diagnosis and/or by consensus among several pathologists?); and (4) flow and timing (did all specimens undergo both the index test and the reference standard?). Each domain was categorized as low risk, unclear risk, or high risk of bias depending on whether data were reported and adequate, not reported, or reported but inadequate, respectively.

Concerns about applicability were also evaluated for the domains 1, 2, and 3, based on whether the criteria used were right but did not fit the objective of our study.

### Data Analysis

In each WHO histologic category of endometrial hyperplasia, the rate of specimens meeting EIN criteria of premalignancy was calculated for each study and as a pooled estimate and reported graphically on forest plots. Given the subjectivity of histologic examination, the random effect model of DerSimonian-Laird was preferred for pooling data. In addition, pooled data according to the fixed effect model were calculated and reported only in figures. The congruity of WHO categories with the EIN system was assessed based on the rate of specimens that met EIN criteria of premalignancy: with complete congruity the rate of EIN diagnosis would be 1.00 in AH and 0.00 in NAH. The congruity of AH with EIN system was categorized as less than 0.60 = null; 0.60 to 0.69 = low; 0.70 to 0.79 = fair; 0.80 to 0.89 = moderate; 0.90 to 0.95 = high; and more than 0.95 = almost perfect. On the other hand, the congruity of NAH was categorized as less than 0.05 = almost perfect; 0.05 to 0.10 = high; 0.11 to 0.20 = moderate; 0.21 to 0.30 = fair; 0.31 to 0.40 = low; and more than 0.40 = null. Heterogeneity among studies was quantified by using the inconsistency index ( $I^2 = 0$ , no heterogeneity;  $0 < I^2 \leq 25$ , minimal heterogeneity;  $25 < I^2 \leq 50$ , low heterogeneity;  $50 < I^2 \leq 75$ , moderate heterogeneity; and  $75 < I^2 \leq 100$ , high heterogeneity).

As additional analysis, a subgroup analysis was performed for both NAH and AH based on the complexity



**Figure 1** Flow diagram of studies identified in the systematic review (PRISMA template, preferred reporting item for systematic reviews and meta-analyses). <sup>a</sup>The sample of Widra et al<sup>18</sup> overlapped with Dunton et al,<sup>19</sup> which was subsequently excluded due to the use of D-score. <sup>b</sup>D-score give results different from subjective EIN criteria.<sup>10,12,20</sup>

of glandular architecture. Four subgroups were obtained: SH, CH, SAH, and CAH. The congruity of WHO categories with the EIN system was assessed for each subgroup, as reported below for NAH and AH.

The data analysis was performed by using Review Manager 5.3 (Cochrane Collaboration) and Comprehensive Meta-Analysis (Biostat).

## Results

### Selection and Characteristics of the Studies

Eight studies were finally included in the systematic review.<sup>10-17</sup> The whole process of study selection for MEDLINE is presented in **Figure 1**. Out of a total of 1,352 EH specimens, 865 were NAH and 487 were AH; by using the EIN system, 807 were benign and 545 were EIN. Characteristics of the included studies are presented in **Table 1**.

### Risk of Bias Assessment

For the patient selection domain, all studies were considered at low risk of bias, due to the inclusion of consecutive patients. Concerns about applicability were raised for five studies, due to the inclusion of only patients that were followed for longer than 1 year,<sup>10,11</sup> or that underwent hysterectomy within a certain period (2 weeks,<sup>13</sup> 3 months,<sup>12</sup> or 1 year<sup>14</sup>).

For the index test domain, the risk of bias was considered low for seven studies (all histologic slides were reviewed to confirm the WHO diagnosis<sup>10-12,14-17</sup>) and unclear for one study.<sup>13</sup>

For the reference standard domain, the risk of bias was considered low for six studies (blinding to WHO diagnosis<sup>12,13,16</sup> or diagnosis by consensus<sup>10,11,17</sup>) and unclear for two studies.<sup>14,15</sup>

For the flow and timing domain, all studies were considered at low risk, because all included specimens were evaluated with both WHO and EIN systems,<sup>13,15,17</sup> or every loss was adequately explained (presence of cancer, artefacts, or other conditions that prevented a correct diagnosis<sup>10-12,14,16</sup>).

No further concerns about applicability were raised. Results of risk of bias assessment are shown in **Figure 2**.

### Main Analysis

In the WHO category of NAH, the rate of premalignant hyperplasias according to EIN criteria was 0.241 (95% confidence interval [CI], 0.117-0.432), indicating a fair congruity with EIN system. There was high heterogeneity among studies ( $I^2 = 94\%$ ).

In the WHO category of AH, the rate of premalignant hyperplasias according to EIN criteria was 0.815 (95% CI, 0.743-0.870), indicating a moderate congruity with the EIN system. Heterogeneity among studies was moderate ( $I^2 = 62\%$ ) **Figure 3**.

### Subgroup Analysis

In the subgroup of SH, the congruity with the EIN system was high, with a rate of EIN diagnosis of 0.065 (95% CI, 0.032-0.130) and moderate heterogeneity among studies ( $I^2 = 71\%$ ).

In the subgroup of CH, the congruity with the EIN system was null, with a rate of EIN diagnosis of 0.517 (95% CI, 3.16-7.13) and high heterogeneity among studies ( $I^2 = 86\%$ ) **Figure 4**.

In the subgroup of SAH, the congruity with the EIN system was null, with a rate of EIN diagnosis of 0.148 (95% CI, 0.052-0.355) and no heterogeneity among studies ( $I^2 = 0\%$ ).

In the subgroup of CAH, the congruity with the EIN system was high, with a rate of EIN diagnosis of 0.901 (95% CI, 0.840-0.940) and with minimal heterogeneity among studies ( $I^2 = 17\%$ ) **Figure 5**.

## Discussion

### Main Findings and Interpretation

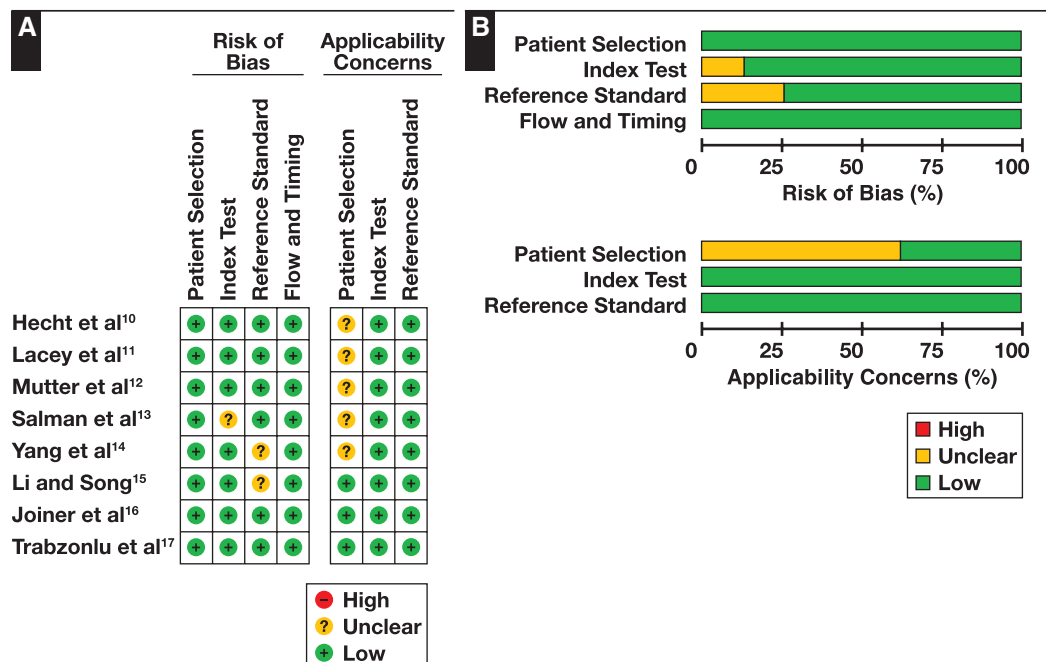
Our study showed that, in the collapsed 1994 WHO categories of NAH and AH, the congruity with EIN

**Table 1****Characteristics of the Included Studies**

| Study                               | Country         | Institution                                                                   | Period of Enrollment | Sample Size | WHO            |                 | EIN |     | Sampling Method                       |
|-------------------------------------|-----------------|-------------------------------------------------------------------------------|----------------------|-------------|----------------|-----------------|-----|-----|---------------------------------------|
|                                     |                 |                                                                               |                      |             | NAH (SH + CH)  | AH (SAH + CAH)  | BH  | EIN |                                       |
| Hecht et al, 2005 <sup>10</sup>     | Israel          | Beth Israel Hospital                                                          | 1998-2000            | 97          | 74 (56 + 18)   | 23 (0 + 23)     | 69  | 28  | Biopsies, curettage                   |
| Lacey et al, 2008 <sup>11</sup>     | USA             | Kaiser Permanente Northwest Department of Pathology                           | 1970-2002            | 239         | 166 (106 + 60) | 73 <sup>a</sup> | 117 | 122 | Not reported                          |
| Mutter et al, 2008 <sup>12</sup>    | Europe, America | Multicenter                                                                   | 1998-2003            | 189         | 0              | 189             | 36  | 153 | Curettage, pipelle, vacuum aspiration |
| Salman et al, 2010 <sup>13</sup>    | Turkey          | Hacettepe University                                                          | 2007-2009            | 49          | 12 (0 + 12)    | 37 (3 + 34)     | 12  | 37  | Vacuum aspiration, curettage          |
| Yang et al, 2012 <sup>14</sup>      | China           | Shilong People's Hospital; 2000-2011<br>The People's Hospital of Jieyang City |                      | 139         | 46 (5 + 41)    | 93 (8 + 85)     | 36  | 103 | Biopsy (unspecified)                  |
| Li and Song, 2013 <sup>15</sup>     | China           | General Hospital of Tianjin Medical University                                | 2008-2010            | 474         | 427 (379 + 48) | 47 (16 + 31)    | 428 | 46  | Curettage                             |
| Joiner et al, 2015 <sup>16</sup>    | USA             | University of Arkansas for Medical Sciences, Little Rock                      | 2005-2013            | 57          | 32 (7 + 25)    | 25 (0 + 25)     | 21  | 36  | Biopsies, curettage                   |
| Trabzonlu et al, 2017 <sup>17</sup> | Turkey          | Kocaeli University School of Medicine                                         | 2006-2011            | 108         | 108 (95 + 13)  | 0               | 88  | 20  | Not reported                          |
| Total                               |                 |                                                                               |                      | 1,352       | 865            | 487             | 807 | 545 | —                                     |

AH, atypical hyperplasia; BH, benign hyperplasia; CAH, complex atypical hyperplasia; CH, complex hyperplasia; EIN, endometrial intraepithelial neoplasia; NAH, nonatypical hyperplasia; SAH, simple atypical hyperplasia; SH, simple hyperplasia; WHO, World Health Organization.

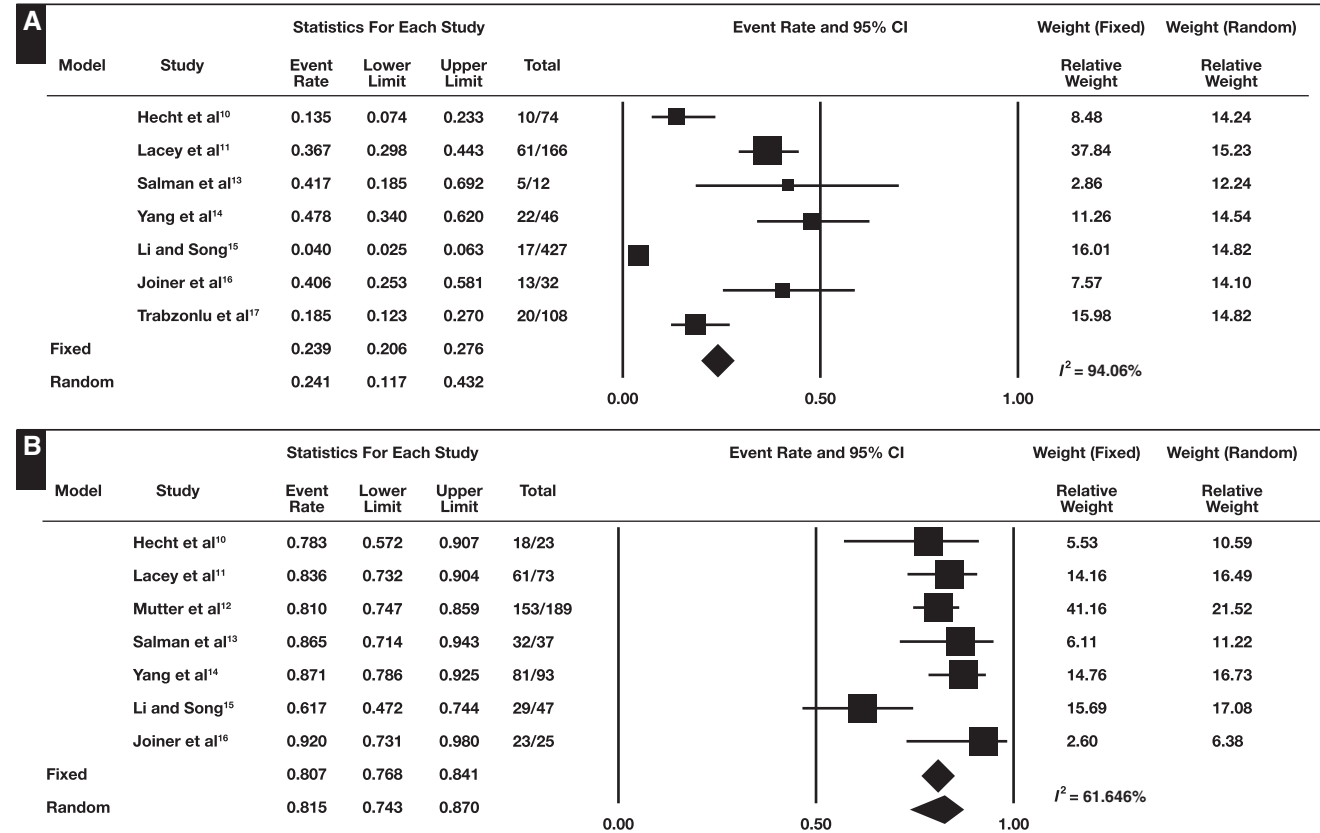
<sup>a</sup>Data refer to the diagnoses made by the centralized panel of pathologists.



**Figure 2** Assessment of risk of bias. **A**, Summary of risk of bias for each study. **B**, Risk of bias graph with each risk of bias item presented as percentages across all included studies.

criteria was moderate; this result was strongly influenced by the complexity of glandular architecture, as shown through subgroup analysis.

Although the association between endometrial hyperplasia and endometrioid adenocarcinoma has long been known, the risk stratification is still a problem.



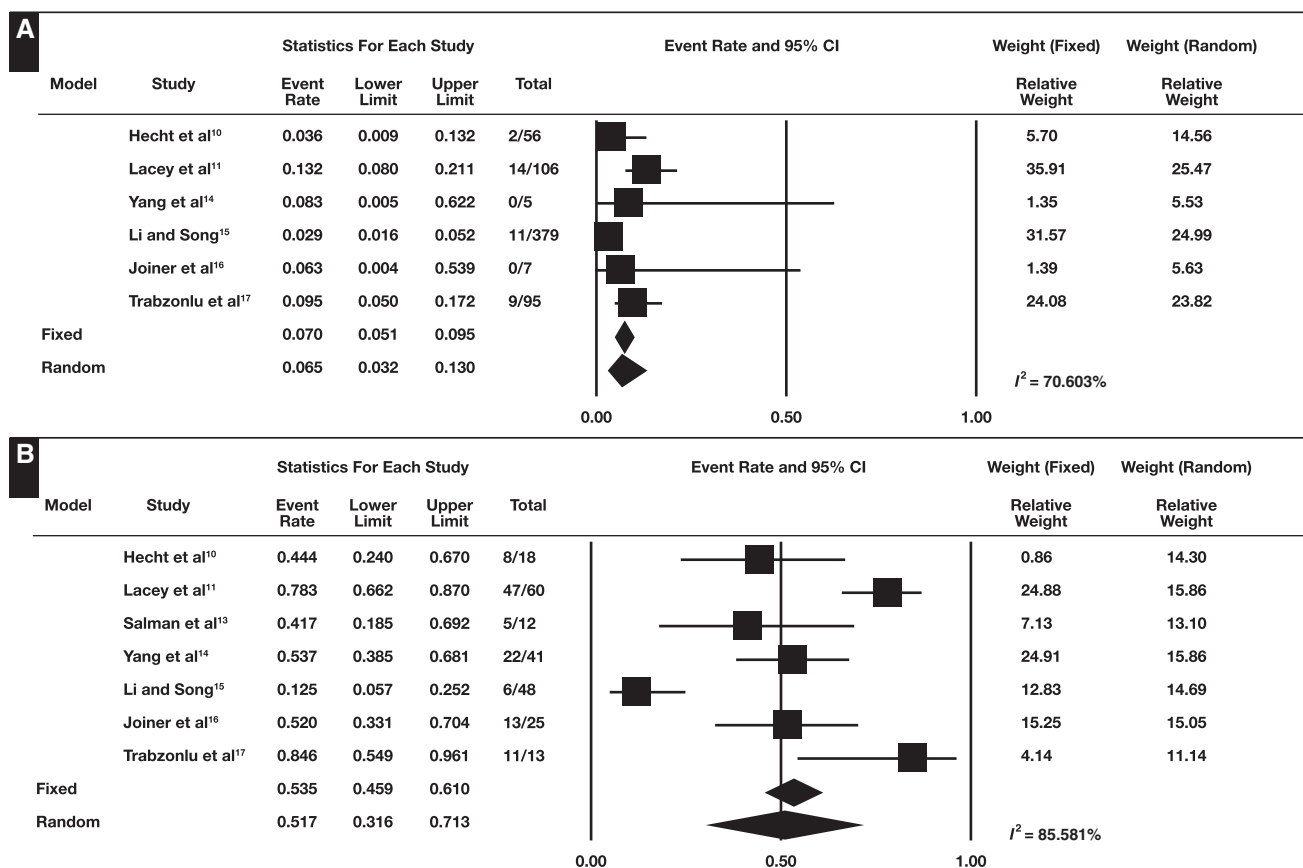
**Figure 3** Forest plot of individual studies and pooled rate of specimens diagnosed as endometrial intraepithelial neoplasia within the World Health Organization categories of nonatypical hyperplasia (A) and atypical hyperplasia (B). CI, confidence interval.

Several histomorphologic classifications have been proposed through the years.<sup>2,5</sup> The 1994 WHO classification had defined four categories of endometrial hyperplasia (SH, CH, SAH, and CAH) based on the complexity of glandular architecture (closely packed glands with irregular profile) and cytologic atypia (loss of polarity, nuclear enlargement and rounding, and presence of nucleoli).<sup>1-3</sup> However, such classification did not have a solid pathogenic and molecular basis and was poorly reproducible.<sup>2,3,21</sup> On the other hand, morphometric and molecular studies have demonstrated that endometrial hyperplasia may be either a benign proliferation or a premalignant lesion.<sup>2,7,18-20,22-26</sup> Therefore, the EIN system was developed to differentiate between these two conditions.<sup>2,3,7</sup> In our previous studies, we found that the EIN systems correlated with immunohistochemical markers of precancer better than the WHO system<sup>27,28</sup> (except for the loss of protein phosphatase and tensin homolog, which, however, appeared to have little accuracy as a marker<sup>29</sup>).

The 2014 WHO classification has acknowledged the dual nature of endometrial hyperplasia as proposed by the EIN system. After such revision, NAH is clearly defined as a reactive proliferation and benign hyperplasia is

reported as a synonym of NAH. On the other hand, AH is defined as a premalignant lesion and EIN is reported as a synonym of AH. The main concern with such classification is that, despite referring to the EIN system, it does not clearly state the changes in the criteria adopted to categorize endometrial hyperplasia. In fact, some definitions such as “crowded aggregates of cytologically altered glands” refers to the EIN system, while other ones such as “cytologic atypia superimposed on NAH defines AH” seems to refer to the previous WHO criteria. Furthermore, SH and CH are listed as synonyms of NAH, while SAH and CAH are listed as synonyms of AH. In this way, cytologic atypia might appear as the only crucial parameter for recognizing precancer; this would define the 2014 WHO system as a collapsed version of the 1994 one.<sup>1</sup>

In the current study, we found the collapsed 1994 NAH category (SH + CH) was only fairly congruent with the EIN system, with about one-fourth of NAH meeting EIN criteria of premalignancy. On the other hand, almost one-fifth of the 1994 AH category (SAH + CAH) was benign according to EIN criteria, with a barely moderate congruency. These findings point to a clear discrepancy between the 1994 WHO system and the EIN system.



**Figure 4** Forest plot of individual studies and pooled rate of specimens diagnosed as endometrial intraepithelial neoplasia within the World Health Organization categories of simple nonatypical hyperplasia (**A**) and complex nonatypical hyperplasia (**B**). CI, confidence interval.

By performing a subgroup analysis, we found that such a difference was partially attributable to the complexity of glandular architecture, which has been disregarded in the current WHO terminology. In fact, in the NAH subgroups, the rate of EIN diagnosis was only 6% in SH but over 50% in CH. This means that, by applying EIN criteria, SH is congruently benign, while more than half of CH are premalignant.

In the AH subgroups, CAH appeared congruently premalignant, with a rate of EIN diagnosis of over 90%, while SAH met EIN criteria of premalignancy only in 15% of cases.

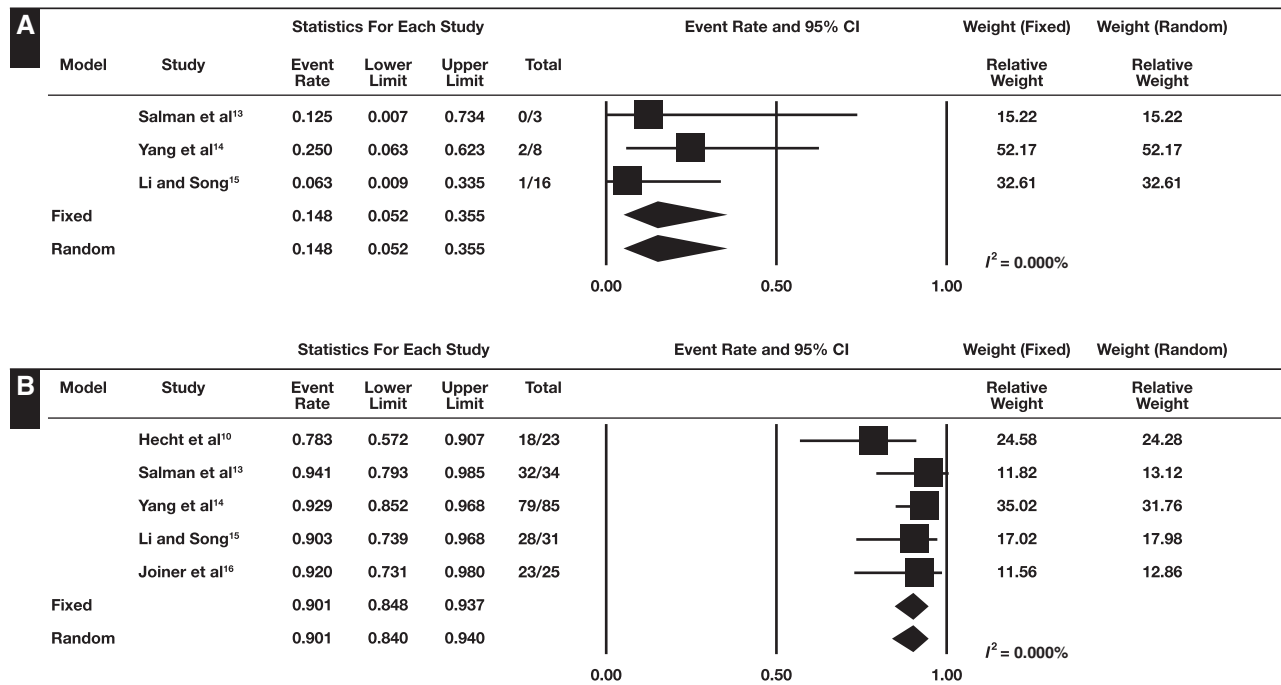
Our results highlight that the presence of a complex glandular architecture may be a crucial premalignant feature, independent from the presence of overt cytologic atypia.

Regarding the AH category, although the current WHO classification lists SAH and CAH as synonyms of AH/EIN, it clearly states that AH is characterized by closely packed glands, in agreement with EIN criteria of premalignancy.<sup>1,3</sup> In this respect, cytologic atypia in the absence of glandular crowding should not be considered

for the diagnosis of precancer, as it may reflect metaplastic, regenerative, or inflammation-related changes.<sup>21</sup> For this reason, the diagnosis of SAH has rarely been made and several authors have not even acknowledged its existence.

Regarding the NAH category, in the EIN system the presence of overt atypia is not necessary to make a diagnosis of premalignancy. In fact, it has been shown that cytologic changes in endometrial precancer may be very subtle; sometimes, premalignant cells may appear even more polarized than benign endometrial cells.<sup>10</sup> In these cases, glandular architecture may be the crucial factor to identify the premalignant clone, in particular when comparison with adjacent endometrium is not possible. Indeed, as discussed above, endometrial precancers are characterized by closely packed glands; furthermore, morphometric analyses that have led to the development of the EIN system have also suggested that irregularity of glandular profile may be relevant in determining the risk of progression to cancer.<sup>18,19,22-25,30,31</sup>

Based on this evidence, complexity of glandular architecture should not be disregarded in the classification



**Figure 5** Forest plot of individual studies and pooled rate of specimens diagnosed as endometrial intraepithelial neoplasia within the World Health Organization categories of simple atypical hyperplasia (A) and complex atypical hyperplasia (B). CI, confidence interval.

of endometrial hyperplasia. An application of the WHO system based on only cytologic atypia would cause many precancers to be missed, with a significant risk of progression to malignancy. Given the excellent outcomes of conservative treatment for endometrial hyperplasia,<sup>32</sup> it appears fundamental not to miss these patients. On the other hand, unless fertility preservation is required, the treatment of choice for premalignant hyperplasia is total hysterectomy<sup>33</sup>; therefore, an erroneous diagnosis of precancer would result in a significant overtreatment. By applying the only criterion of cytologic atypia, noncrowded glands with altered cytology would be overdiagnosed as precancer. Similarly, by applying the only criterion of architecture complexity, all patients with CH would be addressed to hysterectomy; this does not appear reasonable because the risk of cancer linked to architecture complexity is definitely lower than that linked to cytologic atypia.<sup>4,11,22</sup>

The value of the EIN system lies in the clear criteria used for the diagnosis of premalignancy. First of all, the EIN system specifies that the architectural criterion of glandular crowding is necessary for a diagnosis of precancer. Furthermore, the EIN system proposes an alternative method to assess cytologic atypia, based on comparison with background endometrium rather than on absolute criteria. Finally, lesion size and thorough exclusion of mimics are additional criteria that make the

EIN system more complete than the 1994 WHO system. In our opinion, the current WHO system should better specify the criteria used for diagnosing precancer. If the current WHO system aims to recognize the EIN system, a more precise description might be advisable.

In our previous study, we raised the possibility of further stratifying the diagnosis of EIN into low-risk/low-grade EIN and high-risk/high-grade EIN, based on the presence of overt atypia. Given the availability of several different conservative treatments, and the lack of valuable prognostic and/or predictive markers,<sup>32,34-39</sup> a more stratified diagnosis might allow a more tailored management of patients. Further studies are necessary to investigate this issue.

Strengths and Limitations

To the best of our knowledge, this is the first meta-analysis assessing the congruity of the WHO criteria with the EIN criteria for the differential diagnosis between benign and premalignant endometrial hyperplasia. Our results might indicate the need for some revisions in the terminology of the 2014 WHO classification of endometrial hyperplasia.

Major limitations to our results are the retrospective design of the included studies, the differences in the patient cohorts (which underlie the concerns about

applicability, as discussed above), and in particular the low reproducibility of histomorphologic assessment of endometrial biopsies.<sup>40-44</sup> These limitations are probably the cause of the high statistical heterogeneity observed in the analysis of NAH. However, these findings further highlight the concerns with the current classification criteria of endometrial hyperplasia.

## Conclusion

Although the current WHO classification has equated AH to EIN, it is not clearly stated if the EIN criteria should be used and if the former WHO criteria for defining AH should be rejected. Our study showed that a direct translation of the 1994 WHO criteria into a dual classification would result in a significant discrepancy with the EIN system, with the risk of over- or undertreatment of many patients. In our opinion, the current WHO system should better specify the changes in the criteria to be used for diagnosing precancer.

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