Review article

CA 125 and HE4: Impact on diagnosis and treatment of early-stage endometrial cancer

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Abstract
Endometrial cancer is a major concern in women's health, being one of the most common gynecological cancers. With favorable prognoses in early stages, diagnostic accuracy and surgical treatment are the challenges. Tumor biomarkers cancer antigen 125 and human epididymis protein four emerge as potential tools, improving early detection. A review was conducted with the aim of evaluating the impact of tumor markers cancer antigen 125 and human epididymis protein four on diagnostic accuracy and surgical treatment of endometrial cancer in early stages. Narrative bibliography generated in scientific review articles, original articles with a maximum of five years of obsolescence 2019-2024 in PubMed, Elsevier and Google Scholar. Combined cancer antigen 125 and human epididymis protein four offer significant sensitivity to detect endometrial cancer in early stages. Although not ideal for primary detection, their combined use in suspected or diagnosed cases provides value in clinical evaluation, and in the prediction of 5-year disease-free survival. This combination of tumor biomarkers emerges as a promising strategy for the diagnosis and preoperative evaluation of endometrial cancer in early stages.

Keywords
Endometrial Neoplasms, Epididymal Secretory Proteins, CA-125 Antigen, Biomarkers, Tumor.

Resumen
El cáncer endometrial es una preocupación importante en la salud de las mujeres, al ser de los cánceres ginecológicos más comunes. Tiene pronóstico favorable en etapas tempranas; la precisión diagnóstica y el tratamiento quirúrgico son los desafíos. Los biomarcadores tumorales antígeno del cáncer 125 y la proteína cuatro del epidídimo humano surgen como herramientas potenciales que mejoran la detección temprana de la enfermedad. Se realizó una revisión bibliográfica en PubMed, Elsevier y Google Académico con el objetivo de evaluar el impacto de marcadores tumorales antígeno del cáncer 125 y proteína cuatro del epidídimo humano en la precisión diagnóstica y el tratamiento quirúrgico del cáncer endometrial en etapas tempranas. Se seleccionaron artículos científicos de revisión y artículos originales publicados de 2019-2024. La combinación de estas pruebas ofrece una sensibilidad significativa para detectar el cáncer endometrial en estadios tempranos. Sin embargo, su uso conjunto no es ideal para la detección primaria, se reserva para casos sospechosos o diagnosticados, ya que aporta valor en la evaluación clínica, y en la predicción de supervivencia libre de enfermedad a los cinco años. La combinación de estos biomarcadores tumorales emerge como estrategia prometedora para el diagnóstico y la evaluación preoperatoria del cáncer endometrial en etapas tempranas.

Palabras clave
Neoplasias Endometriales, Proteínas Secretorias del Epidídimo, Antígeno Ca-125, Biomarcador Tumoral.

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Introduction

Early and accurate detection of endometrial cancer is essential to improve treatment outcomes and patient survival. In this context, both cancer antigen 125 (CA 125) and human epididymis protein 4 (HE4) have emerged as potential tumor markers (TMs) for disease detection.[i] Endometrial cancer (EC) is a malignant neoplasm of the epithelial layer of the uterus, comprising different histological types and molecular phenotypes.[ii]

According to the most recent incidence data from the 2020 Global Cancer Statistics (GLOBOCAN), there were 417 336 new cases, making it the sixth most common cancer among women. Risk factors such as age, race, nutrition, and sociodemographic conditions influence the incidence and mortality of the condition.[iii]

In El Salvador, data collected in 2022 from the National Women's Hospital by the Observatory of Sexual and Reproductive Rights showed a 55 % increase in hospitalizations due to endometrial cancer.[iv] This trend coincides with the high prevalence of obesity among women (33 %), a condition that constitutes the main risk factor due to its association with metabolic states that increase estrogen exposure.

However, a gap persists in clinical practice due to the absence of specific screening tests for this neoplasm, underscoring the importance of exploring the potential role of biomarkers in early detection and risk stratification.[v]

Furthermore, there is currently no standardized test or tool to detect EC at early stages, so diagnosis is usually made once the neoplasm is already established and confirmed by biopsy. In the search for such a tool, tumor markers have been studied because they are molecules associated with malignant neoplasms. Examples include alpha-fetoprotein for hepatocellular carcinoma, human chorionic gonadotropin for germ cell tumors, and calcitonin for thyroid cancer, among others.[vi]

Among these TMs, the cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) molecules have been identified as potentially useful for detecting EC in early stages. According to the ESMO-ESGO consensus on EC, these two molecules have shown correlations with tumor stage, histologic grade, and even lymph node metastasis.[vii]

Njoku *et al.*, indicated that blood CA 125 measurement has high specificity for EC, with an area under the curve (AUC) of 96 % when combined with ultrasound techniques. Similarly, a meta-analysis by Li *et al.*, reported that HE4 showed combined sensitivity, specificity, and AUC of 65 %, 91 %, and 84 %, respectively.[viii]

In this context, the use of tumor markers such as CA 125 and HE4 has emerged as a promising strategy to improve diagnostic accuracy and risk stratification in patients with EC.

A narrative review was conducted using MEDLINE via PubMed, ELSEVIER, Cochrane Library, SciELO, and Google Scholar databases. Original and review articles published in Spanish and English were included. Boolean operators and the following keywords were used: "Ca125 AND HE4 in endometrial cancer," with publication filters set to 2019-2024, free full-texts, and studies conducted in humans. The objective was to synthesize recent evidence on the impact of CA 125 and HE4 biomarkers in the diagnosis and surgical management of early-stage endometrial cancer.

Discussion

Epidemiological Overview and Challenges in Early Diagnosis

CA 125: Usefulness and Limitations

The American Cancer Society estimated that in 2024, approximately 2001 140 new cases cancer would be diagnosed, translating to about 5480 cases per day. Regarding uterine body cancer, an estimated 67 880 new cases and 13 250 deaths were reported.[ix]

However, early detection and surgical treatment at early stages result in a survival rate of 97 %, which contrasts with less than 20 % survival in advanced stages.[x]

Bokhman's classification divides endometrial cancer into two subtypes: Type I (endometrioid), which accounts for more than two-thirds of cases and is associated with obesity and hyperestrogenic environments, and Type II, which includes the remaining third, is unrelated to those factors, and is more malignant and aggressive.[xi]

Screening is used only for diagnosis in high-risk populations and includes transvaginal ultrasonography and biopsy, which, combined, yield a negative predictive value (NPV) of 96 %.[xii]

Hysteroscopy may be used when diagnostic uncertainty exists, providing a cancer scoring system with 88 % sensitivity, 92 % specificity, and an AUC of 97 %.[x]

In the search for a standardized, simpler, and less invasive screening test for EC, tumor markers are being explored, as they contribute to staging, treatment assessment, and recurrence monitoring.

The usefulness of serum CA 125 and HE4 markers in endometrial carcinoma has been evaluated in various clinical settings. In preoperative evaluation, they have been associated with risk stratification and surgical planning, including predicting lymph node involvement and deciding surgical extent. Likewise, elevated levels correlate with worse disease-free and overall survival, making them potential prognostic predictors.[xiii]

Tumor Markers

Tumor markers (TMs) are quantitatively measurable molecules, often identified through immunohistochemistry, that are overexpressed in tissues in the presence of neoplasms.[xiv]

The Prostate-Specific Antigen (PSA) is a widely used TM that is expressed only in prostate epithelium; its elevation and presence in circulation indicate malignant growth.[xv] Another TM used is Carcinoembryonic Antigen (CEA), primarily for intestinal and colorectal cancer. In a systematic review by Hall *et al.*, CEA was found to play an important role in the diagnosis, staging, prognosis, and monitoring of colorectal cancer.[xvi] The carbohydrate antigen 19-9 has genetic limitations related to blood antigen types, both ABO and Rh systems, as well as the expression of certain genetic products.[xvii]

In recent years, various international guidelines and consensus statements have emphasized the role of serum biomarkers as complementary tools in the preoperative evaluation of endometrial carcinoma. [xviii] However, these documents agree that therapeutic decisions should rely on a multimodal approach integrating clinical assessment, imaging, clinicopathological findings, and molecular profiles.[xix]

Furthermore, the 2023 International Federation of Gynecology and Obstetrics (FIGO) and European guidelines have incorporated molecular classification of endometrial carcinoma, modifying both prognostic stratification and interpretation of biomarker value. This transition reflects the current trend toward precision medicine, where biomarkers are no longer interpreted in isolation but within the context of tumor biology and molecular characterization.[xx]

In gynecology, the CA 125 antigen is mainly used for epithelial ovarian neoplasms, although it lacks specificity for any particular tumor type. Nonetheless, a decrease in this molecule indicates cancer cell death in the ovary, confirming treatment effectiveness, whereas its increase suggests recurrence.[xxi]

Because of its expression in the genitourinary tract, HE4 has been identified as a potential biomarker for early detection and monitoring of tumors, primarily in ovarian and endometrial cancer. This aligns with finding noninvasive methods that help standardize screening tests, stage disease, and monitor response to oncological therapies.[xxii]

CA 125 is a protein that is elevated in the blood in certain types of cancer, especially ovarian cancer. Normal CA 125 levels under physiological conditions are below 35 units per milliliter (U/mL).[xxiii] However, it may rise in other conditions such as endometriosis, uterine diseases, breast cancer, and benign reproductive system disorders, with 52 % sensitivity and 80 % specificity for EC.[xxiv]

CA 125 is used as a primary detection test for EC, unlike ovarian cancer, but it lacks sensitivity to identify patients requiring staging.[xxv] Kubelac *et al.*, demonstrated through a comparative study of two oncO-VARIAN models-using β-HCG, CA 19.9, CEA, AFP, CA 125, and HE4 versus the "Risk of Malignancy Algorithm" (ROMA),that sensitivity, specificity, positive predictive value (PPV), and NPV for malignancy detection were 76.66 % vs. 60 %, 95 % vs. 100 %, 95 % vs. 100 %, and 73 % vs. 62 %, respectively.[xxvi]

Pinyada *et al.*, in a retrospective study of 128 patients with stage I-III endometrial cancer, showed that HE4 and CA 125 had higher sensitivity for EC detection (80 %). At a concentration of 20 U/mL, CA 125 had 64 % sensitivity and 72.3 % specificity (AUC = 0.72, p = 0.002). At a concentration of 113 pmol/L, HE4 had 64 % sensitivity and 77.3 % specificity (AUC = 0.7, p = 0.006). The combination of both markers yielded 80 % sensitivity, 55.8 % specificity, and a PPV of 64.4 %. Patients with high CA 125 and HE4 levels had lower disease-free survival compared to others (78.4 % and 100 %, respectively; p = 0.01).[xxvii]

In diagnosed or suspected EC cases, CA 125 helps evaluate disease extent, monitor treatment response, and detect recurrences.[xxviii] The cost-effectiveness of CA 125 is evaluated based on its cost and clinical benefits, such as improved recurrence detection and optimized treatment strategies.[xxix]

Epidemiological overview and challenges in early diagnosis

HE4: current evidence

HE4 is a secretory protein and a member of the whey acidic protein (WAP) domain family. It is expressed in the epididymis, where it contributes to sperm maturation, and in other tissues such as the mammary gland, kidneys, and female reproductive tract, with limited expression in the ovaries and uterus.[xxx]

It is used as a standard serum biomarker for epithelial ovarian cancer because it is associated with the EGFR-MAPK signaling pathway.[xxxi] This pathway regulates numerous cytoplasmic processes, including cell proliferation, migration, differentiation, and apoptosis.[xxxii]

Due to its expression in tissues of the female reproductive system, particularly the

glandular epithelium, HE4 has also been used in recent years as a predictor for endometrial cancer. In healthy women, HE4 levels vary up to a maximum of 150 pmol/L.[xxxiii] These levels can be influenced by factors such as body mass index, smoking, age, and chronic obstructive pulmonary disease. However, unlike CA 125, HE4 values do not fluctuate with the ovarian cycle, pregnancy, or oral contraceptive use-one of its key advantages.[xxxiv]

In the study by Angionili *et al.*, a predictive tool called Endometrial Malignancy Risk was developed to assess symptomatic patients using ultrasound techniques, age, and serum HE4 and CA 125 levels. Although still experimental, 79 % of their control group was found to be in stage I of EC.[xxxv]

In the experimental study by Yang *et al.*, several tumor markers were evaluated, and HE4 demonstrated the best diagnostic performance for EC, with an AUC of 74 %, the highest in the study.[xxxvi] Liu *et al.*, reported that serum HE4 levels vary depending on the specific uterine condition and show promising utility for EC staging.[xxxvii]

In a prospective study by Cuestas *et al.*, HE4 showed higher sensitivity compared to CA 125 in detecting EC, with a very similar specificity.[xxxviii] This indicates that HE4 is highly promising as a tumor marker for EC; however, larger population studies are still needed for more robust conclusions.

Combined use and predictive algorithms: ROMA, CPH-I

Clinical implications and perspectives

In recent years, the most commonly used methods for screening endometrial masses have included abdominopelvic anamnesis, transvaginal ultrasound, and quantification of serum CA 125 levels.[xxxix]

CA 125 has shown high diagnostic sensitivity but low specificity, as it can be elevated in nonmalignant inflammatory states and physiological conditions such as pregnancy, leading to false positives. In a study by Anastasi *et al.*, blood samples from 50 healthy women, 17 with benign ovarian tumors, 57 with ovarian endometrioma, and 39 with ovarian cancer were examined.

CA 125 levels increased in patients with ovarian endometriosis and ovarian cancer, but not in those with other benign masses. In contrast, HE4 levels did not rise in patients with endometriosis or benign masses but did increase in all ovarian cancer patients ($p = 0.05$).[xl]

Given the need to optimize diagnostic methods, conventional tumor markers such as CA 125 and HE4 have been evaluated in relation to non-modifiable factors, including age and menopausal status. Notably, HE4 levels have been observed to increase with age in postmenopausal women, suggesting that reference values should be adjusted according to demographic parameters.[xli]

In recent years, HE4 has become a more promising marker for early and accurate EC diagnosis. It is more specific than CA 125 and is unaffected by menstrual changes or inflammatory diseases such as endometriosis. However, it may be overexpressed in older women and those with chronic kidney disease.[xlii]

Studies comparing the effectiveness of both markers in combination often use the Risk of Ovarian Malignancy Algorithm (ROMA), which includes the woman's age, menopausal status, and serum CA 125 and HE4 levels in women with a prior ultrasound diagnosis of indeterminate neoplasia.[xliii]

Moore *et al.*, developed the multivariate ROMA index by combining serum CA 125 and HE4 levels with menopausal status through a logistic regression model. This index received FDA approval in 2010[xliv] for the diagnosis of cervical and uterine cancer and has been shown to have a predictive capacity superior to that of individual detection of CA 125 or HE4.[xlv]

A meta-analysis of 13 studies conducted by Cui *et al.*, (2018), which evaluated the ROMA index in 5.954 cases, showed a sensitivity of 90 %, specificity of 91 %, AUC of 0.96, PPV of 90 %, and NPV of 93 %. These results indicate that the ROMA index provides a reliable foundation for the clinical diagnosis of ovarian cancer.[xlvi]

The ROMA score takes menopausal status, results may vary; therefore, it is essential to determine menopausal status. Shen *et al.*, (2019) stated that menopausal status is established based on the duration of amenorrhea combined with FSH and estrogen levels. For future ROMA applications, determining each patient's menopausal status will be necessary, requiring effective communication between laboratories and treating physicians.[xlvii]

More recently, the Copenhagen Index (CPH-I), developed by Karlsen *et al.*, in 2015, has been validated. It also aims to distinguish benign from malignant neoplasms in the preoperative stage, incorporating both tumor markers and the patient's age. The Copenhagen Index offers the advantage of not depending on ultrasound or menopausal status, and

age is an easily collected, simple, and objective variable. Comparisons between the indices (ROMA vs. CPH-I) show similar performance, with some analyses favoring CPH-I for its simplicity (using age and markers without requiring ultrasound or menopausal data).[xlviii]

These two indices show comparable values, as both rely partly on CA 125 and HE4.[xlix] Since serum concentrations of CA 125 and HE4 can be influenced by several factors, such as age, smoking, uterine fibroids, pregnancy, endometriosis, pelvic inflammatory disease, and gallstones, these factors may affect both the Copenhagen Index and ROMA scores.[l]

Tran *et al.*, (2021) analyzed data from 475 patients with diagnosed ovarian masses: 408 benign, five borderline, and 62 malignant tumors. Both indices showed similar discriminatory performance without significant differences ($p > 0.05$). Using optimal cut-off points, the sensitivities/specificities of ROMA and CPH-I for ovarian cancer detection were 74.2 % and 91.8 %; 87.1 % and 78.5 %, respectively. The optimal cut-off point for CPH-I was 1.89 %. AUC values for ROMA and CPH-I were 0.882 (95 % CI: 0.849-0.909) and 0.898 (95 % CI: 0.867-0.924), respectively.[li]

Overall, CPH-I and ROMA show similar sensitivity and accuracy. CPH-I differs from the ROMA in that it is independent of ultrasound tests and menopausal status. The menopausal status can be determined based on age, hormonal concentration, or annual duration of amenorrhea; however, there is no diagnostic. Therefore, CPH-I could serve as a simpler method to optimize management by assessing women with suspected endometrial or adnexal cancer, incorporating age rather than menopausal status.[lii]

Song *et al.*, (2023) performed a statistical regression by comparing CPH-I and ROMA nomograms, and found that the combined nomogram had a higher AUC than either parameter alone.[liii]

Saffarieh *et al.*, (2022) evaluated serum levels of 170 pmol/L for HE4 and 320 pmol/L for CA 125 as optimal cut-off points, obtaining preoperative NPVs of 81 % and 82 %, respectively, in 110 women aged 20 to 80 years with uterine cancer (stages I-IV), despite the limited sample size. This suggests that in EC and adnexal cancer cases, if HE4 serum levels are below 140 pmol/L or CA 125 values below 320 pmol/L, optimal cytoreductive surgery is achievable in approximately 80 % of cases.[liv]

Despite the presented findings, this review of CA 125 and HE4 in early-stage EC diagnosis and treatment presents several limitations. First, variability in study methods and populations may affect generalizability. Moreover, the lack of large-scale observational studies limits the ability to establish definitive conclusions about these biomarkers' effectiveness in different clinical contexts. Further robust research, including controlled, multicenter clinical trials, is recommended to more accurately evaluate the roles of CA 125 and HE4 in managing endometrial cancer. Additionally, exploring the combination of these biomarkers with other clinical and molecular factors could improve diagnostic precision and risk stratification in women with suspected EC.

Conclusion

The CA 125 marker has been shown to be less specific and less stable than HE4 for diagnosing endometrial and ovarian cancer, as its levels can vary significantly due to factors such as the ovarian cycle, pregnancy, or contraceptive use. Recent studies indicate that HE4 may outperform CA 125 in sensitivity for EC detection, showing superior performance in comparative studies. In several recent studies and reviews, HE4 demonstrates moderate sensitivity but high specificity for detection of EC, making it more useful as a confirmatory or stratification marker rather than for population-wide screening.

The combination of CA 125 and HE4 offers significant sensitivity for detecting EC in its early stages. However, their joint use is not ideal for primary detection; instead, it is reserved for suspected or already diagnosed cases, as it provides clinical value in assessment and in predicting five-year disease-free survival.

The combined use of CA 125 and HE4 emerges as a promising strategy for the diagnosis and preoperative evaluation of early-stage endometrial cancer. At the same time, predictive tools such as ROMA and CPH-I offer further improvement in diagnostic accuracy. Nonetheless, continuous evaluation of their efficacy and cost-effectiveness in clinical settings is required for optimal implementation. There remains a need for observational studies and standardized cut-off points validated in Latin American populations; in practice, it is important to validate local thresholds and adjust for age and renal function.

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