OncoTargets and Therapy

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REVIEW

Clinical value of serum human epididymis protein 4 assay in the diagnosis of ovarian cancer: a meta-analysis

This article was published in the following Dove Press journal:
OncoTargets and Therapy
22 July 2013
Number of times this article has been viewed

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Objective: Human epididymis protein 4 (HE4) has been approved for diagnosing ovarian cancer. The goal of this meta-analysis was to evaluate the clinical value of the serum HE4 in the diagnosis of ovarian cancer.

Methods: The PubMed and Embase databases were searched to identify suitable studies. The sensitivity (SEN), specificity (SPE), and positive and negative likelihood ratios (PLR and NLR, respectively) of HE4 for the diagnosis of ovarian cancer were commonly used as bivariates. Summary receiver operating characteristic curves were used to summarize overall test performances. Meta-Disc 1.4 software was used to analyze the data.

Results: A total of 6,269 patients from 31 trials were subjected to meta-analysis. The summary estimates of HE4 for ovarian cancer diagnosis were as follows: SEN 0.73 (95% confidence interval [CI] 0.71–0.75); SPE 0.89 (95% CI 0.88–0.90); PLR 7.30 (95% CI 5.42–9.84); and NLR 0.15 (95% CI 0.10–0.23). SEN 0.74 (95% CI 0.72–0.76); SPE 0.89 (95% CI 0.88–0.90); PLR 7.35 (95% CI 5.55–9.73); NLR 0.14 (95% CI 0.09–0.21).

Conclusion: Our study demonstrates that the sensitivity and specificity of HE4 was higher than that of cancer antigen 125. The results indicated that HE4 could be a useful tumor marker for ovarian cancer diagnosis. However, the results of this meta-analysis should be interpreted with caution, due to the heterogeneity among study designs. Further study should pay more attention to the possibility that HE4 can be a marker for monitoring recurrence of ovarian cancer.

Keywords: ovarian cancer, HE4, CA125, meta-analysis

Background

Ovarian malignant tumor ranks third in female reproductive tract tumors. Only 25% of patients can be identified at stage I. Compared with stage I, 5-year survival of ovarian cancer patients of stage III and IV has decreased from 95% to 20%–25%.[1–3] With this high mortality, early diagnosis of ovarian malignant tumor is of great importance. Serum tumor markers are widely used in screening, diagnosis, recurrence detection, and efficacy judgment. Serum cancer antigen (CA)-125 can elevate in 85% of ovarian cancer patients, with clinical value in preoperative diagnosis and progress monitoring of ovarian cancer. Nevertheless, CA125 levels do not elevate in the early stage of some ovarian cancer patients. It is difficult to establish an early diagnosis of ovarian cancer based on CA125 levels, and they can elevate in some benign gynecological diseases, such as endometriosis, benign ovarian tumors, pelvic inflammatory disease, the menstrual phase, early pregnancy, and laparotomy. Therefore, it is a hot issue for study to search and separate new markers for early diagnosis and disease surveillance of ovarian cancer.

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Human epidermis protein 4 (HE4) is an ovarian cancer marker suggested recently. A study revealed that HE4 is highly expressed in ovarian cancer tissues, whereas it is expressed comparatively lower in precancerous, benign, and normal tissues. Detection of HE4 might have a certain value for diagnosis and monitoring of ovarian cancer. Now, HE4 is studied mostly by individual research centers; the role of the HE4 assay for diagnosing ovarian cancer has not been well-established. Application of evidence-based medicine provides a reliable research method that can integrate the results from different research centers and provide reliable scientific conclusions to guide clinical practice. Therefore, we conducted a meta-analysis based on relevant and available trials to assess the value of serum HE4 for the diagnosis of ovarian cancer to guide clinical treatment.

Materials and methods

Literature search and inclusion criteria

Literature searches of the PubMed and Embase databases (January 2000 to May 2013) were performed. Index words included HE4, WFDC2, human epididymis protein 4, human epididymis-specific protein 4, OC, ovarian cancer, ovarian carcinoma, and ovarian neoplasm.

English-language restriction was imposed. In addition, the reference lists of identified studies were manually checked to include other potentially eligible trials. This process was performed iteratively until no additional articles could be identified.

Inclusion criteria

All papers with pathological diagnosis of ovarian cancer and serum HE4 value were included. All papers were published from January 2000 to May 2013. There was a clear threshold reference value.

Exclusion criteria

Papers published before January 2000 or after May 2013 were excluded, as were case reports and reviews and papers without a serum HE4 test value of ovarian cancer, or where there was no clear threshold reference value.

Quality assessment

The methodological quality of each trial was evaluated by the quality-assessment tool for diagnostic accuracy studies (QUADAS). We requested the relevant information from authors if data were unreported.

The quality and bias of independent research was assessed based on the following aspects: whether the experimental design was scientific, whether inclusion criteria and basic structural characteristics of research objects were clear, whether factors and methods of treatment were accurate, whether statistical methods were appropriate, and whether biases in the study were discussed. Research that met one of these conditions scored 1 point. Quality was reliable when the total score was $\geq$3 points.

Statistical analyses

This meta-analysis was performed using Meta-Disc 1.4 software provided by the Cochrane Collaboration (Oxford, UK). Analysis of heterogeneity between studies was done using the χ^2 test. When there was no significant heterogeneity between studies ($P > 0.1$, $I^2 \leq 50\%$), we used fixed-effect meta-analysis and analyzed bias to obtain sensitivity, specificity, positive predictive, and negative predictive values. If there was statistical heterogeneity between studies, the meta-analysis was performed using the random-effects model ($P \leq 0.1$, $I^2 > 50\%$).

Table 1 Basic information about included papers

Study	TP	FP	FN	TN
Hellström et al[4]	20	1	17	18
Moore et al[5]	49	20	18	146
Havrilesky et al[6]	172	54	28	342
Dong et al[7]	19	0	11	182
Montagnana et al[8]	42	13	0	98
Huhtinen et al[9]	10	3	4	66
Abdel-Azeez et al[10]	34	3	7	46
Andersen et al[11]	31	0	1	158
Chen et al[12]	12	6	0	31
Ke and Liu[13]	29	11	0	92
Liu et al[14]	53	39	0	95
Ma et al[15]	56	38	0	95
Wang et al[16]	26	2	4	100
Xu et al[17]	19	6	0	31
Yao et al[18]	21	9	0	61
Lu et al[19]	45	33	0	25
Liu et al[20]	29	7	0	46
Montagnana et al[21]	42	6	13	92
Van Gorp et al[23]	119	34	42	194
Moore et al[24]	83	6	36	287
Kim et al[25]	57	4	21	77
Jacob et al[26]	25	10	4	61
Holcomb et al[27]	16	16	2	179
Escudero et al[28]	95	32	0	101
Chang et al[29]	38	2	14	64
Bandiera et al[30]	90	23	3	137
Zheng and Gao[31]	103	28	0	126
Karlsen et al[32]	230	22	298	511
Kadija et al[33]	19	10	63	20
Hamed et al[34]	27	3	1	29
Azzam et al[35]	49	11	3	57

Abbreviations: TP, true positive; FP, false positive; FN, false negative; TN, true negative.

Table 2 Quality-assessment tool for diagnostic accuracy studies (QUADAS) measure for included papers

Study	Risk of bias			Applicability concerns		
	Patient selection	Index test	Reference standard	Patient selection	Index test	Reference standard
Hellström et al[4]	↑	?	?	↑	↑	↑
Moore et al[5]	?	↑↑	↑	↑	↑	↑
Havrilesky et al[6]	↑	↑	↑	↑	↑↑	↑
Dong et al[7]	?	↑	↑	↑	↑	↑
Montagnana et al[8]	↑	↑↑	↑	?	↑	↑
Huhtinen et al[9]	?	?	↑	?	?	↑
Abdel-Azeez et al[10]	?	?	?	↑	↑	↑
Andersen et al[11]	?	↑	↑	?	↑	↑
Chen et al[12]	↑	↑↑	↑	↑	↑	↑
Ke and Liu[13]	↑	↑	↑	?	↑	↑
Liu et al[14]	?	↑	↑	↑	↑	↑
Ma et al[15]	↑	↑	↑	↑	↑	↑
Wang et al[16]	↑	↑↑	↑	↑	↑	↑
Xu et al[17]	↑	↑	↑	↑	↑	↑
Yao et al[18]	↑	↑	↑	↑	↑	↑
Lu et al[19]	↑	↑	↑	↑	↑↑	↑
Liu et al[20]	↑	↑↑	↑	↑	↑	↑
Montagnana et al[21]	?	↑	↑	?	↑	↑
Van Gorp et al[23]	↑	↑	↑	↑	↑↑	↑
Moore et al[24]	↑	↑	↑	↑	↑	↑
Kim et al[25]	↑	↑	↑	↑	↑↑	↑
Jacob et al[26]	?	↑	↑	?	↑↑	↑
Holcomb et al[27]	↑↑	↑	↑	?	↑↑	↑
Escudero et al[28]	↑	↑	↑	↑	↑	↑
Chang et al[29]	?	↑	↑	↑	↑	↑
Bandiera et al[30]	↑	?	?	↑	↑	↑
Zheng and Gao[31]	↑	↑	↑	↑	↑	↑
Karlsen et al[32]	↑	↑↑	↑	↑	↑	↑
Kadija et al[33]	↑	?	?	↑	↑	↑
Hamed et al[34]	↑	?	↑	?	↑	↑
Azzam et al[35]	↑	?	?	↑	↑	↑

Notes: ↑, Low risk; ↑↑, high risk; ?, unclear risk.

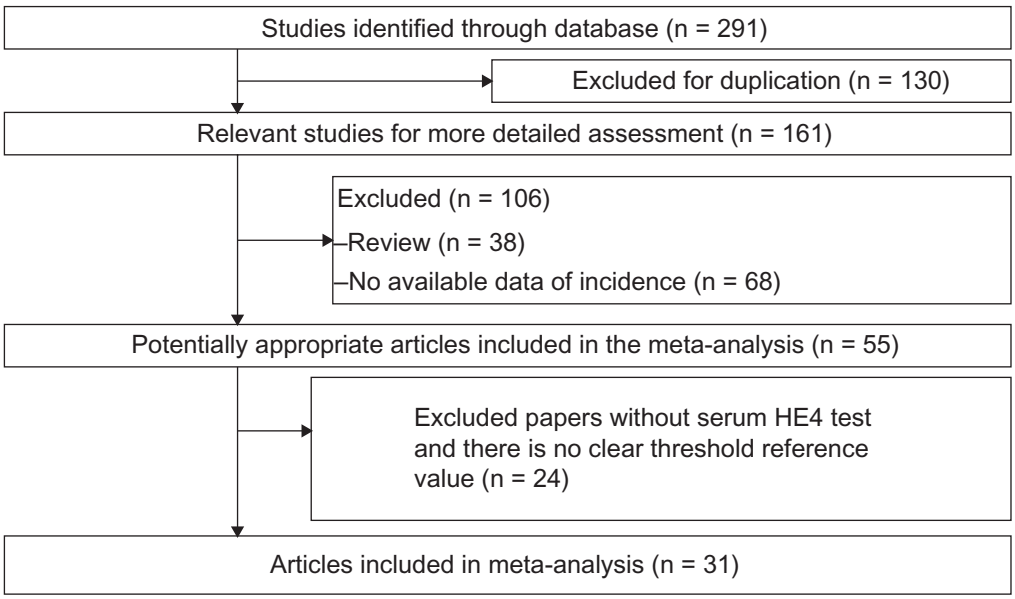


Figure 1 Selection process for articles included in the meta-analysis.

Results

Basic information and quality evaluation of document retrieval

Basic information on studies included is shown in Table 1. A total of 291 potentially relevant papers were identified based on the search terms. Finally, 31 papers were scrutinized in full text as appropriate. The selection process for articles included in the meta-analysis is shown in Figure 1. These studies were published between 2010 and 2013. The size of the articles ranged from 49 to 1,061 (total 6,269) words.

Quality evaluation of literature

The quality and bias of 31 papers were evaluated based on the evaluation criteria. Risk of bias and applicability concerns were used to evaluate the quality of the literature. Most studies were regarded as being at high risk of bias, and patient selection was unclear (description of QUADAS is shown in Table 2).

Meta-analysis

The heterogeneity analysis revealed a less homogeneous ($P < 0.00001$, $I^2 = 96.0\%$). The meta-analysis was

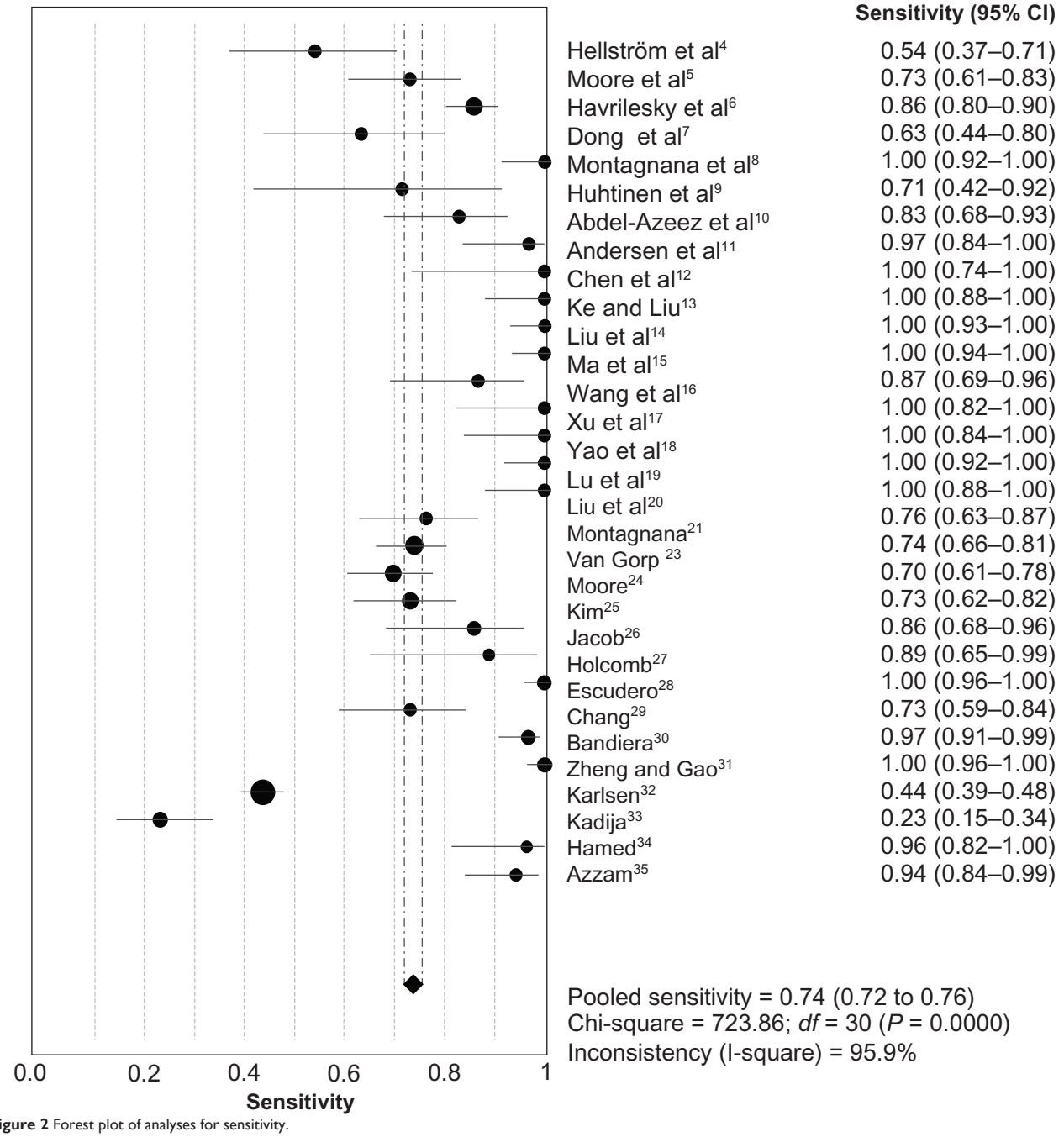


Figure 2 Forest plot of analyses for sensitivity.
Abbreviations: CI, confidence interval; df, degrees of freedom.

performed using the random-effects model. The results showed sensitivity and specificity of serum HE4 in the diagnosis of ovarian cancer was 0.74 (95% CI 0.72–0.76), and 0.89 (95% CI, 0.88–0.90), respectively (Figures 2 and 3). The positive and negative predictive values of serum HE4 in the diagnosis of ovarian cancer were 7.28 (95% CI 5.48–9.68), and 0.14 (95% CI 0.09–0.22), respectively (Figures 4 and 5). The area under the summary receiver operating-characteristic curve was 0.96 (0.95–0.98) (Figure 6). The asymmetry of the funnel plots using Egger's and Begg's tests showed that there was publication bias among the included studies (Egger's test, $P = 0.010$; Begg's test, $P = 0.009$) (Figure 7).

Discussion

Ovarian cancer is the most lethal gynecological malignancy. Unfortunately, the majority of patients remain clinically undetected until they have developed late-stage disease, and only a mere 25% of cancers are detected as stage I disease, due to the fact that there are no typical clinical symptoms. The tumor marker is of great significance for early cancer detection and disease surveillance. CA125 is the most studied and widely used in the clinical setting. However, it has been reported[4] that about 40%–50% of patients with early stage epithelium ovarian cancer did not have abnormal CA125. Therefore, it is necessary to find a new tumor marker to supplement CA125.

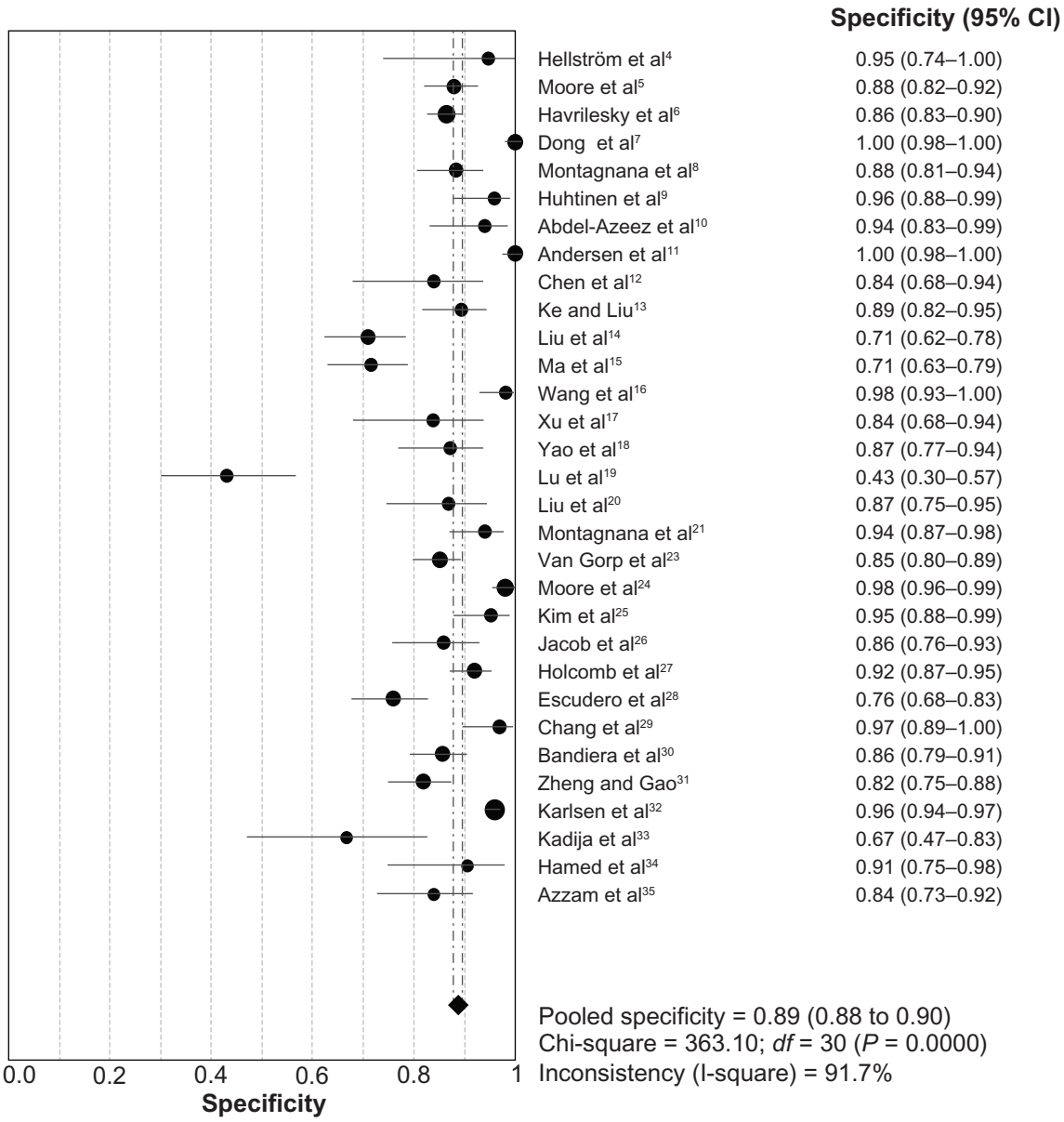


Figure 3 Forest plot of analyses for specificity.
Abbreviations: CI, confidence interval; df, degrees of freedom.

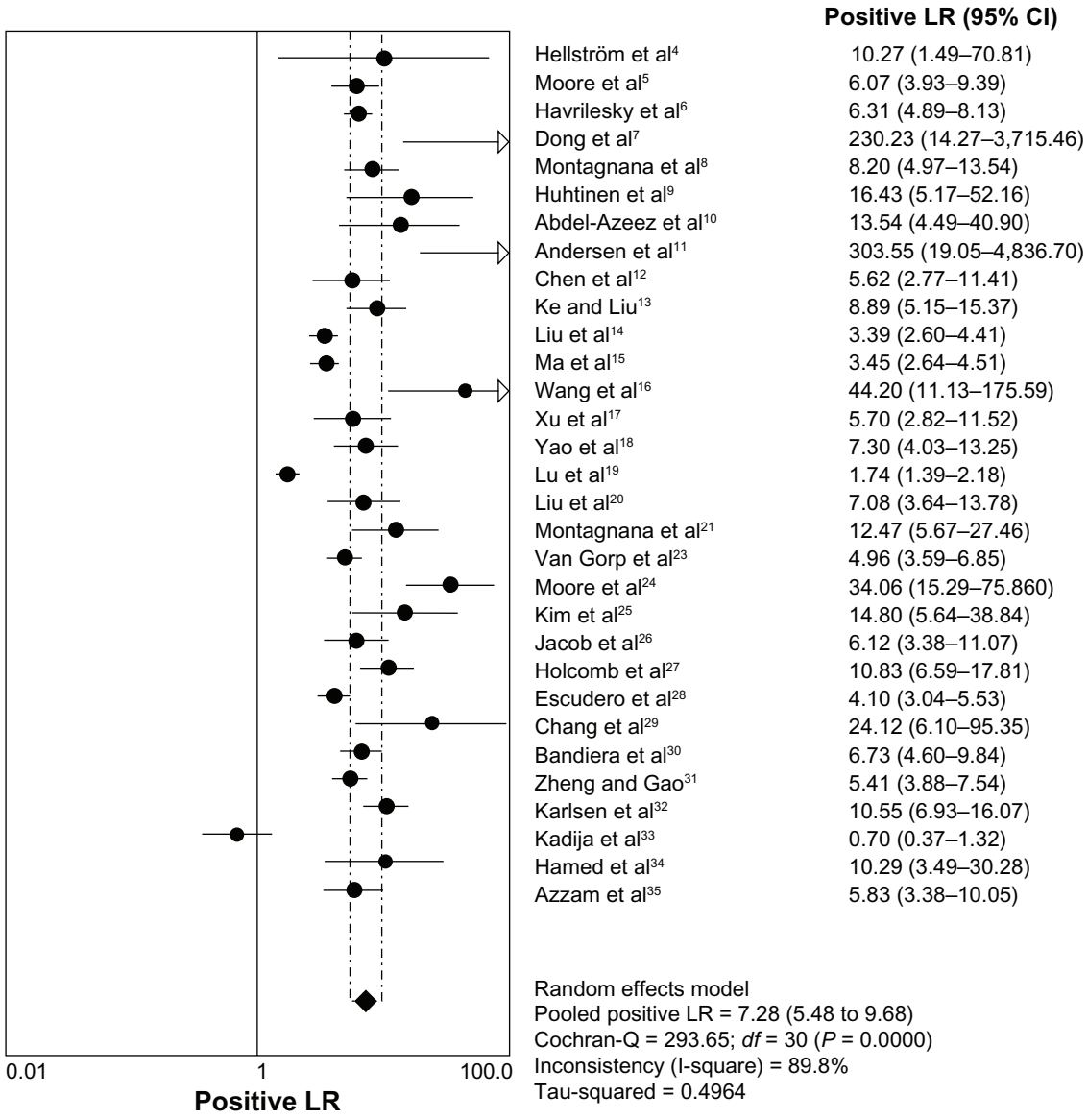
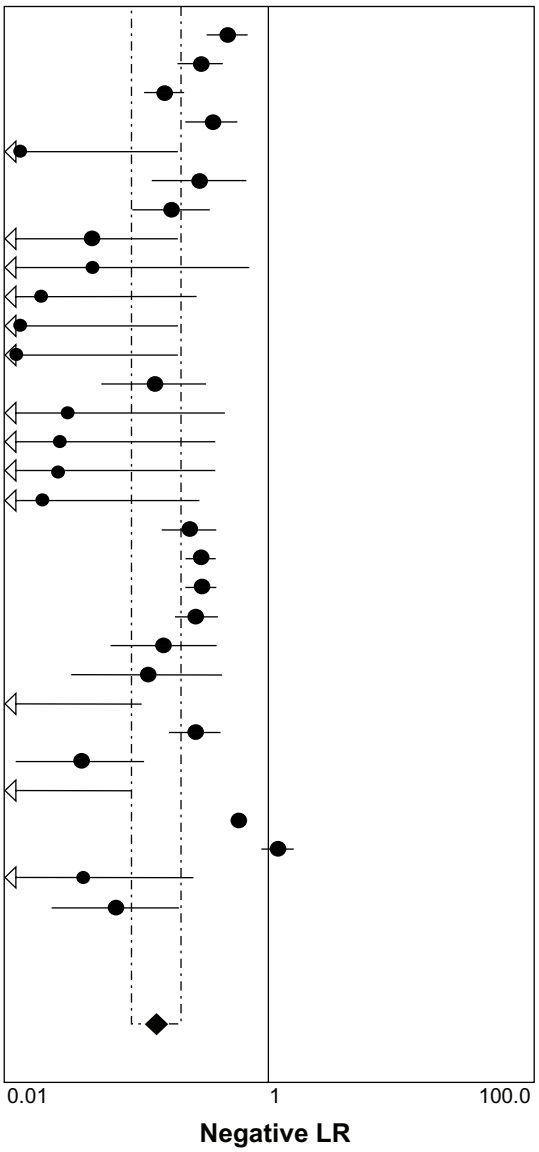


Figure 4 Forest plot of analyses for positive LR.
Abbreviations: CI, confidence interval; df, degrees of freedom; LR, likelihood ratio.

HE4 is also known as WAP four-disulfide core domain protein 2, the coding gene of which was separated from the distal epithelium epidermis in 1991. The encoded protein is mainly composed of WAP four-disulfide core. Hellström et al[4] was the first to subject the HE4 protein to a double-blind test by enzyme-linked immunosorbent assay (ELISA), and found the sensitivity of HE4 in the detection of ovarian cancer was equal to CA125 and the specificity even higher than CA125.

This is a comprehensive systematic review and meta-analysis of 31 articles to evaluate the clinical value of the serum HE4 assay in the diagnosis of ovarian cancer. We reached a contradictory conclusion. Wu et al[38] and Yu et al[36] suggested that HE4 was better than CA125. However Li et al[37] showed that HE4 was not better than CA125, for either epithelial ovarian cancer or ovarian cancer prediction. The main finding of our meta-analysis seems to strengthen the conclusions of Wu et al[38] and Yu et al.[36] However, the results of this meta-analysis should be interpreted with caution, due to the heterogeneity among study designs. In detail, the previous meta-analyses included nine, twelve, and eleven articles, respectively, including twelve studies described here. Meanwhile, articles published in 2012 and 2013 were also included. Two previous meta-analyses[36,38] and



	Negative LR (95% CI)
Hellström et al[4]	0.48 (0.34–0.70)
Moore et al[5]	0.31 (0.20–0.46)
Havrilesky et al[6]	0.16 (0.11–0.23)
Dong et al[7]	0.37 (0.24–0.59)
Montagnana et al[8]	0.01 (0.00–0.21)
Huhtinen et al[9]	0.30 (0.13–0.68)
Abdel-Azeez et al[10]	0.18 (0.09–0.36)
Andersen et al[11]	0.05 (0.01–0.22)
Chen et al[12]	0.05 (0.00–0.71)
Ke and Liu[13]	0.02 (0.00–0.29)
Liu et al[14]	0.01 (0.00–0.21)
Ma et al[15]	0.01 (0.00–0.19)
Wang et al[16]	0.14 (0.05–0.34)
Xu et al[17]	0.03 (0.00–0.47)
Yao et al[18]	0.03 (0.00–0.41)
Lu et al[19]	0.03 (0.00–0.40)
Liu et al[20]	0.02 (0.00–0.30)
Montagnana et al[21]	0.25 (0.16–0.41)
Van Gorp et al[23]	0.31 (0.24–0.40)
Moore et al[24]	0.31 (0.23–0.41)
Kim et al[25]	0.28 (0.20–0.41)
Jacob et al[26]	0.16 (0.06–0.40)
Holcomb et al[27]	0.12 (0.03–0.45)
Escudero et al[28]	0.01 (0.00–0.11)
Chang et al[29]	0.28 (0.18–0.44)
Bandiera et al[30]	0.04 (0.01–0.11)
Zheng and Gao[31]	0.01 (0.00–0.09)
Karlsen et al[32]	0.59 (0.55–0.64)
Kadija et al[33]	1.15 (0.87–1.52)
Hamed et al[34]	0.04 (0.01–0.27)
Azzam et al[35]	0.07 (0.02–0.21)

Random effects model
Pooled Negative LR = 0.14 (0.09 to 0.22)
Cochran-Q = 620.25; *df* = 30 (*P* = 0.0000)
Inconsistency (I-square) = 95.2%
Tau-squared = 1.0137

Figure 5 Forest plot of analyses for negative LR.
Abbreviations: CI, confidence interval; df, degrees of freedom; LR, likelihood ratio.

our meta-analysis showed that the sensitivity and specificity of HE4 was higher than that of CA125. These results are not conclusive, as they are not adequately powered for unified cutoff, control group (healthy women or women with benign disease), and different methods to evaluate HE4 in serum (ELISA, chemiluminescent microparticle immunoassay, bead-based array system).

In 2008, Moore et al[5] reported that as a single ovarian tumor marker, the sensitivity of serum HE4 in diagnosis of ovarian cancer was 72.9% When HE4 combined with CA125, sensitivity and specificity were 76.4% and 95%, respectively, but when HE4 combined with other tumor markers, the increase in sensitivity was very low. HE4 may be the best marker used alone for stage I disease, because the sensitivity of combination with CA125 or other ovarian cancer markers cannot increase. Montagnana et al[8] assayed the preoperative serum concentration of both HE4 and CA125 in patients with different forms of benign and malignant pelvic masses. The results showed that the median CA125 and HE4 serum levels were significantly higher among ovarian cancer patients compared with healthy subjects and with those with benign mass. The receiver operating characteristic-curve analysis on healthy controls and patients with ovarian cancers revealed that HE4 had a significantly higher area under the curve when

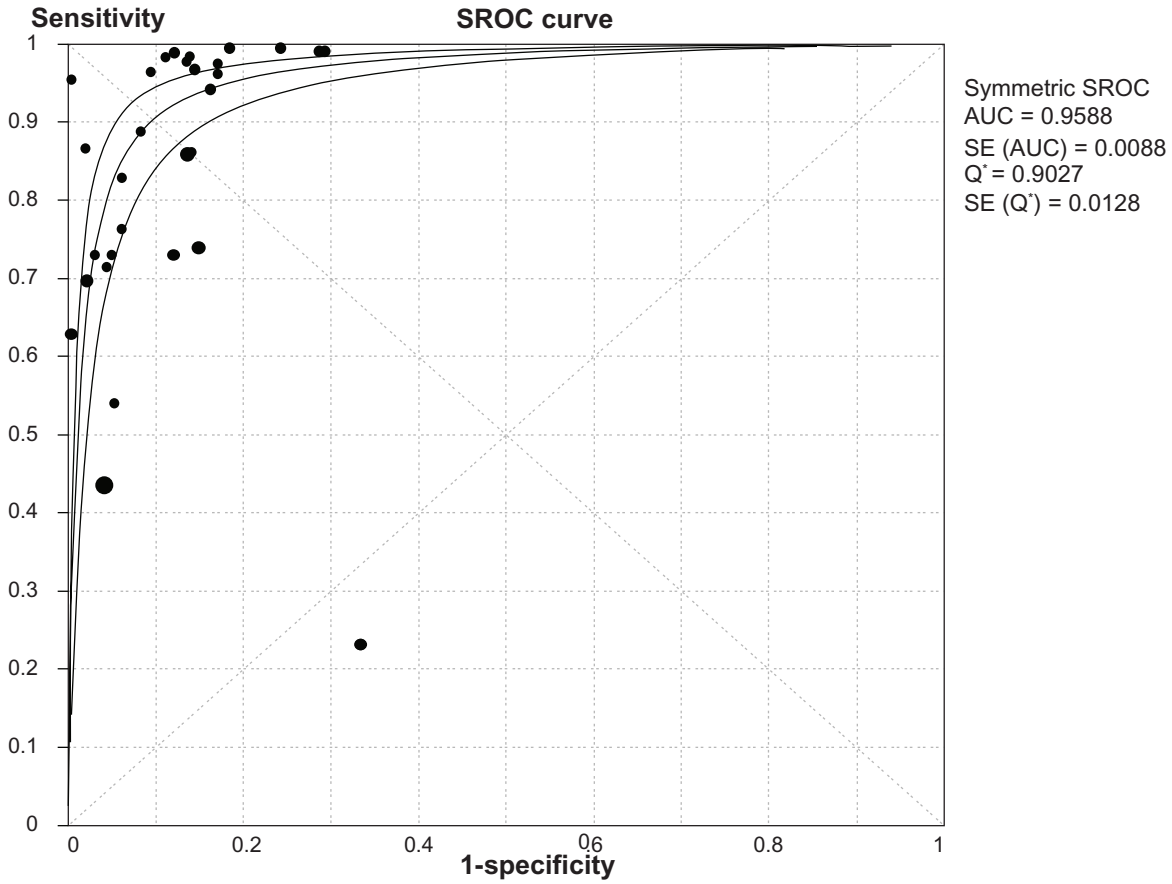


Figure 6 SROC curves from the bivariate model.
Abbreviations: SROC, summary receiver operating characteristic; AUC, area under curve; SE, standard error; Q*, index.

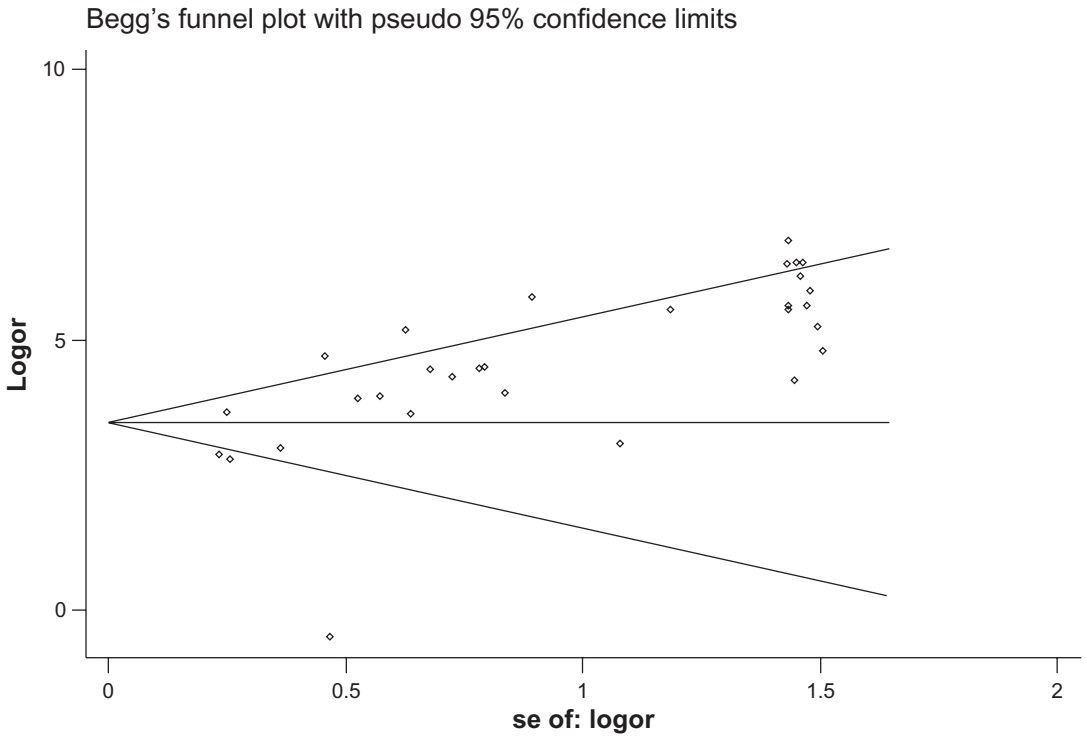


Figure 7 Tests for publication bias.
Abbreviations: se, standard error; logor, log odds ratio.

compared with CA125 (0.99 vs 0.91), with sensitivity and specificity of 98% and 100%, respectively. The sensitivity and specificity of HE4 are higher than CA125. Thus, HE4 is considered a promising ovarian cancer marker. In this study, we conducted a meta-analysis to explore further the value of HE4 in the diagnosis of ovarian cancer. The specificity was 95% (95% CI 0.88–0.90). The positive predictive value was 7.35 (95% CI, 5.55–9.73). The negative predictive value was 0.14 (95% CI, 0.09–0.21). The results and reports revealed that the sensitivity of HE4 in detection ovarian cancer is the same as CA125, but specificity is higher than CA125. It suggested that HE4 is a promising marker of ovarian cancer for clinical application. In addition, this study shows the funnel plot is asymmetric. An unfilled corner at the bottom of the graph indicated that there was bias in the research. It is necessary to collect more data to improve the quality of research. In addition, there are still many papers in which HE4 serum was tested but concentration of HE4 in serum was not classified as positive or negative. These only mentioned the median value or range of ovarian cancers, benign diseases, and the control group.

One potential limitation of the present meta-analysis is that the cutoff values of HE4 used among the studies were various. There is no gold standard for the cutoff value and method to evaluate HE4. The heterogeneity with regard to the cutoff value of HE4, assay method, menopausal status, and small samples may also account for the lack of clear evidence to support HE4 as a potential tumor marker for ovarian cancer diagnosis. The second limitation is that we were unable to assess the impact of unpublished papers on publication bias. The third limitation is that the stage of ovarian cancer has insufficient statistical power. Although the evidence of diagnostic effectiveness in detecting early stage tumors is of pivotal relevance, there are currently not enough studies for estimating HE4 performance in this clinical scenario. Additional studies or data are warranted, particularly to evaluate HE4 capability to identify ovarian cancer at an early stage.

Several articles have reported on HE4 in the early diagnosis of ovarian cancer, and found its sensitivity (76.9%–82.7%) to be higher than CA125 (45.9%).[4,7] HE4 is also reported in some literature for ovarian cancer disease surveillance. Allard et al[22] reported that 83.8% of patients' CA125 or HE4 levels matched the clinical state. Meanwhile, more and more research has focused on the clinical performance of the risk of ovarian malignancy algorithm (ROMA) and on CA125 and HE4. Sandri et al[39] demonstrated that the ROMA index combined the advantage of each single marker and reached a sensitivity of 89.3% and a specificity of 81.7%. However, the results should be interpreted with caution due to heterogeneity. Such heterogeneity means there cannot be a uniform standard in ROMA projects, at least in the beginning. Further indicated that HE4 can be a marker to monitor recurrence of ovarian cancer, which is consistent with the CA125.

Conclusion

The studies described indicate that HE4 is valuable as an ovarian tumor marker in diagnosis and monitoring the disease state. The value of serum HE4 in diagnosis and disease monitoring of ovarian cancer still needs large-scale and multicenter randomized study.

Acknowledgment

This work was supported by a grant from the Provincial Research Project Funding of Guangxi, People's Republic of China (2010GXNSFD013053 and 2011Z2011217).

Disclosure

The authors report no conflicts of interest in this work.

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