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REVIEW

Significant risk of occult cancer in complex non-atypical endometrial hyperplasia

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Abstract

Background In the 2014 WHO classification of endometrial hyperplasia (EH), complex EH is lumped together with simple EH in the benign category of non-atypical EH.

Objective To assess the risk of coexistent cancer in complex EH and simple EH without atypia, through a systematic review and meta-analysis.

Methods Electronic databases were searched from their inception to January 2019 for relevant articles.

Results Twelve studies assessing a total of 804 non-atypical EH were included. The risk of coexistent cancer was significantly higher in complex EH (12.4%) than in simple EH (2%), with an OR of 6.03 ($p = 0.0002$).

Conclusion Even in the absence of cytologic atypia, complex EH is associated with a significant risk of coexistent cancer. Further studies are necessary to investigate the need for a revision in the WHO classification.

Keywords Endometrial hyperplasia · Coexistent cancer · Endometrial intraepithelial neoplasia · Complex hyperplasia

Introduction

Endometrial hyperplasia (EH) is a pathologic proliferation of endometrial glands, which may precede endometrial cancer of endometrioid type [1–4]. The stratification of the risk of cancer in EH is crucial to adopt an adequate and tailored patient management [5–8].

The endometrial intraepithelial neoplasia (EIN) classification system highlights that some EH are benign hormone-driven proliferation, which are referred to as "benign hyperplasia", while other ones are monoclonal lesion, which are termed "EIN" and constitute true precursors of endometrial cancer [1, 3, 4, 9, 10]. The EIN system indicates glandular crowding, lesion size > 1 mm and cytologic features different from background uncrowded endometrium as the crucial features to differentiate EIN from benign hyperplasia [1, 3, 4, 9]. On the other hand, the current WHO classification gives crucial importance to cytologic atypia, defining "atypical EH" as premalignant and synonym of EIN, and "non-atypical EH" as benign and synonym of benign hyperplasia [1–4, 9]. However, as we have pointed out in previous studies, non-atypical EH might include a significant number of premalignant lesions, which may be identified based on the complexity of glandular architecture [3, 11, 12].

In the present study, we aimed to assess how the complexity of glandular architecture affects the risk of occult cancer in non-atypical EH. For this purpose, we first assessed the association between glandular complexity and risk of occult cancer, and then we quantified such risk separately for simple non-atypical EH (SEH) and complex non-atypical EH (CEH).

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Materials and methods

Review authors defined a priori criteria for electronic search, study selection, risk of bias assessment, data extraction and data analysis. All review stages were performed independently by three authors (AT, AR, MM); in the case of disagreement, a solution was achieved by consensus among the three authors and with another author (GS).

The study was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [13].

Search strategy

Scopus, MEDLINE, Ovid, Web of Sciences; EMBASE, ClinicalTrial.gov, Cochrane Library and Google Scholar were searched from the inception of each database to January 2019. Several different searches were performed using a combination of the following text words: endometrial, endometrioid, endometrium, hyperplasia, intraepithelial neoplasia, complex, simple, atypia, atypical, precancer, premalignant, precursor, cancer, carcinoma, adenocarcinoma, coexistent, occult, concurrent, hysterectomy, and risk. The search also involved all relevant references from eligible studies. No language restrictions were applied.

Study selection

All studies assessing the rate of occult endometrial cancer in women diagnosed with SEH and CEH were included. Occult endometrial cancer was defined as a cancer diagnosed on hysterectomy specimen after a preoperative diagnosis of endometrial hyperplasia. Exclusion criteria, defined a priori, were: overlapping patient data, case reports, reviews, and presence of endometrial cancer not assessed on hysterectomy sample.

Risk of bias within studies assessment

The revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) were used to assess the risk of bias within studies [14]. The four domains assessed were: (1) patient selection (were patients included consecutively or randomly?), (2) index test (were preoperative histological slides reviewed by expert pathologists?), (3) reference standard (was hysterectomy specimens reviewed by expert pathologists?), and (4) flow and timing (was the time to hysterectomy < 1 year? In fact, cancers found after 1 year from the index diagnosis are usually considered as subsequently developed rather than coexistent [4, 9, 15, 16]). Authors' judgements were "low risk", "unclear risk" or "high risk" of bias for each domain and in each study. Concerns about applicability of the domains 1, 2 and 3 were also assessed (i.e., if the criteria adopted in the included study were correct but did not suit the aim of our review).

Data extraction

Data were extracted according to the PICOS: "Population" consisted of women diagnosed with non-atypical EH who underwent hysterectomy after a preoperative diagnosis of EH; "Intervention" (or risk factor) was the presence of a complex glandular architecture (CEH diagnosis); "Comparator" was SEH; "Outcome" was the presence of endometrial cancer on histologic examination of hysterectomy specimen after the diagnosis of EH; "Study design" was the study design of the included studies.

Data analysis

The association of glandular complexity with occult cancer was assessed using odds ratio (OR) with 95% confidence interval (CI); a p value < 0.05 was considered as significant.

Subsequently, the pooled rate of occult cancer with 95% CI was assessed separately for SEH and CEH and reported graphically on forest plots to quantify the risk.

Statistical heterogeneity among studies was categorized based on the inconsistency index (I^2) as follows: $I^2 = 0$: null; $0 < I^2 < 25$: minimal; $25 < I^2 < 50$: low; $50 < I^2 < 75$: moderate; $I^2 > 75\%$: high.

A fixed effect model was adopted in the case of $I^2 < 50$, while a random effect model was used in the case of $I^2 > 50$.

The risk of bias across studies (publication bias) was assessed by reporting the studies on funnel plots of the logarithm of the OR by the standard error and of the rate of cancer by the standard error.

Comprehensive meta-analysis and Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) were used for the analysis.

Results

Selection and characteristics of the studies

Twelve retrospective studies assessing a total of 804 EH were included [17–28]. Out of these, 566 were SEH and 238 were CEH. The process of study selection is schematized in Supplementary Fig. 1. Sampling methods included hysteroscopic biopsy, Pipelle biopsy, dilation and curettage and vacuum aspiration.

Characteristics of the included studies are shown in Table 1.

Table 1 Characteristics of the included studies

Study	Country	Period of enrolment	Sample		Age (mean)	BMI	Sampling method	Time to hysterectomy
			SEH	CEH				
1996 Dunton	USA	1988–1993	18	4	34–81 (55.7)	n.r	Hysteroscopy, curettage, biopsy (unspecified)	Preoperative (mean 2.4 months)
2001 Bettocchi	Italy	1988–1991	25	11	(43)	n.r	Curettage	≤2 months
2002 Xie	China	1992–2000	53	11	31–76 (48.5)	n.r	Curettage	4–90 days
2008 Obeidat	Jordan	2003–2007	26	24	35–74 (51.8)	n.r	Curettage	1–33 weeks
2010 Yarandi	Iran	2000–2005	30	4	30–86 (46.6)	n.r	Curettage	≤2 months
2011 Daud	UK	1998–2009	117	34	(55.7)	n.r	Pipelle, curettage	2 weeks to 3 years (2 months)
2012 Yang	China	2000–2011	5	41	37–69	n.r	Biopsy (unspecified)	≤1 year
2014 Sirimusika	Thailand	2000–2012	14	12	27–86 (47)	(26.8)	Curettage, hysteroscopy, biopsy (uspecified)	≤1 year
2015 Dolanbay	Turkey	2009–2013	20	9	(54.6)	(29.27)	Pipelle, biopsy (unspecified)	<6 weeks
2015 Kadirogullari	Turkey	2006–2012	109	9	(50.5)	(30.4)	Biopsy (unspecified)	Preoperative (unspecified)
2015 Matsuo	USA	2003–2014	24	58	(45.2)	(35.6)	Pipelle, curettage vacuum aspiration,	4–2514 days (105 days)
2016 Boyraz	Turkey	2007–2014	125	21	34–82 (50.4)	n.r	Biopsy (unspecified)	Preoperative (unspecified)
Total	–	–	566	238	–	–	–	–

Risk of bias assessment

For the domain 1 (patient selection), all studies were considered at low risk of bias, since they specified inclusion criteria and period of enrolment of patients.

For the domain 2 (index test), five studies were considered at low risk and the other ones at unclear risk. High concern about applicability was raised for one study, due to the possibility of SEH (non-atypical) being lumped together with simple atypical EH.

For the domain 3 (reference standard), the risk of bias was low in five studies and unclear in the other ones.

For the domain 4 (flow and timing), the risk of bias was low for eight studies (all patients underwent hysterectomy within 1 year from index diagnosis) and unclear for four studies (time to hysterectomy not specified, or inclusion of some patients with a time-to-hysterectomy > 1 year).

Authors' judgements are shown in Supplementary Fig. 2.

Meta-analysis

Among non-atypical EH, a diagnosis of CEH was significantly associated with the presence of occult cancer on histologic examination of hysterectomy specimen ($p = 0.0002$), with an OR of 6.02 (95% CI 2.35–15.42) and null statistical heterogeneity among studies ($I^2 = 0\%$) (Fig. 1). The funnel plot of OR was symmetrical, excluding a significant risk of publication bias (Fig. 2).

Among SEH, the pooled rate of coexistent cancer on hysterectomy specimen was 0.020 (95% CI 0.010–0.038), with null statistical heterogeneity among studies ($I^2 = 0\%$).

Among CEH, the pooled rate of coexistent cancer was 0.124 (95% CI 0.084–0.181), with low heterogeneity among studies ($I^2 = 27\%$) (Fig. 3).

The funnel plot of the rate of coexistent cancer was symmetrical for both SEH and CEH, excluding a significant risk of publication bias (Fig. 4).

Discussion

Main findings and interpretation

Our study showed that the complexity of glandular architecture in EH was significantly associated with the presence of occult cancer, with a risk of 2% in SEH and of 12.4% in CEH.

The classification of EH has long since been a crucial issue [29–34]. It is essential to estimate the risk of cancer in women diagnosed with EH, as it determines the management of patients [35–39]. In fact, benign EH has a very low risk of coexistence or subsequent development of cancer (< 5%) and, thus, may be managed even by observation alone. On the other hand, the risk of cancer is high in EIN, making total hysterectomy the standard approach for this condition [4, 6, 9, 40].

To date, the WHO classification is the most widely used one for the diagnosis of EH [2, 4, 9]. According to the WHO,

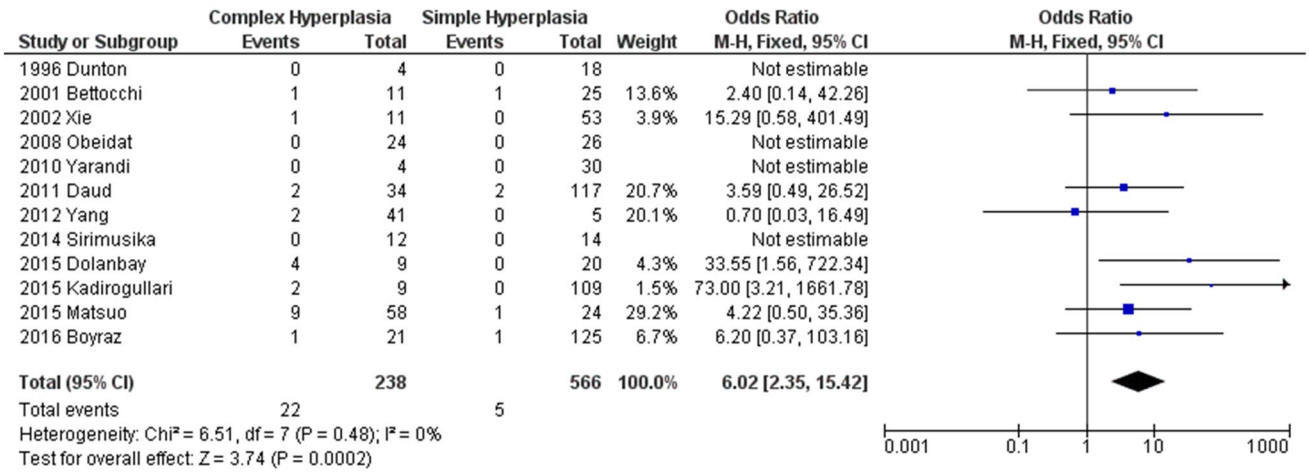

Fig. 1 Forest plot of individual studies and pooled odds ratio (OR) for occult cancer in complex non-atypical hyperplasia (CEH) vs simple non-atypical hyperplasia (SEH)

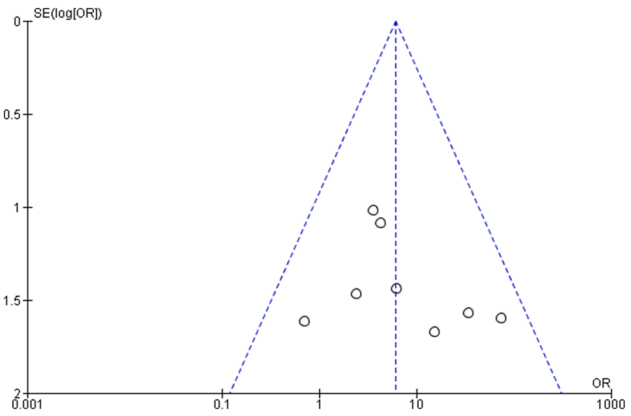

Fig. 2 Funnel plot of odds ratio (OR) by standard error (SE) for the risk of occult cancer in complex non-atypical hyperplasia (CEH) vs simple non-atypical hyperplasia (SEH)

non-atypical EH is assimilated to benign EH, while atypical EH is assimilated to EIN [2, 4].

Our results showed that the risk of occult cancer is only 2% in SEH, consistently with it being a benign condition. On the other hand, the risk of occult cancer is over 12% in CEH, i.e., about six times higher than SEH; this indicates that CEH cannot be simply regarded as a benign lesion.

In our previous studies on EH, we found that the EIN system was more sensitive than the WHO system stratifying the risk of occult cancer [4]. On the other hand, no significant difference was found with regard to the risk of progression to cancer, probably due to the limited available data on the EIN system [9].

Furthermore, we showed that the altered expression of molecules involved in endometrial carcinogenesis, such as Bcl-2, β-catenin and PAX2, correlated better with the EIN criteria of premalignancy than with the WHO ones [11, 41, 42]. By contrast, no difference was found regarding PTEN expression [43]; such finding may be due to overall low accuracy of PTEN loss as a marker of premalignancy [44, 45].

Moreover, our results suggested the inconsistence of non-atypical EH as a benign category. In fact, our previous studies showed that a complex glandular architecture increased the risk of progression to cancer of about six times [12] and that about half of CEH met EIN criteria of premalignancy [46].

All these findings suggest that the WHO criteria for benign hyperplasia might need a revision. In fact, considering CEH as an innocuous lesion may lead many patients to be undertreated, with the risk of progression to malignancy. However, it is clear that the risk of cancer in CEH is sensibly lower than in atypical EH; therefore, it appears excessive to address all CEH patients to hysterectomy, resulting in patients' overtreatment instead.

As we proposed in our previous studies, a hypothetical solution might be the combination of WHO and EIN systems together to obtain a new integrated classification [4]. As the EIN system is more sensitive than WHO and better reflects molecular alterations, it could be used to distinguish benign functional EH from true premalignant lesions. On the other hand, the WHO criterion of cytologic atypia could distinguish premalignant lesions at lower risk (L-EIN) from premalignant lesion at higher risk (H-EIN) of coexistent cancer. Such a stratified diagnosis might be useful for the patient management. Firstly, a diagnosis of L-EIN might ensure that premalignant lesions without significant atypia are not misclassified as benign condition and then undertreated.

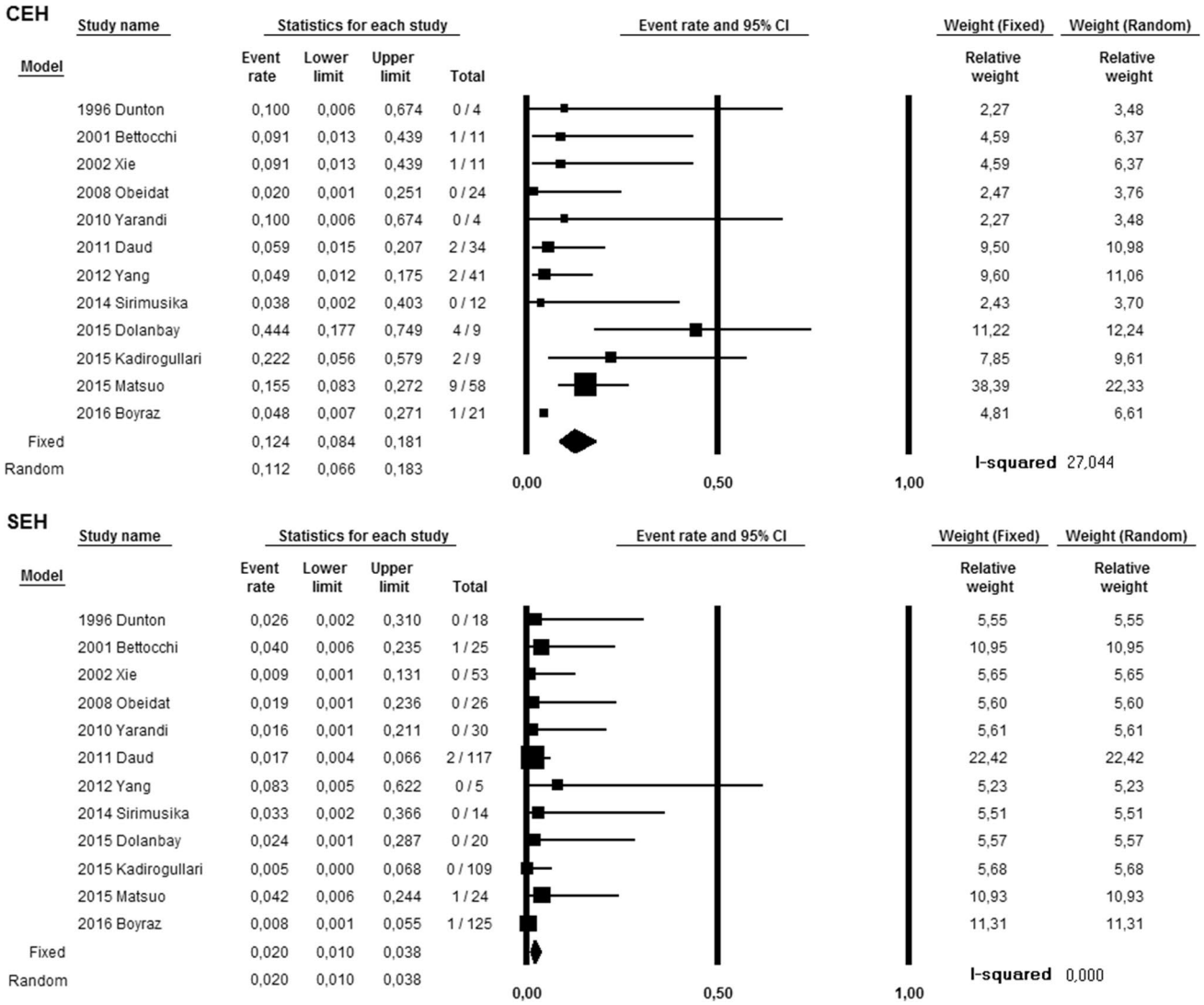

Fig. 3 Forest plot of individual studies and pooled rate of occult cancer in complex non-atypical hyperplasia (CEH) and simple non-atypical hyperplasia (SEH)

Secondly, patients with H-EIN might require hysterectomy in a shorter time compared to H-EIN, and a closer follow-up if conservatively treated. Thirdly, when the decision making between hysterectomy and conservative treatment is difficult (e.g., patient's age older 40 years, low couple fertility potential, wish to get pregnant not in the short term, pluriparity), a diagnosis of L-EIN might direct the choice towards a conservative approach.

Further studies are of course needed to investigate the feasibility of such an integrated classification.

Strengths and limitations

To best of our knowledge, this is the first systematic review and meta-analysis assessing the risk of coexistent cancer in SEH and CEH.

A limitation to our results may lie in the selection of patients within the included studies. In fact, even though patients were selected consecutively, the selection was restricted to only those women who underwent hysterectomy within a short term. If we assume that the ratio between the risks of occult cancer in SEH and CEH is the same that in the general population, then the included studies could be considered as cohort studies, and the level of evidence for prognostic studies would be II; otherwise, the level of evidence would be III [47]. Large prospective studies are of course needed to confirm our results.

The low reproducibility in the classification of EH might be another limitation of our meta-analysis, as it is intrinsic to the topic assessed [48]. For this reason, we considered the index test (i.e., pathologic examination) at low risk of bias only if diagnoses were reviewed by expert pathologist.

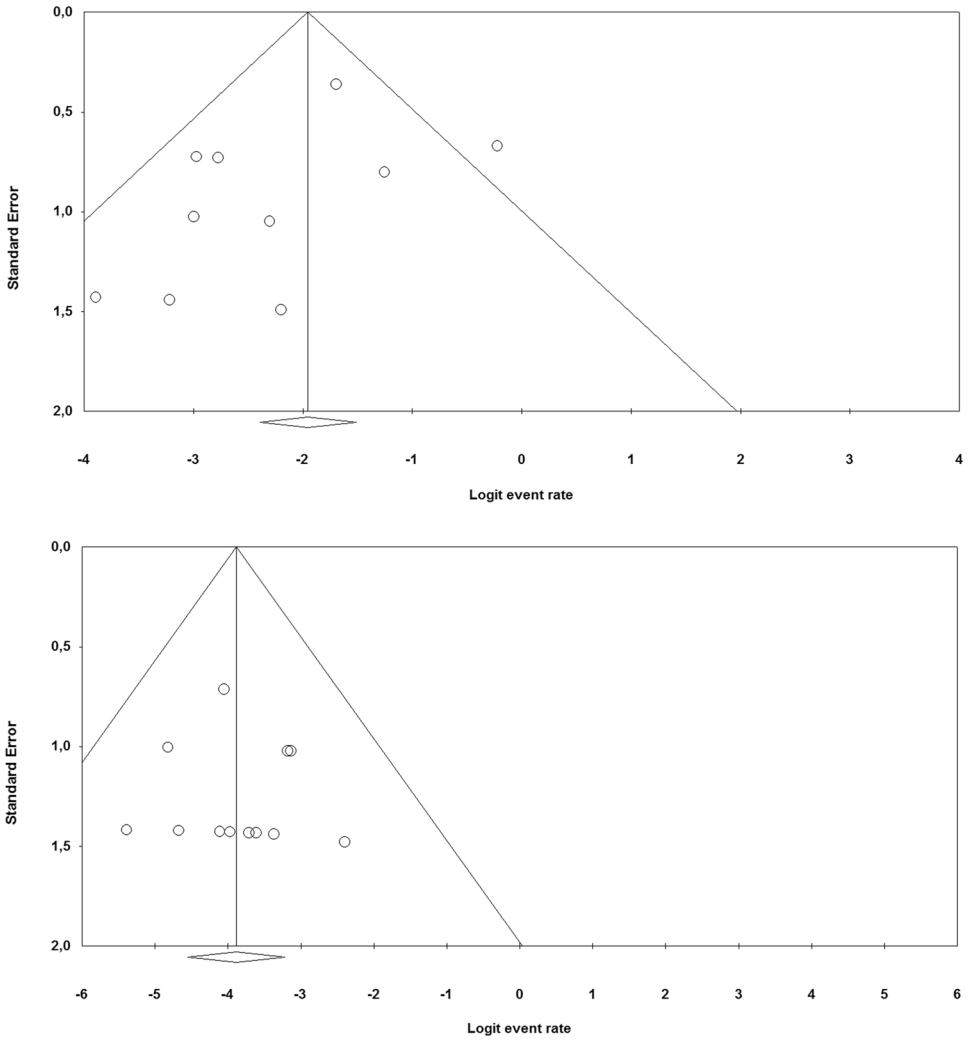

Fig. 4 Funnel plot of odds ratio (OR) by standard error (SE) for the risk of occult cancer in complex non-atypical hyperplasia (CEH) and simple non-atypical hyperplasia (SEH)

Although the risk of bias in this domain was unclear for some studies, the statistical heterogeneity was null in the OR analysis, giving strength to our results.

Finally, the primary studies did not allow extracting demographic data separately for SEH and CEH. This might be a limitation, since factors as diabetes mellitus might affect the behavior of EH [49, 50]. However, the only study that reported demographics separately for the two groups [24] did not show significant differences.

Conclusion

CEH is associated with a significant risk of coexistent endometrial cancer, about six times higher than SEH. Considering such category as benign may cause many patients to be undertreated. Therefore, a revision in the 2014 WHO classification criteria might be advisable; they do not consider complexity of glandular architecture in non-atypical EH.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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