

# EARLY DIAGNOSIS OF OVARIAN CANCER: CURRENT CHALLENGES AND THE ROLE OF EMERGING BIOMARKERS

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**Abstract:** Introduction: Ovarian cancer is one of the most lethal gynecological cancers worldwide, primarily due to its often late diagnosis, the silent progression of the disease, and the nonspecific nature of early symptoms—factors that make it difficult to detect in the early stages and significantly compromise patient prognosis. Although methods such as transvaginal ultrasound and serum CA-125 testing are widely used, they still have significant limitations regarding sensitivity and specificity, especially in population-based screening. In this context, research into emerging biomarkers emerges as a promising strategy to improve diagnostic accuracy and facilitate earlier interventions. Objective: to analyze the main current challenges related to the early identification of ovarian cancer, with an emphasis on the role of emerging biomarkers as promising tools for improving diagnostic accuracy, risk stratification, and patient prognosis. Methodology: This is an integrative literature review of a

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descriptive, exploratory, and qualitative nature, conducted through searches in the PubMed/MEDLINE, Scopus, Web of Science, SciELO, and Virtual Health Library (VHL) databases, using DeCS and MeSH descriptors related to the topic, such as “Ovarian Cancer,” “Early Diagnosis,” “Biomarkers,” “Tumor Markers,” “Screening,” and “Precision Medicine,” combined using the Boolean operators AND and OR. Studies published between 2020 and 2026, available in full in Portuguese, English, and Spanish, that addressed early diagnosis, traditional and emerging biomarkers, and screening strategies were included. Results and Discussion: The studies showed that CA-125, although still widely used, has low specificity when used alone, especially in the early stages of the disease. In contrast, biomarkers such as HE4, the ROMA algorithm, liquid biopsy, exosomal microRNAs, circulating tumor DNA, epigenetic biomarkers, and multi-omic approaches demonstrated higher diagnostic sensitivity and better predictive capacity. The combination of multiple biomarkers has shown superior performance compared to traditional methods used in isolation. Furthermore, it has been observed that the incorporation of technologies such as artificial intelligence and precision medicine has significantly expanded the identification of new biomarkers and individualized risk stratification, facilitating earlier diagnoses and more effective therapeutic interventions. However, challenges remain regarding large-scale clinical validation, methodological standardization, high costs, and limited access to these tools in public health systems. Conclusion: it is concluded that emerging biomarkers associated with new diagnostic technologies represent an important advancement in the fight against ovarian cancer, with the potential to reduce morbidity and mortality and improve patient survival. Despite these advances, the consolidation of these strategies depends on the expansion of multicenter studies, economic feasibility, and the incorporation of these tools into clinical practice, thereby strengthening a more preventive, personalized, and effective approach to oncology.

**Keywords:** Ovarian cancer; Early diagnosis; Biomarkers; Liquid biopsy; Precision medicine.



## INTRODUCTION

Ovarian cancer represents one of the most lethal gynecological neoplasms in the world, mainly due to its often late diagnosis and the absence of widely effective screening methods for the general population. It is estimated that the disease remains among the main causes of cancer death among women, with a high mortality rate when compared to other gynecological tumors, especially due to the silent progression and non-specificity of the initial symptoms, which makes it difficult to identify it in early stages (BRAY et al., 2024; SUNG et al., 2024).

From an epidemiological point of view, factors such as advanced age, genetic predisposition, mutations in the BRCA1 and BRCA2 genes, family history, and hormonal factors are directly associated with increased risk for the development of ovarian cancer. In addition, the biological heterogeneity of the tumor contributes to the diagnostic and therapeutic complexity, requiring increasingly individualized approaches based on precision medicine (REID; PERMUTH; SELLERS, 2024).

Historically, methods such as transvaginal ultrasonography and serum measurement of the CA-125 marker have been used as auxiliary strategies in the diagnostic investigation, but they have important limitations in terms of sensitivity and specificity, especially in the early stages of the disease. In this context, population screening still remains controversial, since large studies have not shown a significant reduction in mortality with traditional methods alone (MENON et al., 2024).

Given this scenario, the search for emerging biomarkers has become one of the main research fronts in gynecologic oncology. New markers, such as HE4, multibiomarker predictive algorithms, molecular signatures, and tests based on artificial intelligence have been investigated with the aim of increasing diagnostic accuracy and allowing earlier interventions, directly impacting the prognosis and survival of patients (MOORE et al., 2024; URICK; BELL, 2024).

The combination of multiple biomarkers has superior performance compared to the use of classical markers alone, favoring greater sensitivity for early detection and better risk stratification. In this sense, the incorporation of these tools into clinical practice may represent a significant advance



in reducing morbidity and mortality associated with ovarian cancer, especially when associated with individualized diagnosis and surveillance of higher-risk groups (SANTANA et al., 2024).

In view of the high mortality associated with ovarian cancer and the limitations of traditional screening and early diagnosis methods, this study aims to analyze the main current challenges related to the early identification of this neoplasm, with emphasis on the role of emerging biomarkers as promising tools for improving diagnostic accuracy, risk stratification, and improving patient prognosis.

## **METHODOLOGY**

This is an integrative literature review, descriptive, exploratory and with a qualitative approach, developed with the objective of analyzing the current challenges related to the early diagnosis of ovarian cancer, as well as investigating the role of emerging biomarkers in increasing diagnostic accuracy, screening attrition of at-risk populations, and improving patient prognosis.

The construction of the research was carried out through a bibliographic survey in the main national and international scientific databases, namely: PubMed/MEDLINE, Scopus, Web of Science, Scientific Electronic Library Online (SciELO) and Virtual Health Library (VHL). These databases were chosen due to their academic relevance and the wide indexation of studies in the area of gynecological oncology and diagnostic medicine.

For the search strategy, controlled descriptors present in the Health Sciences Descriptors (DeCS) and in the Medical Subject Headings (MeSH) were used, including the terms: “Ovarian Cancer”, “Early Diagnosis”, “Biomarkers”, “Tumor Markers”, “Screening”, “CA-125”, “HE4”, “Liquid Biopsy” and “Precision Medicine”. These descriptors were combined with each other using the Boolean operators AND and OR, allowing greater sensitivity and specificity in the identification of relevant studies. As an example of the applied strategy, the following combination was used: (“Ovarian Cancer” AND “Early Diagnosis”) AND (“Biomarkers” OR “Tumor Markers” OR “Liquid Biopsy”).



The following inclusion criteria were established: original scientific articles, systematic reviews, meta-analyses, and observational studies published between 2020 and 2026, available in full, in Portuguese, English, and Spanish, and that directly addressed early diagnostic methods, traditional and emerging serum biomarkers, diagnostic algorithms, liquid biopsy, molecular biomarkers, and new technologies applied to the screening and early detection of cancer ovary.

As exclusion criteria, editorials, letters to the editor, simple abstracts of congresses, dissertations, theses, duplicate studies between databases, articles without access to the full text, and publications that did not have a direct relationship with the proposed theme or that exclusively addressed surgical and therapeutic treatment without a diagnostic focus were discarded.

The selection of studies was carried out in three sequential stages. Initially, the titles were read to exclude works evidently unrelated to the theme. Next, the abstracts of potentially eligible studies were analyzed, observing the compatibility with the research objectives. Finally, the selected articles were submitted to complete reading, allowing a critical evaluation of the methodological quality and scientific relevance for the composition of the final sample.

After selection, the data were organized in a specific instrument containing information such as: author, year of publication, country of origin, type of study, objectives, main biomarkers investigated, diagnostic methods used, and main results found. The analysis was conducted in an interpretative and comparative manner, seeking to identify convergences, divergences and scientific advances related to the use of emerging biomarkers in the early diagnosis of ovarian cancer.

The selection of studies was carried out in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020), aiming to ensure greater methodological rigor, transparency, and reproducibility of the screening process and inclusion of scientific articles. Initially, a comprehensive search was carried out in the PubMed/MEDLINE, Scopus, Web of Science, SciELO and Virtual Health Library (VHL) databases, using descriptors previously defined and combined by Boolean operators.

In the identification stage, 548 records were found, distributed among the databases consulted



as follows: PubMed/MEDLINE (n = 213), Scopus (n = 145), Web of Science (n = 92), SciELO (n = 28) and VHL (n = 70). After export to the reference manager and removal of duplicate studies (n = 112), 436 unique articles remained for the screening stage.

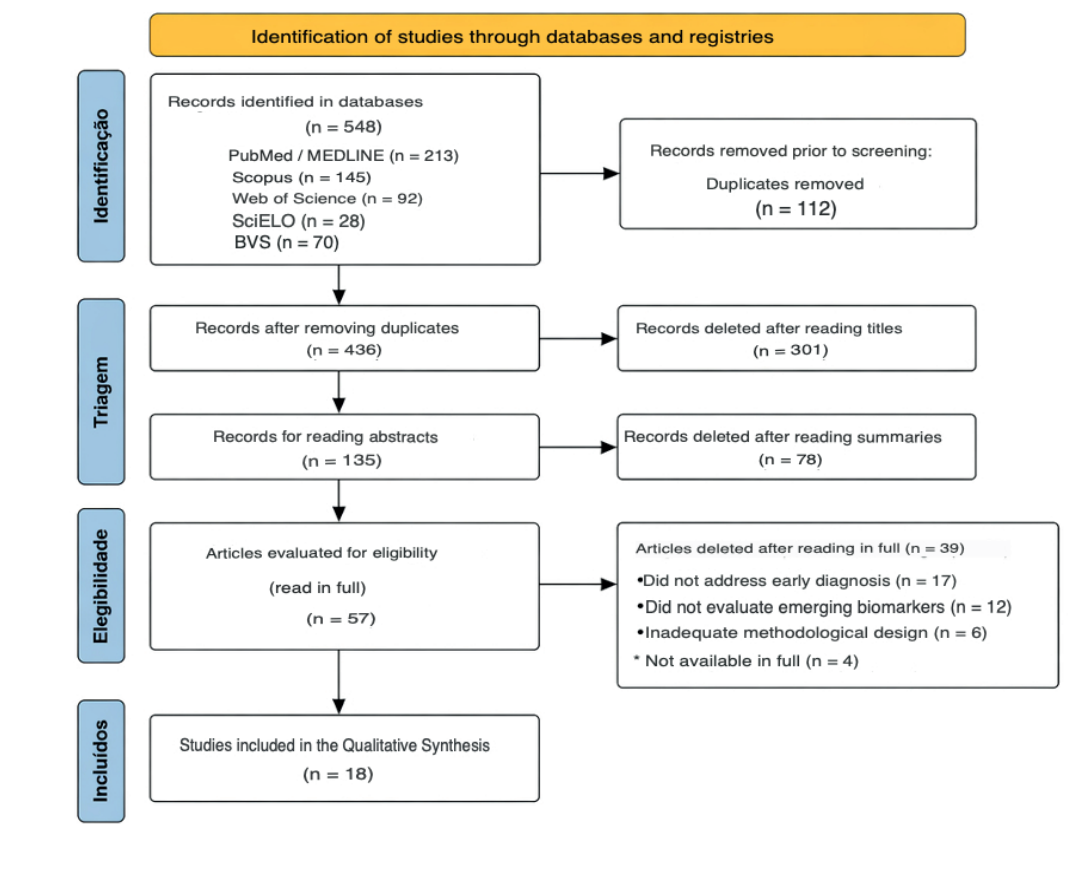
In the screening phase, the titles were initially read, resulting in the exclusion of 301 studies that did not have a direct relationship with the early diagnosis of ovarian cancer or with biomarkers applied to the early detection of the disease. Subsequently, 135 articles were selected for reading the abstracts, and 78 studies were excluded because they did not meet the previously established inclusion criteria, such as lack of relevant data on biomarkers, exclusive focus on surgical or therapeutic treatment, and narrative reviews without robust methodological foundations.

Subsequently, 57 articles were submitted to full reading for eligibility evaluation. At this stage, 39 studies were excluded because they were inadequate to the objective of the review, namely: lack of specific information on early diagnosis (n = 17), lack of evaluation of emerging biomarkers (n = 12), methodological design incompatible with the study proposal (n = 6), and unavailability of the full text (n = 4).

At the end of the selection process, 18 studies made up the final sample of this integrative review, being included in the qualitative analysis and synthesis of the results. The entire process of identification, screening, eligibility and inclusion is represented in the flowchart prepared according to the PRISMA 2020 model and illustrated in the figure below.



Figure 1: Flowchart of the study design



Source: Authors. 2026.

## RESULTS AND DISCUSSION

Chart 1 presents the synthesis of the 18 main studies selected for this integrative review, organized in descending chronological order, from the most recent publication to the oldest. National and international research addressing the early diagnosis of ovarian cancer was included, with emphasis on the current challenges related to screening for the disease and the role of emerging biomarkers as promising tools for increasing diagnostic sensitivity. The analysis includes aspects such as objectives, main results and conclusions of the studies, allowing a comparative view of the most recent scientific evidence on the subject and contributing to the understanding of the advances and limitations still present in clinical practice.



Table 1: General aspects of the study

Authors	Year	Title (translated into Portuguese)	Objective	Result	Conclusion
BRAY et al.	2024	Global Cancer Statistics 2024: GLOBOCAN Estimates of Incidence and Mortality	Present global data on cancer incidence and mortality	Ovarian cancer remains among the gynecological neoplasms with the highest mortality	Late diagnosis contributes significantly to the worse prognosis
SUNG et al.	2024	Global Cancer Statistics 2024: Burden and Mortality Trends	Assess the worldwide burden of cancer and mortality trends	High mortality associated with ovarian cancer in low- and middle-income countries	Early detection is essential to reduce deaths
REID ; PERMUTH; SELLERS	2024	Epidemiology of ovarian cancer: a review	Review epidemiological and risk factors of ovarian cancer	Age, BRCA Mutations, and Family History Increase Risk	Recognition of risk factors favors targeted screening
MENON et al.	2024	Screening and Early Detection of Ovarian Cancer in the Age of Precision Medicine	Discuss screening strategies and early diagnosis	CA-125 and ultrasonography have important limitations	New molecular approaches are more promising
MOORE et al.	2024	Use of multiple tumor biomarkers in the detection of ovarian carcinoma	Evaluate combined biomarkers in pelvic masses	The combination of markers increased diagnostic sensitivity	Combined use outperforms the isolated use of traditional markers
URICK; BELL	2024	New Advances in Ovarian Cancer Screening and Early Detection	Review recent diagnostic advances	HE4, ROMA, and liquid biopsy showed better performance	Emerging Biomarkers Improve Clinical Accuracy
SANTANA et al.	2024	Efficiency of tumor markers in the early detection of ovarian cancer	Analyze the effectiveness of traditional and new tumor markers	HE4 associated with CA-125 showed better results	Combined strategies favor early diagnosis
ROCHA et al.	2024	Advances in the early detection of ovarian cancer	Investigate promising strategies for early diagnosis	Molecular methods and biomarkers increase diagnostic accuracy	Incorporating these techniques may improve the prognosis
BARIONI et al.	2024	Artificial intelligence for identifying biomarkers in cancer	Evaluate the use of AI in biomarker discovery	Algorithms expand diagnostic predictive capacity	AI represents an important tool in precision oncology
BAST et al.	2024	Novel Tumor Markers: CA-125 and Beyond	Discuss the evolution of tumor markers	CA-125 alone has low specificity in early stages	New biomarkers are needed for greater sensitivity



ZHANG et al.	2024	Emerging Biomarkers for Early Detection of Ovarian Cancer	Circulating Biomarkers for Early Detection of Ovarian Cancer	Review innovative circulating biomarkers	microRNAs and ctDNA showed high diagnostic potential	Liquid biopsy could transform future screening
WANG et al.	2024	Exosomal microRNAs as novel biomarkers in ovarian cancer	Exosomal MicroRNAs in Diagnosis and Prognosis	Evaluate MicroRNAs in Diagnosis and Prognosis	High sensitivity in early identification of the disease	They are promising and minimally invasive biomarkers
LIU et al.	2024	Liquid biopsy in ovarian cancer: advances and clinical applications	Liquid biopsy	Review the clinical use of liquid biopsy	ctDNA and circulating tumor cells showed predictive value	The technique can anticipate diagnosis and monitor progression
KIM et al.	2024	HE4 and ROMA algorithm in the diagnosis of ovarian cancer	Analyze evidence on HE4 and ROMA	Analyze evidence on HE4 and ROMA	Improved performance when compared to CA-125 alone	The ROMA algorithm assists in risk stratification
GAO et al.	2024	DNA methylation biomarkers for early detection of ovarian cancer	Investigate epigenetic biomarkers	Investigate epigenetic biomarkers	Methylation changes were detected early	Epigenetic biomarkers have strong diagnostic potential
CHEN et al.	2024	Multimomic biomarkers in ovarian cancer: present and future	Review multimomics biomarkers	Review multimomics biomarkers	Genomic and proteomic integration increases diagnostic accuracy	Multimomics approach strengthens personalized medicine
LUO et al.	2024	AI-assisted biomarker discovery for early diagnosis	Evaluate AI applied to biomarker discovery	Evaluate AI applied to biomarker discovery	Predictive models showed high accuracy	AI can speed up early and individualized diagnosis
DOMINGUEZ JÚNIOR et al.	2023	Advances in early detection and treatment of ovarian cancer	Analyze recent diagnostic methods and therapies	Analyze recent diagnostic methods and therapies	New laboratory and molecular tests have improved detection	Diagnostic advances have a direct impact on patient survival

Source: Authors, 2026



The discussion of the findings shows that the main challenge related to the early diagnosis of ovarian cancer remains associated with the non-specificity of the initial clinical signs and the absence of population-based screening methods with high sensitivity and specificity. In most cases, the disease is identified in advanced stages, when there is already peritoneal spread and a worse prognosis, which directly contributes to the high mortality rates observed worldwide. In this context, the limitation of conventional methods, such as transvaginal ultrasonography and serum CA-125 dosage, reinforces the need for new, more accurate and individualized diagnostic approaches (DOMINGUEZ JÚNIOR et al., 2023; ROCHA et al., 2024).

Although the tumor marker CA-125 remains widely used in clinical practice, its low specificity in early stages and its elevation in benign conditions such as endometriosis and pelvic inflammatory processes reduce its effectiveness as an isolated screening tool. Bast et al. (2024) highlight that, despite its historical relevance, the exclusive use of this marker has significant limitations, especially in asymptomatic patients. Similarly, Santana et al. (2024) demonstrate that the association between CA-125 and other biomarkers, such as HE4, has better diagnostic performance, increasing sensitivity and specificity in the early identification of the disease.

The HE4 biomarker and the ROMA algorithm have stood out as promising tools in the risk stratification of malignancy in adnexal masses. According to Kim et al. (2024), HE4 has less interference by benign diseases when compared to CA-125, making it more reliable in certain clinical contexts. In addition, the ROMA algorithm, by combining laboratory variables and clinical characteristics, offers better predictive capacity, contributing to earlier and more targeted therapeutic decisions. These findings reinforce the importance of the combined use of biomarkers rather than the isolated analysis of traditional markers.

In recent years, liquid biopsy has gained prominence as an innovative and minimally invasive strategy for the early diagnosis of ovarian cancer. The identification of circulating tumor DNA (ctDNA), circulating tumor cells, and exosomes allows the detection of molecular alterations even before the evident clinical manifestation of the disease. Liu et al. (2024) point out that this technology



offers potential not only for initial diagnosis, but also for therapeutic monitoring and detection of recurrences. In addition, Zhang et al. (2024) point out that emerging circulating biomarkers have high predictive capacity and may represent the future of personalized cancer screening.

Among these innovative biomarkers, exosomal microRNAs have demonstrated particularly relevant results. Wang et al. (2024) show that these small RNA molecules have high biological stability and a strong association with carcinogenesis processes, allowing their use in both diagnosis and prognostic evaluation. Its minimally invasive nature favors future clinical application, especially in screening programs aimed at populations at higher genetic and familial risk.

Another promising field involves epigenetic biomarkers, especially DNA methylation patterns. Gao et al. (2024) demonstrate that epigenetic alterations can be identified at very early stages of the disease, even before the development of anatomical alterations detectable by imaging tests. This aspect significantly expands the possibility of early intervention and improved survival rates, consolidating epigenetics as an important diagnostic frontier in gynecologic oncology.

The multiomics approach also represents a significant advance in precision medicine applied to ovarian cancer. The integration between genomic, proteomic, transcriptomic and metabolomic data allows a greater understanding of tumor heterogeneity and favors the identification of specific molecular signatures. Chen et al. (2024) highlight that this strategy enables greater diagnostic and therapeutic accuracy, in addition to contributing to the development of individualized screening and clinical follow-up protocols.

In addition, the use of artificial intelligence has transformed the discovery and validation of new biomarkers. Barioni et al. (2024) describe that machine learning algorithms are capable of analyzing large volumes of clinical and molecular data with high precision, identifying patterns that are often imperceptible to conventional analysis. Luo et al. (2024) reinforce that artificial intelligence applied to early diagnosis can significantly accelerate clinical decision-making, increase predictive accuracy, and reduce diagnostic failures, especially when associated with multiomics strategies.

Thus, the studies analyzed converge in demonstrating that the future of early diagnosis of



ovarian cancer is directly related to the combination of multiple biomarkers, the use of advanced molecular technologies, and the incorporation of artificial intelligence into clinical practice. Despite promising advances, there are still important challenges related to the high cost, laboratory standardization, large-scale clinical validation, and accessibility of these tools, especially in public health systems. Therefore, the consolidation of these strategies will depend on the expansion of multicenter studies and the integration between scientific research, technological innovation, and public health policies (ROCHA et al., 2024; SANTANA et al., 2024).

## **FINAL CONSIDERATIONS**

Throughout this review, it was possible to understand that ovarian cancer continues to be one of the gynecological neoplasms with the greatest impact on public health, especially due to the difficulty of identification in the early stages and the high rates of morbidity and mortality associated with late diagnosis. The analysis of the literature showed that the diagnostic methods traditionally used, although still relevant in clinical practice, have important limitations when used in isolation, especially in the early screening of the disease.

In this context, emerging biomarkers show important potential in increasing diagnostic sensitivity, risk stratification, and building more individualized and effective approaches. Tools such as HE4, ROMA algorithm, liquid biopsy, exosomal microRNAs, epigenetic biomarkers, and multiomics analyses have been consolidating new perspectives for early diagnosis, especially when associated with advances in artificial intelligence and precision medicine. These resources represent not only technological innovation, but also a concrete possibility of reducing mortality and improving the prognosis of patients.

As a potential of this study, the gathering and analysis of recent and relevant scientific evidence that allows a broad and updated view of the main diagnostic advances related to ovarian cancer is highlighted, favoring a critical understanding of the challenges that still exist and the future



perspectives for clinical practice. The integrative approach made it possible to compare different diagnostic strategies and identify the growing trend of replacing isolated methods with combined and more accurate models.

However, some limitations should also be considered, such as the methodological heterogeneity among the studies analyzed, the diversity of the biomarkers investigated, and the still limited standardization of diagnostic protocols, which makes it difficult to directly compare the results and the immediate application of certain technologies in the care routine. In addition, many emerging biomarkers still depend on large-scale clinical validation and greater economic viability for their incorporation into health services, especially in the context of public systems.

Thus, the need for continuity of scientific investigations, the strengthening of multicenter studies and the expansion of access to new diagnostic technologies is reinforced, aiming to transform the current scenario of ovarian cancer. The consolidation of these strategies can significantly contribute to a more resolute, preventive, and humanized care, in line with the principles of early detection and improvement of patients' quality of life.

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