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Advances in Biomarkers for Early Detection and Prognosis of Ovarian Cancer

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Abstract

Ovarian cancer (OC) remains the leading cause of gynecological cancer-related deaths worldwide due to its asymptomatic nature in the early stages and lack of effective early detection methods. Despite advances in diagnostic techniques, the high mortality rate associated with OC is largely attributed to late-stage diagnoses. Current diagnostic biomarkers, such as CA-125 and transvaginal ultrasonography, have limitations in early detection, especially in premenopausal women. This review explores the latest advancements in ovarian cancer biomarkers, focusing on cancer antigens, kallikrein enzymes, osteopontin (OPN), HE4, genetic mutations, epigenetic changes, and newer candidates such as exosomes and circulating tumor DNA (ctDNA). The review highlights how combinations of existing biomarkers, alongside emerging technologies like gene expression profiling and liquid biopsy, can improve early detection sensitivity. miRNAs, such as let-7e, miR-30c, and miR-200a, are identified as key players in ovarian cancer diagnosis, prognosis, and treatment response.

Furthermore, ctDNA and exosomes show promise as non-invasive tools for monitoring disease progression and therapeutic response. Ultimately, this review emphasizes the potential of combining novel biomarkers with traditional methods to enhance early diagnosis, improve patient outcomes, and facilitate personalized treatment strategies for ovarian cancer.

Keywords

Ovarian cancer, biomarkers, early detection, circulating tumor DNA, microRNA, gene expression, exosomes

Introduction

Ovarian cancer remains the leading cause of mortality among gynecological malignancies, responsible for approximately 140,000 deaths annually worldwide [1]. Due to its asymptomatic nature in the initial stages, ovarian cancer is often referred to as a "silent killer," with only 20% of cases being identified at an early stage [2]. Studies using computer modeling suggest that earlier detection of the disease could improve survival rates by 10-30% while also being cost-effective [3]. Symptoms tend to manifest only as the disease advances, which partly explains its high mortality rate compared to other gynecological cancers [2].

Currently, diagnostic methods rely on transvaginal ultrasonography and the measurement of cancer antigens such as CA-125. Although CA-125 has proven useful in diagnosis and prognosis, the absence of highly sensitive biomarkers for early-stage detection remains a critical challenge, contributing to the disease's significant fatality rate [4]. Research is actively investigating combinations of biomarkers, including HE4, FOLR, kallikrein, miRNA, ROMA, and CA-125, with the goal of improving diagnostic sensitivity in early ovarian cancer [5]. This review highlights existing biomarkers, advances in gene-based approaches, newly identified markers, and other promising tools aimed at achieving early detection of ovarian cancer.

Review

Characteristics, Impact, and Challenges in Early Detection

Ovarian cancer (OC) encompasses a diverse range of diseases, each exhibiting unique biological characteristics in terms of appearance and behavior. Although it occurs less frequently compared to breast cancer, OC accounts for a disproportionately large number of cancer-related fatalities. In advanced stages, particularly stage III, the prognosis is poor for most patients, with approximately 75% experiencing recurrence following surgical intervention and chemotherapy. Globally, OC is the deadliest gynecological malignancy and ranks as the fifth leading cause of cancer-related mortality among women in Western countries. Enhancements in diagnostic tools, such as biomarker testing, may significantly increase the likelihood of early detection [6].

Current Biomarkers in Ovarian Cancer

Cancer Antigen 125 (CA-125)

CA-125 has been utilized as a tumor marker for over 30 years, mainly for diagnosing ovarian cancer, monitoring treatment response, and detecting recurrence [7]. This well-established biomarker has a sensitivity of 50-60% and a specificity of 90% in early-stage postmenopausal women, with elevated levels in 90% of epithelial ovarian cancer cases [8]. Despite its common use, CA-125 alone lacks the sensitivity required for early-stage detection, particularly in premenopausal women, as various benign conditions can also cause elevated levels, limiting its effectiveness for routine cancer screening. To improve CA-125's sensitivity, clinical trials like the Risk of Ovarian Cancer Algorithm (ROCA) combine it with other markers, achieving an 86% sensitivity for early detection [9]. The ROCA algorithm stratifies women based on CA-125 levels and risk scores, determining subsequent actions for low, intermediate, and high-risk groups [10]. Furthermore, CA-125 is the only marker that is elevated in cases of endometriomas, with a 40% sensitivity and 91% specificity

when using a 35 U/ml cut-off [11].

Kallikrein Enzymes (KLKs)

Kallikreins (KLKs) are a family of 15 serine proteases encoded by genes located on chromosome 19q13, which are involved in various cellular functions and pathways by regulating proteolytic cascades [12]. They are expressed in both epithelial and endocrine tissues, where they are hormonally regulated, and are detectable in human body fluids [13]. Out of the 15 KLKs, 12 are found to be upregulated in ovarian cancer, with certain KLKs (4-7, 10, and 15) being associated with poor prognosis, advanced disease stages, and chemoresistance to paclitaxel (KLK 4 and 7) [2]. Bioinformatics studies of KLK6 and KLK7 suggest their potential as biomarkers for early-stage and low-malignant ovarian carcinomas, with their sensitivity improving when combined [5].

Osteopontin(OPN)

Osteopontin (OPN) is a secreted extracellular glycoprotein produced by vascular endothelial cells and osteoblasts [10]. Initially identified through a cDNA microarray analysis of ovarian cell lines and human ovarian surface epithelium, it was found to be elevated in ovarian cancer compared to healthy tissues [12]. OPN holds promise as a potential diagnostic biomarker for ovarian cancer and may also play a role in influencing cancer therapies and the development of new anti-tumor treatments [14]. In a study of 40 peritoneal metastatic biopsies, 32 samples showed significantly higher OPN levels than primary ovarian tumor tissues in women with stage III epithelial ovarian cancer (EOC). Elevated OPN levels were independently associated with a very poor prognosis in these patients, whereas 75% of women without increased OPN levels had a 36-month survival rate. Additionally, high osteopontin levels were detectable in urine samples of patients with high-grade ovarian cancer, suggesting the potential use of this test as a noninvasive tool for early diagnosis [2].

HE4 (Human Epididymis Protein 4)

HE4 (Human Epididymis Protein 4), a member of the whey acidic four disulfide core (WFDC) protein family, was first identified in the digital epididymis epithelium [15]. Research suggests that when combined with CA-125, HE4 provides a more specific biomarker for ovarian cancer than either marker individually. As a single marker, HE4 demonstrates a sensitivity of 72.9% at 95% specificity, and when paired with CA-125, this sensitivity increases to 76.4% (at 95% specificity) [8]. HE4's superior specificity compared to CA-125 may explain its better performance, as it remains unaffected by benign conditions like endometriosis. Recent meta-analyses have confirmed that HE4 outperforms CA-125 in distinguishing between benign pelvic diseases and ovarian cancer [12]. Variations in HE4 levels have been examined in different contexts. For instance, Bolstad et al. observed changes in HE4 levels based on Body Mass Index (BMI), while Ferraro et al. found no significant differences in HE4 levels among 103 patients categorized by BMI. This inconsistency may be due to Ferraro et al.'s inclusion of both sexes, which could introduce bias. Overall, BMI appears to have no significant effect on serum HE4 levels, similar to CA-125 [11]. This emphasizes HE4's potential as a reliable biomarker for evaluating treatment response and predicting ovarian cancer outcomes.

Genetic Biomarkers for Ovarian Cancer

Since the first successful sequencing of the human genome in 2001, advancements in genomic technology have enhanced cancer diagnosis and treatment selection. Cancer is thought to arise from genetic alterations, environmental influences, or a combination of both. Given the strong connection between genetic mutations and ovarian tumor development, it is clear that gene-level research will uncover new biomarkers for ovarian cancer [16].

Gene expression

Gene expression profiling, which analyzes thousands of genes in a small tumor sample, holds clinical value in differentiating normal ovarian tissue from ovarian tumors. This approach can offer valuable insights for identifying novel biomarkers [16]. Using oligonucleotide arrays, researchers pinpointed 275 genes likely to encode proteins with altered expression in ovarian cancer [17]. Analyzing gene expression in FFPE samples from five high-grade stage 1 serous carcinomas and five stage 1 broad-line tumors revealed increased levels of surviving, MCM3, E2Fs, VTCN1, and SYNE1, while AKAP14, KNDC1, and DLEC1 were found to be underexpressed in serous carcinoma [18]. Beyond serving as an early detection biomarker, gene expression profiling can provide crucial information for ovarian cancer research, including insights into prognosis, chemotherapy response prediction, and mechanisms of chemoresistance [16].

Inherited gene mutations

At least 20% of all epithelial ovarian cancers (EOCs) are hereditary, with germline mutations in the breast cancer susceptibility genes (BRCA1 and BRCA2) responsible for about 90% of these cases. The remaining 10% are primarily attributed to germline mutations in the DNA mismatch repair (MMR) genes, mainly hMLH1 and hMSH2, which are associated with Lynch syndrome [19]. Typically, 1 in 280 women carries a germline BRCA mutation, and genetic testing for the BRCA gene should be conducted following genetic counseling by professionals in cancer genetics. Previous research has shown that both BRCA proteins are involved in several processes, including DNA repair, transcriptional regulation, and cell cycle control. Over 250 mutations can occur in both BRCA genes, with frameshift or nonsense mutations accounting for 80% of these [16]. The lifetime risk of ovarian cancer is 40% to 50% for BRCA1 carriers and 20% to 30% for BRCA2 carriers. Mutations in MMR genes play a crucial role in correcting mutations that arise during DNA replication or damage repair [7]. Collectively, the genes mentioned above could help identify patients at higher risk for developing ovarian carcinoma [17]. As a result, some experts suggest that comprehensive genetic testing should be offered to all women diagnosed with invasive ovarian carcinoma, regardless of age or family history [16].

Epigenetic changes

Epigenetic mechanisms, such as DNA methylation and histone modifications, play crucial roles in tumor initiation and progression by regulating gene expression. Since abnormal DNA methylation occurs early in cancer development and is easily detectable in clinical samples, assessing methylation status holds significant potential as a biomarker for early-stage ovarian cancer detection [16]. Using sensitive methylation-specific PCR, the methylation status of six tumor suppressor gene promoters, including BRCA1, RASSF1A, APC, p14ARF, p16INK4a, and DAPKinase, was analyzed [20]. At least one or more hypermethylations were detected in tumor DNA from 41 of 50 patients with ovarian or primary peritoneal tumors, showing 82% sensitivity. Furthermore, no hypermethylation was observed in non-neoplastic tissue or serum from 40 control women, indicating 100% specificity [21]. Additionally, epigenetic markers can be measured in circulating DNA from blood, offering the potential for a non-invasive diagnostic test [19].

Newly Identified Biomarkers for Ovarian Cancer

Exosomes

Exosomes are membrane-bound vesicles that are released by various types of cells through endocytosis, and they can be visualized using electron microscopy [2]. These exosomes carry a range of molecules, including proteins, metabolites, RNAs, DNAs, and lipids, and play a key role in cell communication. They can be detected and isolated using various labels, particularly cell surface proteins that are unique to the originating

cells. MAGE3/6 proteins are notable cell surface biomarkers specifically associated with ovarian cancer [22]. Recent clinical trials have shown that exosome levels are three to four times higher in ovarian cancer patients compared to healthy individuals [23]. Although exosomes are considered ideal biomarkers for cancer detection due to their distinctive properties, significant progress is still needed to develop exosome-based diagnostic assays.

Circulating tumor DNA (ctDNA)

Circulating tumor DNA (ctDNA) enables non-invasive detection of mutations in ovarian cancer, such as PIK3CA and KRAS, with potential applications for individual diagnosis and prognosis in liquid biopsies. Unlike lymphocyte DNA, cfDNA has a distinctive fragmented size [6]. ctDNA is likely to be abundantly present in serum due to its small molecular size and the fact that tumors often metastasize via the bloodstream [12]. Swisher et al. identified tumor-specific TP53 mutations in cfDNA using traditional PCR, achieving a 30% detection rate in tube or serum samples. ctDNA analysis holds promise as a non-invasive method for identifying cancer-specific mutations at various stages [6]. Advanced sequencing technologies, such as tagged amplicon sequencing (TAm-Seq) and duplex sequencing, improve ctDNA detection with high sensitivity (down to 2 allelic fragments) and specificity (97% for TAm-Seq). When combined with CA125 in a multi-cancer study, ctDNA demonstrated a high sensitivity of 98% for detecting ovarian cancer, particularly in advanced-stage tumors [22]. ctDNA offers valuable insights for risk assessment and monitoring ovarian cancer progression. Genomic profiling often reveals mutations in TP53, ARID1A, KRAS, and PIK3CA. The analysis also suggests that ctDNA could act as an independent risk factor and a potential biomarker for assessing ovarian cancer prognosis [24].

MicroRNA (miRNA)

The study of the microRNA (miRNA) class has garnered significant attention among all small non-coding RNAs (sncRNAs) to date. Currently, over 2800 human mature miRNAs have been identified and are registered in miRbase Release 22. miRNAs play a crucial role in post-transcriptional regulation of gene expression by binding to complementary targets. Depending on where they bind, they can either repress or degrade the target [25]. miRNA genes are transcribed to produce miRNA, which is processed into pre-miRNA, further processed in the cytoplasm to form a miRNA duplex. The mature miRNA regulates gene expression by targeting mRNA for degradation or translational suppression, based on miRNA–mRNA complementarity [6]. Aberrant miRNA expression in ovarian cancer (OC) has been linked to chemoresistance, including miRNAs such as let-7e, miR-30c, miR-125b, miR-130a, miR-335, miR-340, miR-381, and miR-520f [26]. Changes in miRNA expression in OC correlate with disease stage, treatment response, and overall survival. miR-21, miR-200a, and miR-200c have diagnostic and prognostic significance, while let-7f and miR-141 are associated with poorer progression-free survival. miR-193a functions as a tumor suppressor [27]. In a study by Yokoi et al., distinguishing early-stage ovarian cancers from benign tumors was achieved with a sensitivity of 86% and specificity of 83% using a panel of eight miRNAs. Similarly, miRNAs were detected in exosomes isolated from cultured ovarian cancer cell lines [6].

Conclusion

In conclusion, the early detection of ovarian cancer remains a significant challenge due to its asymptomatic nature in the early stages and the limitations of current diagnostic methods. However, advancements in biomarker research, including the identification of circulating tumor DNA (ctDNA), microRNAs, exosomes, and genetic alterations, offer promising avenues for improving diagnostic accuracy and prognosis. The integration of these biomarkers with existing methods like CA-125 testing holds potential for more sensitive

and specific detection, particularly in the early stages of the disease. Furthermore, the ongoing exploration of genetic mutations, epigenetic changes, and novel biomarkers provides a more comprehensive understanding of ovarian cancer biology, which could lead to better patient management, personalized treatment strategies, and improved survival outcomes. Continued research and clinical validation of these biomarkers will be crucial in transforming ovarian cancer screening and early detection approaches, ultimately reducing the disease's high mortality rate.

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