Indian Journal of Pharmacy Practice., 2024; 17(1):17-20.
https://www.ijopp.org

Review Article

A Review on Emerging Biomarkers for Early Detection of Ovarian Cancer

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ABSTRACT

Ovarian cancer is a serious and complex disease that primarily affects the ovaries. Detecting it in its early stages is important for successful treatment and improved outcomes. While common symptoms such as abdominal pain, bloating, and changes in bowel or urinary habits may raise suspicion, they are often nonspecific, making early diagnosis challenging. Age, family history, and gene mutations are some common risk factors. Emerging biomarkers for early detection of ovarian cancer are CA-125, HE4, osteopontin and genetic testing. Medical professionals usually perform a combination of imaging tests and biopsy to confirm the presence of ovarian cancer. Surgery, chemotherapy, and targeted therapy are some of the possible treatments that can be chosen depending on the stage and type of cancer. Early detection and efficient treatment depend on regular checkups and awareness of possible signs.

Keywords: Ovarian cancer, Detection, Risk factors, Biomarkers.

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Received: 12-10-2023;
Revised: 24-11-2023;
Accepted: 07-12-2023.

INTRODUCTION

Ovarian cancer is a formidable and often deadly disease that poses a significant threat to the health and well-being of women worldwide. This malignancy originates in the ovaries, which are crucial reproductive organs responsible for producing eggs and hormones. Ovarian cancer is a complex and multifaceted condition that presents numerous challenges in terms of diagnosis, treatment, and management.[1] It represents the seventh most commonly diagnosed cancer among women in the world with a 5-year survival rate of 46%. The following are the American Cancer Society's projections for ovarian cancer in the US in 2023: An estimated 19,710 women will be newly diagnosed with ovarian cancer. The estimated 13,270 female deaths from ovarian cancer.[2] Unlike some other cancers, ovarian cancer is notorious for its insidious nature, often remaining asymptomatic in its early stages. This stealthy development frequently leads to late-stage diagnosis, when the disease has already spread to other parts of the body, making it more challenging to treat effectively. As a result, ovarian cancer is associated with a high mortality rate and ranks among the leading causes of cancer-related deaths in women This disease encompasses several different types of ovarian tumors, each with its unique characteristics and treatment approaches. In terms of origin, etiology, molecular changes, risk factors, and prognosis, epithelial OC is the most common pathologic subtype. It has five primary histotypes. Rare hereditary mutations with high- to moderate-penetrance levels cause genetic vulnerability to develop.[3] A mix of both genetic and epigenetic changes, plus increasing genetic diversity found in tumor cells as cancer progresses, are the major factors hindering a cure.[4]

Nonetheless, from 20% to 40% of patients show no response to this primary therapy. Moreover, 80% of patients who exhibit a positive initial response, especially those with the subtype classified as High-Grade Serous Ovarian Cancer (HGSOC), develop a platinum-resistant recurrence over time.[5] Given the complexity of ovarian cancer, ongoing research aims to improve early detection methods and develop more effective treatment strategies.[6]

Additionally, raising awareness about the risk factors and symptoms of ovarian cancer is crucial for earlier diagnosis and better outcomes for those affected by this challenging disease. This review article comprises the risk factors and different biomarkers for early detection of Ovarian Cancer.

Risk Factors

There are various risk factors associated with ovarian cancer. It mostly affects postmenopausal women, where increasing age is associated with increased incidence, advanced stage of the disease, and lower reported survival rates. Parity plays a protective role according to several case-control studies with higher age at childbearing associated with reduced risk of ovarian cancer. The strongest risk factor for ovarian cancer is a positive family

DOI: 10.5530/ijopp.17.1.3

history of breast or ovarian cancer, while a personal history of breast cancer also increases the risk. The most commonly seen risk factors are:

- Age: Ovarian cancer is rare in women younger than 40. Most ovarian cancers develop after menopause. The risk increases significantly after the age of 50.
- Gene mutations: Certain genetic mutations, such as BRCA1 and BRCA2, are associated with an increased risk of ovarian cancer. Women carrying these mutations are more likely to develop the disease.
- History of breast or colorectal cancer: Women who have had breast cancer, colorectal cancer, or certain other cancers have a slightly increased risk of ovarian cancer.
- Endometriosis: A condition where tissue similar to the lining of the uterus grows outside the uterus, linked to an increased risk of ovarian cancer.
- Family history: A strong family history of ovarian cancer or certain other cancers, such as breast or colorectal cancer, may increase the risk.
- Never been pregnant: Women who have their first full-term pregnancy after age 35 or who have never been pregnant may be at slightly higher risk.
- Hormone therapy: Long-term use of estrogen alone or with progesterone after menopause may increase the risk, especially in women who have used it for five years or more.
- Obesity: Obese women (those with a Body Mass Index [BMI] of at least 30) have an increased risk of developing ovarian cancer, but not necessarily the most aggressive types, such as high-grade serous cancer.[7,8]

Biomarkers

Early detection of ovarian cancer is challenging, but several biomarkers have been studied for this purpose. The most common biomarkers are discussed below.

Transvaginal sounds

Doctors utilize a specific kind of pelvic ultrasound called a transvaginal ultrasound, also known as an endovaginal ultrasound, to look at the female reproductive system. The uterus, fallopian tubes, ovaries, cervix, and vagina are included in this.[9] To view the ovaries more closely, this imaging procedure entails inserting an ultrasound probe into the vagina. All ultrasound transducers send out high-frequency sound waves, which are reflected in various ways by the body's soft tissues, structures, and organs. These sound waves are transformed into electrical impulses that create a moving image on a screen. It is incredibly safe because it causes no discomfort and uses no radiation. There are no injections unless your doctor has specifically requested one. The high-frequency sound waves ensure images show very high detail, capable of looking at the very tiniest parts of the body.[10] It may help locate ovarian anomalies or masses. They can also evaluate- the shape, position, and size of the ovaries and uterus, the thickness and length of the cervix blood flow through the organs in the pelvis the shape of the bladder, and any changes in the thickness and presence of fluids near the bladder or in the fallopian tubes and myometrium.[11]

CA-125

A key factor in the setting of ovarian cancer is the protein biomarker CA-125 (Cancer Antigen 125). This glycoprotein, which is frequently assessed in the blood, is located in the cells lining the female reproductive canal. The reference range of CA-125 is 0-35 units/mL. Most women with OC have elevated CA125 levels in their serum, however, women with occult tumors found during preventive surgery and in around 50% of clinically recognized stage I cases have pre-operative serum CA125 levels that are below the usual cutoff of 35 U/mL.[12]

It is recommended to combine CA-125 with transvaginal ultrasound every 6 to 12 months for those at very high risk. However, CA-125 levels can also be elevated for other reasons, such as endometriosis, menstruation, pregnancy, uterine fibroids, or benign ovarian cysts.[13]

Human Natural Killer (NK) cells can be inhibited by CA125 from launching cytotoxic attacks, and this suppression is associated with a marked decrease in CD16 expression on the NK cell surface. It is possible to inhibit cytotoxic responses *in vitro* at native purified CA125 concentrations that are 10,000-100,000 U/mL lower than those found in the tumor microenvironment, which suggests that CA125 derived from tumors acts as a suppressor of the anti-tumor immune response. CA125 modulates NK cell-mediated cytotoxicity and tumor-derived CA125 may act as a suppressor of the immune response that is directed against ovarian tumors.[14]

With the incidence of elevation coinciding with the clinically diagnosed stage, higher serum CA 125 levels are present in up to 80% of women with ovarian cancer of epithelial origin.[15]

HE4

The epithelium of the distal epididymis is where the whey acidic protein known as HE4 (Human Epididymis Protein 4) was initially discovered.[16] For more accurate ovarian cancer detection, this protein is frequently combined with CA-125 and tested in the blood.[17] The reference range of HE4 is 85 pmol/L which becomes 73 pmol/L and 93 pmol/L for pre and post-menopausal subgroups respectively.[18]

In comparison to healthy and benign gynecological controls, HE4 is higher in women with EC. Ovarian cancer cells are encouraged to migrate and adhere when exposed to HE4 (*in vitro* studies).

Tumor development was inhibited in *in vitro* tests where HE4 was silenced. The proliferation of cancer cells both *in vivo* and *in vitro* was stimulated by endometrial cancer cell lines' overexpression of HE4, providing evidence that HE4 is involved in the development of tumors.[19] It was discovered that HE4 functions as a protease inhibitor, reducing the activity of the serine proteases Prss35 and Prss23 that break down the type I collagen that builds up in kidney fibrosis. Inhibition of fibrosis by HE4-neutralizing antibodies was shown in three mouse models, suggesting HE4 as a potential therapeutic target for renal fibrosis.[20]

By using meta-analysis, it was determined that HE4 had an overall diagnostic accuracy of 0.74 and a pooled specificity of 0.87 for distinguishing benign gynecological disorders from malignant ovarian tumors.[21]

Genetic testing

The majority of hereditary ovarian cancer can be attributed to germline BRCA1 and BRCA2 pathogenic variants. HBOC is an inherited genetic condition. This means that the cancer risk is passed from generation to generation in a family. There are 2 primary genes linked with most families who have HBOC: BRCA1 and BRCA2. A "mutation," or harmful genetic change, in either BRCA1 or BRCA2, gives a woman an increased lifetime risk of developing breast and ovarian cancers.[22]

BRCA1 and BRCA2 are responsible for producing proteins that are meant to repair damaged DNA. These types of genes are sometimes referred to as "tumor suppressor" genes because when they function well, they can repair damaged DNA and keep abnormal cell growth in check. When they are damaged, as with BRCA1 and BRCA2 mutations, they are unable to repair damaged DNA, which can lead to errors in proteins and possibly cancer. A positive result means you carry a gene mutation that increases your risk of cancer.[23] Women with BRCA1 mutations have a significantly higher risk of developing ovarian cancer, with estimates suggesting that the risk may be as high as 44%. Women with BRCA2 mutations also have an increased risk, although it is somewhat lower, estimated at around 17-27%. One notable characteristic of BRCA-associated ovarian cancer is that it often occurs at a younger age than sporadic cases of ovarian cancer, especially before menopause.[24]

Osteopontin

OPN is a glycoprotein found in various tissues and while the exact mechanism of action of OPN in cancer, including ovarian cancer, is complex and not fully understood, it is believed to contribute too many processes related to tumor development and progression.[25]

Cell adhesion and migration

OPN has adhesive properties that allow it to interact with cell surface receptors. In ovarian cancer, elevated levels of OPN can enhance adhesion of cancer cells to the ECM and promote their migration and invasion into surrounding tissues. This can help the cancer spread to other organs.[26]

Inflammation and Immune Regulation

OPN is involved in the regulation of inflammation and immune responses. In the tumor microenvironment, OPN can modulate immune cell activity, affecting the balance between anti-tumor and pro-tumor immune responses. This can affect the immune system's ability to recognize and eliminate cancer cells.

Angiogenesis

OPN has been linked to the promotion of angiogenesis, the process by which new blood vessels form to supply nutrients and oxygen to growing tumors. By facilitating angiogenesis, OPN may contribute to the continued growth and survival of ovarian cancer cells.[27]

Matrix remodeling

OPN can influence the remodeling of the ECM, which is crucial for cancer cell invasion and metastasis. It can alter the expression of ECM components and enzymes involved in ECM degradation, making it easier for cancer cells to infiltrate and invade surrounding tissues.

Interaction with signaling pathways

OPN can interact with various signaling pathways within cells, including cell survival, proliferation, and migration. Dysregulation of these pathways by OPN may contribute to cancer progression.[28]

CONCLUSION

It's crucial to remember that no one biomarker is sufficiently sensitive or specific for early detection on its own. As a result, the risk of ovarian cancer is often assessed using a combination of tests and risk assessment tools, together with clinical examination and imaging and, if necessary, these tools are used to direct subsequent diagnostic procedures. Women who are at risk or who have troubling symptoms need to see their doctor frequently for checkups and consultations. Clinical trials often involve studying the genetic and molecular characteristics of tumors, which can help build individualized treatment plans that are based on each patient's unique cancer profile. Clinical trials enable researchers to test novel cures, medications, and treatments, perhaps paving the way for the creation of more efficient and specific ovarian cancer treatments. Including patients who have experienced recurrence in clinical trials will shed light on novel therapeutic approaches. It is essential to raise awareness about the importance of early detection and the significance of clinical trials in driving innovation in ovarian cancer care. By supporting research efforts and advocating for improved screening methods, we can move

closer to a world where ovarian cancer is not the devastating disease it is today.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ABBREVIATIONS

OPN: Osteoponti; **ECM:** Extracellular matrix; **BRCA1:** Breast Cancer gene 1; **BRCA2:** Breast Cancer gene 2; **HBOC:** Hereditary Breast and Ovarian Cancer syndrome.

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Cite this article: Fernandes B. A Review on Emerging Biomarkers for Early Detection of Ovarian Cancer. Indian J Pharmacy Practice. 2024;17(1):17-20.