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# POTENTIAL EPIGENETIC CANDIDATES FOR EARLY BIOMARKERS IN OVARIAN CANCER: A LITERATURE REVIEW

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**Abstract:** Ovarian cancer remains one of the most challenging malignancies to detect at an early stage, often resulting in delayed diagnosis and high lethality. This literature review examines potential epigenetic candidates as biomarkers for early detection, with a particular focus on those with higher accuracy and reproducibility in early stages of ovarian cancer. Despite the limited specificity of CA125 in early detection, its combination with HE4 showed improved performance in stage II cases, suggesting a potential diagnostic enhancement when used together. Exploring epigenetic mechanisms, especially the role of miRNAs such as miR29b and miR199a, shows promise in identifying prognostic markers, offering insights into patient outcomes based on favorable or unfavorable genetic profiles. Furthermore, the review highlights the need for a broader study of endocrine disruptors and the integration of advanced imaging techniques, such as ultrasound, in association with CA125 and HE4, aiming to refine early detection and risk assessment strategies. These findings highlight the potential for epigenetic biomarkers to play a significant role in the early detection and treatment of ovarian cancer, paving the way for improved diagnostic approaches.

## INTRODUCTION

Ovarian cancer is a disease with low incidence but high lethality, often diagnosed in advanced stages. According to the Oncoguia Institute (2024), the risk of a woman developing ovarian cancer over the course of her life is 1 in 78, and the chance of dying from the disease is approximately 1 in 108. It is estimated that, in 2020, approximately 313,959 women were diagnosed with ovarian cancer worldwide. Early detection is essential to increase the chances of a cure, but identifying specific signs and symptoms is challenging since, in the early stages, patients often present with nonspecific symptoms or remain asymptomatic. This scenario is even more complex due to the overlap of symptoms with other benign gynecological diseases and chronic noncommunicable diseases.

The pathophysiology of ovarian cancer involves a set of complex biological processes, resulting in cellular, genetic, and molecular alterations in ovarian tissue. Most ovarian cancers are epithelial in origin, beginning in the cells that line the surface of the ovary. This type of cancer is the most common, followed by germ cell tumors and gonadal stromal tumors, each with distinct pathological characteristics.

Malignant transformation of ovarian epithelial cells is marked by genetic mutations, such as those in the BRCA1 and BRCA2 genes, which are responsible for repairing damaged DNA. These mutations, as well as other alterations in genes such as TP53 and PTEN, lead to a loss of control over cell division and death, promoting uncontrolled cell proliferation. Cancer cells then accumulate additional mutations and evade the natural mechanisms of apoptosis, or programmed cell death, allowing them to grow and multiply.

Angiogenesis, the process of formation of new blood vessels, is another important aspect of pathophysiology, essential for supplying nutrients and oxygen to growing tumor cells. This process is promoted by pro-angiogenic factors such as VEGF (vascular endothelial growth factor), which increase tumor vascularization and aid in its spread.

Ovarian cancer also has a strong tendency to metastasize, especially in the abdominal cavity, through mechanisms such as the direct spread of tumor cells across the peritoneal surface, in addition to invading nearby tissues such as the uterus and colon. This local and, later, distant spread contributes to the high lethality of ovarian cancer, as it allows the invasion of healthy tissues and the formation of secondary foci in other organs, making treatment difficult and reducing the chances of a cure in advanced stages.

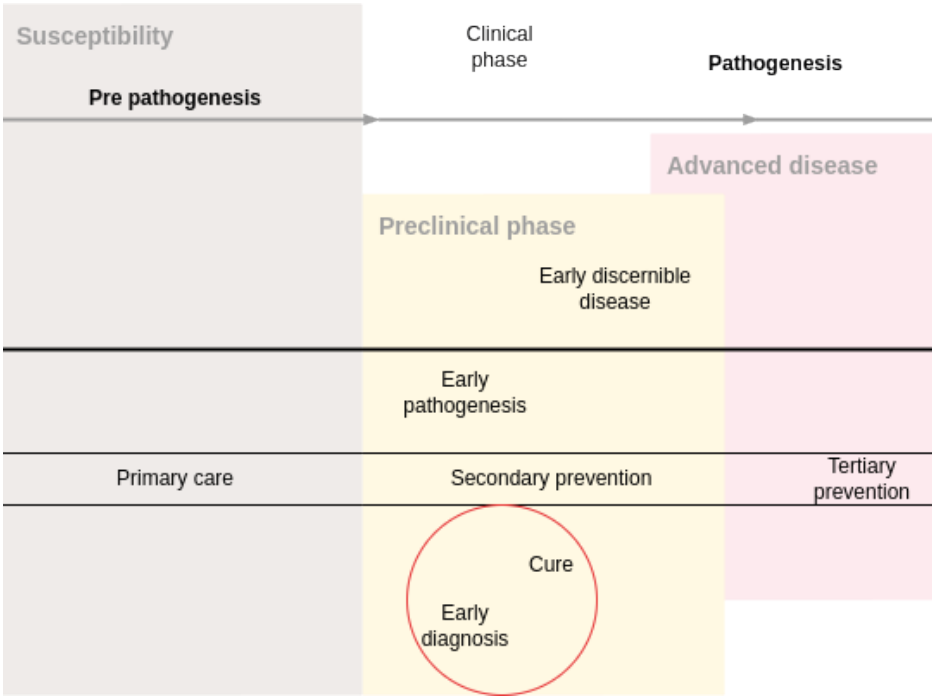


**Figure 1** - Natural history of the disease, the red circle indicates the early diagnosis phase.

The natural history of the disease refers to the set of changes that a disease undergoes from its origin to its possible outcome without medical interference (Figure 1).

This process can be divided into phases: it begins with the susceptibility phase, where risk factors make the organism vulnerable to the disease-causing agent. Next comes the incubation phase or asymptomatic period, also known as silent disease, where the agent is present but without visible symptoms, developing in the organism without noticeable clinical signs. In the clinical phase, visible symptoms and signs appear, resulting from the interaction of the agent with the organism, which reflects the pathogenesis, that is, the mechanism by which the agent causes the disease. In the absence of treatment, the disease can evolve to spontaneous cure, chronicity or fatal outcome, depending on the type of pathogen and the characteristics of the host (BENSON et. al., 2015).

Furthermore, in Figure 1, it can be seen that early diagnosis, during the pathogenesis phase, is essential to increase the chances of a cure. However, this phase presents a considerable clinical challenge, given the complexity of identifying specific signs and symptoms or systemic relationships that clearly indicate a developing disease. This is because, at this stage, patients often present with nonspecific symptoms or remain asymptomatic, creating a scenario in which different diseases can present similar clinical manifestations. This challenge is even greater when the symptoms of benign gynecological diseases overlap with those of chronic noncommunicable diseases, such as ovarian cancer (BEHBAKHT et. al., 2011; BELL-MCGUINN et. al., 2011; BERI et. al., 2018).

Due to the complexity of stratifying data on signs and symptoms in relation to ovarian cancer, we began a search for studies related to molecular biomarkers that play a crucial role in the study of cancer, offering valuable information for diagnosis, prognosis and therapeutic monitoring. Biomarkers represent genetic, epigenetic, protein and metabolic alterations that reflect the biological behavior of tumors and can be used to predict patient response to

specific treatments. In the field of oncology, biomarkers allow a more personalized approach, identifying the molecular profiles of tumors and helping to guide therapeutic decisions based on the individual characteristics of the disease (ANDRIOLE et.al., 2012; ASHCROFT et. al., 2018; BACKEN et. al., 2014). Furthermore, they are essential for the development of targeted therapies, since certain mutations or specific alterations in biomarkers can indicate vulnerabilities in the tumor.

In ovarian cancer, the use of molecular biomarkers has been intensively investigated due to the aggressive and often silent nature of the disease, which is usually detected in advanced stages. Biomarkers such as CA-125, HE4, in addition to mutations in BRCA1 and BRCA2 (HODGSON et. al., 2018), are studied to aid in early diagnosis, risk stratification and personalized treatment. Advances in the identification of molecular biomarkers specific for ovarian cancer continue to be a critical focus to improve early detection and increase survival rates (ALVAREZ SECORD et.al., 2020; BAIS et. al., 2017).

Given the importance and depth of the pathophysiology of ovarian cancer, which comprises diffuse signs and symptoms in the pathogenesis period and the low specificity of molecular biomarkers, a literature review was carried out to identify other potential biomarkers potentially involved in the differential diagnosis of ovarian cancer.

## MATERIAL AND METHODS

This study is a bibliographic review. In order to select the works used in this article, the Pubmed, Bireme, Scielo, and Google Scholar databases from 2011 to 2024 were accessed. In the DeSC/MeSH platform, the following descriptors were used: "Tumor Biomarkers" and Alternative Term(s): "Ovarian Cancer". For the Pubmed platform, the search used validated descriptors and separated articles and/or journals with information on Tumor Biomarkers in Ovarian Cancer.The inclusion criterion adopted was all works published between 2011 and 2024, written in Portuguese and/or English, available free of charge, that addressed topics related to Ovarian Cancer, Tumor Biomarkers using AND in the search for the descriptors and Clinical Trial. As exclusion criteria, studies with publication dates prior to 2011 were applied, as well as those that were not available in full and did not address the themes of the descriptors simultaneously in the same article and/or journal. In relation to the search, we used a crawler to perform the search and extract tumor biomarkers from the text (Figure 2).

## RESULTS

Through searches in the databases and using the selection criteria, 91 articles were found in Pubmed, which were used to prepare this review. At the end, the articles were divided into groups, as follows (Figure 3).

## DISCUSSION

The high heterogeneity of biomarkers in ovarian cancer shows that CA125 (TREDAN et. al., 2022), alone or in combination with other markers, has not yet demonstrated strong efficacy in detecting the disease in its early stages. However, in more advanced stages, CA125 has proven to be an efficient biomarker (SCHUMMER et. al., 2013; CARTMEL et. al., 2015; FRISK et. al., 2023). This cancer presents a considerable variability of signs and symptoms, suggesting a complex etiology with genetic and epigenetic factors. These changes may be associated with environmental factors, daily habits and diet, which mainly affect the epithelial cells of the ovary, where approximately 95% of ovarian cancer cases occur. This multifactorial and heterogeneous nature makes early identification difficult, especially in individuals with limited

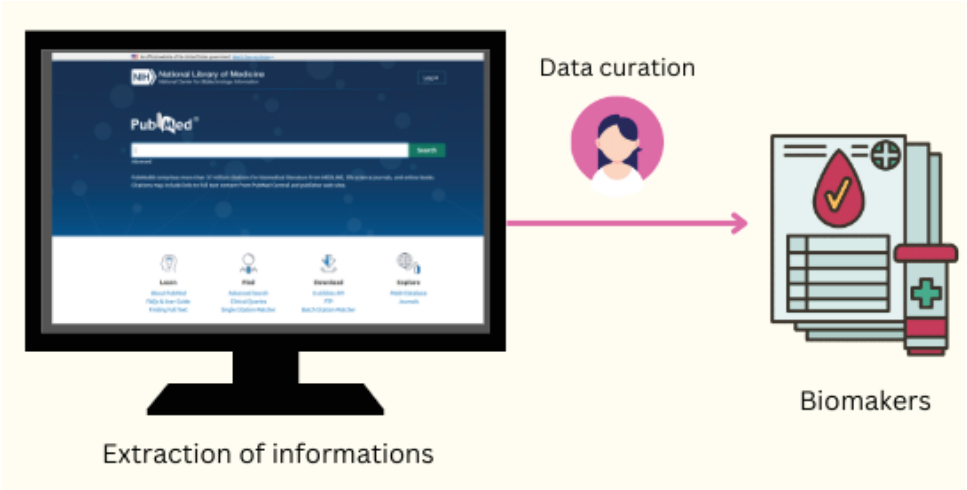


**Figure 2** - Information extraction from pubmed and curation for biomarker searches

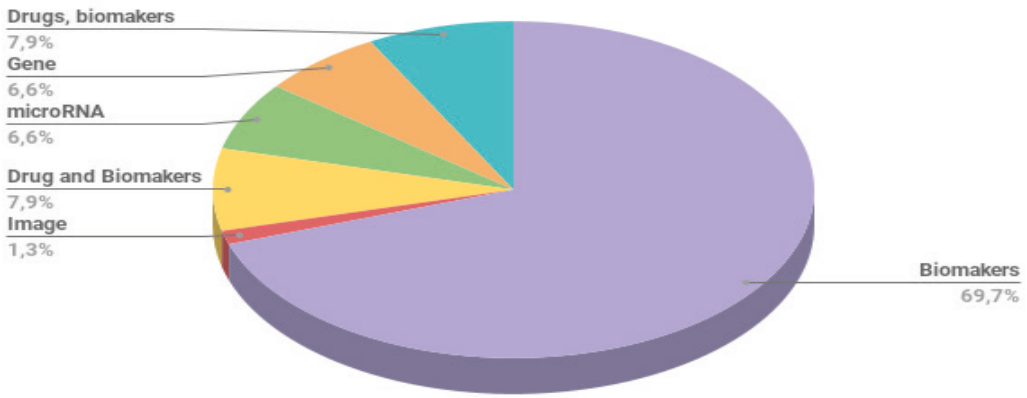


**Figure 3** - Percentage of publications related to research topics.

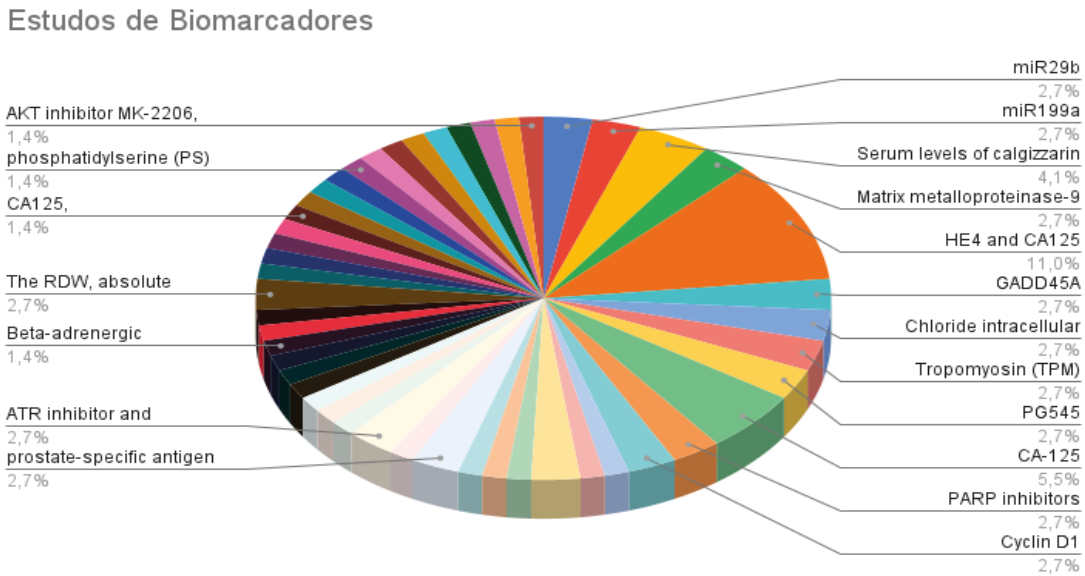


**Figure 4** - Biomarkers studied in different publications.

| Biomarkers | Articles |
|---|---|
| miR29b | 2 |
| miR199a | 2 |
| miR200 | 1 |
| Serum levels of calgizzarin (S100A11) | 3 |
| Matrix metalloproteinase-9 (MMP9) | 2 |
| HE4 and CA125 | 8 |
| GADD45A | 2 |
| Chloride intracellular channel (CLIC) | 2 |
| Tropomyosin (TPM) | 2 |
| PG545 | 2 |
| CA-125 | 4 |
| PARP inhibitors | 2 |
| Cyclin D1 | 2 |
| S100A1 | 1 |
| miR-200c | 1 |
| TP53 | 2 |
| FLT4, AGP, and CA-125 | 1 |
| CTP | 1 |
| PDGF-AB/BB, PDGF-AA, CRP, sFas, CA125, SAA,sTNFRII, sIL-6R, IGFBP6 and MDC | 1 |
| prostate-specific antigen (PSA) | 2 |
| Pyroglutamine, gamma-glutamylphenylalanine, phenylpyruvate, N-acetylcitrulline, and stearoylcarnitine showed the strongest metabolite-risk signals | 1 |
| ATR inhibitor and progression-free survival (PFS) | 2 |
| progression-free survival (PFS) and overall survival (OS). | 1 |
| PD-L1 | 1 |
| PFS | 1 |
| Ang1 and Tie2 | 1 |
| IL-6R blocking | 1 |
| $ER^+$ and/or $PR^+$ ROC and CA125 | 1 |
| Beta-adrenergic | 1 |
| anti-programmed death-1 (PD-1) | 1 |
| FGF2 | 1 |
| The RDW, absolute neutrophil count (N), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and cancer antigen 125 (CA-125) concentration were significantly higher in the ovarian cancer than control group. The hemoglobin concentration (Hb) and absolute lymphocyte count (L) | 2 |
| (CD31) and tumor VEGF-A | 1 |
| PRUNE2 and BARD1 | 1 |
| Thrombocytosis and platelet | 1 |
| ATCdx | 1 |
| CA125, phosphatidylcholine-sterol acyltransferase, vitamin, K-dependent protein Z and C-reactive protein | 1 |
| IGFBP2, LCAT and CA125 | 1 |
| Insulin-like growth factor (IGF) | 1 |
| cancer antigen 125 (CA-125) serum testing and transvaginal ultrasound (TVU) | 1 |
| phosphatidylserine (PS) | 1 |
| VEGF | 1 |

| | |
|---|---|
| miR-148b-5p and PSF | 1 |
| Tie2 and Ca125 | 1 |
| AKT inhibition | 1 |
| PSF | 1 |
| HRG expression and focus on cancers with low HER2 | 1 |
| Aurora A Kinase Inhibitor | 1 |
| AKT inhibitor MK-2206, mTOR inhibitor ,NOTCH inhibitor MK-0752 | 1 |

**Table 1** - List of 73 biomarkers studied for ovarian cancer

| Study | Number of patients | Protocol | Design study | Sample type | Marker type | Biomarker |
|---|---|---|---|---|---|---|
| Steffensen, 2014 | 144 | BEV | prospective | plasma | DNA | cfDNA |
| GAO, 2020 | 62 | CT+BEV | retrospective | tissue | DNA | EGFR status |
| | | | | | | HER2 status |
| | | | | | | MYC status |
| Ribeiro, 2021 | 124 | CT +- BEV | retrospective | tissue | protein | CCNE1 |
| Fabbi, 2022 | 309 | PC + BEV | prospective | tissue | protein | ADAM17 |
| Califano, 2021 | 336 | PC + BEV | prospective | tissue | protein and RNA | MVD |
| Boisen, 2016 | 140 | BEV | prospective | plasma | protein | CA125 |
| | | | | | | VEGF |
| | | | | | | YKL-40 |
| | | | | | | OPN |
| | | | | | | IL6 |
| | | | | | | Ang2 |
| | | | | | | SDF1 |
| | | | | | | IL6R |
| | | | | | | GP130 |
| | | | | | | VEGF-D |
| Slaughter, 2014 | 21 | CT+BEV | retrospective | patients | image | BMI |
| | | | | | | SFA |
| | | | | | | SFD |
| | | | | | | VFB |
| | | | | | | VFA |
| Ng, 2017 | 76 | PC+-BEV | prospective | patients | image | BF |
| | | | | | | BV |
| | | | | | | PS |
| Lorusso, 2020 | 441 | PC+-BEV | retrospective | clinical records | patient characteristics | BRCA |
| | | | | | | PDS/NACT |
| | | | | | | RT |
| Tate, 2021 | 28 | PC+-BEV | retrospective | blood | patient characteristics | PS |
| | | | | | | CR |
| Robelin, 2020 | 119 | PC+- ninedanib | prospective | plasma | miRNA | miR-15b-5p |
| | | | | | | miR-34a |
| Bauerschlag,2013 | 43 | subitinib | prospective | serum | protein | VEGF |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | Ang2 |
| | | | | | | sVEGFR3 |
| Sharma, 2020 | 16 | P+pazopanib | prospective | patients | image | SUV(60_mean) |
| Nixon, 2022 | 70 | olaparib+cediranib | prospective | plasma | protein | OPN |
| | | | | | | IL6 |
| Halvorsen, 2017 | 207 | PC+-BEV | prospective | plasma | protein | Ang1 |
| | | | | | | Tie2 |
| Collinson, 2013 | 121 | CT+BEV | prospective | serum | protein | Mesothelin |
| | | | | | | FLT4 |
| | | | | | | AGP |
| | | | | | | CA125 |
| Backen, 2014 | 205 | CT+BEV | prospective | plasma | protein | Ang1 |
| | | | | | | Tie2 |
| Secord, 2020 | 751 | PC+BEV | prospective | plasma | protein | OPN |
| | | | | | | IL6 |
| | | | | | | Ang2 |
| | | | | | | SDF-1 |
| | | | | | | IL6R |
| | | | | | | GP130 |
| | | | | | | VEGF-D |

**Table 2** - Selection of 21 most used articles to establish as a biomarker for Ovarian Cancer.

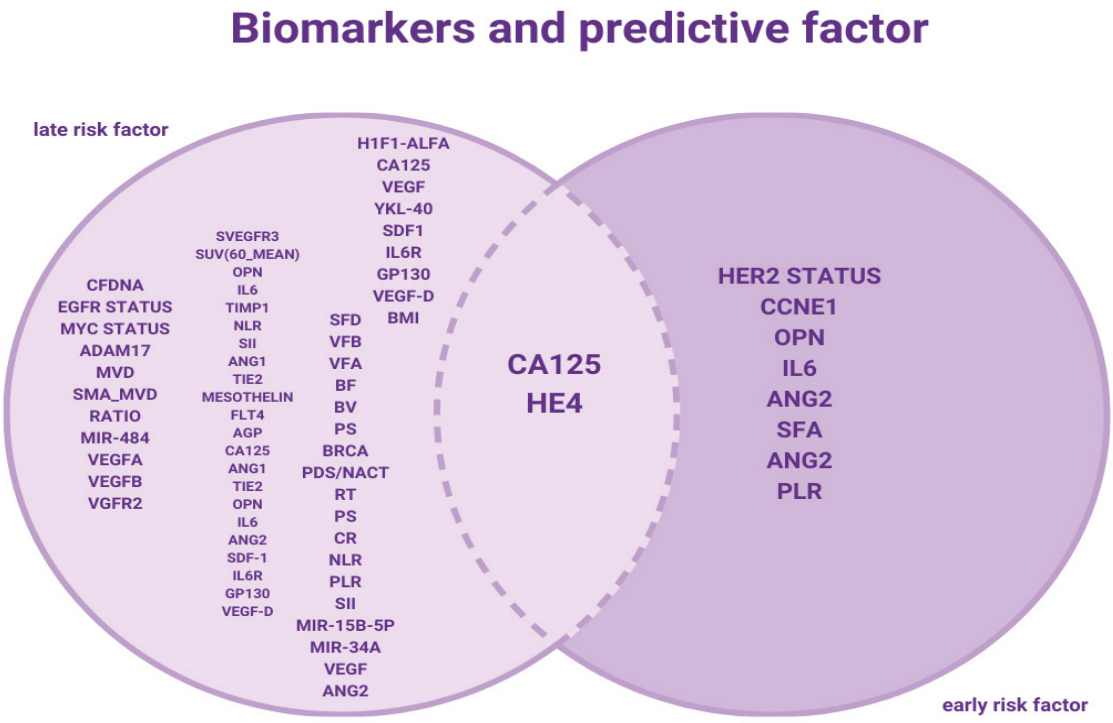


**Figure 5** - Venn diagram (late risk factor) genes that are expressed in advanced stages of ovarian cancer, (early risk factor) are potential factors that can identify ovarian cancer in early stages, in the center we have CA125 and HE4, which have greater expression in cases with advanced stage than in early stages.

family history or without clear clinical signs (BERI et. al., 2019; Blyuss et. al., 2019; TIAN et. al., 2017; SHIELS et. al., 2011; KARLSSON et. al., 2024).

In addition, factors such as hyperandrogenism, exposure to endocrine disruptors, obesity, use of anabolic steroid medications and the presence of metabolic syndrome may increase the risk of developing ovarian cancer. These elements are often associated with hormonal changes that can promote the disordered growth of ovarian cells (MOORE et. al., 2019). The investigation of hormonal and metabolic factors, in addition to genetic and epigenetic factors, highlights the importance of a comprehensive approach to understanding and preventing the disease. These findings reinforce the need to develop more specific biomarkers and to perform screenings that consider multiple risk factors, aiming at a more accurate and early detection of ovarian cancer (COLLINSON et. al., 2013; KARLAN et. al., 2014; NIU et. al., 2017; RUSSELL et. al., 2017).

Given this scenario, there is a need to further explore the relationship between epigenetics and ovarian cancer, considering that epigenetic changes may play a fundamental role in the origin and progression of this type of cancer. Epigenetics involves hereditary changes in gene expression without modifying the DNA sequence, and these changes may be influenced by environmental factors such as diet, stress, and exposure to chemical substances. In ovarian cancer, studies have shown that epigenetic modifications such as DNA methylation and histone alterations may contribute to the inactivation of tumor suppressor genes or the activation of oncogenes, facilitating uncontrolled cell proliferation. Thus, further studies on these changes may elucidate new paths for early diagnosis and treatments to reduce disease progression (PINSKY el. al., 2014; ERICKSON et. al., 2014; KONECNY et. al., 2021).

Another important aspect is that epigenetics may help explain the variability of signs and symptoms in ovarian cancer, which manifests itself in different ways among patients. This heterogeneity suggests that epigenetic modifications may be influenced by individual factors, such as lifestyle and environmental exposure, which directly impact ovarian cells (LIU et. al., 2016; FLEMING et. al., 2017). The analysis of specific epigenetic patterns in patients with ovarian cancer may provide valuable information for the development of biomarkers capable of aiding in the early detection of the disease and in the assessment of prognosis. Larger studies on these relationships may promote the development of personalized epigenetic interventions that take into account the epigenetic profile of each patient, enabling more effective treatments adapted to the individual characteristics of ovarian cancer (COLEMAN et. al., 2014; DIJKGRAAF et. al., 2015; HUANG et. al., 2016; KOMMOSS et. al., 2020).

Regarding the biomarkers HER2, CCNE1, OPN, IL6, Ang2, SFA and PLR play crucial roles in the epigenetics of ovarian cancer, as they influence the regulation of gene expression and tumor behavior. HER2, traditionally associated with breast cancer, can also be overexpressed in cases of ovarian cancer and is related to increased cell proliferation and tumor aggressiveness. CCNE1, a gene that encodes cyclin E1, is frequently amplified in ovarian tumors, contributing to the dysregulated cell cycle, a common characteristic in cancer cells (CHANG et. al., 2013; DIJKGRAAF et. al., 2015; KAZARIAN et. al., 2017; LEA et. al., 2017; REICHARD et. al., 2017; VALLIUS et. al., 2017; CARDUCCI et. al., 2018; RUSSELL et. al., 2019; BUECHEL et. al., 2021). These epigenetic alterations promote an environment conducive to cancer progression, showing how the regulation of genes involved in cellular control can be affected, resulting

in unbridled cell growth (GRUESSNER et.al., 2014; DESPIERRE et. al., 2018; EMBLETON et. al., 2018; ZAMARIN et. al., 2020).

Furthermore, markers such as OPN (osteopontin), IL6 (interleukin 6), and Ang2 (angiopoietin-2) are involved in inflammation and angiogenesis, processes fundamental to tumor progression. OPN and IL6, for example, can be regulated by epigenetic modifications that intensify the inflammatory response and favor the invasion and dissemination of malignant cells (TANG et. al., 2013; KIM et. al., 2014; SCHAIRER et. al., 2017; KOK et. al., 2019; LANDY et. al., 2020; LOIBL et. al., 2020). Increased levels of Ang2, frequently observed in ovarian cancer, facilitate the formation of new blood vessels, allowing the tumor to receive more nutrients and oxygen for its growth. In addition, PLR (platelet-to-lymphocyte ratio) and SFA (insulin-like growth factor) have been associated with exacerbated inflammatory responses and epigenetic alterations that promote resistance to treatment and greater tumor aggressiveness (COTTU et. al., 2018; KONSTANTINOPOULOS et. al., 2021). These biomarkers reflect how epigenetic alterations not only favor tumor growth, but also create a more aggressive and resistant microenvironment, which directly impacts the prognosis and therapeutic approaches of ovarian cancer (HALVORSEN et. al., 2017; JONES et. al., 2019; LI et. al., 2021).

Another promising study is the role of microRNAs (miRNAs) in ovarian cancer, which has been intensively investigated, especially due to the regulatory role they play in gene expression and cancer progression (TUMMERS et. al., 2016). MiRNAs such as miR-29b and miR-199a have emerged as important modulators in ovarian cancer biology, impacting critical cellular processes such as proliferation, apoptosis and cell invasion. miR-29b is particularly relevant, as it regulates the expression of genes involved in DNA methylation and modulation of the extracellular matrix, such as DNMT3A and MCL1 (LAKSHMANAN et. al., 2017; NG et. al., 2017; YU et. al., 2020; MURAKAMI et. al., 2021 LI et. al., 2024). Repression of miR-29b has been associated with tumor progression and resistance to treatments, especially by increasing methylation and promoting a permissive environment for carcinogenesis. In addition, it influences pathways that promote cell survival and invasion, which are essential for ovarian cancer progression and metastasis. Another miRNA that plays an important role is miR-199a, which is commonly downregulated in ovarian cancer cells and is involved in the regulation of pathways such as vascular endothelial growth factor (VEGF), which is known to promote tumor angiogenesis (MOORE et. al., 2011; YUAN et. al., 2015; WINTERHOFF et. al., 2015; QIN et. al., 2017; JAYSON et. al., 2018). Low expression of miR-199a increases angiogenesis and invasion, processes that are key to ovarian cancer progression. In addition to miR-29b and miR-199a, other miRNAs, such as miR-200c, miR-21, and miR-125b, also have significant implications, acting on multiple pathways that contribute to chemotherapy resistance, tumor proliferation, and disease progression (PETERSON et. al., 2013; SURYAWANSHI et. al., 2013; WANG et. al., 2013; ZHOU et. al., 2013; YANG et. al., 2021; QUINTANILHA et. al., 2022; SAVOLAINEN et. al., 2022). Together, these miRNAs influence tumor epigenetics through changes in DNA methylation and modulation of DNA repair genes, creating a complex network that can promote cancer cell growth and survival. Therefore, miRNAs are promising targets for new therapies and biomarkers for the early diagnosis and prognosis of ovarian cancer (BRANA et. al., 2014; SHERMAN et. al., 2014; LEMPIAINEN et. al., 2017; LOU et. al., 2019).

The review of all articles highlights a clear need for further studies on more accurate and reproducible biomarkers for early-stage ovarian cancer, as seen in advanced stages. Although CA125 alone has limited specificity in early stages, its association with HE4 shows potential for improved outcomes, particularly in patients with stage II ovarian cancer. Consequently, the study of epigenetic mechanisms, especially the role of miRNAs, appears promising for identifying markers of favorable and poor prognosis. Additionally, a more comprehensive investigation of endocrine disruptors in association with CA125 and HE4 (Widschwendter et. al., 2011; WANG et. al., 2013) could provide valuable insights into early detection and risk assessment strategies.

## CONCLUSION

The review of all articles highlights a clear need for further studies on more accurate and reproducible biomarkers for early-stage ovarian cancer, as seen in advanced stages. Although CA125 alone has limited specificity in early stages, its association with HE4 shows potential for improved outcomes, particularly in patients with stage II ovarian cancer. Consequently, the study of epigenetic mechanisms, especially the role of miRNAs, appears promising for identifying markers of favorable and poor prognosis. Additionally, a more comprehensive investigation of endocrine disruptors or ultrasound images in association with CA125 and HE4 could provide valuable insights into early detection and risk assessment strategies.

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