**Minireview Article**

**EMERGING TECHNOLOGIES IN OVARIAN CANCER: ADVANCEMENTS IN TREATMENT STRATEGIES**

**ABSTRACT:**

In the Western world, ovarian cancer is the most fatal and second most prevalent gynecologic cancer. Ovarian cancer is usually diagnosed in an advanced stage. Ovarian cancer is a dangerous tumor that affects women’s reproductive systems and poses a significant threat to their health. Researching ovarian cancer is tough due to its genetic heterogeneity, complex pathophysiology, restricted availability of human tissue, unique metastatic mechanisms, and unknown genesis. To gain anatomical knowledge of the pathophysiology of ovarian cancer, novel experimental models must be created. The WHO identifies six main types of ovarian cancers, specifically epithelial tumors which are serous, mucinous, endometrioid, clear cell, seromucinous, and Brenner carcinoma. Although the exact etiological pathways are still undetermined, it is mostly believed that the ovarian surface epithelium is the main site of most ovarian carcinoma. Abdominal discomfort and distension usually appear for a few months in postmenopausal women. Less is known about the potential ovarian cancer risks connected to other gynecological disorders and operations, including as polycystic ovarian syndrome, pelvic inflammatory disease, and surgery. Environmental and lifestyle variables include exposure to powdered talc and asbestos, as well as smoking cigarettes, are other possible risks. The epidemiology offers indications about the cause, early identification, primary prevention, and treatment approaches.A diverse category of neoplasm ovarian cancer is typically categorized according to their kind and level of differentiation. It is becoming clear that every major histological form of ovarian carcinoma has distinctive genetic abnormalities that deregulate particular signaling pathways in the tumor cells, even if the present clinical therapy of this heterogeneity is mostly ignored. Furthermore, the molecular etiology of low-grade and high-grade cancers seems to differ significantly within the most prevalent histological categories. Ovarian carcinoma is a worldwide issue that lacks an efficient screening method and is usually discovered at an advanced stage. For newly diagnosed cancer, platinum-based chemotherapy and cytoreductive surgery are the standard treatments.

**KEYWORDS:** Ovarian carcinoma, tumor, pathophysiology

**INTRODUCTION:**

Ovarian cancer is the seventh most prevalent carcinogenic tumor and the fifth major cause of mortality in female reproductive illnesses. As life expectancy increases, the number of cases detected continues to rise. However, prevention measures and effective therapies still need to catch up. The condition is often not recognized until it has evolved, leading to significant hospitalization and fatality rates **[1].** In a single year, 220,000 new cases of ovarian cancer are identified, and approximately 140,000 women suffer from this cancer globally. Ovarian cancer has multiple subtypes that differ in molecular biology and clinical behavior. Despite limited treatment options over the last decade, overall survival remains minimal. Targeted therapies have been developed due to an increase in understanding of the disease's molecular biology **[2].** The most common cancer in women that results in ovarian cancer death **[3].**

Implementing cell lines with the same characteristics is crucial for the early phase of research. Cell lines are chosen based on the individual history, histopathological type at evaluation, gene sequence, and signal pathways. Cell lines are naturally derived by using carcinomas at various stages of pathways. Cell lines were originally generated by using carcinomas at various stages of the disease’s progression based on histology studies. These cell lines are primarily researched in vitro, beneath the standard cell cultural practices **[4].** Cell lines employed in studies frequently lack in identifying the genetic components typically associated with malignancies. The study explores the potential of such cell lines for preliminary research **[5].** The developed cell lines have been identified by morphological cell culture, surface marker expression, chromosomal evaluation, and cell survival **[6].**

The ovarian surface epithelium or surface epithelial inclusion cysts are hypothesized to be the precursors of ovarian carcinoma, an epithelial malignancy. Because ovarian cancer has a molecular genesis, it is possible to develop novel treatment targets and biomarkers that facilitate advanced diagnosis. Typically, ovarian epithelial cancers are identified solely by their cell structure.**[7].**

**EPIDEMIOLOGY AND RISK FACTORS:**

The epidemiological studies of ovarian cancer (ESOC) emerged in 1998 to centralize and evaluate individual participant data from all ovarian cancer studies, examining the risks related to hormonal and various other causes **[8].** Having ancestry of ovarian malignancy is a major threat. First-degree descendants of individuals have a 3 to 7 times greater chance of developing it, especially if many families are affected and the first sign occurs at an early age **[9].** In 2020, there were 21,400 new instances of ovarian malignancy, corresponding to 1.2% of cancer instances. Females have a 47.3% five-year survival rate **[10].** Epithelial ovarian cancer has been regarded as a single disease in epidemiological and research studies, including those that corroborate established risk factors like infertility and lack of oral contraception. Histologic kinds have not been distinguished. Risch first reported variances in warning signs for epithelial ovarian cancer based on histology **[11].**

Despite an increased understanding of ovarian cancer’s indications, the accuracy of their identification remains extremely poor. Ovarian cancer is sometimes referred to as a “silent killer” since most patients receive the diagnosis at the advanced stages, with no noticeable signs in the initial stages. Over the past few years, a lot of studies have been done on using symptoms to identify ovarian cancer. Patients with ovarian cancer may experience signs for months before being diagnosed **[12].**

Women with pathogenic variants in BRCA1 or BRCA2 are at a higher danger of developing ovarian cancer over their lifetime. Carriers of BRCA1 mutations have a 40% lifetime potential for developing ovarian cancer, whereas those with BRCA2 mutations have a 20% risk **[13].** Whereas genetic variants in breast cancer BRAC1 and BRCA2 have been linked to 20% of ovarian cancer cases, most of them remain isolated **[14].**

Earlier investigation has found an important positive association between menopausal hormone therapy (MHT) and endometrioid malignancies, but not always. Studies on non-reproductive exposures have found no persistent variations in histological subtypes based on BMI, physical activity, consumption of alcohol or tobacco use **[15].**

There is a weak established link between BMI or obesity and ovarian cancer. Obesity may have no relationship with ovarian cancer, which is subtype-specific. Elevated BMI of 30 or above among post-menopausal females has been linked to a high risk of developing Ovarian malignancy relating to limited cohort studies **[16].**

**TECHNOLOGIES USED IN OVARIAN CANCER CELL LINES**

**XENOGRAFTS:**

Xenografts mimic the primary tumor's variability while retaining its properties. The transplantable ovarian tumor tissues with the same genetic and biological characteristics as the original patients. The research suggests that using this can lead to new therapeutic options for ovarian cancer **[17].**

At the moment, the main focus on novel cancer therapy is the in vitro testing of medications utilizing human cancer cell lines and their xenograft models. However, recognized cancer cell lines and their xenograft models do not precisely mirror the original phenotypic or gene features of distinct cancer types since the cell lines have irrevocably lost critical biological qualities of their original organ location. By promptly transplanting tumor tissue removed after surgery into immunodeficient mice, patient-derived xenografts (PDXs), as opposed to cell lines and their xenografts, can be created directly from a patient’s tumor tissue without the need for previous in vitro cultivation.

PDX models can be regarded as effective instruments for pre-clinical investigations of targeted therapy approaches that close the gap between laboratory bench discoveries and clinical implementation as they can faithfully recreate the complexity and heterogeneity of the patient’s tumor. In precision medicine, the importance of PDX is highlighted for cancer types that exhibit heterogeneity. Preclinical drug testing and biomarker discovery for several malignancies, including breast, lung, pancreatic, brain, and colon cancers have been conducted using PDX models**[18].**

The tumor dissociation kit was used to eliminate mouse cells from patient-derived xenograft tumors[PDX] and extract only human tumor cells. PDX tumor tissues were extracted and processed under septic circumstances, eliminating fat, fibrous, and dead tissue while keeping usable tumor material. To dissociate tumor tissue into single cells, 1g of healthy tissue was employed and PDXs were incubated with digesting enzymes for 60 minutes at37°C. after incubating with digestive enzymes, these samples were centrifuged, restored in a new medium, and tallied **[19].**

The combination of antibodies suppresses the growth of human ovarian cancer cells in culture in dormant xenografts **[20].**

**FLOW CYTOMETRY:**

The flow cytometric approach can detect tumor cells in samples with low quantities **[21].**

Flow cytometry is used to assess the DNA content of human neoplastic cell populations and determine the percentage of cells in various phases of the cell cycle. Circulating tumor cells released by ovarian cancer, disseminated to remote organs through the bloodstream, majorly aided the spread of ovarian cancer. The circulating tumor cells of epithelial ovarian cancer of their significance **[22].**

An established intracellular staining technique of PBMCs(Peripheral blood mononuclear cells) maintained their safe at day in 0.4% paraformaldehyde at 4°C and then stained. Antibody molecules for single color cytometry contained rabbit. During tests, a single-color flow technique was employed to optimize excitation settings. Later, a dual stain procedure was optimized with antibodies from several species. These techniques are used to analyze biomarkers like MRE11(A protein expression by immunohistochemistry)**[23].**

**2D AND 3D CELL CULTURE SYSTEMS:**

Three-dimensional (3D) cancer models are revolutionizing research by allowing the recapitulation of an in-vivolike response through the use of a more complex and physiologically appropriate system in the laboratory than typical monolayer cultures. For instance, ovarian cancers are often deadly drug-resistant and would greatly benefit from the improved modeling that 3D cultures simulate. However, existing models often fail to provide the anticipated response, when the lack of standard process limits repeatability and procedures set. This meta-analysis aims to assess the extent of 3D OvCa models to date because of the variability in genetic profiles that a wide variety of 3D cultures exhibit**.[24].**

Sustain ovarian tissue is a successful approach for sustaining female fertility and maintain endocrine function. Several studies have used ovarian tissue culture to improve transplant life span and reduce neoplastic cell reimplantation. This is a standard (2D) culture to an alginate matrix (3D) guideline for ovarian tissue culture **[22].** Experiments utilized both 3D OvCa models and 2D analyses. Also, information from sequencing arises and RNA sequencing is accessible **[25].**

Research has demonstrated that 2D and 3D cell culture models are effective for studying ovarian cancer in vitro, capturing many characteristics of the illness across numerous levels of complexity. Having multiple possibilities is beneficial since no single model, no matter how complicated, can fully stimulate ovarian cancer. Combining results from several methodologies can provide an increased awareness of the process under consideration **[26].**

**LENTIVIRAL VECTORS:**

Lentiviral vectors are frequently employed in investigations into biology, operational genomics, and therapy with genes. Lentiviral vectors (LVs) work efficiently for transferring genes in both proliferating and non-dividing cells **[27].**

Local gene therapy could be a therapy for ovarian carcinoma, a potentially fatal cancer, due to disease containment within the peritoneal cavity in most patients. Lentiviral vectors, as potentially capable of stable transgene expression, may be useful to vehicle therapeutic agents for long term production in these cancers. When compared to gene transfer by other carriers, the transfer of genes by lentivirus vectors is more advantageous. It is possible for cells to become infected even if they are actively dividing or fully differentiated, they can still become infected. Furthermore, lentiviruses quickly integrate into the host genome and don’t produce gene products**[28].**

Lentiviral vectors were come up using triple transfection of 293 T-cells and successfully transduced the human ovarian cancer cell line IGROV-1 in vitro. Initial titration testers with several vectors on 293 A-Cells revealed titers. After incubating samples of a vector containing the residues at 37°C for different durations and testing their transmission on IGROV-1 cells.

The results showed that the viral particle's half-life in vitro was similar to that in vivo **[29].**

**CRISPR/CAS 9 GENE EDITING:**

CRISPR/CAS 9 gene editing can be improvised in SKov3 ovarian cancer cell line culture and examine its impact on self-factors associated with cancer development and death **[30].**

In the realm of cancer research, CRISPR-Cas9 has been extensively utilized to generate animal models of cancer and identify gene functions. Additionally, CRISPR-Cas9 has demonstrated significant promise in cancer gene therapy, including the ability to disrupt mutations the promote tumor growth and deactivate oncogenic virus genes by introducing insertion and deletion mutations(indels) at particular cancer cell genome loci.

The crucial nuclear enzyme of DNA methylation, DNA methyltransferase 1(DNMT1), is a crucial molecular target for cancer epigenetic treatment.

The aberrant overexpression of DNTM1 is essential for the upkeep of cancer stem cells and inactivates tumor suppressor genes. Furthermore, ovarian cancer growth, recurrence and resistance are all strongly correlated with DNTM1 and patients with poor prognoses have often had elevated DNTM1 levels. Contrary to this finding, a number of investigation’s have demonstrated that DNMT1 suppression reduced ovarian cancer resistance and growth. As a result, DNTM1 is a viable molecular target for the therapy of ovarian cancer. In a wide range of cell types and species, endogenous genes have been edited using CRISPR-Cas 9, a targeted genome editing technique. Thus, one possible strategy for ovarian cancer treatment is to modify the DNTM1 of ovarian cancer cells utilizing the CRISPR-Cas9 system**[31].**

Ovarian cancer SKov3 cells with lentivirus-encoded eGFP and eGFP-stable cells (SKOV-3eGFP+) were isolated using green fluorescence sorting. Fluorescence microscopy and flow cytometry studies revealed that inhibitor eGFP of expression as approximately 70% of SKOV-3eGFP+ cells. The genome modification efficiency was comparable to previous cationic lipids.

The CRISPR plasmid was modified to recognize DNMTI 1, and F-LP was employed to deliver the gDNMT1 plasmid and decrease DNMT1 expression in cancerous ovarian cells **[32].**

**CONCLUSION:**

Ovarian cancer is a serious condition often detected lately, but early diagnosis significantly improves the result. Advances in treatment and awareness, along with genetic testing for high-risk individuals are essential for better prevention and outcomes. Many technologies are used in the treatment of ovarian cancer some of them are xenografts, flow cytometry, 2D and 3D cell culture systems, lentiviral vectors, and CRISPR/CAS9 gene editing plays a crucial role in both detection and treatment. Technological advancements are essential to enhance early diagnosis and develop effective therapies.

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