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New Updates in Ovarian Cancer

Edited by Samuel Evans Adunyah



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Volume 14

Aims and Scope of the Series

The field of oncology has undergone extraordinary change and progress over the past several decades. Today, information is evolving at a rapid rate, with standards of management far different than standards of care applied during the training of most practicing oncologists. Oncology practitioners in all disciplines must remain current to optimize patient care. Basic and translational science remain critical in developing process improvements for patient care. The closer we understand the mechanism, the more we can improve targeted therapies and apply them to patient care. The pace of information is moving faster than at any previous time in history, and all oncology disciplines must remain current to provide excellent service to patients. The modern oncologist must be fluent in using big data and the volume of information generated in clinical trials. As we move closer to personalized patient care based on genomics and molecular biomarkers, the modern oncologist has to be nimble in assessing all available information and how this would be applied to each patient, balanced by the clinical status and medical co-morbidities of each patient. Targeted therapies can bring new and different sequelae, and oncology teams need to remain fluent in managing the consequences of therapy and primary management. In this book series, we will present how modern care has progressed in multiple disease areas and how modern oncology teams need to adapt in order to manage the cancer patients of today successfully. Surgery, radiation therapy, and medical oncology are practiced today with the support of exceptional modern technology, and in this series, we will review how these improvements are applied to each disease site to maintain excellence in patient care.

Meet the Series Editor



Dr. FitzGerald is the professor and chair of the Department of Radiation Oncology at UMass Chan Medical School in the USA. He serves as one of the principal investigators of the Imaging and Radiation Oncology Core (IROC) service for the National Cancer Institute clinical trials program and is directly involved in the quality assurance of clinical trials in the National Clinical Trials Network (NCTN). Dr. Fitzgerald manages NCTN clinical trials with a real-time pre-therapy review of imaging and radiation therapy treatment objects to ensure the care plan complies with study objectives and the patient stage has been assigned to the correct study. His basic science interest is in hematopoietic stem cell biology and cellular adhesion molecules as they pertain to therapeutic resistance and mitigation of injury from therapy.

Meet the Volume Editor



Dr. Samuel Evans Adunyah received a BSc (Hons) in Biochemistry from Kwame Nkrumah University of Science and Technology, Ghana, in 1978, followed by postgraduate research training at ETH-Zurich, Switzerland. He has a Master's in Biochemistry from Oklahoma State University and a Ph.D. in Biochemistry from the University of Louisville, Kentucky, USA. He is a Tenured Professor of Biochemistry and Cancer Biology and Distinguished Chair of Biochemistry, Cancer Biology, Neuroscience, and Pharmacology at Meharry Medical College, USA. His research focuses on how cytokines regulate cancer growth. He is the PI/PD of an NCI U54 grant to study Cancer Health Disparities and of an American Cancer Society grant to train more minorities in cancer research. He has co-authored several book chapters on cytokines and edited a book on the tumor microenvironment.

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Preface

Ovarian cancer ranks second among the deadliest gynecological cancers in women. Globally, over 210,000 women die every year from ovarian cancer. As such, there is a strong global interest in learning more about this disease. Hence, providing ongoing updates on various aspects of this disease is extremely important. The content of this book is intended to provide readers with new updates on ovarian cancer. The subject matter covered in this book includes a global epidemiological report on ovarian cancer, basic science aspects of ovarian cancer, ovarian cancer risk factors, ovarian cancer clinical symptoms, new biomarkers for ovarian cancer detection, and new treatment strategies for ovarian cancer. The book will also cover some aspects of biological factors and signaling mechanisms that are utilized by chemokines and other biological factors to regulate ovarian cancer development, progression, and differentiation. In addition, the book discusses the roles of factors that affect ovarian cancer patient survival.

The chapters in this book include (1) *Introductory Chapter: New Updates in Ovarian Cancer*, (2) *Tumor Microenvironment of Epithelial Ovarian Cancer*, (3) *Secondary Prevention of Ovarian Cancer*, (4) *Impact of Chemokine Axes on Survival and Tumor Progression in Ovarian Cancer*, (5) *Biomarkers in Ovarian Cancers*, and (6) *Perspective Chapter: The Use of Fluorescence in Ovarian Cancer Surgery*. The book is expected to enrich current knowledge of ovarian cancer and to educate readers outside the ovarian cancer field with vital information about this disease. Lastly, the information provided in this book will help stimulate further global discussions on ovarian cancers from basic and clinical sciences aspects to ovarian cancer anti-drug development to combat this deadly gynecological cancer in women.

First, I would like to express my sincere gratitude to all the international scientists, including Dr. Deok-Soo Son, who contributed vital chapters to make this new book project successful. I greatly enjoyed working with them. Next, I want to thank the Publishing Process Manager, Ms. Karmen Daleta at IntechOpen, for her efficient, effective, and outstanding technical assistance throughout the preparation of this book. Her critical and indispensable advisory role is sincerely appreciated. Lastly, I want to express my gratitude to all the editors and technical and publishing staff at IntechOpen for their invaluable roles in preparing this vital book on ovarian cancer.

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Chapter 1

Introductory Chapter: New Updates in Ovarian Cancer

Samuel Evans Adunyah

1. Introduction

1. This introductory chapter succinctly introduces the main subject matter of this book, which focuses on new updates on ovarian cancer.

Cancers of the ovary are considered the most common forms of neoplasia in women. Among all the cancers that affect the genital tract of females, ovarian cancer incidence ranks only second to carcinoma of the cervix and the endometrium [1, 2].

In the United States, ovarian cancer accounts for at least 6% of all cancers in females and ranks fifth among the most common forms of cancer in women, excluding skin cancer. Unfortunately, because ovarian cancers cannot be detected early during their development, they constitute a disproportionate percentage of all cancer deaths among U.S. women [3]. There are many types of ovarian cancer, including both benign and malignant, with approximately 80% being benign and occurring mostly in young women between the ages of 40 and 69 years. Globally, ovarian cancer forms about 1.1% of all cancer deaths in women. The Center for Disease Control (CDC) and the American Cancer Society (ACS) indicated that in 2025 there were 20,890 new ovarian cancer diagnoses and 12,720 ovarian cancer deaths in the United States. Global estimates show that about 207,000 women die annually from ovarian cancer [3, 4].

1.1 Ovarian cancer statistics: Top ten countries with ovarian cancer incidence and death rates

Ovarian cancer affects all the continents, including Africa, Asia, Europe, and South America. In Africa, ovarian cancer is quite common in the sub-Saharan countries. According to the 2022 World Cancer Research Fund, Asia recorded the highest ovarian cancer incidence and death rates in comparison to any other continent. In 2022, globally, there were a total of 324,603 new ovarian cancer diagnoses. Notably, the ranking order among the top ten countries with ovarian cancer incidence was China (61,060) > India (47,333) > US (21,179) > Indonesia (15,130) > Russia (14,606) > Japan (10,693) > Brazil (7,710) > Germany (7,547) > Philippines (6,453) > UK (6,390). Certainly, the incidence in China, India, and Indonesia together exceeded 129,000 new diagnoses. During the same year, a total of 206,952 ovarian cancer deaths were recorded globally. The ranking order of the top ten countries with the highest ovarian cancer death rates was India (32,978) > China (32,645) > US, (13,273) > Indonesia (9,673) > Russia (9,333) > Germany (5,366), Brazil

(5,235) >UK (4,159) >Philippines (4,073) [3–5]. The global ovarian cancer incidence is likely to continue to increase by 40% within the next 15–20 years, with most increases likely to occur in Asia and Africa [4–6].

1.2 Ovarian cancer types

The diagram in **Figure 1** depicts the site in the female reproductive system where ovarian cancer develops. The diagram in the figure shows ovarian cancer involving the right ovary.

There are several types of ovarian cancer, which include epithelial ovarian cancer, germ cell ovarian cancer, stromal cell ovarian cancer, and carcinoma. Among these, epithelial ovarian cancer is the most common, constituting 90% of all ovarian tumors, with the remaining types being rare. It is well known that epithelial ovarian cancer begins in the surface layer covering the ovary. There are different types of epithelial ovarian cancers, including high-grade serous, endometrioid, clear cell, low-grade serous, and mucinous [6, 7]. Ovarian germ cell tumors are considered to be teratomas and dysgerminomas, while stromal tumors are considered granulosa tumors [7]. The germ cell ovarian tumors start in the ovarian cells that develop into eggs (germ cells). This type of ovarian cancer is rare but commonly affects young women who are in their early 30s [7].

The stromal cell ovarian cancers are very rare, and they originate from the connective tissues (stroma) of the ovaries [7]. Several different types of stromal cell ovarian cancers, which have been characterized, include granulosa cell tumors, Sertoli-Leydeg cell tumors, and sex cord stroma tumors [6, 7]. Stromal cell ovarian tumors are very rare and constitute 1.2% of all ovarian tumors [6, 7].

The diagram in **Figure 2** shows the various organs and tissues to which metastatic ovarian cancers (stages 3 and 4 ovarian cancers) metastasize. These major sites of

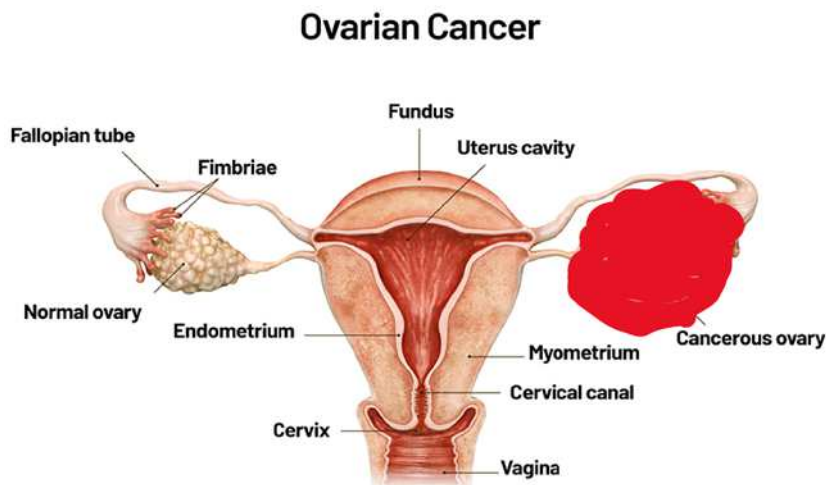


Figure 1.

Diagram of a female reproductive system showing ovarian cancer involving one of the ovaries. Modified from <https://www.saintjohnscancer.org/gynecology/conditions-we-treat/ovarian-cancer/>.

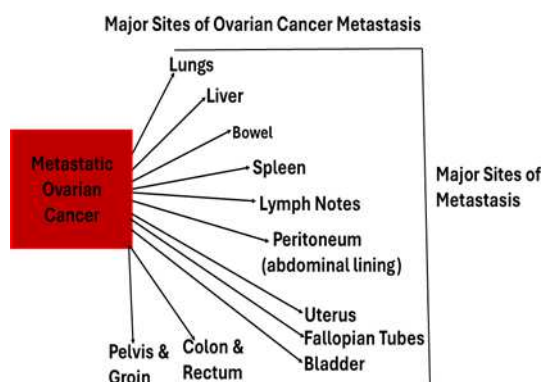


Figure 2.
 A diagram showing major sites where stages 3 and 4 ovarian cancers metastases.

ovarian cancer metastasis include the liver, lungs, bowel, spleen, lymph nodes, abdominal walls, colon and rectum, pelvis, groin, and omentum. Ovarian cancer rarely metastasizes to the brain, with ovarian cancer metastasis occurring in less than 3% of all advanced ovarian cancer cases [8].

1.3 Genes associated with ovarian cancer

Several genes are associated with the development and progression of ovarian cancers. It is well-known that BRCA1 and BRCA2 are strongly associated with an increase in a woman's risk of developing ovarian cancer. Inheritance of BRCA1 gene increases a woman's chance of developing ovarian cancer by 50%. Hence, a woman who develops BRCA1-type ovarian cancer also has an increased chance of developing BRCA1-type breast cancer. The TP53, PTEN, STK11, PALB2, and Lynch syndrome-associated genes are also known to enhance ovarian carcinogenesis [9]. These genes trigger malignant transformations among the ovarian epithelial cells and initiate the carcinogenesis processes leading to ovarian cancer. In addition to these genes, it is known that the PI3-KCa gene is altered in a number of ovarian tumors [7, 9].

1.4 Ovarian cancer incidence and death rates

A woman's lifetime chance of dying from ovarian cancer is about 1 in 143. According to 2018–2022 NCI data, 10.3 per 100,000 women were diagnosed with ovarian cancer per year, and the ovarian cancer death rate was 5.9 per 100,000 per year [4]. In 2018, Lindsey A. Torre et al. [3] reported that among women of various racial/ethnic groups in the US, the highest incidence of ovarian cancer was in Non-Hispanic White women. This was followed, in ranking order, by Alaska Indians > American Natives > Hispanics > Non-Hispanic Black women > Asian Pacific Islanders. The ovarian cancer death rates were highest in Non-Hispanic Whites followed in that order by Non-Hispanic Blacks > Alaska Indians > American Natives, Hispanics > Asian Pacific Islanders. According to the ACS, ovarian cancer incidence has declined by 2% per year since 2012 [5–8].

1.5 Ovarian cancer survival rates

The ovarian cancer survival rates depend on the various stages of the disease, the ovarian cancer types, and the age of the patient. Based on these factors, survival rates are as indicated in **Tables 1–3** below [4–6].

As mentioned earlier, the diverse types of ovarian cancers include epithelial ovarian cancer, germ cell ovarian cancer, and stromal cell ovarian cancer. Each type is associated with its own 5-year survival rate, as indicated by the National Cancer Institute (NCI), Center for Disease Control (CDC), and American Cancer Society (ACS). In the United States, the relative 5-year survival rate for all types of ovarian cancer is 51%.

1.6 Risk factors of ovarian cancer

There are many risk factors that predispose a woman to ovarian cancer. Most ovarian cancer risk factors are less clear than those for other forms of genital cancers in women. However, nulliparity and family inheritable mutations play a significant

Ovarian cancer stages	5-year survival rates	Comments
Stage I (localized)	93 %	The cancer has not spread outside where it started.
Stage II (regional)	71 %	The cancer has spread to nearby tissues and areas.
Stage III (distant)	41 %	The cancer has spread to distant organs, including the lymph nodes in the pelvic areas and abdomen.
Stage IV (Advanced)	15 %	The cancer has spread outside the ovaries to other parts of the body, including the liver, bones, lungs, and brain.

Table 1.
Stage-specific 5-year survival rates for ovarian cancer.

Ovarian cancer types	5-year survival rates
Epithelial ovarian cancer	49%
Germ cell ovarian cancer	93%
Stromal cell ovarian cancer	90%

Table 2.
Ovarian cancer type-specific 5-year survival rates.

Ovarian cancer patient's age	5-year survival rates
65 years and under	72%
65–79 years	54%
80 plus	34%

Table 3.
Age-specific adjusted ovarian cancer survival rates.

role in ovarian tumor development. There are mutations in many genes, including BRCA1 and ERB-B2, that are known to play a role. There are distinct types of ovarian cancer and their respective incidence among women in any country. Because the symptoms of the initial stages of ovarian cancer are, to a great extent, undetectable, it is exceedingly difficult to diagnose at the initial stages [7–9].

In addition to being influenced by certain genes, other factors, including chemokines, trigger multiple signaling pathways that culminate in ovarian cancer progression and a reduction in survival rates [10–12].

Other factors, including smoking, obesity, inactivity, and other sedentary lifestyle habits, all contribute to increasing a woman's risk of developing the less common histotypes of ovarian cancer. However, these factors do not appear to enhance a woman's risk of developing the common high-grade serous ovarian cancer. Hence, lifestyle modifications, including smoking cessation and weight loss, are more likely to reduce a woman's risk for rare ovarian cancers [13]. Also, factors such as surgery to remove certain reproductive organ(s), oral contraceptives, intrauterine devices (IUDs), breast feeding, and pregnancy can reduce ovarian cancer risks [14].

1.7 Current techniques for ovarian cancer diagnosis and treatment

There are many different techniques and approaches to achieving accurate ovarian cancer diagnosis. Traditionally, ovarian cancer diagnostic techniques include a combination of imaging, blood tests, and biopsy. Images generated by computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, positron emission tomography (PET) scan, and transvaginal ultrasound (TVUS) scan are dependable for detecting ovarian tumors and ovarian abnormalities. These diagnostic techniques are followed by biopsy for confirmation [15]. In addition, blood tests for the detection of the presence of ovarian tumor markers are useful for diagnosis.

1.8 Ovarian cancer treatment options

The traditional treatment of ovarian cancer includes surgery, chemotherapy, targeted cancer drugs, hormone treatment, and radiotherapy [15]. However, the type of treatment selected for individuals will depend on several factors, including (i) the type of epithelial cancer, (ii) the size of the individual's cancer and whether it has spread (the stage), (iii) how abnormal the cells look under the microscope (the grade), and (iv) the overall health of the newly diagnosed patient [15]. During the last couple of decades, there have been advancements in the methods for treatment modalities of ovarian cancer, including surgery, radiation, chemotherapy, immunotherapy, and other non-conventional/traditional approaches for treating ovarian cancer patients around the world. However, because of late diagnosis, it is exceedingly difficult to achieve effective and efficient treatment of ovarian cancer [15].

2. Conclusion

In this book, we will discuss several types of ovarian cancer, the epithelial ovarian cancer microenvironment, the roles of various risk factors, modifiable risk factors, ovarian cancer survival rates, inheritable gene mutations, nutrition, and

environmental factors contributing to ovarian cancer incidence and mortality. The book will also offer insights into new biomarkers for ovarian cancer diagnosis and prognosis, as well as new techniques for treatment, including fluorescence techniques. Furthermore, the book will provide a current update on the basic molecular mechanisms, including the signal transduction mechanisms mediated by various chemokine receptors and other growth factors that regulate ovarian cancer pathogenesis.

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Tumor Microenvironment of Epithelial Ovarian Cancer

Rachel S. Perkins, Won-Young Choi, Matthew S. Jung and Wenjing Zhang

Abstract

The tumor microenvironment (TME) of epithelial ovarian cancer (EOC) is a dynamically integrated system that significantly influences disease progression, metastasis, and treatment resistance. This dynamic niche is composed of diverse components, including immune cells, stromal cells, and vasculature that are embedded within a remodeled extracellular matrix (ECM). This chapter explores the critical crosstalk between EOC cells and the TME, with a particular focus on how this interaction fosters a favorable environment for cancer stem cells (CSCs). We also review current therapeutic strategies targeting the TME and discuss advanced research tools, such as multiomics and 3D modeling, that are essential for developing effective treatment approaches for EOC.

Keywords: tumor microenvironment, cancer stem cells, TME modeling, fibroblasts, adipose stem cells, epithelial ovarian cancer

1. Introduction

1.1 Heterogeneity of epithelial ovarian cancer

Epithelial ovarian cancer (EOC) represents a group of highly heterogeneous tumors that differ significantly in their cellular origin, molecular alterations, clinical behavior, and response to therapy. This heterogeneity occurs on multiple levels: intertumoral (differences between patients), intratumoral (differences within a single tumor), temporal (evolution over time), and spatial (differences across tumor sites and microanatomical regions). Understanding this complexity is crucial for improving diagnostics, prognostication, and therapeutic targeting.

1.1.1 Histological and molecular subtypes

EOC is the most prevalent form of ovarian malignancy and is characterized by five distinct subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometrioid, clear cell, and mucinous carcinoma [1]. Each subtype has unique molecular features and clinical behavior. Of these,

the most common and aggressive subtype is HGSC, characterized by *TP53* mutations (>96%), high chromosomal instability [2–5], and frequent homologous recombination deficiency due to *BRCA1/2* mutations – making it responsive to PARP inhibitors (PARPis) [3]. It is thought to originate from secretory epithelial cells of the fallopian tube, particularly from serous tubal intraepithelial carcinoma (STIC) lesions [4]. LGSC shows less genomic instability and often carries *KRAS*, *BRAF*, or *NRAS* mutations, with a slower-growing clinical course [2]. Predisposing factors of endometrioid and clear cell carcinomas include a history of endometriosis. Endometrioid tumors often have mutations in *PIK3CA*, *PTEN*, *ARID1A*, and *CTNNB1* and tend to respond well to hormone-based therapies [6, 7]. Clear cell carcinomas are marked by *ARID1A* and *PIK3CA* mutations, platinum resistance, and a distinct metabolic and immune profile, including glutathione dependency and elevated HIF-1 α signaling [8–10]. Mucinous carcinoma, though rare as a primary ovarian tumor, frequently harbors *KRAS* mutations, often mimics gastrointestinal metastases, and responds poorly to standard chemotherapy [11].

1.1.2 Intratumoral, spatial, and metastatic heterogeneity

Intratumoral heterogeneity in EOC is marked by the coexistence of diverse tumor cell clones with varying mutational profiles, epigenetic states, differentiation levels, and therapy responses [12–14]. Single-cell RNA sequencing (scRNA-seq), multiplex immunohistochemistry, and spatial transcriptomics studies have revealed complex subclonal architectures and phenotypic plasticity within both primary and metastatic lesions [12, 15–17]. For example, even within HGSC tumors, multiple transcriptional subtypes – such as mesenchymal, immunoreactive, proliferative, and differentiated – can coexist, reflecting diverse cell states and microenvironmental influences [2]. Spatial heterogeneity is further compounded by the metastatic behavior of EOC. Unlike many solid tumors, ovarian cancer (OC) preferentially spreads via the transcoelomic route. Tumor cells exfoliate into the peritoneal cavity, survive in ascitic fluid as multicellular spheroids, and adhere to peritoneal surfaces such as the omentum, mesentery, and diaphragm. These sites are rich in adipocytes, mesothelial cells, and stromal elements that create a permissive microenvironment for colonization. The tumor microenvironment (TME) at these secondary sites is not passive – it actively shapes metastatic success through immune modulation, metabolic support, and extracellular matrix (ECM) remodeling [18, 19]. The metastatic process itself contributes to spatial heterogeneity, as different lesions may harbor distinct clonal compositions, immune profiles, and stromal interactions. These differences are clinically relevant, as they can influence therapeutic responses and resistance patterns [19].

1.1.3 Temporal heterogeneity and treatment resistance

Temporal heterogeneity in EOC reflects the dynamic evolution of tumor cell populations over time, particularly in response to therapeutic pressure. As the disease progresses, recurrent tumors often exhibit distinct genomic and transcriptomic landscapes compared to their origin [20]. This divergence is driven by clonal selection and expansion of resistant subpopulations, influenced by both inherent and acquired factors, including the evolving TME.

1.2 Cancer stem cells in epithelial ovarian cancer

Cancer stem cells (CSCs) are a subtype of cells residing in a tumor that maintain stem-like qualities and are highly associated with initiation, metastasis, drug resistance, and relapse [21]. The theory of CSCs was first discussed in mice in lymphoma cells in 1963 [22]. In humans, CSCs were initially described in 1997 using models of acute myeloid leukemia (AML) [23]. Since the first report of CSCs in AML, over 100,000 papers have been published establishing the relevance of CSCs in cancer pathology. CSCs have been identified in almost every solid tumor, including pancreatic, colorectal, breast, lung, and EOCs [21]. They are driving factors in chemotherapy resistance due to their slow division, ability to become dormant, and ability to upregulate drug pumps and drug resistance genes such as ATP-binding cassette (ABC) transporters and aldehyde dehydrogenases (ALDHs) [21, 24]. CSCs also promote metastasis via epithelial-to-mesenchymal transition (EMT). Recently, evidence suggested that cells undergoing EMT acquired CSC properties and that EMT and CSCs can be regulated by the same agents [25, 26]. CSCs were first identified in EOC in 2005 by Bapat et al. They found that one tumorigenic clone isolated from EOC patients' ascites possessed stem-like traits, including the capacity to initiate tumors in vivo and differentiate [27]. As with other CSCs, ovarian CSCs (OCSCs) contribute to drug resistance, metastasis, prognosis, and relapse [28]. Recent studies focus on the importance of the interplay between CSCs and the TME, suggesting a bidirectional communication between the two niches [29].

1.3 Tumor microenvironment in epithelial ovarian cancer

The TME in EOC is an intricate, immunologically active, and highly dynamic niche that plays a central role in tumor development. Rather than being a passive backdrop, the TME actively interacts with tumor cells to facilitate proliferation, metastasis, immune escape, and therapy resistance. It consists of diverse cell types – including fibroblasts, mesenchymal stem cells (MSCs), adipocytes, endothelial cells (ECs), and immune cells – embedded within an ECM and surrounded by secreted factors such as growth factors and cytokines. These elements engage in constant crosstalk with tumor cells, shaping the local immune landscape and influencing cancer behavior. Importantly, the composition and function of the TME vary across tumor sites and change dynamically over time, particularly in response to therapeutic pressure [30]. This plasticity contributes to intratumoral and temporal heterogeneity and significantly influences clinical outcomes. Emerging molecular profiling technologies and model systems have begun to unravel these complex interactions, revealing novel targets within the TME. This chapter focuses on the crosstalk between EOC cells and TME components, with an emphasis on CSCs and their roles in tumor development and treatment resistance.

2. Crosstalk between the tumor microenvironment components, ovarian cancer, and cancer stem cells

2.1 Adipose-derived stem cells

Adipose-derived stem cells (ADSCs) are a type of MSCs residing in adipose tissue. Given the anatomical and metastatic preference of OC for adipose-rich

regions – particularly the omentum – ADSCs are a major source of stromal support and paracrine signaling. Additionally, ADSCs can differentiate into cancer-associated fibroblast (CAF) – or adipocyte-like cells and release fatty acids (FAs) that fuel tumor metabolism [31].

ADSCs secrete cytokines, chemokines, and exosomes that facilitate tumor proliferation, EMT, and immune evasion [31]. Notably, TGF- β present in ADSC-derived secretome induces EMT, enhancing EOC cell migration and invasion in vitro and promoting tumor growth and metastasis in vivo [32]. The coculture of ADSCs with OC cells leads to elevated secretion of matrix metalloproteinases (MMPs), promoting proliferation and invasion [33]. Moreover, conditioned media from omental ADSCs reduces platinum accumulation and apoptosis in EOC cells, contributing to chemotherapy resistance [34]. Compared to ADSCs from normal omentum, those derived from metastatic omentum produce higher levels of vascular endothelial growth factor (VEGF), IL-8, IL-6, and TNF α , further promoting chemotherapy resistance and tumor progression [35]. ADSCs also differentiate into cancer-associated adipocytes (CAAs) and CAFs, which actively reshape the TME to favor tumor growth [31, 36, 37]. EOC-derived exosomes increase the expression of α -smooth muscle actin (α -SMA), TGF- β , and stromal-derived factor-1 (SDF-1) in ADSCs, suggesting that these signals promote CAF differentiation [36].

Beyond this, a distinct population known as cancer-associated-MSCs (CAMSCs) has been identified in EOC tissues. These cells maintain normal morphology and karyotype but are reprogrammed by the tumor and hypoxic microenvironment into a more tumor-promoting phenotype [38–41]. EOC cells secrete Hedgehog (HH) ligands that induce BMP4 expression in CAMSCs, which elevates HH signaling, creating a positive feedback loop that promotes malignancy [38]. RNA-sequencing analysis revealed that CAMSCs arise from the reprogramming of local ADSCs by the TME, not bone marrow-derived MSCs (BMSCs), underscoring the unique and dynamic interaction between ADSCs and EOC cells in driving cancer progression [40].

ADSCs enhance EOC progression by expanding the population of CSCs, partly through elevated expression of BMPs, which enhances their stem cell-supporting capacity; OC cells cocultured with cancer-associated ADSCs show increased sphere formation in vitro and ALDH⁺ CSC expansion in vivo [39]. CAMSCs further reinforce stemness in OC via platelet-derived growth factor (PDGF) secretion, as shown in a 3D coculture model, where PDGF signaling increased CSC stemness, metastasis, and chemoresistance – effects reversed by PDGFB silencing [42]. Additionally, CAMSC-derived IL-6 and LIF activate STAT3 in tumor cells, further promoting ALDH⁺ CSC enrichment and underscoring the function of MSC-derived signals in maintaining stemness and therapy resistance in OC [43].

2.2 Cancer associated fibroblasts

CAFs comprise the largest component of stromal cells in the TME and contribute to worse prognosis, increased tumor proliferation, angiogenesis, tumor immunity, drug resistance, metabolic changes, and EMT [44, 45]. CAFs have vast origins, including normal fibroblasts, MSCs, ADSCs, ECs, and more [44–47]. Markers of CAFs include fibroblast activation protein (FAP), α -SMA, periostin (POSTN), Tenascin-C, PDGF, collagen (COL) I, and Vimentin [48].

Across several OC patient datasets, CAF infiltration and CAF signatures are significantly associated with poor prognosis [49–51]. scRNA-seq identified a subpopulation of CAFs expressing *RGS5* that is associated with increased metastasis and reduced survival in EOC patients [52]. Additionally, there is a strong correlation between CAFs and genes associated with the ECM and EMT [50]. CAFs can secrete factors that promote OC growth, invasion, and metastasis [53]. One factor, fibroblast growth factor 7 (FGF7), is associated with residual disease and higher vascular and lymphovascular invasion following surgery [50]. FGF7 secreted by the CAFs proved essential in driving aggression in A2780 and HO8910 cells by promoting HIF-1 α /ZEB1 signaling. Further, evaluating FGF7 in OC cells instead of CAFs was not significant, reinforcing the interplay between CAFs and OC cells [50]. POSTN, another secreted CAF factor is induced by TGF- β , associated with reduced survival and remodels the metastatic TME to fuel OC migration and invasion [54].

CAF regulate metabolic processes associated with the OC landscape through metabolites, extracellular vesicles (EVs), and autophagy [53]. Stromal expression of a metabolic regulator, nicotinamide N-methyltransferase (NNMT), was correlated with significantly worse survival in the CAF compartment, but not in the tumor compartment, indicating the importance of the CAF and stromal niche [55]. Inhibition of NNMT in OC reversed the phenotype of CAFs, revealing that targeting the metastatic stromal niche is feasible and should be explored [55]. Furthermore, exosomes isolated from omental CAFs, but not normal fibroblasts, increase migration and invasion of OC [56, 57]. CAFs remodel the ECM in the omentum through the production of COL proteins mediated by Discoidin Domain Receptor 2 (DDR2) to increase invasion and metastasis [58, 59].

CAF also have a protective effect against chemotherapy in OC [60–63]. They induce paclitaxel resistance through APAF-1-mediated miR21 signaling [60] and enhance cisplatin resistance in OC cells through the IFNB1-CGAS-STING DNA-sensing pathway [61]. On the other hand, EOC can promote the progression and conversion of normal fibroblasts into CAFs. In SKOV-3 OC cells, POSTN and TGF- β 2 secreted from cancer cells primed ADSCs to express CAF marker genes and promoted tumor advancement [64]. The secretome of OC cells can induce the phenoconversion of fibroblasts into CAFs both by glycolytic shift as well as induction of CAF-associated signaling [65, 66]. Additionally, the inhibition of autophagy could revert CAFs into normal fibroblasts [65]. The exosomal miRNA hsa-miR-141-3p from OC cells can transform fibroblasts into CAFs and promote the peritoneal metastatic niche through the YAP1 signaling axis [67]. CAFs are also linked to the promotion of stemness in OC. In 3D spheroid models, IL-8 from both EOC cells and CAFs promoted chemoresistance and stemness through NOTCH3 signaling [62]. Coculturing CAFs with OVCAR3 cells increased spheroid formation, ALDH1 populations, and tumor cell-initiating frequency, indicating an induction of stemness. WNT5A/ROR1-mediated signaling forms a paracrine network wherein CAFs promote cancer cells to become CSCs, and CAFs promote CSCs to self-renew and maintain stemness [63]. Furthermore, IL-6 secreted from CAFs following platinum treatment induces non-CSCs to de-differentiate into OCSCs through STAT3/ALDH1A1 [68]. Coculturing CAFs with HTBoA ALDH1-high OC cells increased CSC marker expression, enhanced sphere formation, and tumor initiation capacity in vivo through the expression of FGF4 [69]. Taken together, CAFs promote stemness in OC by promoting dedifferentiation, maintaining stemness, and increasing the expression of stemness markers.

2.3 Cancer-associated adipocyte

CAAs are metabolically and phenotypically reprogrammed adipocytes within the EOC TME, particularly prominent in omental metastases. Upon interaction with EOC cells, mature adipocytes dedifferentiate into fibroblast-like cells with reduced lipid content and increased lipolytic activity [70, 71].

CAAs promote tumor progression by supplying energy-rich lipids, supporting oxidative metabolism, and secreting inflammatory factors (IL-6, leptin, and TNF- α), which together facilitate peritoneal implantation and metastatic outgrowth [70, 72]. FABP4 is a mediator of CAA–EOC interactions, promoting lipid transfer and contributing to metastasis and resistance to carboplatin [73, 74]. A hallmark of CAAs is elevated lipolytic activity, leading to free fatty acid (FFA) release, which OC cells uptake via transporters like CD36 and FATP1 to fuel mitochondrial β -oxidation, especially under hypoxic or nutrient-deprived conditions [75]. This metabolic coupling supports tumor growth, stemness, and therapy resistance, correlating with poor clinical outcomes [76].

Moreover, CAAs contribute to CSC maintenance through IL-6, IL-8, and TNF- α secretion, activating STAT3 and NF- κ B pathways – key regulators of stemness and survival in OCSCs [77]. Leptin, another CAA-derived adipokine, enhances CSC traits via JAK/STAT and PI3K/AKT signaling. Leptin binds to the Leptin Receptor, which phosphorylates JAK2 activating the STAT3 phosphorylation cascade to enter the nucleus and increase transcription of key stemness and EMT genes [78]. Simultaneously, the binding of the Leptin receptor recruits PI3K to phosphorylate AKT and upregulate the transcription of Akt3 and SOX2 [78]. Together, this cascade leads to the upregulation of pluripotency markers like NANOG, SOX2, and OCT4, as shown in breast cancer models [78, 79]; however, its direct role in OCSC regulation remains to be fully clarified.

2.4 Immune system

The tumor immune microenvironment (TIME) in EOC is both heterogeneous and frequently immunosuppressive. Consequently, clinical outcomes with immune checkpoint inhibitors (ICIs) have been modest in unselected OC populations, likely due to the immunologically “cold” nature of many tumors [80]. Typically considered an immunosuppressive tumor, EOC exhibits limited infiltration of cytotoxic T cells, abundant suppressive immune populations, and spatial immune exclusion [81, 82]. While CD8⁺ tumor-infiltrating lymphocytes are associated with better survival, their function is often impaired by high levels of M2-polarized tumor-associated macrophages (TAMs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated neutrophils (TANs) [83–87]. M2-polarized TAMs dominate the EOC TME and promote tumor proliferation, invasion, and angiogenesis, while driving immune evasion through IL-10, VEGF, CCL18, CCL22, and TGF- β [88, 89]. Tregs are enriched in both primary tumor sites and ascites, express several immune checkpoint molecules, such as PD-L1, LAG3, and TIM3, and secrete IL-10 and TGF- β , reinforcing immune suppression [90–92]. MDSCs are expanded during tumor progression and suppress T cell activity through the expression of ARG1, IDO, TGF- β , and IL-10 [93, 94]. Increased MDSCs are associated with advanced disease, reduced CD8⁺ T cell infiltration, poor prognosis, and therapeutic resistance. TANs can polarize into

either N1 (antitumor) or N2 (protumor) phenotypes depending on the TGF- β context [95]. TANs frequently exhibit protumoral properties, contributing to immune suppression by recruiting other immunosuppressive cells and impairing CD8⁺ T cell activity [95, 96].

Beyond immune cell-intrinsic effects, oxidative stress and ROS actively shape the TIME. Constitutive activation of the NRF2 antioxidant program in tumor and myeloid compartments can blunt ROS-driven danger signaling and favor immune evasion, while therapeutic NRF2 inhibition tends to resensitize OC cells to oxidative death pathways [97]. By contrast, excess ROS can trigger NF- κ B, fueling IL-6/IL-8/CCL2 and PD-L1 upregulation that recruits and polarizes suppressive myeloid cells and dampens T-cell activity [98, 99].

While the TIME of EOC is broadly immunosuppressive, emerging evidence suggests that a subpopulation of OCSCs exists within an even more specialized and resilient immunosuppressive niche. Moreover, OCSCs are not merely passive residents but active modulators of this immune landscape, using it to maintain stemness, evade immune clearance, and drive recurrence [100, 101]. OCSCs modulate the TIME through multiple, strategically coordinated mechanisms. They secrete cytokines such as VEGF, IL-10, and TGF- β , which impair immune system functions [102]. At the same time, OCSCs attract immunoregulatory cell populations, including Tregs, M2-TAMs, and MDSCs, thereby strengthening the immunosuppressive environment [103]. In addition, OCSCs often express ligands such as PD-L1 and CD47, which further inhibit immune responses [104, 105]. Importantly, the immune system not only fails to eliminate OCSCs but also contributes to their persistence through signals from Tregs, M2-TAMs, and CAFs activating NOTCH, Wnt/ β -catenin, and IL-6/STAT3.

2.5 Extracellular matrix

The ECM is a complex, tissue-specific, multifaceted matrix that is composed of macromolecules, proteins, glycoproteins, receptors, and enzymes [106]. The ECM is essential for providing the structural and organizational support required for cellular functioning [106]. In healthy tissue, the ECM maintains precise regulation of cell adhesion, differentiation, and growth [106]. Meanwhile, in pathophysiology, the ECM undergoes remodeling to facilitate the migration/invasion of cancer cells, making it a fundamental component of the TME [107].

Due to the cyclical nature of the ovarian microenvironment, the ECM is ever-changing in healthy ovaries. Regardless, the core proteins that make up the ovarian ECM are COLs, fibronectin (FN), laminin (LMN), glycoproteins, and proteoglycans [107]. ECM remodeling in EOC development is a critical step and is directly related to the disease state [107]. The ECM is important in primary tumor seeding but perhaps more so in migration, invasion, and seeding at metastatic sites, namely the omentum [107]. ECM remodeling and stiffness are two main factors that prime the TME for tumor growth. The orientation of COL fibrils correlates strongly with disease score [108]. ECM-related markers EDN1/ARRB1, COL1A1 and FN1 directly correlate with worse prognosis [109]. Endothelin-1 (ET-1) regulates FN1 and COL1A1 through β -arrestin-1 (β -arr1) to modulate ECM-remodeling and ECM matrisome expression [109]. Ovarian outgrowths, the initial step in metastasis, are supported by low elasticity ECM [110]. ECM factors that drive these outgrowths include LMN γ 1, COL IV, low shear viscosity, and elasticity [110].

On the other hand, at the omental site, increased stiffness, regulated by TAGLN/RHOA/ROCK, is associated with worse prognosis and increased COL [111]. In the omentum, TGF- β 1 increases fibrillar COL I deposition through activating fibroblasts [112]. This increased COL density enhances cancer proliferation driven by heparin-binding epidermal growth factor (EGF) from the ascites [112]. DDR2 from the stroma is associated with worse prognosis, increased attachment, migration, and invasion through promoting ECM remodeling by regulating fibrillar COL deposition in peritoneal spread [59]. Not surprisingly, the ECM is also affiliated with chemoresistance. Stiffness shields cells from chemotherapy, directed by chemotherapy-related expression of COL6 [113]. Altogether, the ECM contributes to worse prognosis and is essential to the primary and metastatic niche in OC.

The ECM promotes OCSCs by upregulating and maintaining stemness. The ECM protein 1 isoform a (ECM1a) promotes ovarian tumorigenesis, maintains stemness, and increases drug resistance through the integrin α X β 2/hnRNPLL/ABCG1 phosphorylation cascade [114]. The ABC transporter family, often associated with stemness, is upregulated by secreted hyaluronan in OC following carboplatin treatment [115]. ECM markers transglutaminase (TG2), integrin β 1, and FN1 are highly expressed in OCSCs, and their inhibition suppresses stemness properties such as sphere formation, tumor-initiating capacity, and stemness markers [116]. More research is required to holistically decipher the ECM-OCSC reciprocal roles; however, it is clear that the ECM is integral to maintaining stemness in the CSC niche.

2.6 Angiogenesis

Angiogenesis is a critical process in tumor advancement. This neovascularization supplies oxygen and nutrients to rapidly proliferating tumor cells and enables the spread of cancer cells, particularly within the peritoneum.

VEGF is a key driver of angiogenesis, promoting EC proliferation, migration, and capillary formation via VEGFR-1- and VEGFR-2-mediated activation of MAPK and PI3K/AKT pathways [117, 118]. In EOC, VEGF is frequently overexpressed and correlates with advanced stage, increased tumor burden, ascites formation, and poor prognosis [119, 120]. Different cell types in the EOC TME secrete VEGF in response to hypoxia and stress, amplifying angiogenesis. ECs transform into tumor-associated phenotypes under hypoxic conditions and exposure to proangiogenic markers such as VEGF, FGF, and PDGF. These tumor-associated ECs generate aberrant, leaky, and disorganized vessels that facilitate tumor growth, metastasis, and intravasation [121]. Additionally, ECs actively shape the immunosuppressive TME by interacting with TAMs and CAFs and regulating T cell trafficking and activation [122]. In EOC, ECs display distinct features compared to their normal counterparts, including elevated expression of ICAM-1 and VCAM-1 (adhesion molecules), which promote tumor–endothelial interactions, along with elevated secretion of IL-6 and CXCL12, assisting tumor cell survival, immune escape, and metastatic potential [123].

Importantly, ECs also preserve CSCs by forming a specialized vascular niche. Crosstalk between ECs and CSCs, mediated through pathways such as VEGF/VEGFR2, NOTCH, and IL-6/STAT3, has been shown to stimulate resistance, survival, and CSC self-renewal during chemotherapy [29]. For example, VEGF stimulation can enhance the stemness of OCSCs by upregulating Bmi1 expression via VEGFR2-dependent Src activation [124]. These interactions suggest that

angiogenesis promotes bulk tumor growth and reinforces the CSC compartment, further contributing to disease recurrence and treatment resistance.

2.7 Other tumor microenvironment modulators: Cytokine and chemokine network, exosomes, hypoxia, and metabolites

The cytokine and chemokine network in the OC TME is an interactive signaling system that plays a central role in disease advancement. It modulates immune response and promotes tumor cell proliferation, angiogenesis, ECM remodeling, and EMT. Central cytokines, such as ILs, VEGF, IFNs, and TGF- β , contribute to the establishment of a protumorigenic TME. Meanwhile, chemokines like CCL2 and CXCL12 facilitate the recruitment of immunosuppressive immune cells. This coordinated signaling network drives immune evasion, metastasis, and therapeutic resistance [125].

Exosomes are key mediators of communication between EOC cells and the TME, carrying proteins, miRNAs, and lncRNAs. Exosomal miRNAs are particularly important, as they drive angiogenesis (e.g., miR-130a, miR-205) [126, 127] and chemoresistance (e.g., miR-21, miR-214, miR-125b) [60, 128, 129]. Similarly, exosomal lncRNA *MALAT1* has been implicated in chemoresistance by modulating autophagy and activating the PI3K/AKT signaling pathway [130, 131]. Hypoxia is a major driver of TME remodeling in EOC. Stabilization of HIF1 α and HIF2 α under low oxygen induces gene networks promoting angiogenesis, immune suppression, and EMT [132–134], thereby enhancing tumor cell migration/invasion and platinum-based therapy resistance. Under hypoxic conditions, metabolic patterns are transformed to increase aerobic glycolysis and lipid metabolism, resulting in lactate accumulation, acidifying the TME, fostering angiogenesis, and suppressing immune response [135, 136].

OCSCs release exosomes carrying stemness-promoting miRNAs (e.g., hsa-miR-1246) and may transfer drug-resistance genes, such as *ABCB1* and modulate their surrounding environment [137, 138]. Exosomal communication enables OCSCs to reshape the TME, promote OCSC niche formation, and even convert non-stem cells into stem-like phenotypes. Hypoxia sustains OCSC quiescence and survival by stabilizing HIF1 α , which upregulates SOX2, NANOG, and ALDH1A1 to maintain self-renewal and an undifferentiated status [139, 140]. Unlike EOC, OCSCs rely on FA oxidation and oxidative phosphorylation rather than glycolysis, enabling metabolic flexibility that promotes long-term survival, low-proliferation, and drug resistance [141].

2.8 Cancer stem cell niche

In healthy tissue, stem cells reside in the “stem cell niche”, which is a precisely regulated microenvironment consisting of stromal and immune cells that promote stem cell maintenance [142]. Similarly, CSCs rely on the “CSC niche” for self-renewal, differentiation, and overall stem cell maintenance [143, 144]. Furthermore, it is recognized that the TME of the CSCs promotes not only primary tumor growth but also migration and invasion, which suggests the existence of a separate metastatic niche [144].

The specific composition of the TME, inflammatory network, and growth factors makes up the OCSC niche [29]. The various cell types involved in the OCSC niche

include adipocytes, MSCs, fibroblasts, and immune cells such as macrophages [143]. As described above, the specialized ovarian TME can dynamically influence the CSCs and vice versa to promote disease progression [143]. Specifically, these TME cells can induce stemness phenotypes such as spheroid formation, metastasis, and chemoresistance through growth factor, cytokine, and chemokine signaling [143].

As the predominant site of ovarian metastasis, the omentum provides a special environment for CSCs [145]. The omentum, located in the peritoneal mesothelium, consists of visceral adipose tissue and fat-associated lymphoid clusters [146, 147]. Adipocytes in the omentum provide FAs that support metastatic growth [74]. Likewise, the CSCs can also prime themselves for the metastatic niche. Spheroids detached from primary sites undergo metabolic reprogramming, increasing lipid metabolism, autophagy, and FA oxidation to enhance cell survival at metastatic sites [148]. Omental macrophages drive the CSC phenotype of OC to promote invasion into the metastatic niche [147]. The specialized niches provided by the ovary and omentum support and promote the development of aggressive disease.

3. Therapeutics

Surgical debulking with subsequent platinum and taxane chemotherapy regimens, PARPi, and antiangiogenics are recommended as first-line therapy by The American Society of Clinical Oncology [149]. While initially effective, disease recurrence and platinum resistance develop in 70% of cases [150]. New therapeutics seek to address this relapse by moving beyond nonspecific therapies and exploiting the molecular vulnerabilities of EOC and the TME [151].

Reduction of TIME immunosuppression is of significant clinical interest for effective therapy regimens. The most common therapy against the TIME is ICIs, designed to block CTLA-4, PD-1, PD-L1, IDO, LAG3, or TIM3 to prolong TIL function [81, 152–154]. However, the objective response rate to single PD-1/PD-L1 inhibition is 10% in EOC [81]. Clinical trials investigating combination therapies are being pursued; however, recent phase III trials failed to demonstrate efficacy [81, 155–158]. Therefore, further research on combinations of ICIs, immunotherapies, antiangiogenics, and chemotherapies is of great importance.

Inhibition of tumor stromal cells and vascular remodeling has also been a validated strategy for the treatment of EOC. VEGF blockade with the monoclonal antibody (mAb) bevacizumab has demonstrated strong clinical benefits in conjunction with traditional therapies [149, 159]. However, resistance to antiangiogenic therapy through EC plasticity, vessel cooption, and activation of compensatory angiogenic pathways remains a major hurdle, necessitating the development of new antiangiogenics [160]. Preclinical studies reveal that targeting CAFs can decrease EOC tumor progression. Studies inhibiting CAF populations take three main approaches: selective killing of CAFs via surface markers like FAP or PDGF-receptor (PDGF-R), inhibiting CAF activation, and targeting CAF signaling and regulatory networks [161]. Specifically, CAR-T cells targeting both FAP and folate receptor alpha (FRa) target both the cancer and stromal cells to overcome “cold” tumor regions and induce tumor death [162]. Depletion of available FAs can also effectively restrict EOC growth, making CAAs a reasonable target for EOC treatment [163]. Inhibition of EOC-CAA-induced CD36 expression with mAbs decreased FA uptake and reduced CAA-mediated tumor development in vitro and

in vivo [164]. Similarly, targeting the ECM has shown potential in preclinical studies due to its reciprocal interaction with cancer cells, but it has not yet yielded clinical impact in EOC [165].

Preclinical studies are exploring how ADSC EVs can be leveraged as a therapeutic delivery mechanism for direct cellular inhibition [166, 167]. These studies involve preloading ADSC EVs with taxanes [168, 169], enzyme/prodrug payloads that activate only in the TME upon ADSC association [170–172], targeting moieties for nanoparticle-delivered therapies [167], or oncolytic viruses (NCT02068794) to induce targeted cell death in combination with traditional therapeutics or as solo agents.

As previously discussed, resistance and recurrence are driven by OCSCs sheltered by the cellular subpopulations within the TME, such as ADSCs, CAAs, and CAFs [107, 173]. There are many strategies for targeting OCSCs: signaling pathway inhibitors (WNT, SHH, NOTCH, PI3K/PTEN, or MAPK), OCSC targeting via surface markers (CD133, CD44/CD117, CD24, EPCAM, ALDH1), immunotherapies (CAR-T), epigenetic regulation, and miRNAs [174–176]. Given the heterogeneity of EOC and its TME, the development of novel and combinatorial therapies – including CAR-T, ICIs, nanoparticles, or even targeted radiopharmaceuticals – that address both EOC and TME holds strong potential.

4. Researcher's toolkit

4.1 In vitro and in vivo modeling for tumor microenvironment

Modeling EOC and its TME is challenging due to their heterogeneities and complex interactions. Effective models must reflect both tumor architecture and TME interactions that drive progression, metastasis, immune evasion, and therapy resistance [177].

In vitro models offer controlled, reproducible, and cost-effective platforms for studying the complex OC TME. While traditional 2D monolayer culture is frequently applied, it fails to recapitulate the structural and cellular complexity of the TME. To address this, advanced 3D systems have been developed. Aggregate cultures – formed via the hanging droplet method [178, 179], ultra-low attachment plates [180, 181], or spinner flasks – create multicellular systems that mimic tumor architecture, hypoxia, and cell-cell interactions. These systems can be cocultured with stromal or immune cells to study invasion, signaling, and drug responses in a TME-like context. Scaffold-based 3D models further enhance physiological relevance by incorporating ECM components like Matrigel, COL, or synthetic polymers, providing structural and biochemical cues that simulate the tumor matrix and support tumor–stroma interactions. Microfluidic platforms (“tumor-on-a-chip” systems) enable dynamic modeling of TME processes such as immune cell infiltration, angiogenesis, and therapy response under fluid flow and nutrient gradients [182, 183]. Organoids, derived from patient tumors, retain key genetic and phenotypic features [184] and can be cocultured with TME components to study immune evasion and personalized drug responses.

In vivo models remain indispensable for illustrating the full intricacy of the TME. Xenografts and patient-derived xenografts (PDX) enable human tumor growth in mice and are widely used for preclinical drug testing [185], though their

immunocompromised hosts limit immune-TME studies. Humanized mouse models partially restore human immunity [186], allowing immunotherapy testing but with limitations such as incomplete immune function and graft-versus-host risk. Genetically engineered mouse models and syngeneic models using gene-edited murine cells (e.g., ID8) provide immune-competent settings to study tumor initiation, immune surveillance, and therapy response [187, 188]. These systems mimic native TME interactions and are well-suited for immunological studies. Together, in vitro and in vivo models offer complementary strengths. Combining both approaches provides a comprehensive TME-relevant model of OC progression and therapy resistance, supporting the development of effective treatments.

4.2 Cancer stem cell models

Modeling the TME with CSCs can be approached in a similar manner to whole tumor modeling, but with the additional CSC isolation steps. Classically, CSCs are modeled through side population exclusion assays (e.g., Hoechst 33342), flow sorting for CSC surface markers (e.g., CD133/CD34), enzymatic activity of ALDH, or 3D-tumor spheroid culturing [189]. Spheroids, one of the most common CSC models, apply culturing techniques originally used for neural stem cells. These spheroids are grown in suspension without serum and with added neural stem cell factors B27 and N2, as well as fibroblastic and EGFs [190, 191]. Spheroids are arguably the gold-standard in vitro method for CSCs due to their reliable expression of CSC markers, in vivo tumorigenicity, and capacity to differentiate into heterogeneous cancer cells [192]. Perhaps the most compelling application of CSC-spheroids to OC research is their morphological resemblance to the free-floating metastatic aggregates seen in ascites [27, 192, 193]. To study CSCs with spheroids, size, shape, sphere number, and sphere-forming capacity provide insight into stemness and proliferation, and assays to measure migration and invasion are performed with biocompatible materials like Matrigel [194–196].

4.3 Multiomics approach

Understanding the complex interactions in the TME requires tools capable of resolving overlapping molecular signals across cell populations. Advances in next-generation sequencing and computational methods now allow high-resolution analysis through bulk, single-cell, and spatial omics approaches.

Bulk RNA-seq remains the most widely used platform for analyzing tumor samples but lacks the capacity to determine contributions from diverse cell populations within the TME. Therefore, computational deconvolution methods have been developed to estimate the cellular composition and functional states. Tools such as CIBERSORTx, xCell, and EPIC use predefined gene expression profiles (bulk and single-cell level) to infer the relative abundance of cell types [197–199]. For example, studies using TCGA and GEO datasets have identified immune-enriched versus immune-depleted subtypes, where the immune-enriched group exhibited increased cytotoxic T cell infiltration and better survival outcomes [200, 201]. Single-cell-omics has revolutionized our comprehension of the TME by empowering high-resolution profiling of individual cells within tumors. In OC, scRNA-seq has uncovered previously unrecognized cell types, lineage hierarchies, and dynamic cellular states such as EMT, therapy-induced reprogramming, and CSC-like

phenotypes [15, 202–204]. In HGSC, recent scRNA-seq studies have identified tumor cell subpopulations characterized by stemness-associated transcription factors (e.g., SOX2), exhausted T cell phenotypes, and TAM subsets expressing immunosuppressive cytokines such as IL-10 and TGF β 1 [81, 205, 206]. Recent applications of spatial transcriptomics, particularly through platforms like 10x Genomics Visium and NanoString GeoMx Digital Spatial Profiler, have begun to uncover the architectural complexity of the OC TME. These technologies allow researchers to map gene expression patterns within the native spatial context of tumor tissues, revealing how molecular signals are organized across tumor subregions. In HGSC, spatial profiling has identified immune-excluded niches, stromal-immune cell interactions, and subclonal tumor structures that may underlie resistance mechanisms and immune evasion [17, 207].

5. Conclusions

The TME of EOC is a heterogeneous population of malignant ADSCs, CAAs, CAFs, TAMs, and TANs within a remodeled ECM, vasculature, and immune environment that establishes a protumorigenic niche for CSCs to drive tumor relapses and metastasis (**Figure 1**). ADSCs serve as progenitor cells for other stromal cells, CAAs facilitate tumor metabolism and metastasis, and CAFs mediate ECM stiffening and platinum resistance. TAMs, TANs, MDSCs, and Tregs repress immune

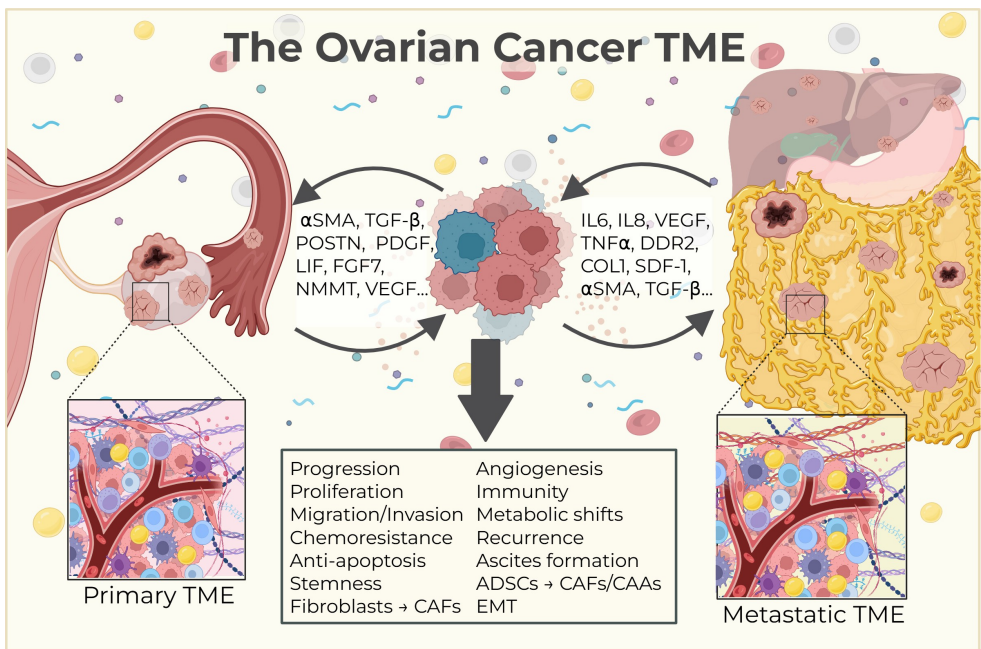


Figure 1. The ovarian cancer TME. Artistic representation of the reciprocal interactions between the heterogeneous tumor, ascites, primary and metastatic TME in EOC. Tumor (center: red represents heterogeneous tumor; blue represents CSCs). Ascites (yellow background with components such as lipid droplets, blood cells, peptides, etc.). Primary site (left: pink background represents collagen-rich ovary). Metastatic site (right: yellow background represents adipose rich omentum). Created in BioRender.

infiltration through factors like IL-10, IDO, and TGF- β 1. The TME is fundamentally involved in the maintenance of the CSC niche. CAFs and ECs secrete factors like IL-6 and VEGF to activate STAT3 and Notch signaling. Hypoxia maintains CSC pluripotency and self-renewal through upregulation of SOX2, ALDH1, and NANOG. Hypoxic conditions also predispose CSCs to FA oxidation, supported by CAAs, further acidifying the TME and suppressing immune infiltration. The TME shields CSCs from cytotoxic immune surveillance and acts as a reservoir for subsequent disease recurrence. Therefore, effective therapeutic strategies for EOC must account for the complexity of the TME, as standard-of-care regimens are undermined by treatment resistance and disease recurrence. Understanding this system requires advanced models to capture the intricate cell-matrix and cell-cell relationships observed in vivo. Patient-derived organoids, microfluidic cocultures, PDXs, mouse models, and multiomic analysis are critical for this purpose. Determining the proper combination and dosing of PARPis, ICIs, antiangiogenics, cytotoxic chemotherapies, and targeted radiopharmaceuticals for efficacious treatment regimens represents the critical next step in treating therapy resistance and improving long-term patient outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

Appendices and nomenclatures

TME	Tumor Microenvironment
EOC	Epithelial Ovarian Cancer
CAF	Cancer Associated Fibroblast
CAA	Cancer Associated Adipocyte
ECM	Extracellular Matrix
CSC	Cancer Stem Cell
ADSC	Adipose-Derived Stem Cell
TAM	Tumor-Associated Macrophage
Treg	Regulatory T Cell
MDSC	Myeloid-Derived Suppressor Cell
HGSC	High-Grade Serous Carcinoma
LGSC	Low-Grade Serous Carcinoma
sc-RNA seq	Single Cell RNA Sequencing
EMT	Epithelial-To-Mesenchymal Transition
OCSC	Ovarian Cancer Stem Cell
AML	Acute Myeloid Leukemia
MSC	Mesenchymal Stem Cell
ABC	ATP-Binding Cassette

MMP	Matrix Metalloproteinase
SDF-1	stromal-derived factor-1
α -SMA	α -Smooth Muscle Actin
CAMSC	Cancer-Associated Mesenchymal Stem Cell
HH	Hedgehog
BMSC	Bone Marrow-Derived Mesenchymal Stem Cell
FAP	Fibroblast Activation Protein
POSTN	Periostin
PDGF	Platelet-Derived Growth Factor
PDGF-R	PDGF-Receptor
COL	Collagen
FGF	Fibroblast Growth Factor
NNMT	Nicotinamide N-Methyl Transferase
DDR2	Discoidin Domain Receptor 2
FA	Fatty Acid
FFA	Free Fatty Acid
TIME	Tumor Immune Microenvironment
TAN	Tumor-Associated Neutrophil
EGF	Epidermal Growth Factor
FN	Fibronectin
LMN	Laminin
ET-1	Endothelial-1
ECM1a	ECM Protein 1 Isoform A
TG2	Transglutaminase
VEGF	Vascular Endothelial Growth Factor
EC	Endothelial Cell
miRNA	MicroRNA
lncRNA	Long Non-Coding RNA
PARPi	Poly (ADP-ribose) Polymerase Inhibitor
ICI	Immune Checkpoint Inhibitor
FRa	Folate Receptor Alpha
EV	Extracellular Vesicle
PDX	Patient-Derived Xenograft
ALDH	Aldehyde Dehydrogenase
mAb	Monoclonal Antibody

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Secondary Prevention of Ovarian Cancer

Gehanath Baral

Abstract

Cancer of uterine cervix and ovaries are the common female genital organ cancers. Cervical cancer is preventable primarily by vaccination and secondarily by treating pre-cancer lesions as the surrogate markers by programmatic screening methods. There is programmatic gap in ovarian cancer care due to lack of screening tool and specific surrogate markers. Ovarian cancer may progress without symptom for longtime because of intra-abdominal location of organ. Therefore, the disease may be revealed incidentally on casual imaging study only. Predicting modality will be clinical, imaging study, biochemical, biomolecular or their combinations for different tools. Its intervention will also be contextual depending on availability and affordability of resources. Thus, the comprehensive clinical practice guideline or diagnostic model or approach should address every level of socioeconomic and geographical sector for the graded care facility.

Keywords: cancer screening, diagnostic accuracy, ovarian cancer, practice guideline, secondary prevention, tumor cytology

1. Introduction

Cancer of the ovary is the second most common cancer after the uterine cervix in the female genital tract. This body organ is located inside the body that is not easily identified without an imaging study, and cancer may occur without notice or apparent symptoms. Incidence of these cancers is increasing over time because of ever-increasing diagnostic resources, increasing life expectancy, and a paradigm shift in disease patterns from communicable to non-communicable diseases like cancers nowadays. Cancer is a deadly and costly disease if not addressed in the early stages or before it becomes symptomatic [1]. Prediction of cancer can be done either by identifying the inciting agent if known or using screening tools if available. Screening by surrogate markers and mitigating it appropriately will prevent ovarian cancer from evolving. Neither do we have a proven and specific surrogate marker yet. Thus, the only intervention left is secondary prevention once the disease is apparent, requiring treatment of the disease either by surgery, medicine, or both. If we intervene in the early stage, we can prevent further progression and complications and improve the quality of life. We are in need to

identify inciting agent for primary prevention or specific surrogate markers for early secondary prevention.

2. Cancer burden and prevention

2.1 Burden of cancer

Reproductive organ cancer is a public health burden in women's lives. The organs involved will be the ovary, fallopian tube, uterine body, uterine cervix, vagina, and vulva from inside the body outwards. Out of all cancers in these organs, only the cancer of the uterine cervix has received public health concern because of its demonstrable precancerous stage for a long duration of 5–14 years [2]; it is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women [3].

On the other hand, global incidence and death of ovarian cancer have increased by 88% and 84% over the period of 28 years since 1990, respectively, and by 176% and 162% in South-East Asia. This is 7–8 times more in the low SDI region than in the high SDI regions [4]. The morbidity has increased by 29–30% since 2007 [5]. According to GLOBOCAN 2022 data, the age-standardized incidence and mortality from ovarian cancer are 6.6% and 4%, respectively [6].

The burden of ovarian cancer is increasing over time because of an aging population and improved medical facilities to detect cancer early. Unopposed influence of gonadotrophins on the ovary for a prolonged period due to changes in reproductive behavior, like delayed marriage and child-bearing, birth-spacing, and low parity, in the present-day society has also contributed a lot. Other lifestyle factors and environmental exposure to carcinogens are also playing some role. Lack of primary preventive measures is the bypass window for ovarian cancer to grow [7]. This brings in the concept of one-health for comprehensive action from all sectors, like biomedical and environmental science.

Such a burden can be measured by its incidence, prevalence, mortality rate, and disability rates. Magnitude of premature death, disability, or both is a public health concern that requires action and requires secondary preventive measures to implement in order to improve quality of life. This costs a lot in terms of loss of resources and life. This yields an unfavorable effect on the health care financing, family sustenance, and economic growth. To address the financial toxicity – the term used for the negative financial impact, especially due to the cost of cancer care – we have to explore the preventive measures at both the primary and secondary levels. It not only depletes the financial capacity but also risks sub-optimal care and disability or premature death. (**Figure 1**)

2.2 Level of disease prevention

There are different levels or stages of disease prevention measures against the occurrence or its sequelae. The target of preventive intervention could be against the causative factor, surrogate markers, or conditions, or progression of disease. Exposure to causative factors can be avoided, removed, or treated. Known factors like human papilloma virus infection causing cervical cancer can be prevented by health education or counselling to avoid its exposure or

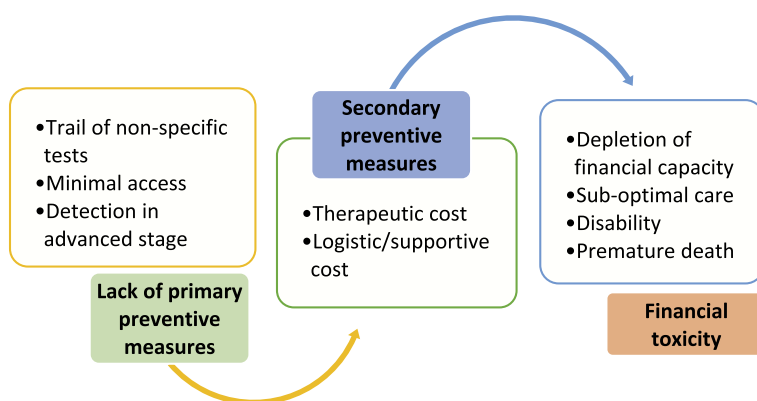


Figure 1.
 Financial toxicity from cancer care (illustration created by author).

immunization at an appropriate time in life as primary prevention [8, 9]. Proven infection-related female genital cancer is cervical cancer, but the carcinogen for ovarian cancer has not been revealed yet to mitigate its occurrence and progression. However, there are some non-genital cancer-causing organisms like hepatitis B virus (HBV) and hepatitis C virus (HCV) for liver cancer; helicobacter pylori for stomach cancer and lymphoma; and Epstein-Barr virus, and human immunodeficiency virus for other cancers. Even when the primary preventive measures addressing known risk factors and causative agents are in place, all cancers can't be prevented. Therefore, secondary preventive measures are important intervention strategies because the known factors and agents for the cancer are few like in ovarian cancer [10]. Controlling the known surrogate markers like treating precancer lesion in uterine cervix or any screening tests marker before it alters the normal health parameters or potentially progresses to a disease or cancer is secondary prevention. Established disease requires either a definite care or a palliative care to improve quality of life. In ovarian cancer, there is no vaccination yet. Still, some predictive and diagnostic tools exist in clinical practice or service delivery such as imaging, tumor markers, and tumor cyto-histology as to target for secondary prevention. Hence, primary and secondary prevention should be taken as a priority for global cancer control [11]. Vaccination and health-promoting activities like diet, lifestyle modification, and healthy living would be primary preventive measures. As the disease condition begins to progress, secondary preventive measures apply, such as early amelioration of abnormality, stabilization of surrogate markers of the disease, stress management, and lifestyle intervention. Once the disease condition is established, then the preventive measures would be risk reduction, palliation, supportive measures, rehabilitation, and psychosocial support. Thus, the integrative effort to mitigate health problems would be an option for healthy living [12, 13].

Secondary preventive measures tend to halt the appearance or progression of disease in order to improve quality of life. Thus, the expected quality of life depends on the intervention at different stages of exposure status [14] (**Figure 2**).

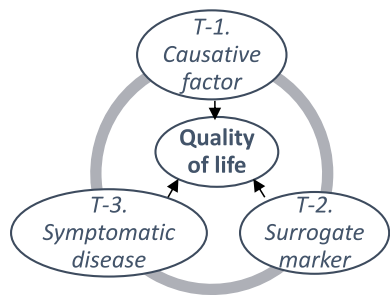


Figure 2.
Intervention targets (T-1, T-2 & T-3) to improve quality of life (created by author).

All patients with epithelial ovarian cancer have an overall probability of BRCA1/2 mutation of over 10%. So, it is better to carry out genetic counseling and testing on all women with this type of tumor [15]. A surgical procedure, salpingo-oophorectomy, reduces the risk of breast and ovarian cancer among women with a BRCA1/2 mutation [16]. This is the implementation of knowledge on the inheritance of familial cancer. Secondary prevention of homologous recombination (HR)-deficient ovarian cancers, including BRCA-mutated ones, by Poly (ADP-ribose) polymerase (PARP) inhibitors used in clinical practice will have targeted tumor cell death [17].

By the perception of disease, also, the patients can be categorized into four sub-groups as true or false perception, and category 1 indicates primary prevention, category 2 is early secondary prevention, categories 3 and 4 for late secondary prevention or clinical treatment of organic disease and mental health, respectively. (**Figure 3**).

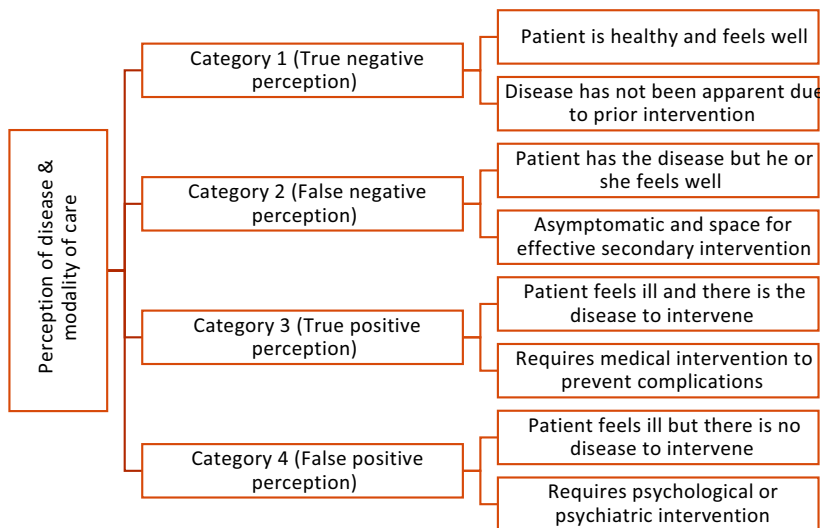


Figure 3.
Category of patients by their perception of disease (created by author based on [13]).

2.3 Prediction of ovarian cancer

Due to a lack of universal primary preventive measures or a screening tool for ovarian cancer, it has become a global challenge for cancer care providers. Currently, one or another clinical practice guideline and recommendations have been used based on the availability of diagnostic and therapeutic services. The diagnostic accuracy of any means may not be sufficient singly. This warrants the adoption of a comprehensive approach or model to be used at different facility levels, wherever the facility permits. Resource-constrained setting would use the model up to a certain point and be guided for further care [18].

Different programmatic interventions like cervical cancer prevention, tuberculosis prevention, and other educational and business programs were evaluated by a logic model considering contextual resources, implemented activities, retrieved outputs, and obtained outcomes resulting in the impact (RAOOI) of the whole process. Similarly, a comprehensive model or approach can be adopted to address ovarian cancer care [18, 19]. (Figure 4).

The Logic model has been tested in a multicentric study in a small sample to explore the status of currently available ovarian cancer services. The overall satisfaction level of specialist service providers in the clinical and diagnostic field for the detection and treatment of ovarian cancer was good against its utility, feasibility, and accuracy domains [18].

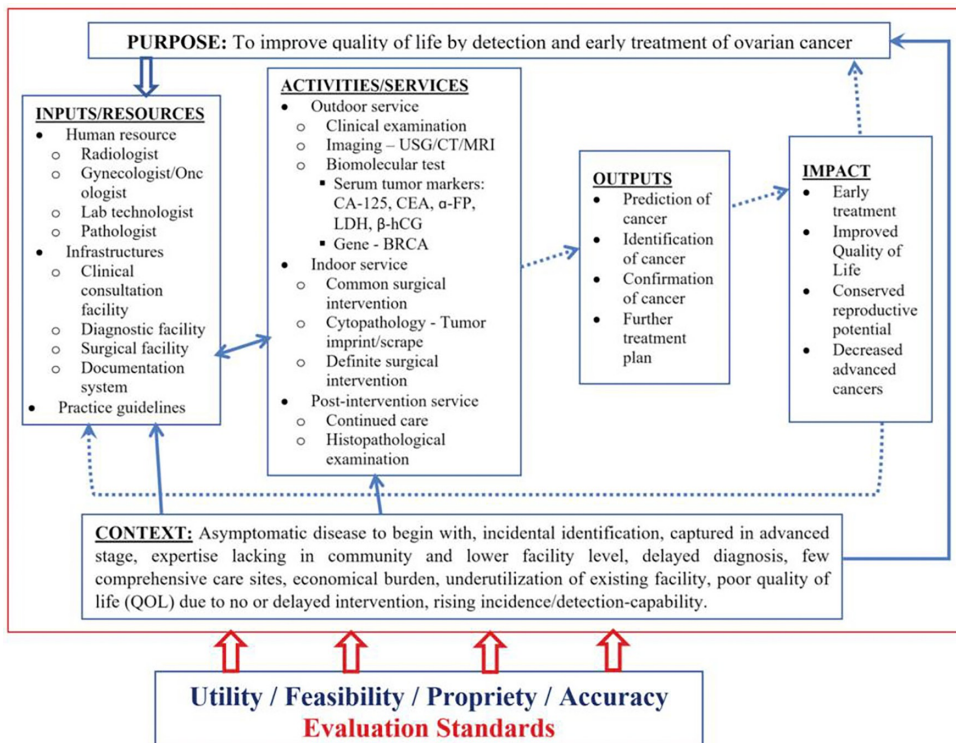


Figure 4.
Logic model for secondary prevention of ovarian cancer: A conceptual framework [18].

“Utility Standards (U) are used to determine the value of the service to see whether it meets the intended needs. Feasibility Standards (F) are used to increase evaluation effectiveness and efficiency. Accuracy Standards (A) are used to increase the dependability and truthfulness of evaluation representations, propositions, and findings, especially those that support interpretations and judgments about quality.” An exploratory analysis of 53 factors was promising, and a larger sample size was recommended to test model fit for confirmatory analysis to validate the current practice of predicting and managing ovarian cancer [18].

Imaging study reveals and characterizes the adnexal masses for further workup by biochemical and biomolecular tests, such as tumor markers and gene tests. The biochemical tests are reasonably sensitive but not specific in predicting ovarian cancer. Cytopathology or histopathology, either retrieved by needle aspiration, tumor imprint, or frozen section, has good diagnostic accuracy while testing against *paraffin section biopsy* [20].

There are several tumor markers to identify different types of ovarian tumors, such as CA-125 (Cancer antigen 125 for serous cancer), CEA (Carcino-embryonic antigen for mucinous cancer), α -FP (Alfa-feto protein for yolk sac tumors), LDH (Lactate dehydrogenase for dysgerminoma), β -HCG (beta-human chorionic gonadotrophin for choriocarcinoma), Inhibin (for granulosa cell tumor), and human epididymis secretory protein 4 (HE4) [21]. The ultrasound results and menopausal status are also considered for risk scoring. The risk of ovarian malignancy algorithm (ROMA), the risk of malignancy index (RMI), IOTA, and OVA1 assays have also been used. Screening by combined transvaginal ultrasound and CA125 is also not effective enough to recommend [21]. The accuracy to differentiate malignant from benign adnexal lesions is better with magnetic resonance spectroscopy (MRS) than with conventional magnetic resonance imaging (MRI) [22]. The novel biomarkers, such as autoantibodies, ctDNAs, miRNAs, and DNA methylation signatures, also provide earlier detection methods for ovarian cancer. Genetic predisposition can be detected in a few cases by a genetic test for BRCA mutation and other tumor suppressor genes, and preventive surgery (prophylactic salpingo-oophorectomy) can be considered in positive cases; two-stage prophylactic surgery, like premenopausal salpingectomy followed by perimenopausal oophorectomy, has also been suggested [1, 23, 24].

Proteomic profiling of biomarker discovery has some value in prognostic evaluation of high-grade serous epithelial cancer of the ovary [25]. Instead of taking the widely used serum biomarker CA125 only to detect ovarian cancer, if we take all three tumor markers together (CA125, CEA, and AFP) along with tumor cytology, the detection rate is increased by 1.3 times. Still, there are some limitations, like these markers can't detect all germ cell tumors, nor stromal tumors of the ovary. Even the higher multiples of serum CA125 level could not correlate with the malignancy [20, 26]. (**Figure 5**).

There are two methods to instantly detect ovarian cancer intra-operatively – frozen section biopsy and tumor cytology. Frozen section biopsy helps to proceed with further surgery to prevent incomplete treatment, but its wide availability is questionable. The alternative procedure in resource-constrained settings is tumor imprint cytology, which is available in most centers with cancer surgery facilities [26, 27]. It is taken by the imprint, scrape, or crush method. While comparing to paraffin section biopsy, the tumor imprint cytology taken intra-operatively had

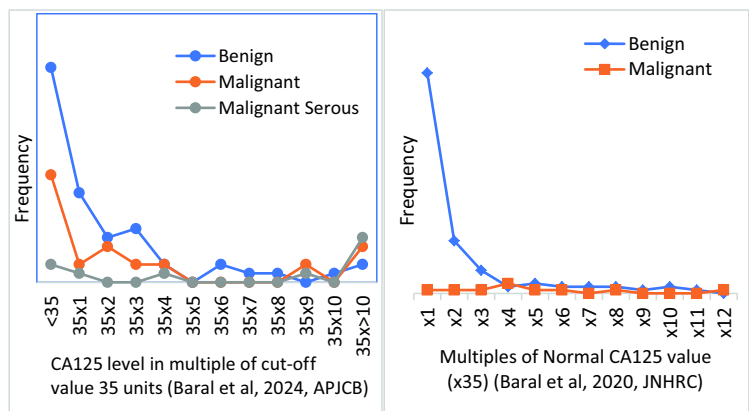


Figure 5.
 Nature of ovarian tumor by multiples of CA125 level.

80.5% overall diagnostic accuracy. Thus, four-fifths of the ovarian cancer cases can be treated confidently to prevent further morbidity and improve quality of life, even with the limited facility. The reactive cytological changes, like increased nuclear-cytoplasmic volume, mild pleomorphism, and prominent nucleoli, mimicked suspicion for malignancy, even in the endometriosis, lowering its accuracy by 3% [28]. (**Figure 6**).

Artificial Intelligence (AI) can also be used to predict cancer, but it also requires input variables, which are already in practice, such as imaging and biomolecular analysis. Still, there may be some ethical issues and loss of human touch in handling a life. Analysis of clinical history (reproductive, family, and genetic history), tumor images, biomarkers, and histopathological reports can be performed by using machine learning models and convolutional neural networks (CNNs) to predict ovarian cancer and decide further intervention [29].

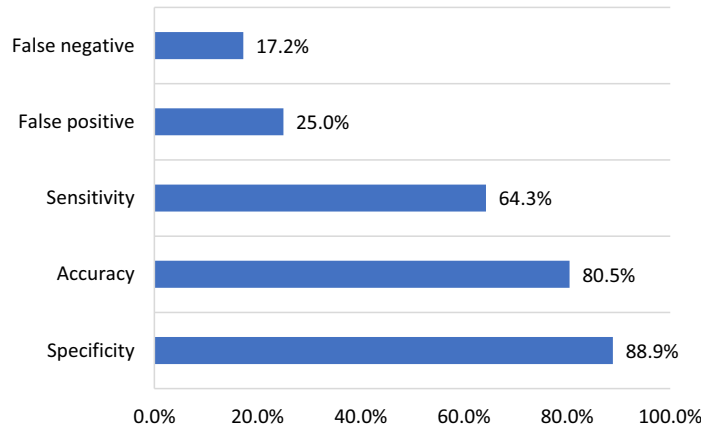


Figure 6.
 Diagnostic accuracy of tumor imprint cytology of ovarian cancer [18].

3. Conclusion

In the absence of a facility-based clinical protocol and an ovarian cancer screening tool, clinical judgment supported by diagnostic aids will be the ultimate means to detect and treat ovarian cancer. Ununiform cancer care practice invites further dilemma to standardize the treatment protocol. Currently, only the secondary preventive intervention is available globally, with spatial discrepancies in its practice due to differential resource distribution. There is a need to mitigate financial toxicity and prevent disability and premature death. Step-wise reorganization of available means of cancer prediction in the form of a model or approach would be the solution for customized care.

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Conflict of interest

The author declares no conflict of interest.

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Impact of Chemokine Axes on Survival and Tumor Progression in Ovarian Cancer

Deok-Soo Son and Samuel Evans Adunyah

Abstract

Chemokines, by binding to specific G protein-coupled receptors, orchestrate cell migration critical for development, inflammation, and immune responses. In cancer, chemokines regulate tumor cell proliferation, angiogenesis, stem-like cell traits, and metastasis, significantly influencing tumor immunity and disease progression. The chemokine profile within the tumor microenvironment shapes immune cell composition and intercellular interactions via distinct chemokine axes, thereby affecting cancer prognosis. Ovarian cancer primarily spreads within the peritoneal cavity through peritoneal dissemination, differently from hematogenous metastasis through blood and lymph vessel spread observed in other cancer types. This review synthesizes the multifaceted roles of chemokines in ovarian cancer, the deadliest gynecologic malignancy with poor survival rates. By integrating evidence from cell lines, animal models, and clinical studies, this work elucidates the pivotal role of chemokines in driving ovarian cancer progression and peritoneal metastasis. It highlights the differential impacts of specific chemokine axes on patient survival: CCL7/8-CCR2 and CXCL13-CXCR5 axes associated with improved outcomes; CXCL7-CXCR2, CXCL14, and CXCL12-CXCR7 axes linked to poorer survival; XCL1/2-XCR1, CCL15/16/23-CCR1, CCL11/15/26-CCR3, CCL4/11/16-CCR5, CCL27-CCR10, CXCL6-CXCR1, and CXCL17-CXCR8 axes showing no significant effect; and the CCL18 and CXCL11-CXCR3 axes yielding controversial results.

Keywords: ovarian cancer, chemokines, tumor microenvironment, peritoneal metastasis, overall survival

1. Introduction

Ovarian cancer is the most lethal gynecological malignancy, primarily due to late-stage diagnosis and nonspecific early symptoms. This heterogeneous disease encompasses epithelial (~90% of cases, originating from the ovaries, fallopian tubes, or peritoneum), germ cell, and sex cord-stromal tumors [1]. Epithelial subtypes include high-grade serous carcinoma (HGSC; 70%), endometrioid carcinoma (10%), clear cell carcinoma (10%), mucinous carcinoma (3%), and low-grade serous carcinoma (<5%) [2]. Malignant ascites, a hallmark of advanced disease, promotes

peritoneal dissemination, therapeutic resistance, and poor clinical outcomes [3]. Ascites and omental tumor microenvironments create a premetastatic niche and immunosuppressive milieu by secreting cytokines and chemokines, thereby driving tumor proliferation, metastasis, and immune evasion [4].

Chemokines are chemoattractant cytokines that recruit immune cells to the tumor microenvironment by interacting with specific receptors, shaping the immune contexture, and influencing cancer progression and prognosis [5]. They are classified into four groups based on the number of amino acids between the first cysteine (C) motifs: C (XCL1-2), CC (CCL1-28), CXC (CXCL1-17), and CX3C (CX3CL1). Each chemokine binds to specific chemokine receptors (XCR1, CCR1-10, CXCR1-8, and CX3CR1), regulating angiogenesis, immune networks, and cellular functions, thus forming distinct chemokine axes as follows: the XCL-XCR axis, the CCL-CCR axis, the CXCL-CXCR axis, and the CX3CL-CX3CR axis (**Table 1**).

Chemokines bind to specific G protein-coupled receptors (GPCRs) on target cell surfaces, initiating intracellular signaling cascades, including PLC, PI3K, MAPK, and JAK pathways. These cascades drive diverse cellular responses, such as migration, adhesion, survival, proliferation, and differentiation (**Figure 1**).

Chemokine axis family	Chemokine axis subfamily
The XCL-XCR axis	The XCL1/2-XCR1 axis
The CCL-CCR axes	The CCL3/5/7/8/14/15/16/23-CCR1 axis
	The CCL2/7/8/13/16-CCR2 axis
	The CCL5/7/11/13/14/15/24/26/28-CCR3 axis
	The CCL17/22-CCR4 axis
	The CCL3/4/5/8/11/14/16-CCR5 axis
	The CCL20-CCR6 axis
	The CCL19/21-CCR7 axis
	The CCL1/16-CCR8 axis
	The CCL25-CCR9 axis
	The CCL27/28-CCR10 axis
The CXCL-CXCR axes	The CXCL6/7/8-CXCR1 axis
	The CXCL1/2/3/5/6/7/8-CXCR2 axis
	The CXCL4/9/10/11-CXCR3 axis
	The CXCL12-CXCR4 axis
	The CXCL13-CXCR5 axis
	The CXCL16-CXCR6 axis
	The CXCL11/12-CXCR7 axis
	The CXCL17-CXCR8 axis
The CX3CL-CX3CR axis	The CX3CL1-CX3CR1 axis
Orphan chemokines CCL18 and CXCL14.	

Table 1.
Human chemokine axis.

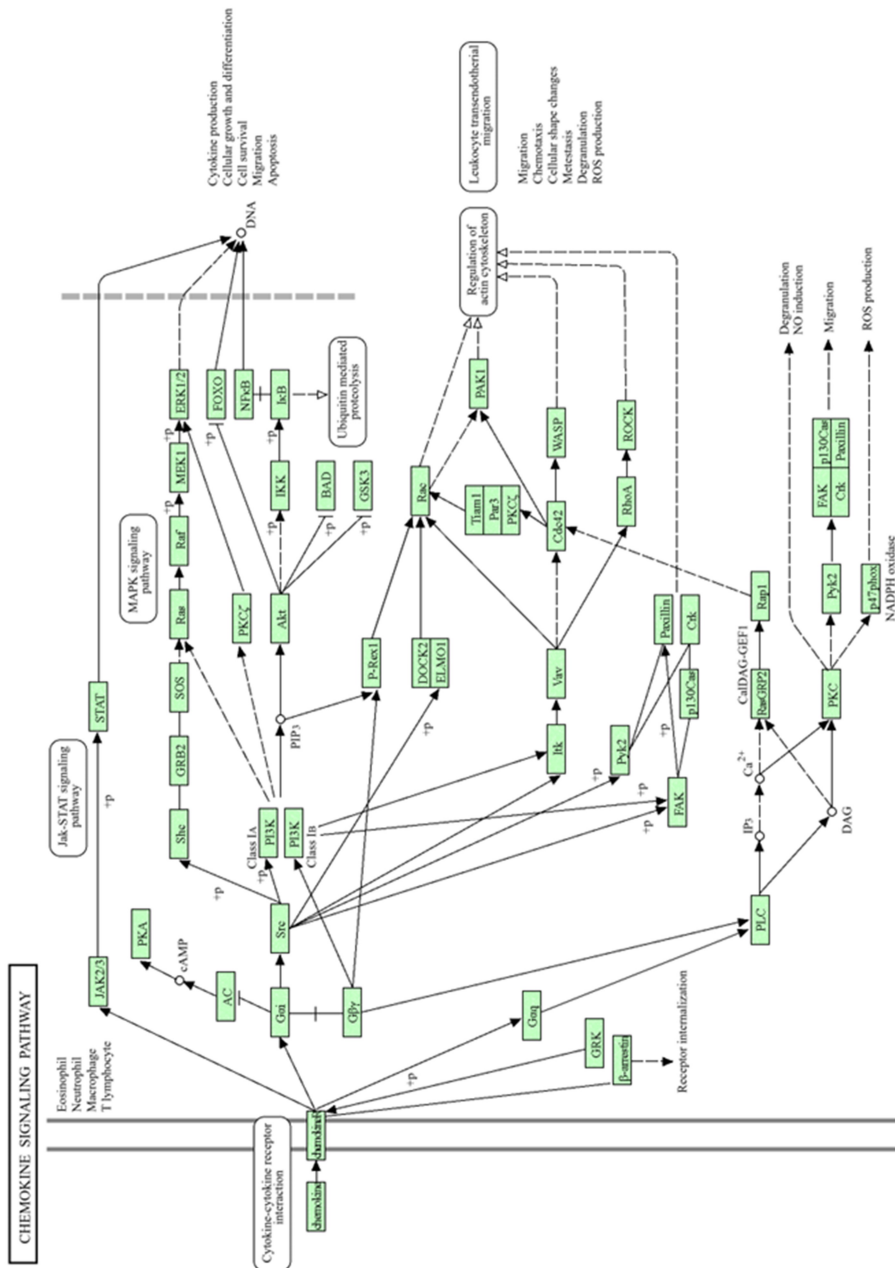


Figure 1. Chemokine-mediated signaling pathway. Modified and simplified from the KEGG PATHWAY database (<https://www.kegg.jp/pathway/hsa04062>). Arrow and block lines indicate positive and negative effects, respectively. PLC: phospholipase C; PKC: protein kinase C; PI3K: phosphoinositide 3-kinase; akt: protein kinase B; IKK: ikkappa kinase; iκb: inhibitor of nuclear factor kappa B; nf-κb: nuclear factor kappa-light-chain-enhancer of activated b cells; FOXO: forkhead box O; src: proto-oncogene tyrosine-protein kinase src; SHC: SHC adaptor protein; GRB2: growth factor receptor-bound protein 2; SOS: son of sevenless; ras: ras sarcoma virus; raf: rapidly accelerated fibrosarcoma; MEK1: mitogen-activated protein kinase 1; erk1/2: extracellular signal-regulated kinase 1/2; JAK: janus kinases; STAT: signal transducers and activators of transcription.

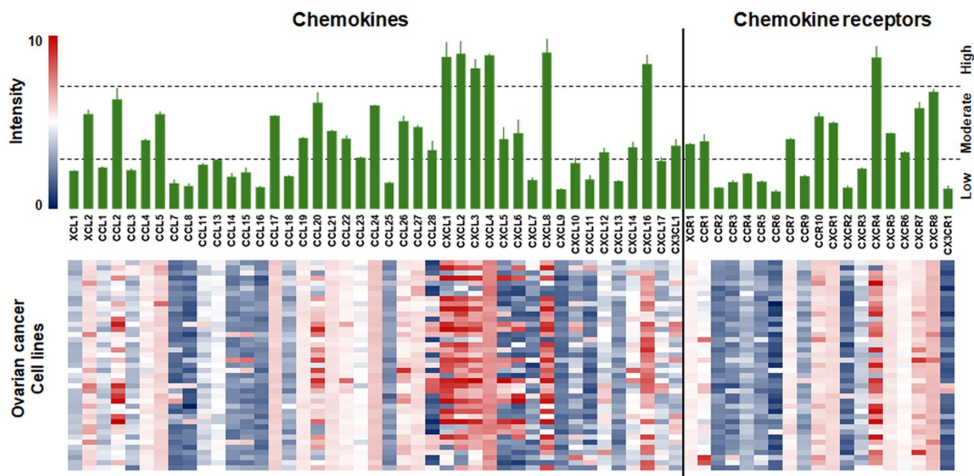


Figure 2. Chemokine expression profiles in ovarian cancer cell lines. Heatmaps illustrating the expression profiles of chemokines and chemokine receptors in 41 ovarian cancer cell lines, sourced from the NCBI GEO database (GSE34615; <http://www.ncbi.nlm.nih.gov/geo/>). The intensity, represented by green bars, reflects the average expression values and SEM across the 41 cell lines. Dotted lines delineate low, moderate, and high expression levels.

The chemokine signaling axis orchestrates the peritoneal tumor microenvironment in ovarian cancer by facilitating communication among cancer, immune, and stromal cells (**Figure 1**).

Chemokine signatures in ovarian cancer reveal distinct expression profiles between cell lines and tumor tissues, driven by the heterogeneity of the tumor microenvironment [6]. In human ovarian cancer cell lines, dominant expression of chemokines CXCL1-4, CXCL8, CXCL16, and the receptor CXCR4 was observed (**Figure 2**). Notably, ovarian cancer exhibits a high frequency of p53 mutation compared to other cancer types [7]. These mutations correlate with distinct chemokine signatures and differential overall survival outcomes between p53 wild-type and mutant ovarian cancers [7]. This chapter compiles comprehensive literature data on chemokines in ovarian cancer, encompassing clinical characteristics in patients, in vitro findings from ovarian cancer cell models, and in vivo results from animal models for ovarian cancer. This chapter elucidates the functional roles of chemokine axes in ovarian cancer, focusing on chemokine signature, overall survival, and clinicopathologic features in patients. Additionally, it explores the molecular mechanisms of chemokines derived from ovarian cancer cells and tumor-bearing animal models. Overall survival data for serous ovarian cancer (n = 1207) were sourced from the Kaplan-Meier Plotter database (<https://kmplot.com/analysis/index.php?p=service&cancer=ovar>).

2. The XCL1/2-XCR axis

XCL1, XCL2, and XCR1 expression levels do not significantly influence survival [7].

3. The CCL-CCR axis

3.1 The CCL3/5/7/8/14/15/16/23-CCR1 axis

High CCL3 levels correlate with improved survival in the serous subtype (HR = 0.75; 95% CI = 0.62–0.90), but show no association with TP53 mutation status (mutant vs. wild-type) [7]. CCL3 antibody reduces tumor metastasis in animal models [8]. CCL5 is associated with improved survival in the serous subtype (HR = 0.81; 95% CI = 0.68–0.97) and TP53 mutant tumors [7]. Elevated CCL5 expression correlates with tumors harboring DNA damage repair gene somatic mutations [9, 10] and T-cell infiltration [11]. Macrophage (M ϕ)-derived CCL5 promotes tumor-mesothelial cell adhesion [12]. CCL5 increases cell proliferation through MEK/Erk activation and Jun, NF- κ B2, and Traf2 expression [13], and stromal-secreted CCL5 induces chemoresistance via IL-6/PYK2 signaling [14]. CCL5 was elevated in cancer stem-like cells (CSCs) [15], driving endothelial differentiation and tumor angiogenesis through CCR1/3/5-dependent NF- κ B and STAT3 pathways [16]. In non-CSCs, CCL5 promotes epithelial-mesenchymal transition (EMT), MMP9, and tumor invasion via NF- κ B activation [17, 18]. Cisplatin-induced CCL5 secretion from cancer-associated fibroblasts (CAFs) promotes cisplatin resistance through STAT3 and Akt activation [19]. Additionally, CCL5 enrichment in immune cells (T and NK cells) may support cancer cell survival in ascites [20]. CCL5 antibodies boost the antitumor effects of PARP inhibitors in murine models [21].

CCL7 levels correlate with improved survival in the serous subtype (HR = 0.75; 95%CI = 0.63–0.90), but show no association with TP53 mutation status [7]. Peritoneal M ϕ s from patients exhibit increased CCL7 expression, which promotes tumor cell invasion [22]. CCL8 levels correlate with improved survival in the serous subtype (HR = 0.77; 95%CI = 0.66–0.90), but show no association with TP53 mutation status [7]. CCL14 levels are linked to poor survival in the serous subtype (HR = 1.28; 95%CI = 1.07–1.52), but show no association with TP53 mutation status [7]. Contrarily, CCL14 upregulation in tissue microarray samples is associated with better prognosis [23]. Neither CCL15 nor CCL16 impacts survival outcomes [7]. CCL23 shows no impact on survival outcomes [7], although high CCL23 levels are detected in ascites and sera of patients [24]. CCL23, secreted by M ϕ s, contributes to immunosuppression by inducing T-cell exhaustion [24] and promotes tumor colonization in the omentum via CCR1 by activating Erk1/2 and PI3K pathways [25]. CCR1 shows no impact on survival outcomes [7]. Blocking CCR1 reduces the invasion of CSCs [18].

3.2 The CCL2/7/8/13/16-CCR2 axis

CCL2 is associated with improved survival in the serous subtype (HR = 0.78; 95% CI = 0.65–0.94), but shows no association with TP53 mutation status [7]. CCL2 promotes cell proliferation, migration, and invasion via the MEK/Erk/MAP3K19 and PI3K/Akt/mTOR pathways [26–28]. CCL2 is expressed at higher levels in the ascites of obese mice [29]. Serum CCL2 levels are elevated in primary ovarian cancer, correlating with histological grade and age at diagnosis, but not with overall survival [30], while both the lowest and highest values of CCL-2 show poor prognosis [31]. CCL2 is highly expressed in tumors with intraepithelial T cells [11], but is downregulated in most cancer cell lines and primary adenocarcinomas [32].

Increased tumoral CCL2 expression correlates with improved survival [33]. However, low CCL2 expression in tissue microarray is a feature of HGSOC and does not correlate with survival [34]. CCL2 contributes to paclitaxel resistance via NF- κ B-mediated PI3K/Akt activation, while CCR2 inhibitors enhance paclitaxel sensitivity in murine models [35]. Similarly, CCL2 antibodies improve paclitaxel and carboplatin therapy outcomes [36]. CCL2 from cancer-associated mesothelial cells drives peritoneal metastasis via the p38-MAPK pathway [37], and stromal CCL2 induces IL-6/PYK2-dependent chemoresistance [22]. Omental adipocyte-derived CCL2 enhances cell migration and metastasis via the PI3K/Akt/mTOR pathway [28].

CCL7, CCL8, and CCL16 are described within the context of the CCL3/5/7/8/14/15/16/23-CCR1 axis. CCL13 levels correlate with improved survival in the serous subtype (HR = 0.67; 95% CI = 0.57–0.79), but show no association with TP53 mutation status [7]. Conversely, high tumoral CCL13 expression is associated with shorter survival and promotes migration and invasion while inhibiting apoptosis [38]. CCL13 upregulates MMP-2, MMP-9, N-cadherin, vimentin, and Bcl2/Bax, downregulates E-cadherin, and activates the p38 MAPK pathway, thereby enhancing cancer progression [38]. CCR2 levels correlate with improved survival in the serous subtype (HR = 0.82; 95%CI = 0.69–0.97), but show no association with TP53 mutation status [7]. CCR2 facilitates leukocyte recruitment to the tumor microenvironment, and its genetic deletion reduces tumor burden [39]. CCR2 inhibitors enhance paclitaxel sensitivity in murine models [35] and, when combined with bevacizumab, sustain anticancer effects [40]. CCR2 antagonists reduce CCL2-induced cell invasion and adhesion [41].

3.3 The CCL5/7/11/13/14/15/24/26/28-CCR3 axis

CCL5, CCL7, CCL13, CCL14, and CCL15 are described within the context of the CCL3/5/7/8/14/15/16/23-CCR1 axis and the CCL2/7/8/13/16-CCR2 axis. CCL11 does not affect survival [7]. CCL11 promotes cell proliferation, migration, and invasion, effects that are inhibited by antibodies against CCR2, CCR3, and CCR5, through the activation of Erk1/2, MEK1, and STAT3 [42]. In the serous subtype, CCL24 is associated with favorable survival (HR = 0.83; 95% CI = 0.70–0.97), but shows no association with TP53 mutation status [7]. CCL26 has no survival impact [7]. Conversely, CCL28 is linked to poor survival in the serous subtype (HR = 1.39; 95% CI = 1.10–1.75). CCR3 does not impact survival [7]. CCR3 is highly expressed in ovarian cancer cells, and its specific inhibitor reduces cell invasion [22]. Additionally, CCR3 inhibition suppresses CCL11-induced proliferation, migration, and invasion of cancer cells [43], as well as the invasion of ovarian CSCs [18].

3.4 The CCL17/22-CCR4 axis

CCL17 does not significantly affect survival [7], but it improves survival in other studies using Xenabrowser [44]. CCL22 is associated with improved survival in the serous subtype (HR = 0.83; 95% CI = 0.71–0.98), but shows no association with TP53 mutation status [7]. CCL22 is present in ascitic fluid, where it promotes CCR4 + T-cell enrichment [45, 46]. Plasma CCL22 is elevated in stage IV patients compared to stages I and III [47]. CCR4 shows no survival impact [7]. In a CCL22-secreting ovarian cancer humanized mouse model, CCR4 antibody enhances antitumor immunity by modulating tumor-infiltrating Tregs [48].

3.5 The CCL3/4/5/8/11/14/16-CCR5 axis

CCL3, CCL5, CCL8, CCL11, CCL14, and CCL16 are described within the context of the CCR1/CCR2/CCR3 axis. CCL4 shows no survival impact [7]. CCL4 levels were reduced in the sera of patients [49], but it was highly expressed in tumors with intraepithelial T cells [11]. CCR5 has no impact on survival [7]. CCR5 antagonists suppress CCL5-induced intracellular Ca^{2+} flux and proliferation [50]. CD4^{+} T cells delay the progression of MHC class II-negative ovarian cancer by secreting CCL5, which recruits CCR5⁺ dendritic cells [43]. While CCR5 antagonist maraviroc does not affect cell viability, it enhances apoptosis induction, cell cycle blockage, DNA damage, and ROS formation [51].

3.6 Orphan ligand CCL18

CCL18 is associated with improved survival in the serous subtype (HR = 0.78; 95% CI = 0.67–0.90) [52], but shows no association with TP53 mutation status [7]. Serum CCL18 levels are significantly higher in ovarian cancer [52, 53]. High CCL18 expression correlates with worse FIGO staging and poor survival, which is associated with serum levels, not mRNA levels [53, 54]. ZEB1-induced CCL18 expression promotes M2-TAM aggregation and CD8^{+} T-cell apoptosis, aiding immune escape [55]. CCL18 increases cell migration, invasion, and adhesion, but not proliferation, and ascitic CCL18 levels are correlated with enhanced cell migration, which is attenuated by CCL18 antibodies [54, 56]. High CCL18 mRNA levels are linked to increased metastasis and worse survival, mediated partly through the mTORC2 pathway [57].

3.7 The CCL20-CCR6 axis

CCL20 shows improved survival in the serous subtype (HR = 0.84; 95% CI = 0.70–1.00) but no association with TP53 mutation status [7]. Serum CCL20 levels are elevated in ovarian cancer [58]. The CCL20-CCR6 axis drives metastasis by promoting migration and invasion in high-CCR6 cancer cells, with effects reversed by CCR6 blockade [59]. CCL20 upregulates N-cadherin and versican while downregulating E-cadherin, with CCR6 knockout blocking these changes [59]. Cisplatin-stimulated M ϕ s increase CCL20 production, activating CCR6 on ovarian cancer cells and inducing EMT to enhance cell migration [60]. CCL20 promotes paclitaxel resistance in CD44^{+} CD117^{+} cells via Notch1 signaling [61] and doxorubicin resistance by regulating ABCB1 expression [62]. NF- κ B-mediated CCL20, potentiated by CXCR2, is a key chemokine network in the peritoneal dissemination of ovarian cancer [6]. CCR6 has no impact on survival in the serous subtype [7], while high CCR6 correlates with increased metastasis and poor prognosis in TP53 mutant tumors [60].

3.8 The CCL19/21-CCR7 axis

CCL19 has no overall survival impact [7]. CCL21 has no overall survival impact [7]. However, CCL21 is associated with poor survival in TP53 wild-type tumors [7]. Serum CCL21 levels are elevated in ovarian cancer patients [63]. CCR7 is associated with improved survival in serous ovarian cancer (HR = 0.84; 95% CI = 0.70–1.00),

but shows no association with TP53 mutation status [7]. CCR7 is overexpressed in ovarian cancer, correlating with advanced FIGO stage and lymph node metastasis [64].

3.9 The CCL1/16-CCR8 axis

CCL1 has no overall survival impact [7]. CCL16 is described within the context of the CCL3/5/7/8/14/15/16/23-CCR1 axis. CCR8 is associated with improved survival in serous ovarian cancer (HR = 0.78; 95% CI = 0.67–0.91), but shows no association with TP53 mutation status [7]. The CCL1-CCR8 axis promotes the migration and infiltration of CD4 + CCR8 + Tregs into ovarian tumors [65].

3.10 The CCL25-CCR9 axis

CCL25 is associated with improved survival in the serous subtype (HR = 0.78; 95% CI = 0.66–0.91), but shows no association with TP53 mutation status [7]. CCL25 is linked to a decreased risk of ovarian cancer [44]. High CCL25 and CCR9 expressions are observed in serous adenocarcinoma [66]. CCR9 has no impact on survival [7]. The CCR9-CCL25 axis reduces cisplatin-induced apoptosis by enhancing anti-apoptotic signaling, including Akt activation, as well as GSK-3 β and FKHR phosphorylation [67]. CCR9 antibody inhibits CCL25-induced migration and invasion of cancer cells [66].

3.11 The CCL27/28-CCR10 axis

CCL27 and CCR10 have no overall survival impact [7]. CCL28 is described within the context of the CCL5/7/11/13/14/15/24/26/28-CCR3 axis.

4. The CXCL-CXCR axis

4.1 The CXCL6/7/8-CXCR1 axis

CXCL6 has no overall survival impact [7]. CXCL7 is associated with poor survival in the serous subtype (HR = 1.19; 95%CI = 1.01–1.40), but shows no association with TP53 mutation status [7]. CXCL8 is highly expressed in ovarian cancer cells (**Figure 2**) and is associated with improved survival in the serous subtype (HR = 0.81; 95% CI = 0.69–0.96), but shows no association with TP53 mutation status [7]. Consistently, high CXCL8 expression correlates with better prognosis [68]. CXCL8 is significantly elevated in cancerous tissue, ascites, serum, and recurrent tumors, and is associated with ovarian cancer stage, grade, and lymph node metastasis [69–71]. Proinflammatory cytokines (IL-1, TNF) induce CXCL8 via NF- κ B signaling, while IFN γ upregulates it through JAK1/STAT1 and NF- κ B pathways, promoting proliferation, migration, and invasion [72–74]. TAMs-derived CXCL8 enhances invasion via Wnt/ β -catenin-mediated TRIM46 upregulation [75]. It drives EMT, metastasis, and angiogenesis by acting on endothelial CXCR1/2 receptors, activating the Erk pathway, and promoting endothelial cell proliferation, tube formation, and migration [70, 76, 77]. CXCL8 contributes to paclitaxel resistance via GSK-3 β /p70S6K1 signaling and reduces

bortezomib effectiveness, which is improved by IKK inhibition [78–80]. Proteasome inhibition increases CXCL8 expression, contributing to resistance [78]. CXCL8 knockdown reduces tumor growth and M2 M ϕ infiltration [81]. CXCR1 has no impact on survival [7]. CXCR1 is upregulated in advanced cancer tissues and correlates with stage, grade, and lymph node metastasis [70].

4.2 The CXCL1/2/3/5/6/7/8-CXCR2 axis

CXCL1 is highly expressed in ovarian cancer cells (**Figure 2**) [6, 68, 72]. Serum CXCL1 levels are significantly elevated in patients, increasing with disease stage [82]. High CXCL1 expression in ascites is notable in undifferentiated cancers [83]. CXCL1 promotes tumor progression by: 1) enhancing angiogenesis through CXCR1/2 receptor-mediated endothelial cell proliferation, tube formation, and migration [76]; 2) driving cancer cell proliferation via EGFR transactivation and p38 activation in ovarian fibroblasts [84, 85]. Despite its tumorigenic roles, high serum CXCL1 expression is associated with improved survival [52]. However, CXCL1 mRNA levels have no impact on survival in the serous subtype, with no association with TP53 mutation status [7]. In obese mice, higher circulating CXCL1 levels correlate with earlier ovarian cancer onset, increased peritoneal metastasis, and a trend toward shorter survival [29]. CXCL2 exhibits high expression in ovarian cancer cells (**Figure 2**) and is significantly upregulated in platinum-resistant epithelial ovarian cancer, promoting cisplatin resistance [86]. CXCL2 knockdown or antibody treatment enhances cisplatin sensitivity [86]. CXCL2 is highly expressed in epithelial cancer tissues, correlating with tumor differentiation, stage, and metastasis [87]. However, high CXCL2 expression does not independently predict prognosis [87] and has no impact on survival [7]. CXCL3 expression is high in ovarian cancer cells (**Figure 2**) but significantly reduced in ovarian cancer patients [68]. High CXCL3 expression is associated with better prognosis in the serous subtype (HR = 0.82, 95% CI = 0.70–0.97) and improved outcomes [68], but shows no association with TP53 mutation status [7]. CXCL5 has no impact on survival [7]. Elevated CXCL5 levels are observed in ascites [83]. Bevacizumab combined with paclitaxel and platinum-based chemotherapy reduces serum CXCL5 levels in post-tumor debulking surgery, correlating with improved survival [88]. CXCL6, CXCL7, and CXCL8 are described within the context of the CXCL6/7/8-CXCR1 axis.

CXCR2 expression is elevated in advanced serous ovarian cancer tissues, correlating with higher tumor stage, grade, and lymph node metastasis [70]. High CXCR2 expression is associated with poor survival in TP53-mutant tumors [7] and serves as a prognostic and immunological biomarker, as well as a potential immunotherapeutic target [89]. CXCR2 knockdown reduces tumor growth and M2-M ϕ infiltration [81]. Increased CXCR2 levels in peritoneal fluid, but not serum or tumor tissue, correlate with histological differentiation stage [69]. CXCR2 inhibition re-sensitizes ovarian cancer to cisplatin [90], enhances antitumor and antiangiogenic responses [91], and promotes mitotic catastrophe in both chemo-sensitive and chemo-resistant ovarian cancer cells, independent of p53 status [92]. The CXCL1/8-CXCR2 axis drives progression by upregulating proinflammatory chemokines via EGFR-transactivated Akt and NF- κ B signaling [93]. CXCR2 also negatively regulates p21 via Akt-mediated Mdm2 in a p53-independent manner [94] and enhances metastatic potential through the TAK1/NF- κ B cascade [95]. CXCR2 blockade reduces tumor growth by decreasing tumor-associated

neutrophils and increasing CD8 + T cell activity [96]. CXCR2 promotes ovarian cancer progression through dysregulated cell cycle, reduced apoptosis, and enhanced angiogenesis [97].

4.3 The CXCL4/9/10/11-CXCR3 axis

CXCL4 expression is high in ovarian cancer cells (**Figure 2**) with no impact on survival [7]. CXCL9 is downregulated in ovarian cancer tissues [98]. However, high CXCL9 levels are observed in epithelial ovarian cancer [99] and correlate with tumor stage [100]. High CXCL9 expression is associated with improved overall survival in the serous subtype (HR = 0.76; 95% CI = 0.63–0.92) [68] and TP53-mutant tumors, but not in TP53 wild-type tumors [7]. CXCL9 inhibits tumor growth and enhances anti-PD–L1 therapy in preclinical ovarian cancer models [101]. CXCL9's angiostatic properties may suppress epithelial ovarian cancer progression [102]. CXCL10 expressions are significantly upregulated in ovarian cancer, particularly in serous epithelial tumors and HRD tumors [9, 68, 99]. High CXCL10 expression is associated with longer overall survival in the serous subtype (HR = 0.77; 95% CI = 0.66–0.90) [100] and prolonged prognosis, correlating with increased infiltration of immune cells [103]. Low CXCL10 expression is linked to poor prognosis and reduced immune infiltration [44, 103]. No difference in survival is observed between TP53-mutant and wild-type tumors [7]. CXCL10 inhibits epithelial ovarian cancer progression by enhancing cytotoxic T cell activity and suppressing angiogenesis [104]. It is produced by M1-type TAMs in immune-infiltrated high-grade serous carcinoma [105]. Dendritic cell-derived CXCL10 restrains tumor growth and metastasis by activating cytotoxic T lymphocytes [106]. In contrast, adipocyte-derived CXCL10 in obesity promotes cell migration and invasion [107], and omentum-derived adipose stem cells in ovarian cancer patients are a novel CXCL10 source [108]. CXCL10 overexpression reduces tumor burden and malignant ascites in syngeneic murine high-grade serous carcinoma models, while reduced CXCL10 expression increases ascites and disease progression [109]. Intraperitoneal CXCL10 administration inhibits tumor growth [110]. In BRCA2 wild-type epithelial ovarian cancer, treatment with the CXCL10/CXCR3 antagonist AMG487 attenuates Treg induction and IL10 production [111].

CXCL11 is upregulated in ovarian cancer [68, 104]. High CXCL11 expression is linked to improved survival in the serous subtype (HR = 0.73; 95% CI = 0.61–0.88) and TP53-mutant tumors, but not in wild-type tumors [7]. CXCL11 is associated with reduced ovarian cancer risk [44] and correlates with tumor stage and longer survival [68, 100]. Conversely, high CXCL11 expression in tissue microarray predicts worse survival in HGSOC [112]. CXCL11 promotes M1 M ϕ polarization via the Jak2-Stat1 signaling pathway, acting as a favorable prognostic biomarker [113]. It mediates Twist1-induced angiogenesis in epithelial ovarian cancer [114]. CAFs-derived CXCL11 promotes cell proliferation and migration via CXCR3, which is expressed in malignant cells [115]. CXCR3 expression does not significantly impact overall survival [7]. However, a high CXCR3 immunohistochemistry score in advanced cancer is linked to reduced survival [116], although it is associated with higher tumor grade and lymph node metastasis [115]. CXCR3 mediates cell migration toward malignant ascites, which can be inhibited by CXCR3 antibody [116]. In a p53-negative epithelial ovarian cancer mouse model, CXCR3 antibody treatment reduced tumor ascites and extended survival [111].

4.4 The CXCL12-CXCR4 axis

CXCL12 expression is elevated in tumor tissues [68], in ascites [83], and in obese mouse models [29]. Plasma CXCL12 levels are significantly higher in FIGO stage III patients compared to stage I [117]. High CXCL12 expression is linked to poor survival in the serous subtype (HR = 1.32; 95% CI = 1.13–1.55) [68] and TP53 wild-type tumors [7]. Primary and recurrent serous carcinoma, including CXCL12-positive immune cells, correlate with chemosensitivity and improved overall survival [118]. CXCL12-positive CAFs are linked to poor prognosis and chemotherapy resistance in HGSOC [119]. The CXCL12-3'A polymorphism is associated with poor chemotherapy response and reduced survival rates [120]. CXCL12 promotes cell proliferation, migration, and invasion by activating Erk1/2, Akt [121, 122], $\alpha\beta 6$ integrin [123], and MMP-9/MMP-2 [124], and through EGF receptor transactivation [125]. CXCL12 suppresses ARHGAP10 expression, enhancing cell invasion [126], and elicits intracellular calcium flux, migration, and integrin expression changes [127]. CAF-derived CXCL12 promotes peritoneal metastasis by inducing EMT [128]. CXCL12 knockdown reduces cell proliferation and tumor growth [129].

CXCR4 is highly expressed in ovarian cancer cells (**Figure 2**). High CXCR4 immunohistochemistry score is associated with unfavorable prognosis and reduced chemosensitivity, correlating with lower overall survival [130]. However, some studies link high CXCR4 mRNA expression to better prognosis [131]. CXCR4 expression is linked to improved survival in TP53-mutant tumors [7]. The CXCL12-CXCR4 axis promotes cell proliferation, migration, invasion, and metastasis by activating Erk1/2, Akt [121], integrin $\beta 1/\beta 3$ [132], RhoA, Rac-1/Cdc42 [133], and NF- κ B pathways, and inducing EMT [134]. CXCR4 mediates peritoneal dissemination via Sp1-dependent CXCL12 signaling and extracellular matrix-directed spheroid formation [135]. CXCL12-stimulated growth is abrogated by CXCR4 antibodies [136], while cisplatin-induced CXCR4 expression promotes proliferation of CSCs [137]. The Notch pathway enhances tumor growth and metastasis via the CXCL12-CXCR4 axis [138]. CXCR4 antagonists (e.g., AMD3100) inhibit CXCL12-induced proliferation, migration, and EMT [121, 134], enhance paclitaxel chemotherapy [139], and reduce tumor burden, metastasis, and angiogenesis [140]. They also increase tumor apoptosis/necrosis while reducing Treg infiltration [129]. CXCR4 blockade inhibits tumor growth and metastasis by enhancing CD8 + T cell infiltration and reducing immunosuppression [141]. CXCR4 knockdown inhibits proliferation, invasion, and metastasis, promotes apoptosis via ASK1/c-Jun activation, and enhances chemosensitivity by reducing RhoA, Rac-1/Cdc42, Wnt, vimentin, and Slug expression [130, 133, 140, 142].

4.5 The CXCL13-CXCR5 axis

Ovarian cancer cells typically exhibit low CXCL13 expression [68, 104]. High CXCL13 levels in ascites are observed in obese mice [29] and are linked to improved survival in the serous subtype and TP53 mutant tumors [7, 68, 143]. CXCL13 is generally associated with a decreased risk of ovarian cancer [44], though one study reported an increased risk [144]. The positive association with CXCL13 is stronger in non-HGSOC, overweight/obese women, and postmenopausal women [144]. High CXCL13 expression correlates with increased infiltration of CXCR5-expressing CD8 + T cells, enhancing the immune response [143]. CXCL13 expression is associated

with tumor stage and longer overall survival [100]. CXCR5 expression levels are linked to tumor stages [145]. High CXCR5 expression is associated with improved survival in the serous subtype [145], but shows no association with TP53 mutation status [7].

4.6 Orphan ligand CXCL14

CXCL14 expression is upregulated in ovarian cancer tissues [68, 104], while healthy controls have higher serum CXCL14 levels [146]. High CXCL14 expression is linked to poor survival in the serous subtype (HR = 1.26; 95%CI = 1.08–1.48) [68, 147] but shows no association with TP53 mutation status [7]. Upregulated CXCL14 promotes cell proliferation and metastasis by activating the Wnt/ β -catenin signaling pathway [147].

4.7 The CXCL16-CXCR6 axis

CXCL16 is highly expressed in ovarian cancer cells (**Figure 2**) and tumor tissues [68]. CXCL16 expression does not affect survival [7, 68]. Elevated serum CXCL16 independently predicts poor survival [148]. However, low CXCR6 expression is associated with shorter survival [145]. High CXCL16 levels are linked to aggressive ovarian cancer, promoting disease progression through CXCR6 activation and MMP modulation [149]. TAMs enhance cisplatin resistance in ovarian cancer cells via the CXCL16-CXCR6 axis by increasing RNA methylation [150]. CXCL16 knockdown in TAMs or CXCR6 in ovarian cancer cells reduces cisplatin resistance [150]. High CXCR6 expression is associated with improved survival in the serous subtype (HR = 0.83; 95% CI = 0.70–1.00) but shows no association with TP53 mutation status [7].

4.8 The CXCL11/12-CXCR7 axis

CXCL11 and CXCL12 are discussed within the CXCL4/9/10/11-CXCR3 and CXCL12-CXCR4 axes, respectively. CXCR7 levels are high in ovarian cancer tissues [145]. High CXCR7 expression is associated with poor survival in the serous subtype (HR = 1.26; 95%CI = 1.06–1.50) [145] but shows no association with TP53 mutation status [7]. The CXCL11-CXCR7 axis, under ER α control, promotes EMT and metastasis in ovarian cancer cells [151]. The CXCL12-CXCR7 axis enhances cell invasion by upregulating MMP-9 expression via the p38 MAPK pathway [152].

4.9 The CXCL17-CXCR8 axis

CXCL17 does not affect survival in ovarian cancer [7, 68]. However, CXCL17 levels are elevated in ovarian cancer tissue [68]. CXCR8 has no impact on survival in the serous subtype.

5. The CX3CL1-CX3CR1 axis

CX3CL1 is elevated in the sera of advanced ovarian cancer patients [82]. High CX3CL1 expression correlates with worse survival in advanced HGSOC [153]. However, it shows a better survival in the serous subtype (HR = 0.84; 95%

CI = 0.71–0.99), but shows no association with TP53 mutation status [7]. Through binding to CX3CR1, CX3CL1 promotes Akt activation and cell proliferation, driving intraperitoneal tumor growth despite increased T-cell recruitment [153]. CX3CR1 expression is associated with poor survival in the serous subtype (HR = 1.26; 95% CI = 1.06–1.50) [154], but shows no association with TP53 mutation status [7]. Hypoxia-inducible factor-1 α upregulates CX3CR1 expression, promoting EMT in ovarian cancer cells [155].

6. Summary/conclusion

Chemokines significantly influence ovarian cancer progression by modulating the peritoneal tumor microenvironment through immune cell recruitment, cell-to-cell communication, metastasis, chemoresistance, and tumor growth, ultimately affecting prognosis and survival. Chemokine axes primarily drive cell migration and invasion over proliferation, altering the immune contexture and overall survival. They regulate EMT genes, immune cell infiltration, tumor size, grade, and stage, while some promote tumor growth and angiogenesis by enhancing cell viability and angiogenic gene expression. Certain chemokines also contribute to cancer recurrence and chemoresistance, reducing therapeutic efficacy.

In ovarian cancer, survival outcomes vary by chemokine-receptor axis (**Figure 3A**): The XCL-XCR axis shows unchanged survival. Survival outcomes in the CCL-CCR axis are as follows: good survival in CCL3, CCL5, CCL7, CCL8, CCL20, CCL22, CCL24, CCL25, CCR2, CCR7, and CCR8; poor survival in CCL28; unchanged survival in CCL1, CCL4, CCL11, CCL15, CCL16, CCL19, CCL23, CCL26, CCL27, CCR1, CCR3, CCR4, CCR5, CCR9, and CCR10; controversial survival in CCL2, CCL13, CCL14, CCL17, CCL18, CCL21, and CCR6. Survival in the CXCL-CXCR axis are as follows: good survivals in CXCL3, CXCL8, CXCL9, CXCL10, CXCL13, CXCR5, and CXCR6; poor survivals in CXCL7, CXCL12, CXCL14, CXCR2, CXCR7, and CX3CR1; unchanged survival in CXCL2, CXCL4, CXCL5, CXCL6, CXCL17, CXCR1, and CXCR8; controversial survival in CXCL1, CXCL11, CXCL16, CXCR3, and CXCR4. Orphan chemokines CCL18 and CXCL14 have controversial and poor survival, respectively. Survival in the CX3CL1-CX3CR1 axis shows controversial survival for CX3CL1 and poor survival for CX3CR1.

Chemokine axes associated with patient survival are summarized as follows (**Figure 3B**): CCL7/8-CCR2 and CXCL13-CXCR5 correlate with improved survival; CXCL7-CXCR2, CXCL14, and CXCL12-CXCR7 with poor survival; XCL1/2-XCR1, CCL15/16/23-CCR1, CCL11/15/26-CCR3, CCL4/11/16-CCR5, CCL27-CCR10, CXCL6-CXCR1, and CXCL17-CXCR8 show no significant association; while CCL18 and CXCL11-CXCR3 display conflicting associations. Mechanistically, CCL7/8-CCR2 and CXCL13-CXCR5 likely enhance survival by recruiting leukocytes and cytotoxic CD8⁺ T cells into the tumor microenvironment [39, 143], thereby suppressing tumor progression. In contrast, CXCL7-CXCR2 promotes tumor growth and poor survival by increasing M2-M ϕ infiltration, activating Akt and NF- κ B, and reducing CD8⁺ T cell infiltration and p21 expression [81, 93, 94, 96]. CXCL14 appears to decrease survival by promoting proliferation and metastasis via Wnt/ β -catenin activation [147]. Similarly, CXCL12-CXCR7 likely induces ERK1/2 and Akt activation and upregulates MMP-9, enhancing migration and invasion, and leading to poor survival [121, 122, 124, 152].

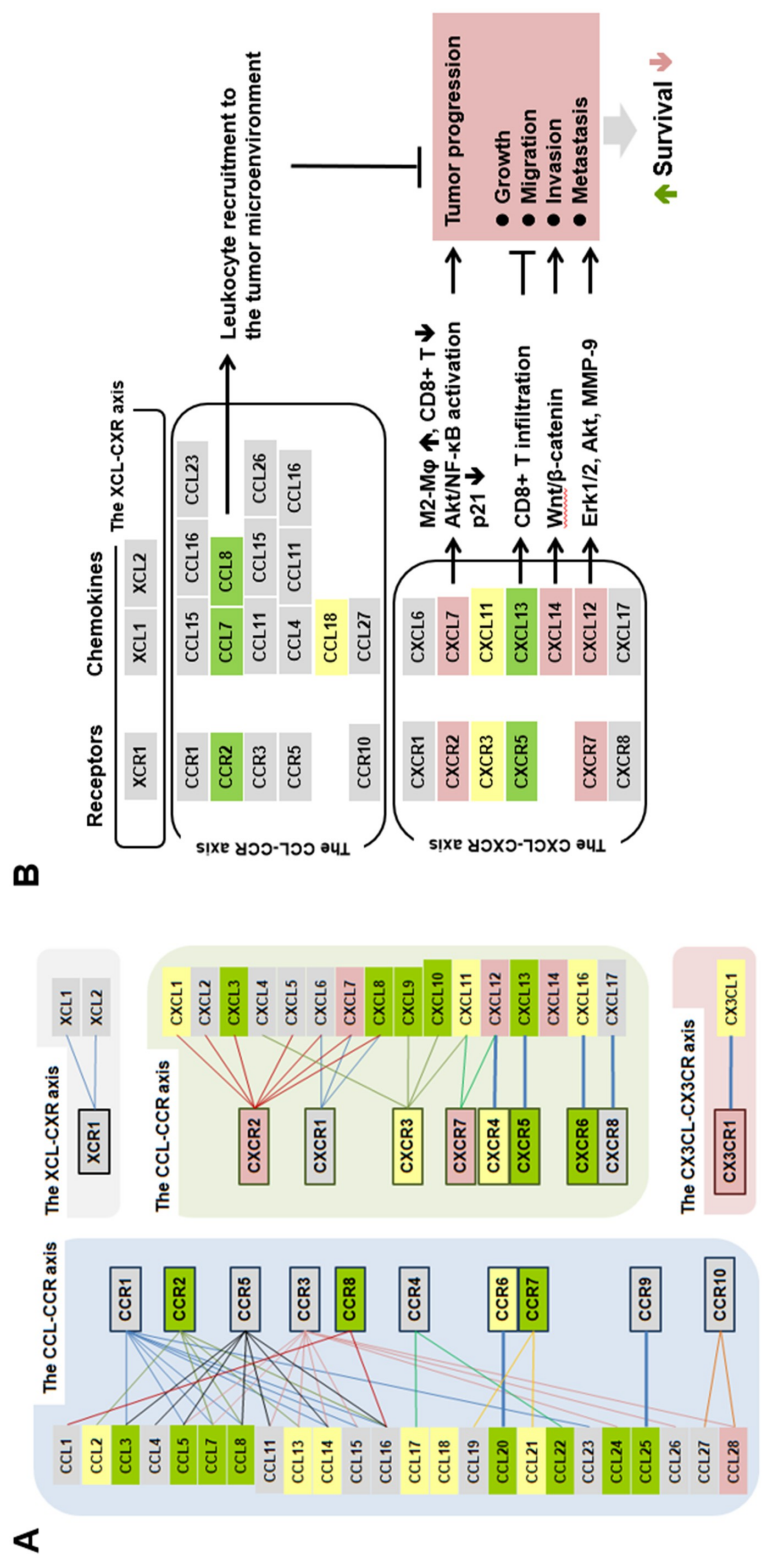


Figure 3. Impacts of chemokine axis on overall survival in ovarian cancers. A) Effects of chemokines and their receptors on patient overall survival. B) Schematic overview of the primary chemokine-receptor axes influencing survival outcomes, with an integrated diagram depicting their downstream functional effects on tumor progression, immune infiltration, and patient prognosis. Green: good survival; pink: poor survival; gray: unchanged survival; yellow: controversial survival.

Conflicts in survival outcomes reported across studies may arise from methodological differences, variations in patient cohorts, or inconsistencies in sample measurement, underscoring the need for additional research. Although a single chemokine may exert a dominant effect in isolated cell models, its influence can vary dramatically when interacting with other cell types within the tumor microenvironment. In the peritoneal tumor microenvironment of ovarian cancer, distinct chemokine expression profiles among tumor cells, stromal cells, immune cells, and adipocytes reveal intricate cell-to-cell communication networks that cannot be explained by any one chemokine alone. Despite extensive study of CXCL12 and CXCR4, the roles of many other chemokines in ovarian cancer remain poorly understood, warranting further investigation. Chemokines drive ovarian cancer progression through specific receptor interactions, modulating the peritoneal tumor microenvironment by recruiting immune cells, facilitating cell-to-cell crosstalk, promoting metastasis and chemoresistance, and enhancing tumor growth, ultimately influencing patient prognosis and survival.

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Biomarkers in Ovarian Cancer

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Abstract

Biomarkers help differentiate between benign and malignant ovarian tumors. Biomarkers are like specialized messengers within the blood: measurable molecules released by cells that can signal changes or abnormalities. In ovarian cancer, they underpin early detection, diagnosis, prognosis, and monitoring of treatment response. Clinically, carbohydrate antigen 125 and HE4 are foundational but perform best when combined and embedded in algorithms such as the risk of ovarian malignancy algorithm, the OVA1 multivariate index assay (OVA1), and the second-generation OVA1/Overa multivariate index assay (OVERA) to refine risk stratification for adnexal masses and to aid surveillance. Additional markers – including kallikreins, prostein, vascular endothelial growth factor, transferrin, transthyretin, and apolipoprotein A-I – can strengthen diagnostic accuracy and convey prognostic insight. Osteopontin is used to assess progression and metastasis and may anticipate a relapse earlier than traditional markers. Histologic differentiation benefits from panels tailored to tumor subtype, with alpha-fetoprotein (AFP), inhibin A/B, lactate dehydrogenase (LDH), human chorionic gonadotropin (hCG), carcinoembryonic antigen, and CA 19–9 particularly informative for germ-cell and mucinous tumors. Beyond single analytes, high-throughput proteomics and glycoproteomics, together with epigenetic and liquid-biopsy approaches – circulating tumor DNA, circulating tumor cells (CTCs), microRNAs, long noncoding and circular RNAs – offer minimally invasive, real-time windows into disease biology and therapeutic response. Because no single marker is sufficient, combining multiple biomarkers and advanced analytical approaches is essential to tailor treatment to individual patients and to move toward earlier detection, more precise prognostication, and truly personalized care in ovarian cancer.

Keywords: ovarian cancer, biomarkers, diagnosis, proteomic markers, epigenetic markers

1. Introduction

Because ovarian cancer (OC) is often asymptomatic until it has progressed to an advanced stage, it is referred to as “the silent killer” and is one of the deadliest cancers in the group. Its five-year survival rates are lower than those of endometrial and cervical cancer, the two most prevalent gynecological cancers. The emergence of

nonspecific clinical symptoms and the absence of reliable biomarkers and testing techniques are two factors that contribute to the diagnostic delay. With survival rates as high as 90% in Stage I, 70% in Stage II after five years, and 20% or fewer in Stages III–IV, the general prognosis for OC remains poor [1]. Poor prognosis is further influenced by a high recurrence rate (70–80%) [2]. Due to the genetic and phenotypic heterogeneity of these cancers, no single tumor marker can identify every variation. Any measurable trait that can be tested and assessed objectively as a sign of a pathogenic process, a normal biological process, or a pharmacologic reaction to a therapeutic intervention is called a biomarker. A variety of macromolecules, such as DNA, mRNA, proteins, metabolites, or processes such as angiogenesis, proliferation, or cell death, can serve as biomarkers. In the diagnosis, prognosis, and therapy monitoring of OC, biomarkers are essential. Glycan structures can be noticeably altered in cancer cell-produced glycoproteins [3]. In addition to being receptors, growth factors, cytokines, or by-products of aberrant metabolism, tumor markers may also include distinct extracellular matrix or cell adhesion molecules. Autoantibodies produced by the body against tumor antigens may also serve as indicators. In a perfect world, tumor markers would objectively reflect tumor burden, be highly tumor-specific, and be produced in sufficient quantities to enable quick, simple, affordable, and noninvasive identification of minimal disease. However, this is not the case in practice today. The guiding principles of serum marker technology demand strict protocols for gathering clinical data, using analytical methods, and interpreting the results. For OC, there is no distinct marker. Many biomarkers have been investigated and employed over time to evaluate the state, course, and effectiveness of medication therapy for this type of illness. Serum-based biomarkers for the clinical management of OC will be the primary focus of this chapter.

This chapter will discuss some well-known biomarkers, in addition to those that have received clinical approval. The final segment will address new areas of ovarian cancer biomarker development, such as proteomics and epigenetic markers, with an emphasis on initiatives fueled by high-throughput technology.

2. Serum markers for ovarian cancer

Currently, several serum biomarkers are utilized in the detection of OC, including carbohydrate antigen (CA-125), human epididymis protein 4 (HE4), kallikreins (KLKs), prostasin (PSN), transthyretin (TTR), transferrin (TF), and vascular endothelial growth factor (VEGF). For plasma-based screening, apolipoprotein A-I (ApoA-I) and osteopontin (OPN) are commonly assessed. In addition to diagnostic markers, prognostic indicators also play a crucial role in OC. Some, such as CA-125, OPN, and VEGF, serve dual roles in both diagnosis and prognosis. Others, including bikunin and creatine kinase B (CKB), are primarily associated with the prediction of cancer development rather than diagnosis.

2.1 Carbohydrate antigen 125

The most popular serum marker for OC diagnosis is CA-125. Elevated amounts of this protein, which is found on the surface of ovarian cancer cells, may be a sign of the disease. For many years, the only marker available for tracking therapy response

and identifying recurrence in OC patients was CA-125. However, CA-125 is not sensitive enough to detect most occurrences of ovarian cancer in its early stages when used alone. CA-125 values usually increase exponentially with tumor progression, matching tumor doubling. About 50% of ovarian cancer cases in their early stages and 92% of cases in their late stages have elevated levels [4]. Sadly, increased CA-125 levels are not exclusive to ovarian cancer; they can also be seen in endometrial, breast, gastric, pancreatic, and lung cancers, among other cancers. Furthermore, people with benign gynecological illnesses such as menstruation, pregnancy, endometriosis, ovarian mature teratoma, and pelvic inflammatory disease may have elevated CA-125 values. Even nongynecological diseases such as pancreatitis and hepatitis can have elevated levels [5]. According to studies by Cho et al. and Ustunyurt et al., individuals with mature cystic teratomas had high CA125 levels in 8.4% and 23.3% of cases, respectively [6, 7]. The possibility that this tumor marker could produce false positives from other illnesses must constantly be taken into account by clinicians. With a sensitivity of 67.39% and a specificity of 86.79%, CA-125 by itself can identify early OC recurrence with a threshold of 35 U/mL [8]. The limitations of CA-125 as an OC screening test have been highlighted by some studies, including PLCO and UKCTOCS [9, 10].

Differentiating primary OC from tumors metastatic to the ovary remains a significant clinical challenge. Yedema and colleagues [11] investigated the preoperative distinction between OC and colorectal cancer. They found that using a combination of a positive CA-125 result (>35 U/mL) and a negative carcinoembryonic antigen (CEA) marker significantly improved specificity (Sp) to 100%, with a sensitivity (Se) of 81%. Furthermore, a CA-125/CEA serum ratio exceeding 25 demonstrated the highest diagnostic accuracy, achieving 100% Sp and 91% Se, with an overall test accuracy of 94%. Similarly, Sørensen and Mosgaard [12] examined the diagnostic value of combining CEA and CA-125 to distinguish between malignant ovarian and nonovarian diseases. They reported that 68% of patients with CEA levels above 5 ng/mL had nonovarian malignancies. Conversely, among those with a CA-125/CEA ratio greater than 25, 82% were diagnosed with OC. When the CA-125/CEA ratio threshold was increased from 25 to 100, the Sp rose to approximately 85% [12].

There is ongoing discussion on the predictive value of pretreatment CA-125. Preoperative CA-125 is not an independent prognostic indicator, according to some research [13, 14], but other studies have shown that it can identify poor-prognosis subgroups regardless of stage, since greater levels are linked to a decreased chance of adequate cytoreduction [15–17]. In roughly 87% to 94% of cases, CA-125 dynamics match responder status (regression, stability, or progression) [5]. According to a model put forth by Arab et al., patients who had CA-125 ≤ 420 IU/mL and no liver metastases or severe ascites were more likely to experience the best possible cytoreduction [18]. In patients who initially revert to normal CA-125 levels after main treatment, elevated CA-125 levels can also be used as a marker of disease progression [19]. In order to detect the course of the disease, Rustin et al. [20] showed that a doubling of CA-125 from the upper limit of normal had a sensitivity (Se) of 86% and a specificity (Sp) of 91%. The false-negative rate is reduced to less than 2% by including a second confirmatory test. Likewise, in patients with consistently high levels following main treatment, a doubling of CA-125 from baseline is a good indicator of the course of the disease [21]. Rising CA-125 values typically occur 70% of the time before clinical symptoms appear, with a median

delay of 4.5 months (range: 0.5–29.5 months) [20]. There is still much disagreement, nevertheless, over whether raising CA-125 levels by themselves should lead to the start of additional treatment. In the usual follow-up of all OC patients, the European Society of Gynecologic Oncologists (ESGO) and the European Society of Medical Oncology (ESMO) have advised against totally stopping the use of CA-125 [22]. Increases in CA-125 levels during follow-up are frequently associated with recurrences in the intra-abdominal and peritoneal areas, including the cul-de-sac, vaginal stump, and lymph nodes. Patients without elevated CA-125 levels (<35 mu/L), on the other hand, are more likely to experience recurrences in supradiaphragmatic regions, such as the brain and lungs.

2.2 Human epididymis protein 4

The WFDC2 gene encodes HE4, a 25 kDa glycoprotein that inhibits serine proteases and is found to be upregulated in OC. By triggering the EGFR/MAPK signaling pathway, it is believed to affect tumor cell adhesion, migration, and proliferation [23]. When it comes to identifying early-stage OC, HE4 shows somewhat less Se than CA-125, but it offers more Sp when differentiating between benign pelvic masses and malignant tumors. For OC detection, comprising both early-stage (62–83%) and late-stage (75–93%) illness, HE4 showed the greatest overall Se (72.9%) among all individual biomarkers [24]. Furthermore, HE4 is significantly overexpressed in some OC subtypes; it is expressed in 93% of serous OC and 100% of endometrioid tumors [25]. In several subtypes of OC, HE4 is significantly overexpressed; it is found in 93% of serous OC and 100% of endometrioid tumors [25]. On the other hand, HE4 levels in endometrioma patients are comparable to those in patients with other benign ovarian cysts (53.0 pmol/L vs. 52.8 pmol/L) [26, 27], suggesting that HE4 is a more useful diagnostic marker for OC linked to endometriosis than CA-125. The diagnostic performance of serum HE4 in OC was assessed in a thorough meta-analysis comprising 38 trials and 14,745 patients. The results showed a clinically relevant Sp of 0.92 and a Se of 0.79, highlighting the diagnostic tool's dependability for OC [28]. Nevertheless, HE4 and CA-125 by themselves are insufficient for the early identification of every OC case. In order to improve diagnostic accuracy, Moore developed the risk of ovarian malignancy algorithm (ROMA) in 2009, which combines HE4 and CA-125 [29]. The cutoff values to place patients in a high-risk category using the Roche Diagnostics Laboratory's ECLIA method are 29.9% for menopausal women and 11.4% for premenopausal women. In contrast, the cutoff levels are set at 7.4% and 25.3%, respectively, using Abbott Diagnostics Laboratory's CMIA technique [30]. To properly evaluate the algorithm's results, it is therefore necessary to know the testing procedure that was employed or to consult the laboratory-specific reference values. With an area under the curve (AUC) of up to 0.96, the combined use of CA-125 and HE4 has demonstrated great diagnostic efficiency [31]. In women under 50, this combination demonstrates superior Se and Sp, whereas ROMA performs best in women over 50. While HE4 alone has greater Se than CA-125, it has lower Sp [32]. Moreover, combining CA-125 with HE4 helps account for variations in HE4 levels influenced by external factors such as smoking or hormonal contraception involving both estrogen and progestin. Notably, HE4 levels are elevated by 20–30% in smokers compared to nonsmokers [33]. Ferraro and colleagues found that women on oral contraceptives had significantly lower HE4 levels than those using other

contraceptive methods ($P = 0.008$). As with CA-125, HE4 concentrations appear unlikely to be influenced by BMI [34]. Patients with chronic kidney disease exhibit significantly higher serum HE4 levels, likely because HE4 is produced in the distal convoluted tubules and reduced kidney function diminishes its clearance [35]. According to Shin et al., MRI demonstrates the highest diagnostic accuracy among imaging modalities for OC, followed by CT, with the ROMA algorithm ranking third [36]. In terms of recurrence detection, Lakshmanan et al. found that serum HE4 had comparable Se to CA-125 (85.3% vs. 84.3%) but superior Sp (91.4% vs. 70.2%), and was capable of signaling relapse approximately three months earlier than CA-125 [37]. Liao et al. also observed elevated HE4 levels in the urine of certain patients prior to relapse, despite normal serum levels of both HE4 and CA-125 [38]. Furthermore, a larger retrospective cohort study reported that HE4 could detect recurrence a median of 126 days earlier than clinical confirmation, with elevated HE4 seen in 75% of recurrent cases, compared to only 50% with CA-125 [39]. Based on such findings, the combined use of HE4 and CA-125 has been approved for monitoring OC during follow-up. Although these results are promising, further validation through large-scale, multicenter randomized studies is necessary to solidify HE4's utility in tracking OC recurrence.

To improve patient classification and clinical decision-making, more OC subtype-specific biomarkers must be identified despite intensive research efforts [40]. To differentiate between the histological subtypes of OC, a number of other markers are used, such as CA 19-9, CEA, alpha-fetoprotein (AFP), inhibin A and B, lactate dehydrogenase (LDH), and human chorionic gonadotropin (hCG). Given the increased risk of uncommon ovarian cancers, such as germ cell and sex cord-stromal tumors in this population, the Royal College of Obstetricians and Gynecologists advises assessing tumor markers such as hCG, LDH, and AFP in women under 40 who present with an adnexal mass [41]. CA 19-9 and CEA are used in mucinous OC patients for both diagnostic purposes and disease recurrence monitoring.

2.3 CA 19-9

About 68–83% of mucinous OC have higher amounts of this monosialoganglioside antigen, which is frequently used to diagnose gastrointestinal adenocarcinomas, than nonmucinous subtypes, which only have 28–29% of this antigen. On the other hand, almost 80% of nonmucinous OC cases have high CA-125 [42, 43]. Preoperative increases in CA 19-9, CA-125, and CEA – along with tumor size – can be useful markers for distinguishing between tumor types, according to a retrospective examination of 314 patients with mucinous ovarian tumors [44].

2.4 Carcinoembryonic antigen

CEA is a 200-kDa glycoprotein present during fetal development, arising from embryonic endodermal epithelium and regulated by fetal oncogenes; it usually disappears from the bloodstream after birth. As a nonspecific serum marker, CEA can be elevated in many cancers – including colorectal [45], medullary thyroid, breast, and mucinous OC. In mucinous OC, reported elevations reach 87–88%, though CEA is still less reliable than CA-125 [46]. Clinically, a serum CEA level $>5 \mu\text{g/L}$ but $<10 \mu\text{g/L}$ generally indicates localized disease, lower recurrence risk, and a favorable prognosis; levels $>10 \mu\text{g/L}$ suggests higher recurrence risk and poorer

prognosis, and titers >20 µg/L are commonly associated with metastatic breast or colon cancer. Due to the variability in CEA expression and secretion, levels below 2.5 µg/L cannot definitively exclude the presence of primary, recurrent, or metastatic disease [45]. Moreover, CEA elevation is not specific to any single tumor site, as increases occur in various malignant and nonmalignant conditions (**Table 1**).

National guidelines, such as those from the American College of Obstetricians and Gynecologists (ACOG), the Society of Gynecologic Oncologists (SGO), and the National Institute for Health and Care Excellence (NICE), do not include CEA measurement as a standard part of evaluating adnexal masses.

2.5 Inhibin A and B

Heterodimeric hormones called inhibins are released by testicular Sertoli cells and ovarian granulosa cells. Each inhibin molecule is made up of a beta A or beta B subunit joined with a common alpha subunit, forming inhibin A and inhibin B. The efficacy of inhibin A and B as accurate biomarkers in premenopausal women is limited by their variable levels over the menstrual cycle. However, circulating levels of inhibin A and B decrease to extremely low or undetectable amounts after menopause, when ovarian follicular activity stops. Postmenopausal women with granulosa cell tumors (GCTs) and mucinous epithelial ovarian cancer (OC) have elevated levels of total inhibin. Anti-Müllerian hormone (AMH) and inhibin B are two indicators of GCTs that are especially sensitive. Although the sensitivity (Se) of inhibin B appears to be 93.5% in GCT diagnoses and 81.3% in tumors originating from Sertoli–Leydig cells, with a specificity (Sp) of 100%, the data must be interpreted in light of the ovaries' functional status [47]. Even ten to twenty years after the original diagnosis, GCTs can spread and recur. Monitoring inhibin B, a marker of tumor burden, can help identify disease recurrence and track therapy response [48]. Inhibin A levels have been found to be high in around 70% of GCTs, frequently exhibiting a 6- to 7-fold increase in comparison to the normal reference range. With increased levels in 20% of patients, inhibin A may be a helpful marker for mucinous epithelial OC. On the other hand, total inhibin is elevated in around

Malignant conditions	Nonmalignant conditions
Thyroid cancer	Gastrointestinal disorders
Lung cancer	Peptic ulcer disease
Breast cancer	Inflammatory bowel disease
Colorectal cancer	Diverticulitis
Pancreatic cancer	Pancreatitis
Prostate cancer	Liver disorders
Ovarian cancer	Alcoholic liver disease
Mucinous adenocarcinoma of the cervix	Chronic liver disease
	Primary biliary cirrhosis
	Obstructive jaundice
	Others
	Smoking
	Renal failure
	Fibrocystic breast disease

Table 1.
Malignant and nonmalignant conditions associated with CEA elevation.

15% to 35% of nonmucinous epithelial OC, making it a weak indicator for nonmucinous epithelial tumors [49]. Some studies show that inhibin B can be elevated in ovarian fibroma or fibrothecoma [50, 51]. Reference values for inhibin B are as follows: females <11 years: < 5 pg/ml, between 11 and 17 years: <98 pg/ml, premenopausal: <98 pg/ml, postmenopausal: <5 pg/ml [52]. While not a reliable standalone screening test for OC, inhibin A and B are useful in monitoring known ovarian tumors after diagnosis. Decreasing levels after surgery are indicative of successful treatment, while elevations may suggest recurrence or progression of the disease.

2.6 Lactate dehydrogenase

Lactate dehydrogenase is a key glycolytic enzyme that catalyzes the reversible conversion between pyruvate and lactate. When cells are injured, LDH is released into the bloodstream, raising serum levels. In neoplastic disease, increased LDH reflects tumor growth and tissue damage. Malignant tissues often upregulate glycolysis even in the presence of adequate oxygen (the Warburg effect), relying on LDH; tumor necrosis further contributes to high circulating LDH. Clinically, serum LDH is a useful tumor marker for ovarian malignant germ cell tumors, aiding diagnosis, guiding therapy monitoring, and supporting posttreatment surveillance for recurrence or metastatic spread [53]. Normal serum LDH levels range from 120 to 246 U/L. When applying a cutoff of 450 IU/mL, serum LDH demonstrated a sensitivity of 60%, specificity of 86%, a positive predictive value of 70%, and a negative predictive value of 75% [54]. Elevated LDH levels are correlated with more advanced stages of the disease. In our practice, we managed a 22-year-old woman with dysgerminoma who reported no prior sexual activity, presenting with elevated serum LDH (485 U/L) and hCG (56.9 mIU/mL). Two weeks postoperatively, LDH declined to 310 U/L. Using the latest International Federation of Gynecology and Obstetrics (FIGO) criteria, the tumor was staged as FIGO II A. On postoperative day 8, speculum examination for persistent vaginal bleeding revealed a vaginal mass; histology confirmed metastatic ovarian dysgerminoma with extensive tumor necrosis and hemorrhage [55].

LDH levels in peritoneal fluid are significantly elevated in OC patients and offer greater sensitivity and diagnostic accuracy than serum LDH, owing to their strong association with advanced tumor stage, unfavorable histologic subtypes, higher tumor grade, and positive peritoneal cytology. Median peritoneal LDH values rise with disease progression – measured at 303 U/L in Stage IA and increasing to 837 U/L in stages II–IV [56]. In contrast, findings by Ikeda et al. indicate that a serum LDH concentration of ≥ 250 U/L may serve as a predictor of platinum resistance and poorer clinical outcomes in OC. The same study also reported significantly higher LDH levels in high-grade serous carcinoma compared to clear cell ($P = 0.009$), endometrioid ($P = 0.002$), and mucinous tumors ($P = 0.006$) [57]. Moreover, cisplatin-resistant OC cells tend to exhibit increased glycolytic activity and reduced mitochondrial function compared to their cisplatin-sensitive counterparts.

2.7 Alpha-fetoprotein

The liver and yolk sac are the main producers of the fetal serum protein known as AFP. For some types of cancer, it serves as a tumor marker. Elevated AFP in

epithelial OC is uncommon and might cause uncertainty in diagnosis, particularly in younger women. AFP can, however, rise, particularly in younger women with aggressive types of clear cell OC. For these patients, the total survival rate is almost 50%. The best chemotherapeutic regimen and the molecular features of AFP-producing clear cell epithelial OC are still unclear, nonetheless, because of their rarity [58]. Though its usefulness in early-stage screening is limited, it is noteworthy that AFP is a significant biomarker for yolk sac tumors (YSTs), a subtype of malignant germ cell tumors. Although YSTs are usually seen in younger patients, elderly women might also experience them. In spite of this, elderly female populations do not commonly undergo serum AFP testing [59]. Elevated AFP has been linked to more aggressive disease and poorer outcomes. In an analysis of multiple tumor markers, Bian et al. showed that AFP – among others – helped distinguish OC from benign conditions and healthy controls [60]. In clear cell OC, AFP appeared more sensitive than CA-125 for postoperative surveillance [61]. Ongoing monitoring of AFP and β -hCG is important for prognostic assessment [62].

2.8 Human chorionic gonadotropin

The expression patterns and diagnostic potential of hCG and its β -subunit (β -hCG) have been studied in patients with OC. hCG has a potential role in OC diagnosis, particularly with germ cell tumors, which can cause elevated hCG levels. The normal value is <5 mIU/mL. In a series of 40 OC specimens, 68% of patients showed elevated serum hCG and positive hCG expression in tumor tissue; tissue expression correlated strongly with tumor grade but not with histologic subtype [63]. Nonetheless, β -hCG's diagnostic performance in epithelial OC is unreliable, with both false positives and false negatives. The biological role of hCG in tumorigenesis remains incompletely defined: acting as a pro-angiogenic factor, hCG enhances vasculogenic mimicry in the OVCAR-3 cell line in vivo and in vitro and markedly upregulates VEGF, CD31, and factor VIII via LH-receptor activation, thereby promoting tumor growth [64]. hCG may also inhibit cancer-cell apoptosis. Immunohistochemical analyses have revealed elevated β -hCG expression in metastatic OC, which correlates with unfavorable clinicopathological features such as advanced disease stage, increased tumor size, poor cellular differentiation, and high-grade serous histology. These observations indicate that β -hCG expression is associated with more aggressive tumor behavior and may serve as an independent prognostic marker in OC [65, 66].

2.9 OVX1

OVX1 is an epitope found on high-molecular-weight mucin-like glycoproteins and can be identified through radioimmunoassay techniques. Notably, OVX1 was elevated in 67% of OC patients who tested negative for CA-125, and it does not show binding affinity to normal ovarian tissue [67]. The cutoff values, sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) for OVX1 and other biomarkers are summarized in **Table 2** alongside relevant data from additional markers [67–71].

Marker	Cutoff/condition	Se (%)	Sp (%)	PPV	NPV
CA-125	>35 U/mL	82.2	67.3	47.1	91.4
	>65 U/mL	75.6	86.6	66.7	90.9
CA 19-9	>40 U/mL	35.6	81.1	40	78
CEA	>3 ng/mL (nonsmoker)	16	93	37	83
	>5 ng/mL (smoker)	–	–	–	–
HE4	>70 pmol/L (premenopause)	72.9	95	NA	NA
	>140 pmol/L (postmenopause)	NA	NA	NA	NA
OVX-1	7.2 µ/mL	70	95	NA	NA

Table 2.
Cutoff values, Se, Sp, NPV, and PPV for some biomarkers in ovarian cancer.

2.10 Apolipoprotein A1

ApoA1, a key protein component of high-density lipoprotein (HDL), is frequently found at reduced levels in patients with OC [72]. A fluorescence spectroscopic system using multiplexed magnetic nanoparticle–antibody conjugates (MNPs-Abs), which combines the detection of CA-125, β 2-microglobulin (β 2-M), and ApoA1, has demonstrated promising performance for early OC detection – achieving a specificity (Sp) of 98% and a sensitivity (Se) of 94% [73, 74].

2.11 Transthyretin

TTR is a transport protein found in plasma and cerebrospinal fluid that carries thyroxine (T4) and retinol to the liver. The human TTR protein is encoded by the TTR gene on chromosome 18q12.1. It is synthesized by the liver and secreted into the bloodstream. In circulation, fewer than 1% of TTR's T4-binding sites are occupied; this low occupancy helps prevent TTR dissociation, misfolding, and aggregation, which can otherwise lead to degeneration of postmitotic tissues. It is a protein whose serum levels are decreased in ovarian cancer (OC) and has shown promise when used in combination with other markers for early detection. TTR has been identified as a potential biomarker for detecting Stages I–II OC, demonstrating a sensitivity (Se) of 78.6% and a specificity (Sp) of 68.8% [75, 76].

The desire to discover new biomarkers that are more effective in the early diagnosis of OC has led to the analysis of numerous markers.

2.12 Proastasin

The 40-kDa trypsin-like protease PSN, which is found on chromosome 16p11.2, is essential for opening sodium channels in the epithelium. PSN was suggested by Mok et al. as a new OC biomarker [77]. Early in the course of the disease, it is overexpressed, and this overexpression continues in later stages and grades [78]. In contrast to normal settings, epithelial and stromal OC exhibit expression levels greater than 100 times higher. It possesses a 94% specificity (Sp) and a 51% sensitivity (Se) [79, 80].

2.13 Creatine kinase B

CK is essential for cellular energy homeostasis. Preoperative serum CKB activity is higher in women with OC (9.6 U/L) than in those with benign ovarian masses [81]. It is highly expressed in early tumoral phases, and has a specificity (Sp) of 94% and a sensitivity (Se) of 92%. It can be used as a diagnostic and prognostic marker [82].

2.14 Kallikreins

KLKs are a subgroup of serine protease-type peptidases, with more than 15 known members. Notably, increased expression of KLK4, KLK5, KLK6, KLK7, KLK10, and KLK15 is associated with poorer prognosis and advanced-stage disease [83]. Overall, 12 of the 15 KLKs are upregulated in OC. Several – KLK4–KLK7, KLK10, and KLK15 – correlate with poor prognosis and advanced stage, and KLK4 and KLK7 are linked to resistance to first-line paclitaxel [84, 85]. In type II OC, higher KLK5–KLK7 expression has been linked to lower rates of optimal cytoreduction and to higher tumor grade [86]. KLK6 may aid in diagnosing and monitoring ovarian and prostate cancers; however, elevated plasma KLK6 is also seen in Alzheimer's disease [87]. KLK7 levels are significantly elevated in both serous and endometrial OCs [88]. Moreover, KLK7 overexpression promotes chemoresistance and upregulates alpha5/beta1 integrins, driving ovarian cell invasion, peritoneal dissemination, and reinvasion [89]. KLK10 functions as a tumor suppressor in breast and prostate cancers but is elevated in the tissues and serum of patients with OC. KLK11, implicated in tissue remodeling and cell migration, is likewise increased in OC. Consequently, differential kallikrein expression may serve as a diagnostic biomarker for serous OC and suggests that these proteases shape the tumor microenvironment, fostering disease progression, chemoresistance, and metastasis. KLKs are upregulated in the serum and ascites of OC patients and are linked to poor prognosis and resistance to paclitaxel [90].

2.15 Interleukins

Inflammatory cells and mediators are abundant within the tumor microenvironment, and the progression of cancer disrupts normal cytokine homeostasis. In OC, interleukin-1 α (IL-1 α) – a key regulator of inflammation and innate immunity – is often elevated. IL-7, involved in hematopoiesis, is also found at increased levels. IL-10, produced by monocytes, dendritic cells, macrophages, natural killer cells, CD4 + and CD8 + T cells, Th17 cells, B cells, and even OC cells themselves, is markedly elevated in OC ascites – a unique immunologic niche. Ascitic IL-10 levels exceed those found in serum and are associated with poorer prognosis, likely due to IL-10's role in enhancing the anti-apoptotic properties of malignant ascitic fluid [91].

IL-6, a multifunctional proinflammatory cytokine secreted by epithelial cells, monocytes, and tumor cells, is nearly undetectable in healthy individuals. Under physiological conditions, IL-6 plasma levels are maintained at low levels (<8 pg/mL; range: 0.2–7.8 pg/mL) to support basal homeostasis. In OC, IL-6 levels rise significantly, particularly in advanced stages, where they closely correlate with tumor size. Biologically, IL-6 promotes cancer progression by stimulating cell proliferation through acceleration of the cell cycle and inhibition of apoptosis. It also

supports the generation of cancer stem cells (CSCs), drives angiogenesis, and contributes to the development of chemoresistance via activation of pro-survival signaling pathways such as JAK/STAT3 and PI3K/AKT [92]. Furthermore, IL-6 enhances OC invasiveness by stimulating the production of matrix metalloproteinases – particularly MMP-9 – which facilitate basement membrane degradation and tumor cell invasion. In ascitic fluid, IL-6 levels can exceed 2000 pg/mL, correlating with rapid disease progression, poor prognosis, and shorter disease-free survival.

The expression of the IL-6 receptor (IL-6 R) also increases during OC development and progression. This upregulation plays a crucial role in promoting cell proliferation, invasion, metastasis, and resistance to therapy, and is associated with poor prognosis. Elevated IL-6 R expression has been observed in the majority of OC cell lines [92].

IL-6 has been extensively studied as both a diagnostic and prognostic marker. Elevated IL-6 levels have been associated with advanced-stage disease in both serum and ascites, contributing to tumor-host interactions and metastatic spread. IL-6 also plays a role in remodeling the tumor microenvironment by promoting VEGF expression and subsequent angiogenesis, as well as facilitating neoplastic invasion through matrix metalloproteinase overexpression [93]. In clinical practice, an IL-6 serum cutoff of > 3.75 pg/mL has been proposed as a primary triage tool for OC, outperforming both CA-125 and the Risk of Malignancy Index (RMI = ultrasound score × menopausal status score × CA-125 in U/mL) [94].

In our clinic, we measured serum IL-6 levels using ELISA in 17 patients with OC and compared them with 13 individuals without ovarian pathology. The mean IL-6 concentration in the cancer group was 47.217 ± 41.4 pg/mL, significantly higher than the control group mean of 5.09 ± 2.54 pg/mL. Using 12.5 pg/mL as the upper limit of normal, 12 of the OC patients exceeded this threshold. ROC curve analysis yielded an AUC of 0.917, indicating excellent discriminatory performance [95].

However, despite its potential, IL-6 has limitations. Its levels may fluctuate in response to stress, diet, inflammation, and other nonmalignant conditions, which can lead to false positives. Additionally, IL-6 levels tend to be lower in early-stage disease, reducing its sensitivity for early detection [96]. Current literature linking IL-6 concentrations to pathological and clinical predictors remains inconsistent, and its standalone diagnostic value remains inconclusive.

Recent studies, however, indicate that combining IL-6 with established markers such as CA-125, HE4, ROMA, and RMI enhances diagnostic accuracy, sensitivity (Se), specificity (Sp), and predictive power while reducing false positives [97]. In a comprehensive meta-analysis covering 37 studies and nearly 7,000 participants, Amer H. et al. found that IL-6 levels in ascitic fluid were significantly elevated in late-stage ovarian cancer (OC) compared to early-stage disease and benign conditions. The pooled sensitivity (Se) and specificity (Sp) for IL-6 were 76% and 72% in serum, and 84% and 74% in ascites, respectively [96]. These findings support the use of ascitic IL-6 as a promising diagnostic marker for advanced-stage OC, though its application in early detection warrants further investigation.

2.16 Transferrin

TF, produced mainly by hepatocytes, transports plasma iron into cells and is integral to cell division and proliferation. As a standalone OC detection marker,

it shows limited performance – Se 72.9% and Sp 74.1% [98]. Consequently, TF should be combined with other biomarkers to achieve meaningful clinical utility.

Even though there are several indicators for OC diagnosis and prognosis, most of them don't have enough sensitivity (Se) and specificity (Sp) when utilized alone. Combinations of multiple biomarkers have also been investigated for their potential to improve diagnostic discrimination. Zhang et al. described an early-detection marker panel of three proteins that achieved 83% sensitivity and 94% specificity for diagnosing early-stage OC: apoA-1, a shortened transthyretin (TTR), and a cleavage fragment of the inter-alpha-trypsin inhibitor heavy chain (H4) [72]. PSN, CA-125, LDH, AFP, and hCG + β are among the blood biomarkers that Bastani et al. evaluated in 2017 for their diagnostic value in detecting epithelial OC and distinguishing it from benign tumors and healthy individuals. According to their findings, patients with OC had noticeably higher levels of PSN, LDH, and CA-125 [99]. Using CA-125, ApoA-I, TF, and TTR, Su et al. created a multiple logistic regression model (MLRM) that produced a sensitivity of 89% and specificity of 97% for early-stage OC. The model showed 95% sensitivity and 92% specificity for separating healthy individuals from those with mucinous OC [100]. Nosov et al. reported 94% sensitivity and specificity for early-stage serous OC and 98% for both sensitivity and specificity in early-stage endometrioid OC using the same MLRM and biomarker combination [101]. With 95% sensitivity and 99% specificity, Visintin et al.'s blood biomarker panel – which included leptin, prolactin, OPN, IGF-II, MIF, and CA-125 – was able to differentiate OC patients from healthy controls [102]. To better distinguish between benign and malignant pelvic tumors, the OVERA test combines CA-125 with TF, ApoA-I, and follicle-stimulating hormone (FSH) [103]. Direct comparisons revealed that OVERA identified more OC cases than ROMA, but it also led to a notably greater number of referrals to gynecologic oncologists for benign diseases [104]. Additional biomarker combinations have been suggested as diagnostic algorithms for OC, including TTR + ApoA-I + TF + CA-125; CA-125 + ApoA-I + β 2-microglobulin; PSN + CA-125; IGFBP2 + LCAT + CA-125 [105]; CA-125 + CA 19-9 + EGFR + G-CSF + eotaxin + IL-2 R + cVCAM + MIF [106]; and CA-125 + vitamin K-dependent protein Z + phosphatidylcholine sterol acyltransferase + C-reactive protein [107]. To classify the malignancy risk of pelvic masses into low-, moderate-, or high-risk categories, OVA1, a multivariate index assay, integrates five markers: CA-125, TTR, ApoA-I, β 2-microglobulin, and TF. Obtaining enough preclinical serum samples to validate these panels and determine the best biomarker combinations remains a major hurdle.

For most of these candidates, despite performing reasonably well diagnostically, they still fail to meet the requirements for clinical settings that rely on serum markers [108]. Although publications have listed more than 35 biomarkers that appear to enhance CA-125's sensitivity for detecting early-stage disease [106, 107, 109], decades of research have not yielded robust early-diagnostic tools. Many markers capture only a small subset of cases missed by CA-125. Compounding this, ovarian cancer has a high likelihood of recurrence with poor postrecurrence outcomes. There is an urgent need for methods that predict progression earlier and strategies to recognize and prevent recurrence at the earliest possible stage.

2.17 Mesothelin

Mesothelin (MSLN) is a GPI-anchored cell-surface glycoprotein encoded by the MSLN gene on chromosome 16p13.3. Under normal conditions, its expression is limited to mesothelial cells of the pleura, pericardium, peritoneum, and vaginal sheath, but it is increasingly examined across solid tumors and is present in roughly 70% of OC. MSLN is actively shed from the cell surface, creating a measurable antigen pool in ascites or blood that enables quantification of circulating MSLN. It is especially prevalent in serous OC and correlates with a more advanced tumor stage. Badgwell et al. reported greater sensitivity for early-stage OC when MSLN was measured in urine versus serum [110]; however, urinary levels depend on glomerular and tubular function, which can complicate interpretation and produce false positives [111]. Prognostically, higher MSLN expression is linked to worse overall and disease-free survival, in part due to its association with chemoresistance; expression is significantly lower in chemosensitive than in chemoresistant cases [112]. Mechanistically, MSLN can blunt paclitaxel-induced cell death by activating the PI3K/AKT and MAPK/ERK signaling pathways [113].

2.18 Bikunin

Bikunin is a glycosylated serine protease (glycoprotein) of the Kunitz family that helps suppress tumor cell invasion and metastasis. Measuring plasma bikunin is simple and relatively inexpensive, and preoperative levels have been reported as a strong prognostic indicator in ovarian cancer (OC): higher levels correlate with a more favorable prognosis. Low plasma bikunin has been linked to late-stage disease, likely suboptimal debulking with > 2 cm residual tumor, poorer chemotherapy response, and shorter survival [114]. Tanaka et al. further suggested that loss of bikunin contributes to a more aggressive course and reduced survival; notably, decreased bikunin mRNA expression carries prognostic value comparable to periaortic lymph-node metastasis and is independent of typical clinicopathological variables [115].

2.19 Vascular epithelial growth factor

VEGF is a signaling protein and a key vascular-permeability factor that drives tumor angiogenesis – an essential prerequisite for tumors to grow beyond small sizes. The VEGF gene family includes seven members (VEGF-A to VEGF-F). Evidence highlights a central role for VEGF-A in the pathogenesis of OC, in both localized and metastatic disease [116]. VEGF levels are elevated in OC and contribute to ascites formation. Expression is higher in metastatic tumors, while among primary tumors, lower VEGF expression has been linked to poorer prognosis [117]. In clear cell OC, VEGF expression correlates with microvessel density. VEGF-C has been associated with increased lymph-node and distant metastases; conversely, a twofold rise in preoperative serum VEGF-C was associated with a 2.79-fold higher likelihood of responding to bevacizumab [118].

2.20 Osteopontin

Different cell types express OPN, a calcium-binding glycoprotein that ranges in size from 44 to 66 kDa. It is widely expressed in many tissues and secreted by

leukocytes, macrophages, and activated T lymphocytes. OPN is found in almost all bodily fluids, the extracellular matrix, and inflammatory areas. It functions as a cytokine for a number of integrins and CD44 receptors and aids in cellular adhesion. It is essential for the development of tumors and inflammatory responses mediated by macrophages. OPN has drawn interest as a potentially useful biomarker for OC diagnosis and treatment [119]. In patients with high-grade OC, elevated OPN levels have been found in their urine, indicating that it may be used as a noninvasive biomarker for early diagnosis. OPN has a high correlation with MTS, invasion, and tumor development. At a specificity (Sp) of 98%, OPN allowed for the detection of 82% of early-stage OC patients when paired with CA-125, macrophage inhibitory factor (MIF), and anti-IL-8 autoantibodies, as opposed to just 64% when CA-125 was used alone [120].

Serum OPN levels were assessed using the ELISA method in a group of 17 OC patients and compared to 13 people without ovarian disease as part of our clinical evaluation. In comparison to the control group, which had a mean serum OPN concentration of 36.72 ± 25 ng/mL (range: 6.4–82 ng/mL), the OC group's mean was 594.55 ± 224.86 ng/mL (range: 325–860 ng/mL). With both sensitivity (Se) and specificity (Sp) equal to 1, OPN showed flawless diagnostic performance in this pilot trial. An ideal cutoff value for OPN was determined using the receiver operating characteristic (ROC) curve to be 199.8 ng/mL [95]. OPN levels decrease after treatment, just like CA-125; however, in 90% of patients who experienced recurrence, OPN levels increased before CA-125, indicating that it can be used as a predictive biomarker [121]. According to these results, OPN might be a viable option for molecularly targeted treatments in the future, particularly for advanced OC that is chemoresistant [122].

2.21 Paraneoplastic antigens

Paraneoplastic antigens are expressed by both tumor cells and neurons, prompting a humoral response that produces onconeural antibodies and can result in paraneoplastic neurologic syndromes. These antigens may serve as biomarkers to predict OC recurrence – even in asymptomatic patients – before conventional signs appear. In a retrospective study, Chatterjee et al. evaluated six antigens (HARS, CDR2, Ro52, 4B7, 4H4, 5H6) for their ability to anticipate recurrence before a CA125 rise (cutoff: 35 U/mL) or radiologic evidence; antibodies against HARS, Ro52, CDR2, and 5H6 predicted recurrence with 90.5% sensitivity, providing a mean lead time of 5.03 months before clinical or symptomatic relapse [123]. Notably, these findings come from a small cohort with CA125 values within the normal range.

Atallah et al. provide an overview of OC biomarkers, highlighting the clinical role, specificity (Sp), and sensitivity (Se) of certain biomarkers for the early stages (Stages I–II) of the disease (**Figure 1**) [124].

Currently, there exist the so-called tumor-agnostic biomarkers: MSI/mismatch repair deficiency and TMB, which predict response to immunotherapy, and HER2 (immunohistochemistry), approved in 2024 for trastuzumab deruxtecan treatment (FDA-approved for 3+ expression; National Comprehensive Cancer Network recommends for 2+ as well).

Other diagnostic and predictive biomarkers are: p53 (distinguishes high-grade from low-grade serous OC), KRAS (expected to become an integrated biomarker for the upcoming MEK/FAK inhibitor combination therapy in low-grade serous OC),

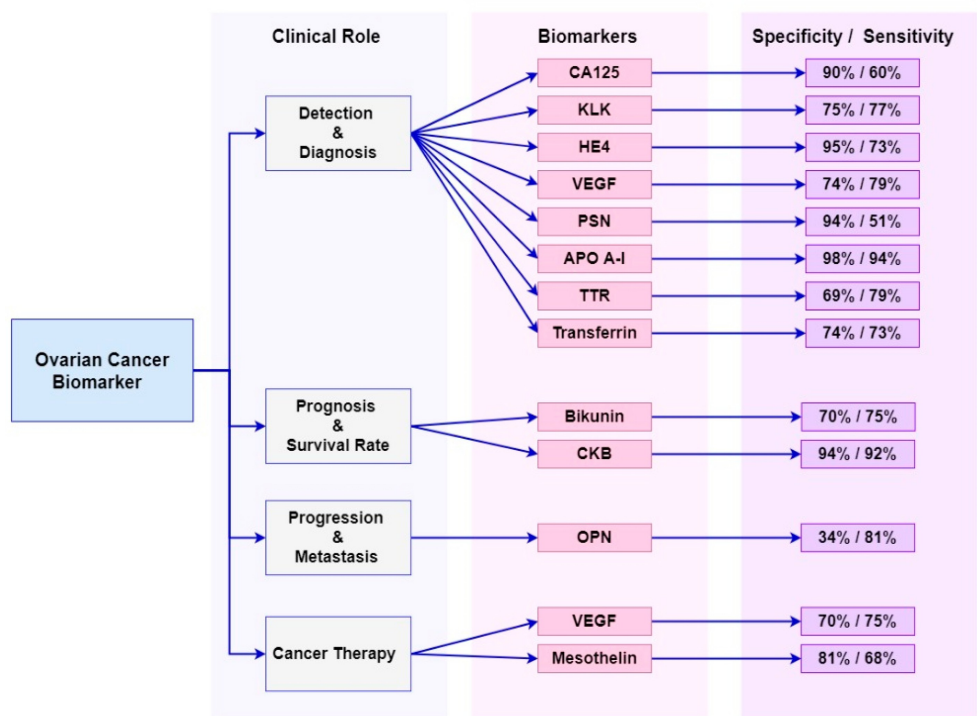


Figure 1.
Ovarian cancer biomarkers Atallah [80].

and CCNE1 amplification (used mutually exclusively with BRCA mutations, associated with platinum resistance, with targeted therapies in development). TP53 is mutated in nearly all high-grade serous OC, and circulating anti-TP53 autoantibodies are reported in about 20–25% of patients. In early-stage disease, anti-TP53 antibodies have been detected in 20% of cases – appearing a median of 8 months before CA-125 elevation and 22 months before clinical diagnosis [125]. In a screen of 5,177 candidate autoantigens, antiprostaglandin F receptor (anti-PTGFR) and anti-protein tyrosine phosphatase receptor type A (anti-PTPRA) were identified as markers that complement anti-TP53 [126].

Additional proteins show promise for diagnosing and prognosticating OC, including aryl-hydrocarbon-receptor-nuclear-translocator-like (ARNTL), runt-related transcription factor 3 (RUNX3), calstabin-1/paired box protein 9 (FKBP1/PAX9), collagen alpha-1(XI) chain (COL11A1), forkhead box protein M1 (FOXO1), retinol-binding protein 4 (RBP4), the proliferation marker Ki-67, aldehyde dehydrogenase 1 (ALDH1), folate receptor- α (FOLR1), and glutathione S-transferase polymorphisms (GSTP) [127, 128]. Beyond traditional OC markers, recent high-throughput molecular approaches have highlighted several new biomarker candidates.

2.22 Folate receptor alpha 1

FOLR1 is a glycoposphatidylinositol (GPI)-anchored glycopolypeptide; part of it is released into circulation as soluble folate receptors (sFRs). FOLR1 is a membrane

receptor involved in folate transport and related cellular processes, but its utility as an early-detection biomarker has not yet been confirmed. Elevated sFR can signal OC recurrence – levels may fail to return to baseline or even rise while CA-125 remains low – likely reflecting clusters of tumor cells with high folate-receptor expression [129]. Overexpression of FOLR1 in OC is often linked to greater tumor aggressiveness and poorer prognosis and can be therapeutically exploited: agents such as mirvetuximab soravtansine-gynx, an antibody–drug conjugate targeting FOLR1, are designed to deliver cytotoxic therapy selectively to receptor-overexpressing cancer cells, aiming to improve efficacy while limiting damage to normal tissue [130, 131].

2.23 Cancer stem cells

Bapat et al. identified and cultivated the first OC CSCs [132]. Because of their ability to self-renew and differentiate, elude defense, and promote inflammation and angiogenesis, CSCs are a tumor subpopulation that is crucial for initiation. They also promote chemoresistance, metastasis, and relapse, which result in recurrence [133]. CSCs exhibit infinite proliferation and survival capacity, significantly more flexibility, and a unique metabolism highlighted by increased glycolysis when compared to typical stem cells. Their expression of VE-cadherin, Notch, MMP-2, MMP-9, and CXCR4 influences endothelial transformation and pro-angiogenic signaling within the tumor microenvironment, and they preferentially overexpress VEGF receptors (VEGFR-1/VEGFR-2), which promote angiogenesis and tumor growth. While CSCs emit cues that recruit and activate niche components, the surrounding niche cells secrete substances that improve CSC survival and plasticity and protect them from chemotherapy. Aldehyde dehydrogenase (ALDH), DNA-repair pathways, and ATP-binding cassette transporters have been identified as the three main resistance mechanisms in CSCs. Certain markers, including CD44 (hyaluronic acid receptor), CD133, ALDH1, CD117 (c-kit), and CD24, or distinctive intracellular enzyme activity, can be used to identify CSCs [134]. Certain histologic subtypes, an earlier FIGO stage, greater differentiation, and increased survival are all correlated with high ALDH1 expression in tumor cells [135]. LGR5, EpCAM, NANOG, SOX2, FOXM1, OCT4, CD166 (ALCAM), and autotaxin (ATX) are other biomarkers associated with CSCs. Although identifying distinct CSC characteristics is still difficult because of their variability and flexibility, targeting CSCs is a viable treatment approach for OC [136].

Promising candidates for more informative blood biomarkers in OC are being produced by recent advancements in clinical proteomics and nucleic acid-based profiling. Many of these markers are currently being researched and validated, and, when combined, they may allow for population screening and predict chemotherapy response.

3. Proteomic markers

Proteomic analysis of biological fluids such as serum, plasma, and ascitic fluid is increasingly being used to identify novel biomarkers for the early detection of OC. Molecular profiling indicates that OC can be stratified based on distinct “-omic” signatures, which may correlate with the tumor’s tissue of origin, patient survival,

and sensitivity to chemotherapy [137]. Among the proteomic candidates reported are glycosylated eosinophil-derived neurotoxins and COOH-terminal fragments of OPN. The most extensively studied dataset is the proteomic profile of OC ascites, from which approximately 80 potential biomarkers have been proposed for early-stage diagnosis.

Proteomic profiling – most often via mass spectrometry (MS) – is currently the most direct route to identify diagnostic and prognostic biomarkers for OC. These methods enable comprehensive interrogation of OC proteomes, supporting the discovery of novel markers and deeper characterization of the disease. Mapping alterations in proteins, signaling pathways, and even metabolites across OC subtypes can aid diagnosis, guide therapy, and potentially improve quality of life and survival. MS-based investigations have examined tumor tissue, blood, ascites, and cell culture.

Ahn et al. profiled peripheral blood from high-grade serous cancer (HGSC) patients, identifying > 1,200 proteins and ~ 400 metabolites (polar lipids and small molecules – 20 amino acids, 7 biogenic amines, 1 monosaccharide – and neutral lipids). They found 197 differentially expressed proteins in OC (108 upregulated, 89 downregulated), enriched in platelet, immune, hemostasis, gluconeogenesis, extracellular matrix, stimulus-response, and signaling pathways – patterns consistent with tumor growth, high-energy metabolism, and microenvironmental influence [138].

Isotopic MS using multicollector ICP-MS to assess copper composition (the $^{65}\text{Cu}/^{63}\text{Cu}$ ratio, often reported as ^{65}Cu) in plasma and ovarian biopsies showed an association with cancer progression; plasma ^{65}Cu was lower in OC patients [139].

Focusing on proteoforms, McGee et al. introduced AutoPiMS, a semi-automated top-down platform performed directly on tissues that reports proteoform mass, spatial distribution, and abundance. Applied to tumor and stromal OC biopsies, it identified ~1,000 proteoforms [140]. Another study comparing OC with normal ovarian tissue (11 paired biopsies) found >2,000 altered proteins implicating mitochondrial proteostasis and protein translation, with marked upregulation of HSP60 in OC [141]. Plasma analyses have likewise shown elevated SPARC and THBS1 versus healthy donors [142].

Dieters-Castator et al. derived an 8-marker panel (KIAA1324, PAM, PGR, WT1, SCGB2A1, PIGR, CTNNB1, TP53) to distinguish endometrioid carcinoma from HGSC. From over 500 differentially expressed proteins, a subset of 106 correctly classified 90% of samples, and KIAA1324 was validated as a particularly discriminating marker for endometrioid carcinoma [143]. Nguyen and colleagues examined cisplatin treatment and resistance in paired patient-derived cell lines, reporting higher levels of phosphorylated sequestosome-1 in the resistant line and proposing it as a candidate marker of drug-resistant HGSC [144]. Coscia et al. quantified over 10,000 proteins across OC cell lines and HGSC tumors and defined a 67-protein signature that classifies samples as originating from ovarian surface epithelium or fallopian tube epithelium [145].

Collectively, proteomics studies have identified over 11,000 distinct proteins in OC, yet inconsistencies across reports underscore the need for meta-analyses to reconcile findings and refine biological interpretation.

4. Epigenetic markers

Mutations, gene amplifications, translocations, and changes in microarray expression patterns are among the genomic changes being investigated as possible OC indicators. Oncogenes and tumor suppressor genes are disrupted during the initiation and progression of OC, as in other malignancies, by both genetic and epigenetic pathways. In OC diagnosis, epigenomics – the study of heritable changes in gene expression that do not alter the underlying DNA sequence – has grown in significance. Important epigenetic alterations, such as histone modifications and DNA methylation, have potential as predictive and diagnostic biomarkers.

Novel biomarkers that can support early identification, expand knowledge of molecular pathways, and direct the creation of cutting-edge treatments and prognostic tools are still desperately needed, especially in epithelial OC. CA-125 is currently utilized to track prognosis and therapeutic response following initial therapy. Nevertheless, it has little predictive value for second-line medicines and insufficient specificity to guide treatment plans.

Crucially, it is possible to identify epigenetic markers in bodily fluids such as blood, providing a less intrusive method for prognostic evaluation and early diagnosis. By employing noninvasive, repeatable blood collection, liquid biopsy promotes the development of precision medicine and allows for real-time tracking of tumor progression. CTCs, circulating tumor DNA (ctDNA), circulating cell-free microRNAs (cfmiRNAs), long noncoding RNAs (lncRNAs), and extracellular vesicles such as exosomes are important analytes in liquid biopsy. Liquid biopsy is already used in OC, and the majority of research to date has focused on the functions of ctDNA and CTCs [146].

4.1 Circulating tumor cells

CTCs are live cancer cells released into the bloodstream by metastases, local recurrences, or the original tumor. CTC shedding was long thought to be low since OC usually spreads by direct peritoneal dissemination, with distant metastases occurring in only approximately one-third of patients. Since the initial immunocytochemical attempts to identify disseminated tumor cells in 1990, detection technologies have significantly improved. Hematogenous dissemination is a significant factor in OC, according to more recent data: CTC positivity is associated with advanced stage, elevated CA-125, and postoperative residual disease [147]. Pradeep et al. also proposed that the ErbB3–neuregulin-1 (NRG1) pathway may be the preferred route of omental metastases via the circulation [148].

Positive immunomagnetic enrichment for typically expressed surface markers is a standard method for detecting CTCs. RT-PCR or immunocytochemistry are then used for visualization and quantification. Although correlations differ depending on isolation and detection techniques, new data indicate that the presence of CTCs is associated with a worse prognosis and more advanced disease. The effect of growing CTC counts is yet unknown, and there is no set cutoff. Response to platinum-based treatment may also be predicted by CTC status.

4.2 Circular RNAs

Circular RNAs (circRNAs) are ncRNAs whose covalently closed structure renders them more resistant to endonucleases – and thus more stable – than linear RNAs. They have clinical relevance across many diseases, including OC [149]. In OC, circ-ITCH expression is reduced and correlates with clinicopathologic features such as tumor size, FIGO/TNM stage, and overall survival [150]. CircPLEKHM3, derived from the PLEKHM3 gene, is among the most markedly downregulated circRNAs in OC and appears to influence tumor initiation and progression; loss of circPLEKHM3 is associated with poorer survival [151]. Based on these observations, circRNA is emerging as a promising molecular biomarker for OC therapy.

4.3 microRNAs (miRNAs)

Treatment planning is aided by the ability of certain epigenetic patterns to anticipate the cancer's aggressiveness and patient survival. The likelihood that a patient will respond to chemotherapy or other targeted medicines can be determined by examining epigenetic biomarkers. It is now widely recognized that, in a variety of pathological circumstances, altered or dysregulated miRNA expression can also influence the onset and/or progression of disease. Crucially, miRNAs play a functional role in the pathophysiology of numerous cancers, including OC. In these cases, miRNAs can act as regulatory molecules, either as tumor suppressors or oncogenes (oncomiRs). In response to the tumor, OCs, nearby stromal tissues, and even other host body tissues express a range of miRNA candidates differently or abnormally. Their stability over time following extraction from plasma and their role in posttranscriptional gene regulation suggest that miRNAs could be used as clinical indicators. The clinical significance of circulating cfmiRNAs and exosomal miRNAs in OC patients' serum and/or plasma must be clarified because the biological properties and mechanisms of the various miRNAs in OC may vary, and there are differences in the methods used to accurately quantify miRNAs, which restricts the applicability of pooled analyses [152]. Poor patient survival is linked to increased levels of miRNA-552 and miRNA-216a [153]. Downregulated levels have been identified for several potential predictive biomarkers, including miR-135a, miR-375, miR-139, and miR-584. This suggests that miRNA profiling may be a potential new tool for screening asymptomatic individuals, biopsy profiling, and early OC identification. Additionally, Yokoi et al. demonstrated that OC patients have altered levels of miR-142-3p, miR-26a-5p, let-7d-5p, miR-374a-5p, miR-766-3p, miR-200a-3p, miR-328-3p, and miR-130b-3p in comparison to the healthy control group [154]. Elias and associates created a neural network prediction model for OC by using bioinformatics tools to validate miRNA sequencing data [155].

4.4 Circulating tumor DNA

Circulating tumor DNA (ctDNA) enables noninvasive detection of OC mutations – such as PIK3CA and KRAS – with potential diagnostic and prognostic utility in liquid biopsy. ctDNA is released predominantly via tumor-cell apoptosis [156]. Using deep sequencing and droplet digital PCR (ddPCR), investigators can identify specific mutations, loss of heterozygosity (LOH), DNA hypermethylation, copy-number changes, and even single-nucleotide variants in very small amounts of

ctDNA [157]. In early-stage OC, ctDNA has been detected in blood and cervical secretions in 55% of cases and has captured cancers missed by CA-125 alone in studies from Johns Hopkins [158]. Collecting cervical samples may be particularly valuable, as tumors larger than 1 cm may be needed to elevate ctDNA levels in blood [159]. Postoperatively, detectable ctDNA predicts poorer outcomes – its presence is strongly linked to shorter recurrence-free survival – and a systematic review of eight studies (627 epithelial OC patients) found ctDNA significantly associated with reduced overall and progression-free survival [160].

4.5 Long noncoding RNAs

Long noncoding RNAs (lncRNAs), transcripts over 200 nucleotides, are illuminating oncogenic mechanisms and are increasingly relevant to diagnosis and prognosis in OC. They regulate diverse biological processes and contribute to malignant phenotypes and metastasis [161]. The lncRNA H19 is present in most OC ascites samples and is upregulated in tumor tissue, suggesting a role in carcinogenesis [162]. FAM83H-AS1 has been proposed as an indicator of OC progression [163]. HOTAIR is aberrantly expressed in OC, with higher levels tied to increased cancer-cell motility [164]. MALAT-1 is likewise significantly upregulated, and its expression correlates with FIGO stage [165].

4.6 Transfer RNA-derived small-non-coding RNAs

Transfer RNA-derived small-non-coding RNAs (tsncRNAs), including tRNA halves (tiRNAs) and tRNA-derived fragments (tRFs), are emerging as potential biomarkers for OC. For example, tRF-03357 downregulates the tumor-suppressor HMBOX1 and thereby promotes aberrant proliferation, migration, and invasion. Although no ncRNA-based clinical diagnostic assays are in routine use, research supports their value in OC detection and monitoring. Jia et al. identified a tRNA fragment, tRF5-Glu, that interacts with breast cancer antiestrogen resistance 3 (BCAR3) and suppresses OC cell growth [166]. Given that their clinical significance remains incompletely defined, large patient-based trials are needed.

5. Conclusion(s)

The blood protein CA-125, which has been the mainstay of clinical detection since its discovery, is still the most well-known and often-utilized biomarker for OC diagnosis. Since then, a number of other biomarkers have been discovered, including HE4, KLKs, PSN, TTR, ApoA1, bikunin, and OPN, although none have attained the same degree of widespread clinical use as CA-125.

Numerous multivariate biomarker panels have been created to improve diagnostic performance, particularly in differentiating between benign and malignant pelvic tumors. These include the OVA1 test, ROMA, and Overa, which all combine several serum indicators to enhance sensitivity (Se) and specificity (Sp). The first of its kind, the OVA1 multivariate index assay (MIA), combines imaging findings, menopausal state, and CA-125 with transthyretin (TTR), transferrin (TF), ApoA1, and β -2 microglobulin. Even though OVA1 can identify

76% of cancers that CA-125 is unable to detect, its high false-positive rate remains a major disadvantage.

The Overa test was developed as a second-generation MIA (MIA2G) to address this, combining TF, FSH, CA-125, HE4, and ApoA1. Although it is not appropriate for general screening, Overa was approved by the FDA in 2016 and is meant to be used in assessing the risk of cancer in women with adnexal masses before surgery.

Despite continuous efforts to enhance biomarker panels, nine candidates with discriminatory potential were identified in a large prospective study of 92 serum proteins by Mukama et al. [167]: CA-125, HE4, FOLR1, KLK11, WISP1, MDK, CXCL13, MSLN, and ADAM8. However, their clinical relevance for early detection techniques was limited because none of these improved the diagnostic performance of CA-125 when used alone [167].

Although cancer biomarkers have enormous potential to improve OC diagnosis, therapy, and monitoring, their practical application is impacted by both clinical validity and utility, as well as financial factors. The viability of implementing biomarkers in various healthcare settings is largely dependent on factors including testing costs, insurance coverage, reimbursement rules, and overall cost-effectiveness.

Cost-effectiveness becomes more important when considering biomarkers that could prevent needless procedures. However, the exorbitant cost of many of these diagnostic technologies makes adoption in low- and middle-income nations extremely difficult. For example, the CA-125 blood test, which is frequently used for screening, can cost approximately \$92 in the United States without insurance, while reimbursements usually fall between \$31 and \$36. The OVA1 assay is significantly more costly, ranging from \$600 to \$650, with Medicare reimbursement stated at \$540. In contrast, the ROMA test is reasonably priced, ranging from \$60 to \$130. OVA1's weaker specificity may lead to more needless referrals for benign illnesses despite its wider diagnostic usefulness, placing a burden on healthcare resources and decreasing overall cost-effectiveness [168].

In the end, a biomarker's economic worth is determined by its capacity to enhance clinical outcomes, such as lowering morbidity and mortality, rather than just cost. Serum metabolic fingerprinting is one of the emerging diagnostic technologies, which shows promise as a more scalable and cost-effective alternative, especially in environments with limited resources [169].

The public healthcare system in Romania, a middle-income nation, currently only pays for biomarker testing for CA-125, CA19-9, and CEA in oncology institutes. This restricts access to more sophisticated but expensive diagnostic assays. This highlights the pressing need for widely available and commercially feasible biomarker techniques that can facilitate earlier diagnosis and individualized therapy, particularly in environments with constrained healthcare budgets.

Conflict of interest

The authors declare no conflict of interest.

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Perspective Chapter: The Use of Fluorescence in Ovarian Cancer Surgery

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Abstract

In this modern era, one might find several innovative treatments that are constantly updating themselves and are thus shaping the future of therapy in ovarian cancer patients. The major challenge confronting the clinician is selecting from a range of established and traditional treatment methods (such as chemotherapy or immunotherapy) versus new nanotechnology advancements and gene therapy, which have newly emerged but are evolving rapidly. In terms of surgery, modern-day updates can offer a more precise and up-to-date treatment, with various options to adapt the technique to the patient's particular needs and indications. An excellent example of surgical modern-day enhancement is fluorescence. Given that complete cytoreduction is a vital prognostic element in advanced epithelial ovarian cancer, surgery enhanced by fluorescence using fluorescent markers might significantly improve the identification of microscopic disease and the prognosis of surgical treatment. Additionally, CD24, a receptor on the cell surface, presents overexpression in 70% of solid tumors and could serve as a predictive and therapeutic biomarker for epithelial ovarian cancer. Recent preclinical studies have demonstrated that CD24-targeted imaging agents enhance tumor removal and noninvasive fluorescence visualization in orthotopic patient-derived xenograft models of epithelial ovarian cancer. Additionally, fluorescence-guided cytoreductive surgery targeting human epidermal growth factor receptor two or folate receptor alpha has demonstrated feasibility in both animal models and individuals with epithelial ovarian cancer. In conclusion, fluorescence-guided surgery may enhance the diagnosis of ovarian cancer micrometastasis and sentinel lymph nodes. More precise future research is required to determine whether the use of this method improves patient outcomes.

Keywords: fluorescence, ovarian cancer, ovarian cancer treatment, fluorescence-guided surgery, cytoreductive, ovarian cancer surgery, modern treatment of ovarian cancer, fluorescent antibody/receptor, epithelial ovarian cancer (EOC), fluorescent tracers

1. Introduction

Ovarian cancer represents the most fatal gynecological malignancy, exhibiting a survival rate of roughly 40% at five years post-diagnosis (see **Figures 1** and **2**), as underlined by Solidoro et al. [1]. The treatment strategy combines cytoreductive surgery with platinum- and taxane-based chemotherapy. Complete surgical resection of tumors, including micrometastases, is crucial for prognosis, as minimal residual disease increases relapse risk. Intraoperative fluorescence imaging may improve outcomes by aiding real-time visualization of tumor lesions.

As presented and emphasized also by Sun et al. [2], fluorescence-guided surgery (FGS) is promising for real-time intraoperative tumor delineation and observation of submillimeter tumor masses (see **Figure 3**) in epithelial ovarian cancer (EOC) cytoreductive surgery. However, most of the EOC-targeted fluorescence probes are in preclinical trials.

Number of new cases of ovarian cancer as shown for different countries in the year 2022. The source of the data is: <https://gco.iarc.who.int/today/en/fact-sheets-populations#countries>

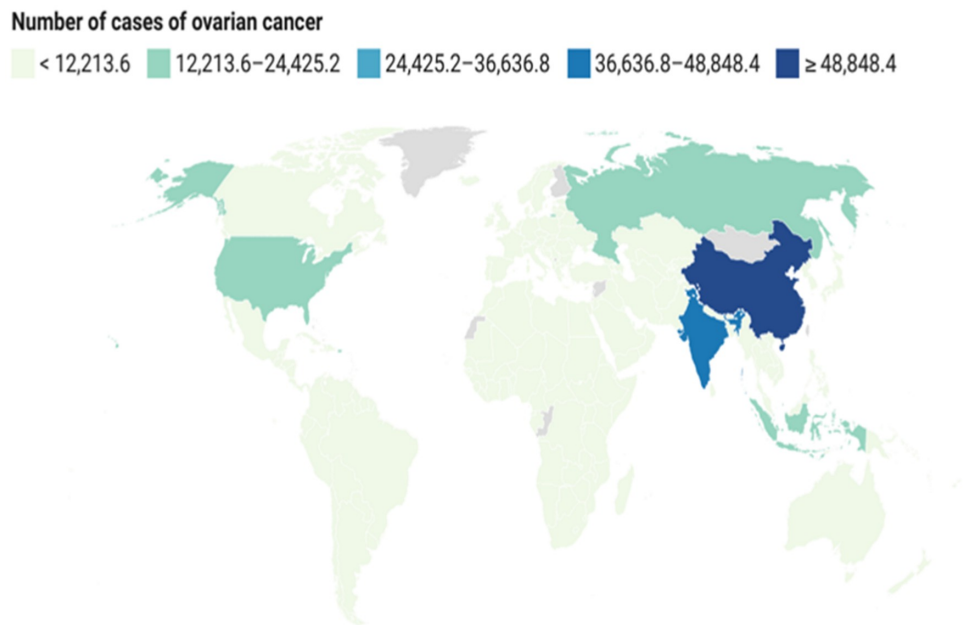


Figure 1.
Number of new cases of ovarian cancer, shown for different countries worldwide in 2022 (according to the data on the site: <https://gco.iarc.who.int>).

Number of deaths of ovarian cancer, shown for different countries, in the year 2022. The source of the data is: <https://gco.iarc.who.int/today/en/fact-sheets-populations#countries>

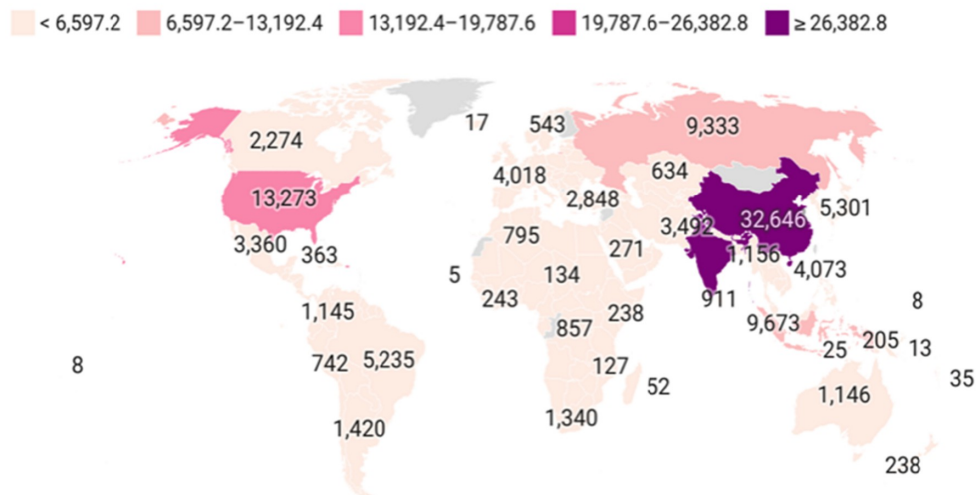


Figure 2.
Mortality of ovarian cancer, shown for different countries worldwide in 2022 (according to the data on the site: <https://gco.iarc.who.int>).

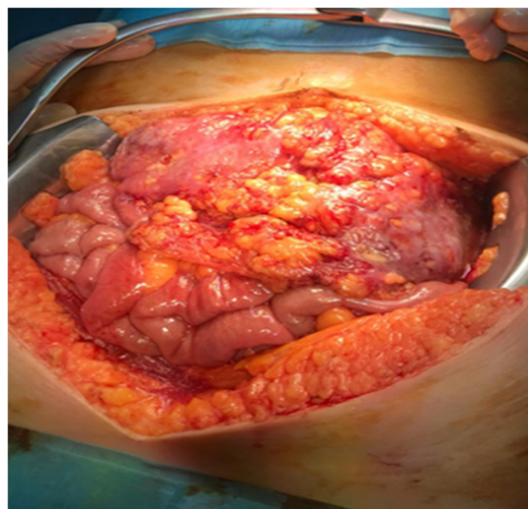


Figure 3.
Submillimeter tumor nodules in advanced ovarian cancer.

2. Results

2.1 Fluorescence-guided surgery in ovarian cancer – general facts

Imaging through the use of NIR-I (near-infrared first-window) fluorescence is limited by the complicated architecture and lymphatic drainage of the anatomically deep ovaries. Ovarian cancer NIR-II imaging studies employed the intraperitoneal xenograft model to identify late-stage metastases. Early-stage cancer detection improves patient survival; thus, finding ovary-restricted tumors is equally important, as demonstrated by Pu et al. [3].

Indocyanine green (ICG) fluorescence imaging is preferred for lymphatic mapping in most gynecologic malignancies. This new technique improves ureteral evaluation, as shown by Zapardiel et al. [4].

As explained by El-Swaify et al. [5], FGS may enhance ovarian cancer micrometastasis and sentinel lymph node (SLN) diagnosis. Additional studies are needed to ascertain whether this enhances patient outcomes.

Xu et al. [6] described that ovarian tumors may be visualized using β -galactosidase (β -gal), a key biomarker for primary ovarian malignancies. A fluorescent chemosensor (LAN- β gal) has the ability to detect β -gal through the use of d-galactose and LAN-OH as its fluorophore, while being membrane-permeable (see **Table 1**), and achieves an unprecedented tumor/normal tissue fluorescence ratio for ovarian cancer diagnostics and treatment.

Types of probes	Fluorophore	Efficiency and success rates	Safety and disadvantages
<i>Probes used in pre-clinical setting</i>			
	CD24-target fluorescent probe	Mostly, but not exclusively in ovarian and colorectal cancers, CD24 can identify otherwise invisible precancerous lesions and small metastases, leading to more complete tumor removal	Although CD24 is a potential target, differences in its expression across various patients and tumor subtypes may pose barriers
	Optical FR α -targeted agent (PPF)	It detected submillimeter tumor tissues	Tumor vascularization influences the probe distribution
	Gonadotropin-releasing hormone receptor (GnRHR)-targeted fluorescent probe = GnRH α -indocyanine green	Revealed submillimeter tumor deposits on the mesentery	Each component has limitations, such as ICG's poor photostability and strong protein binding, possible side effects such as allergic responses and nausea, and liver elimination, making it inappropriate for liver disease patients. Atypical puberty may benefit from GnRH α , but it may also harm body composition
	Human placental lactogen (hPL) -Cy5	To assist surgeons in the detection of tumors from healthy tissue after surgery, hPL-Cy5 highlights prolactin receptor-expressing tumors	Fluorescence imaging performed <i>in vivo</i> showed elevated fluorescence in non-target areas

Types of probes	Fluorophore	Efficiency and success rates	Safety and disadvantages
	COC183B2-Cy7 and COC183B2-800	They offer great specificity and sensitivity for ovarian cancer, identifying malignant lesions that standard imaging may miss, enhancing tumor resection and patient outcomes	The main drawback of COC183B2-Cy7 and COC183B2-800 is the very fluorescent liver signal, which might mask tumor imaging, especially at 48 hours post-injection. Due to hepatic signal competition, tumor-to-background ratio (TBR) and tumor visualization are limited, making it difficult to precisely estimate tumor size
	γ -glutamyl hydroxymethyl rhodamine green	Within 10 minutes of peritoneal injection, submillimeter tumor deposits became visible on the mesentery and peritoneal wall	The fluorescence signal diminishes after 60 minutes
	low-pH response fluorophore (CypH-1)	Fluorescence was uniformly distributed in the tumor and intestine	No detection potential for the micrometastases
	Folic aggregation-induced emission luminogen	Facilitate sentinel lymph node detection; micro to submillimeter peritoneal metastases were detected	It has limited specific-targeting ability, poor biocompatibility in physiological fluids, and low stability
<i>Probes used in clinical trials</i>			
	Fluorescein isothiocyanate (FITC)/EC-17	It is suitable for applications involving bright green fluorescence, has broad compatibility, and offers cost-effective labeling solutions	Fluorescein's quick photobleaching is its main drawback
	OTL38	It identified epithelial ovarian carcinoma with a sensitivity of 85.93%	Its optical qualities necessitate changes in imaging systems optimized for indocyanine green (ICG) and have a reduced tissue depth of detection compared to newer NIR-II fluorophores, thus hindering its ability to detect deep lesions
	ONM-100	The findings demonstrated 100% sensitivity, with no false negatives observed	NIR light cannot detect deeper tumors due to its low penetration depth. Another issue is that the surgeon must precisely separate fluorescent signals from background noise, and external white light may interfere
	Methylene blue	Capable of visualizing arterial structures and pancreatic neuroendocrine neoplasms	The drawbacks include aggregation-caused quenching (ACQ), in which molecules clump together and cause their fluorescence intensity to diminish through non-radiative paths, and low fluorescence efficiency (low quantum yield), which results in weak signals

Types of probes	Fluorophore	Efficiency and success rates	Safety and disadvantages
	IR-780 @albumin	It's photostable. Albumin improves the compound's water solubility and reduces toxicity	It has the potential for unstable binding or incomplete encapsulation, which could cause the dye to escape the nanoparticle and bind to endogenous albumin, affecting its intended biodistribution and clearance; hepatobiliary accumulation (accumulation in the liver and intestines); and possibly high background signals
	ICG in brain surgery	A role in ependymoma and hemangioblastoma surgery	Fewer advantages are brought in the case of intramedullary spinal tumor
	cRGD-ZW800-PEG	It allows for dual-channel NIR fluorescence imaging, enabling precise and simultaneous intraoperative differentiation of lung segment lines and tumor boundaries in various colors	There might be possible difficulties with deep tumor penetration, the potential for high dosages to accumulate in healthy tissues, and the fact that it is an experimental drug with little clinical use
	LGW01-08	Nerve-specific. It makes nerves buried under tissue visible, supports real-time imaging after systemic injection, and allows one to two minutes of direct administration staining	Its high lipophilicity makes it difficult to create an aqueous formulation, and its poor aqueous solubility necessitates the use of hydrogel formulations or specialized co-solvents for administration
	SGM-101	Has the potential to improve liver metastasectomy when used in conjunction with ICG	While SGM-101 may improve tumor diagnosis and be safe, false positives are its main drawback
	(GEBP11)2-ACP-Cy5.5	It is a promising tool for intraoperative fluorescence assistance in gastric cancer procedures	The process of GEBP11 peptide binding to its target receptor is unclear, and its efficacy in metastatic cancer and humans needs additional study
	CY7-4	A significant decrease in recurrence and an enhanced survival rate were found when photothermal therapy and fluorescence were used in the treatment of prostatic cancer	Cy7 molecules' light-absorbing chromophore bleaches due to oxygen radicals. Flat rigid molecules can also congregate and interact non-specifically with other biomolecules, slowing their clearance from the body

Table 1.
Fluorescent probes and examples of their use in surgery.

2.2 Enhancing peritoneal cytoreduction in epithelial ovarian carcinoma through FGS

FR α -targeted imaging has the potential to improve lesion detection in cytoreductive surgery, thereby enhancing the completeness of resection. De Jong et al. [7] showed that both animal models and humans with EOC demonstrate promise for fluorescence-guided cytoreductive surgery targeting HER2 or FR α .

EC17 demonstrates feasibility; however, larger trials indicate the potential of OTL38. According to Ferrari et al. [8], future research should focus on optimizing imaging agents to minimize autofluorescence and evaluate their effects on survival outcomes. Erdemoglu et al. [9] considers that FGS with 5-ALA may improve microscopic disease detection and surgical management in ovarian cancer. CD24, a minor cell surface receptor, is markedly overexpressed in nearly 70% of solid tumors, as noted by Kleinmanns, and has been identified as a prognostic and therapeutic biomarker of particular relevance to EOC. The reliable intraoperative detection of micrometastases underscores the potential of CD24 as a target for FGS in patients with EOC. Complementarily, Zhang et al. [10] demonstrated that Cetuximab–Cy7 selectively binds to EOC xenografts in nude mice, further supporting the feasibility of receptor-targeted fluorescence imaging in ovarian malignancies. Chen et al. [11] showed that the COC183B2–Cy7 probe is sensitive and specific. In FGS, the probe entitled COC183B2–Cy7 may prove to become a new diagnostic instrument in the full and accurate removal of malignant foci.

Fluorophore selection impacts biodistribution and clearance of conjugates, affecting the specificity of target binding. The following examples – ICG, ZW800-1, and IRDye[®] 800CW – are all common NIR fluorophores, but the optimal *in vivo* option is still unclear. The study by de Jalón et al. [12] revealed that fluorophore selection greatly affects biodistribution, specificity, and contrast in an ovarian cancer model. ZW800-1 Forte (2) showed the best performance with a notable specific fluorescence signal. Uwins et al. [13] noticed that ICG may be promising in patients with outstanding treatment response and little tumor deposits during robotic interval cytoreductive surgery for ovarian cancer. Achimas-Cadariu et al. [14] found that ICG improved detection of residual malignant foci after interval debulking, with hypointense regions showing higher predictive value for malignancy than hyperintense areas, potentially due to changes from neoadjuvant chemotherapy. The review by Dindere et al. [15] examines the applications of pafolacianine, an FDA-approved agent, for the precise intraoperative identification of malignant tissues.

According to Josserand et al. [16], FGS utilizing Angiostamp800 and Bevacizumab–IRDye 800CW resulted in an $88.7\% \pm 4.3\%$ increase in total tumor burden resection, while ICG showed no improvement in surgical outcomes. Bevacizumab–IRDye 800CW and Angiostamp800 demonstrate superior detection of ovarian tumors and metastases compared to the commonly used fluorescent tracer ICG, thereby facilitating more complete tumor removal by surgeons, particularly after neoadjuvant chemotherapy. Liu et al. [17] conjugated a GnRH analog peptide with the Rh760 fluorophore and polyethylene glycol to create a GnRHR-targeted NIR fluorescent probe, GnRHa-PEG-Rh760. The findings showed that GnRHa-PEG-Rh760 enhances surgical accuracy via fluorescence.

OCTL14 would provide surgeons with an essential tool for optimum resection, in the context of the bioconjugation strategy by Fukuda et al. [18] of utilizing a non-targeted fluorophore.

Usama et al. [19] introduces fluorogenic probes based on the most widely used NIR chromophore, heptamethine cyanine. These probes might expand fluorogenic imaging to intact tissues and living animals.

According to de Muynck et al. [20], another option would be EpCAM, described as a potential intraoperative imaging target for detecting genuine metastatic EOC lesions.

He et al. [21] showed that chemically connecting ICG to mouse monoclonal antibody 10D7, which recognizes CUB domain-containing protein 1 – an ovarian cancer-enriched cell surface receptor – created a tumor-selective fluorescent agent. *In vitro* and *in vivo*, 10D7ICG displays excellent affinity for pure recombinant CDCP1 and ovarian cancer cell surface CDCP1. The results showed that intravenously injected 10D7ICG accumulates preferentially in ovarian cancer, enabling mice to visualize xenograft tumors. The findings support tumor-specific fluorescence-guided ovarian cancer surgery targeting CDCP1.

In a systematic review, Boussedra et al. [22] showed that the sensitivity and specificity of fluorescence varied from 66.7% to 100% and from 54.2% to 100%, respectively. The negative predictive value (NPV) ranged from 90% to 100%. The differences across the studies prevented any agreement on the best use of fluorescence, such as choosing the dye, timing and method of injection, and the imaging tools employed. No negative incidents were reported. In comparison to this former study, a systematic review and meta-analysis conducted by Luo al. [23] compared various fluorophores utilized in ovarian cancer surgery, yielding the following results: the highest sensitivity value recorded was an EC17 of 98.2%. 5-ALA achieved 96.9% specificity and positive predictive value. Detecting SLNs was greater at ICG doses of 0.625–1.25 mg compared to 0.5 or 2.5 mg. Negative responses varied between 14.3% and 83.3%.

Using the Cell-SELEX technique, the DNA aptamer mApoc46 was developed by targeting patient-derived primary serous ovarian cancer (pSOC) cells. The aptamer mApoc46 is highly selective to pSOC cells. Therefore, according to Wang [24], the aptamer mApoc46 shows promise for rapid cancer detection, diagnosis, and targeted treatments.

2.3 Bimodal approaches (fluorescence and another class of detectors)

2.3.1 Fluorescence and radionuclide detection

A study signed by Kleinmanns et al. [25] presents ovarian cancer biomarkers, highlights the advantages of CD24, and proposes a bimodal strategy combining fluorescence imaging with targeted therapy.

2.3.2 Fluorescence and erythrocyte membrane-camouflaged bioprobes

Current probes yield low-contrast imaging, complicating resections. To overcome this disadvantage, a study by Meng et al. [26] used an engineered erythrocyte membrane-camouflaged bioprobe (AR-M@HMSN@P) to precisely resect tiny metastatic cancers. AR-M@HMSN@P attained highly accurate tumor imaging with an SNR of 15.2 for excisions under 1 mm.

2.3.3 Fluorescence through/with nanotechnology

Marotta et al. [27] developed two generations of up-converting nanoparticles that emit green light when exposed to NIR light. The particles identify ovarian tumors

through tumor-associated macrophages. The findings show that this method can detect tumors during surgery without costly, sophisticated, or large detection equipment.

A research study by Vankayala et al. [28] investigates the effectiveness of virus-mimicking nanoparticles derived from genome-depleted bromine mosaic virus, which have been combined with NIR brominated cyanine dye BrCy106-NHS for the targeted NIR fluorescence imaging of ovarian tumors located intraperitoneally. These particles are called optical viral ghosts (OVGs). The researchers have also altered the OVGs with antibodies that specifically target the HER2 receptor, which is a biomarker excessively expressed in cases of ovarian cancer. Functionalized virus-mimicking NIR nano-structures may serve as a means for the intraoperative imaging of ovarian tumor implants.

Nano-sized red blood cell-derived particles encapsulating the NIR dye ICG were developed for tumor visualization during surgery. This study reports the first application of these nanoparticles in combination with spatially modulated illumination (SMI) at specific spatial frequencies for fluorescence imaging of intra-abdominal ovarian tumors in mice. The findings demonstrate that employing erythrocyte-derived NIR nanoparticles together with structured illumination enables effective intraoperative fluorescence imaging of ovarian tumor nodules, resulting in enhanced image contrast. Potara et al. [29] created a nanotherapeutic platform for ovarian cancer that combines NIR imaging with photodynamic (PDT) and photothermal (PTT) treatments and identification functionality. IR780 was loaded into polymeric Pluronic-F127-chitosan nanoformulation to overcome its hydrophobicity, toxicity, and folic acid functionalization. Nanocapsules exhibit temperature-dependent swelling, enhanced fluorescence, and stability, producing singlet oxygen and increasing temperature by 46°C under NIR laser. They show potential as theranostic agents for dual PDT-PTT and ovarian cancer surgery imaging. On the clinical benefits of PDT and its association with fluorescence to destroy tumor cells and trigger the immune response, another research was conducted by Liu et al. [30]. Ahmmed et al. [31] showed that photosensitizers like Porphyrin-Phospholipid (PoP) and chemotherapeutics like Doxorubicin (Dox) allow light-triggered medication release and targeted tumor death in chemophototherapy (CPT). Laparoscopic systems can measure PoP and Dox fluorescence concentrations, making them useful for intraoperative CPT effectiveness monitoring.

2.3.4 Aggregation-induced emission probe mimicking cancer-associated fibroblasts

Intraoperative fluorescent surgical navigation modalities are inadequate for the complete removal of ovarian cancer lesions, resulting in a persistently high recurrence rate. Dai et al. [32] developed cancer-associated fibroblasts (CAFs)-mimetic aggregation-induced emission (AIE) probe to facilitate comprehensive management of surgical procedures aimed at preventing recurrence. The probe markedly decreased the recurrence rate of ovarian cancer.

2.3.5 NIR fluorophores that are pH-sensitive

Yokomizo et al. [33] reported the following: a pH-sensitive NIR fluorophore exhibiting rapid signal changes in acidic tumor microenvironments due to

reduced intramolecular quenching, along with intrinsic cancer targeting based on chemical structure and mitochondrial/lysosomal retention. Applied topically on peritoneal tumors, it showed increased fluorescence within 10 minutes, lasting over 4 hours. This combination enables the visualization of submillimeter tumors with an elevated tumor-to-background ratio (TBR > 5.0). PH08 has a notable effect on surgical and diagnostic applications, offering a viable, scalable approach for designing cancer therapies. Song et al. [34] developed a novel smart nanoparticle (e.g., FA-IR780&PFOB-SNPs) by leveraging the optical properties of IR780 and the characteristics of the acidic tumor microenvironment, utilizing a pH-responsive nano framework (FA-PEG-PLGA-PEOz) and optimizing the quantity of IR780. The study results suggest that FA-IR780&PFOB-SNPs could improve intraoperative NIR fluorescence guidance for ovarian cancer in precise tumor resections, targeting R0 resection and better outcomes for patients.

2.3.6 Fluorescence and photonic crystals

As presented by Jian et al. [35], photonic crystals with appropriate wavelengths may boost fluorophores' surface excitation and emission intensities, as well as fluorescent compounds' fluorescence signals. Ovarian cancer detection and therapy are fast and accurate using stretchable photonic crystal-assisted glycoprotein identification.

2.3.7 Fluorescence and MRI activation

Yu et al. [36] created an innovative β -gal bimodal imaging sensor that uses NIR fluorescence and MRI to visualize live creature activity in real time. Gal-Cy-Gd-1, upon β -gal activation, enhances NIR fluorescence at 717 nm, improving enzyme labeling, probe accumulation at tumors, and supporting real-time imaging of enzyme activity.

2.3.8 Double immunofluorescent staining

Bogush et al. [37] outlined an innovative double immunofluorescent labeling technique for flow cytometry that can specifically measure the mesenchymal protein vimentin solely in the epithelial cells of a solid tumor with various originating cell types. Among 32 ovarian cancer patients, both the Kaplan–Meier curves and the COX proportional hazards ratio indicated an inverse relationship between the quantitative measure of epithelial–mesenchymal transition and progression-free survival.

2.4 Use of fluorescence in multivisceral resections done for ovarian cancer surgery

Enhancing bowel anastomosis integrity in ovarian cancer surgery is crucial, as complications can hinder recovery and treatment. Traditional assessments are subjective and unreliable for predicting leakage risks. Fluorescence technologies, particularly ICG fluorescence angiography (ICG-FA), show promise in improving diagnostic accuracy and aiding intraoperative decision-making, addressing serious anastomotic failure consequences, as shown also by Salman et al. [38] in enhancing bowel perfusion assessment precision during surgical interventions. Preliminary

results indicate that ICG-FA is a safe and feasible tool in ovarian cancer surgeries, as presented by Gill et al. [39]; however, more research is needed to establish standardized protocols and evaluate its clinical relevance and long-term benefits. Santana et al. [40] also investigated and concluded that ICG-FA may prevent ostomies in ovarian cancer cytoreductive surgery but does not reduce anastomotic leak rates.

ICG fluorescence imaging may promptly identify the ureter's path, avoid ureteral damage, and decrease perioperative and postoperative problems. Intraureteral ICG enables surgeons to safely execute ureterolysis by quickly visualizing the ureter, as emphasized by Yan et al. [30] Complex gynecological cancer, pelvic floor disease, and endometriosis surgery may use the suggested method.

2.5 Fluorescence to check the blood supply and to better identify the lymph nodes

Childhood ovarian masses are the most prevalent abdominal masses in girls. Most newborn masses are benign, but adolescents and teens are at risk of cancer. Ciro et al. [41] conducted a 25-year retrospective examination of the clinical and therapeutic characteristics of ovarian tumors in girls to demonstrate how minimally invasive technology has transformed care. ICG fluorescence is essential at all ages to monitor ovarian vascularization following detorsion or lymph node status in cancer. Remove any probable lesions using an endo-bag.

3. Availability and cost involved in fluorescence surgery for ovarian cancer in different parts of the world

FGS for ovarian cancer is still new and only available at top cancer centers in North America and Europe, but it is spreading worldwide. While cost data vary by region and institution, initial FGS equipment costs can be high (e.g., \$120,000 for a system), but improved outcomes and reduced therapy needs may outweigh them. Due to equipment investment, staff training, and fluorescent probe regulations, FGS implementation cost breakdowns by area are limited.

3.1 Availability

FGS is a growing technology utilized for surgical guiding, including tumor diagnosis, but it is not yet a conventional treatment for all ovarian cancer patients, and its potential risks (see **Table 2**) require further studies and specific testing.

Geographic focus: The technology is more accessible in industrialized countries with established healthcare infrastructure, namely in North America and Europe, but it is growing globally.

FGS is more common at major cancer centers and research hospitals that use novel surgical equipment.

3.2 Cost factors

Surgical institutions must invest in FGS equipment, including imaging systems and optical probes, which can be costly initially.

Patient-related risks	Procedure-related risks
Sun sensitivity: fluorescent dyes can increase skin sensitivity to light for 24 hours; thus, patients should avoid strong lights and sunshine	False positives/negatives: healthy tissue may glow, but malignant tissue may not, making it challenging for surgeons to differentiate between the two
Patients may experience moderate responses, such as a skin rash or stomach problems, or more serious allergic reactions to dye components like iodine	Signal attenuation: tissue might diminish or block the fluorescent signal, making open surgery difficult
Medication interactions: fluorescent dyes can interact with blood pressure and heart medications, causing negative effects	Ambient light interference: surgical lights and ambient white light can disrupt fluorescence imaging
Temporary color changes: the dye can briefly modify the patient's skin or urine color	Increased radiation dose: some fluorescence procedures may expose patients and surgeons to more radiation

Table 2.
Potential risks of various fluorescence surgery techniques.

Hospital staff require specialized training to handle the FGS system and comprehend fluorescent agent behavior.

Fluorescent probes: These injectable probes for cancer cell detection are expensive. Like new pharmaceuticals, they must undergo rigorous regulatory review, which increases access costs.

Despite high initial costs, FGS can reduce long-term healthcare expenditures by increasing tumor resection rates and reducing the need for costly follow-up therapies like chemotherapy and radiotherapy.

Country-specific healthcare systems, economic conditions, and regulatory clearance processes for probes and equipment can considerably impact global cost variations.

3.3 FGS cost impact

Improved resection: FGS enables surgeons to better identify and remove malignant tissue while sparing healthy tissue, which can lead to better patient outcomes.

FGS can reduce surgical problems and costs by improving the visibility of important structures and reducing the need for additional procedures or adjuvant treatments.

4. Point of view on a comparison between fluorescence surgery on one side, and robotic and laparoscopic surgery on the other

While laparoscopic and robotic surgery are surgical techniques for carrying out less invasive treatments, fluorescence surgery is a technology that enhances visibility.

Regardless of the surgical technique selected, fluorescence imaging can be incorporated into a robotic or standard laparoscopic surgery system to enhance the visualization of anatomy or disease.

Fluorescence is an inherent element of robotic systems; however, it takes extra equipment to incorporate fluorescence into routine laparoscopy.

The main advantages of minimally invasive procedures (less trauma, quicker recovery) are provided by laparoscopic and robotic surgeries; however, robotic devices come at a higher cost but offer more precision and visualization. For conclusive results, more high-quality research is necessary because the precise cost-effectiveness of minimally invasive surgery can differ based on the particular technique, the technology (such as robotics), and the cost analysis methodology. Similarly, fluorescence surgery has higher initial and ongoing expenses for supplies and equipment, but it can have major advantages, such as increased tumor removal rates, decreased risks of complications like hypoparathyroidism (hypoPT) or bile duct damage, shorter recovery times, and possibly fewer reoperations. In addition to all those benefits, one could include a reduction in the reliance on adjuvant treatments, like chemotherapy, immunotherapy, and radiotherapy, along with their associated expenses. The particular type of operation and the rate at which the fluorescence technology minimizes problems determine the overall cost-effectiveness, a form of economic analysis open to future studies, with regard to fluorescence-guided ovarian cancer surgery.

5. Conclusions

FGS is an encouraging method for better intraoperative definition of tumors and real-time monitoring of submillimeter tumor masses in EOC cytoreductive surgery. Nevertheless, most of the EOC-targeted fluorescence probes are still in preclinical trials.

Fluorescence is a safe method for evaluating peritoneal metastases, but a randomized controlled trial is necessary to standardize current practice.

FGS, as applied to ovarian cancer, needs more specific investigation to establish whether it improves patient outcomes. Additionally, a cost-effectiveness analysis (CEA) of FGS in ovarian cancer, assessing the costs and health outcomes (like quality-adjusted life years or disability-adjusted life years), could be beneficial in guiding future clinical and health policy planning.

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Cancers of the ovary are considered the most common forms of neoplasia in women. Among all the cancers that affect the genital tract of females, ovarian cancer incidence ranks only second to carcinoma of the cervix and the endometrium. In the USA, ovarian cancer accounts for about 2.5 % of all cancers in females and ranks 5th among the most common forms of cancer in women.

Because ovarian cancers cannot be detected early during their development, they constitute a disproportionate percentage of all cancer deaths among women. There are many types of ovarian cancer, including both benign and malignant, with approximately 80 % being benign and occurring mostly in young women between the ages of 40 and 69 years. Globally, ovarian cancer ranks 18th among the most common cancers. The American Cancer Society predicts there will be 20,890 new ovarian cancer diagnoses and 12,730 ovarian cancer deaths in the USA by the end of 2025. The 5-year survival rate of ovarian cancer is about 50.9%. Worldwide, 1.1 % of women will be diagnosed with ovarian cancer sometime during their lifetime. There are many ovarian cancer risk factors. However, nulliparous families with inheritable mutations in BRCA1, BRCA2, RAD51C, RAD51D, MSH2, MLH1, MSH6, and PMS2 play significant roles in developing ovarian cancer, in particular hereditary forms of ovarian cancer. Because the symptoms of the initial stages of ovarian cancer are undetectable, it is exceedingly difficult to diagnose it at initial stages; hence, it is exceedingly difficult to treat ovarian cancer. In the last 20 years, we have seen advancements in the identification of new biomarkers, methods for efficient diagnosis, and treatment modalities for ovarian cancer. Currently, the main methods for treatment include surgery, radiation, chemotherapy, immunotherapy, and other non-conventional/traditional approaches for treating ovarian cancers. In this book, the authors are invited to discuss the types of ovarian cancer, new markers for early detection, the roles of modifiable and non-modifiable risk factors, the roles of inheritable gene mutations, nutrition and environmental factors, and basic molecular mechanisms mediated by various cytokines/chemokines and other growth factors that regulate ovarian cancer pathogenesis.

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