# Proteomic Landscape of Ovarian Cancer

Subjects: Others

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Keywords: ovarian cancer ; proteomics ; biomarkers

## 1. Overview

Despite recent technological advancements allowing the characterization of cancers at a molecular level along with biomarkers for cancer diagnosis, the management of ovarian cancers (OC) remains challenging. Proteins assume functions encoded by the genome and the complete set of proteins, termed the proteome, reflects the health state. Comprehending the circulatory proteomic profiles for OC subtypes, therefore, has the potential to reveal biomarkers with clinical utility concerning early diagnosis or to predict response to specific therapies. Furthermore, characterization of the proteomic landscape of tumor-derived tissue, cell lines, and PDX models has led to the molecular stratification of patient groups, with implications for personalized therapy and management of drug resistance. Here, we review single and multiple marker panels that have been identified through proteomic investigations of patient sera, effusions, and other biospecimens. We discuss their clinical utility and implementation into clinical practice.

## 2. Ovarian cancer

Ovarian cancer (OC) is often used as an umbrella term referring to malignancies caused by ovarian epithelial inclusion cysts that are trapped beneath the surface of the epithelium of the ovary as well as malignancies in the peritoneum and fallopian tube [1]. Advanced OC is one of the deadliest malignancies in women with a 5-year survival rate below 30% and high incidences of occurrence in the Eastern and Central European population (11.4 per 100,000 and 6.0 per 100,000, respectively) [2]. Although the incidence varies across populations, the average lifetime risk of developing OC is 1.3% [3].

Most OC are epithelial (90%), and it is a heterogeneous disease comprising of a range of subtypes [4]. The most frequent subtype is high-grade serous carcinoma (HGSC) corresponding to around 60 % of cases, whereas low-grade serous carcinoma, mucinous, clear cell, and endometrioid OC are all less abundant [4]. The spread of OC is frequently systematically categorized using a scoring scheme outlined by the International Federation of Gynecology and Obstetrics (FIGO). FIGO scoring is based on the tumor-node-metastasis (T-N-M) approach which systematically describes the extent of the tumor (T) as well as its spread to lymph nodes (N) and potential metastasis (M) and categorizes OC into 4 stages (denoted I, II, III, and IV). Stage I is characterized OC only in the ovary(s) or fallopian tube(s) and Stage II by its spread to a close organ such as the uterus, bladder, or rectum. Stage III is defined by the spread to the abdomen and/or lymph nodes and stage IV by distant metastasis. i.e., pleura. While Stage I tumors are associated with a good prognosis most OC cases are not diagnosed at this stage. Stage II and III OCs are removed by debulking surgery followed by treatment with a combination of platinum and taxane chemotherapy which leads to considerable improvement in survival [5]. Stage III tumors are categorized by the spread to the adjacent peritoneum through metastasis. Stage IV is defined through distant metastasis and frequently treated by a combination of debulking surgery to remove the primary tumor and chemotherapy to target metastases. Due to the lack of efficient tools for early diagnosis, around 10–20% of the OCs are detected at this stage and treatment options remain limited along with poor survival rates [6]. OC tumors are typically also categorized as low or high grade, which reflects the differentiation state of tumor cells. The less differentiated low-grade tumors are typically associated with a better prognosis.Several genetic studies have linked dysregulated gene expression and mutations to OC. However, not all OCs display a similar pattern, emphasizing that the disease is heterogeneous also at the molecular level. For example, and by analogy with malignant breast cancer, mutations in BRCA1 and BRCA2 are linked to OC [7]. Moreover, the high-grade serous OCs display a high frequency of TP53 mutations and other OC histologic subgroups have frequent mutations in ARID1A, PIK3CA, PTEN, CTNNB1, KRAS, and RPL22 [7][8][9][10].

One of the major challenges associated with the diagnosis of OC is the asymptomatic nature of the disease. Early-stage (I and II) OC are therefore challenging to detect. Late-stage (III and IV) OC is associated with more severe symptoms, and invasive surgery is the most viable option for disease management [11]. Although primary complete debulking surgery (PDS) strikingly increases survival for advanced-stage OC, it is not a perfect approach and many patients suffer from the recurring disease. In certain cases, the tumor burden needs to be reduced before PDS. This is frequently achieved through neo-adjuvant chemotherapy and referred to as interval debulking surgery [12].

While the 5-year survival rates for early-stage (I and II) OC can be up to 90% with clinical interventions like cytoreductive surgery and combination chemotherapy, the late-stage (III and IV) OC 5-year survival rate is below 30% [13]. Therefore, diagnostic biomarkers that distinguish benign from malignant tumors at an early stage would be of tremendous value (Figure 1a). Moreover, as OC is a complex heterogeneous disease, biomarkers predicting the responsiveness of tumors to drugs, which would thereby guide personalized treatment, would be of great clinical utility (Figure 1b).

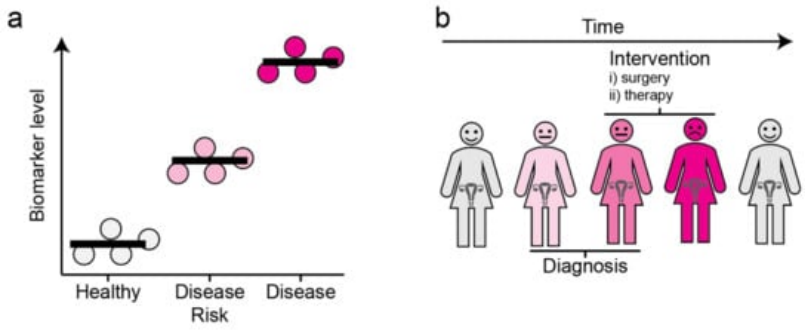


**Figure 1.** The concept and utility of biomarkers. (**a**) Disease biomarkers. Molecules of which the level is associated with a disease state are referred to as biomarkers. (**b**) Clinical utility of biomarkers. The levels of biomarkers can be monitored over time, allowing for early diagnosis and informed decisions regarding clinical interventions. Grey: Healthy, Light Pink: Individuals with disease risk, Dark Pink: Individuals harboring the disease.

## 3. Protein Biomarkers Associated with OC

The identification of biomarkers for improved OC diagnosis and informed clinical decision-making would represent great value for both patients and the healthcare system. Protein markers are most frequently analyzed in the tumor, tumor effusions, or circulating fluids such as blood plasma (Figure 2). Early studies have reported the use of single markers in blood serum such as CA125 (Uniprot ID Q8WXI7, also known as Mucin-16) [14] and HE4 (Uniprot ID Q14508) [14]. With high-throughput semi-automated systems for sample handling and analysis, as well as the implementation of machine learning-based AI approaches, the use of biomarker panels comprising multiple markers has emerged as a superior approach. For example, panels of analytes such as the one proposed by Mor G et al., consisting of Leptin, Prolactin, Osteopontin, and insulin-like growth factor-II (IGF-II) have been proven to be useful for discriminating cancer and non-cancer patients as well as the assessment of stage I/II disease [15]. In a recent study, the assessment of multiple biomarkers, along with CA125, considerably improved the performance of the predictive model for early diagnosis. This panel comprised of CA125, HE4, CHI3L1, PEBP4, and/or AGR2, provided 85.7% sensitivity at 95.4% specificity up to one-year before diagnosis [16]. Moreover, a study by Enroth et al., recently revealed a candidate 11-protein biomarker panel for early OC diagnostics [17]. Currently, studies aimed at uncovering OC biomarkers are increasingly implementing similar multiple-marker models for predictive analysis (Table 1).

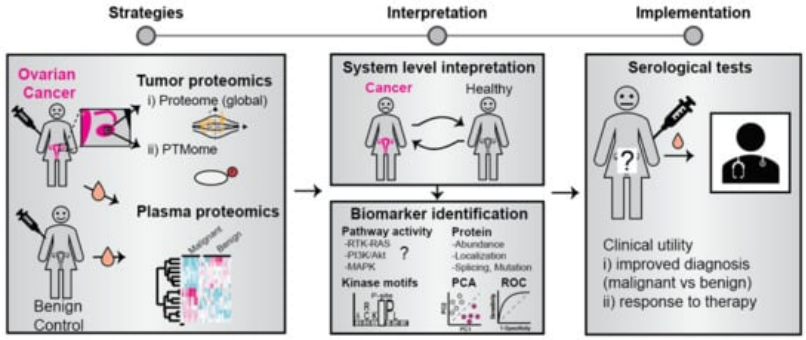


**Figure 2.** Identification and clinical use of OC protein biomarkers. Biomarkers can be identified by a comparative analysis of proteins and their modification state in tumor material and blood plasma from patients and controls. The bioinformatic analysis may involve cellular pathway activity mapping, principal component analysis (PCA), and receiver operator

characteristics (ROC). Identified biomarkers have the potential to improve disease diagnosis and predict response to therapy.

**Table 1.** Examples of key protein markers associated with Ovarian Cancer.

| Marker(s) | Gene ID (If Applicable) | Source | Type (Circulatory/Tumor-Specific | Utility (Early/Late-Stage Pre/Post-Menopausal) | Platform & Study Design | Reference |
|---|---|---|---|---|---|---|
| CA-125 | MUC16 | Serum/Plasma | Serum marker-high molecular weight glycoprotein | Monitoring response to chemotherapy and disease activity in clinical trials. | Immunoassays from patient sera using OC125 and M11 antibodies | [18][19][20] [21] |
| HE4 | WFDC2 | Serum/Plasma | HE4 is also a secreted glycoprotein that is overexpressed in OCs | FDA approved biomarker for monitoring disease activity | Immunoassays from patient sera | [19][20] |
| MCSF and LPA | CSF1 | Blood/Tumor tissue ascites | Components of the tumor microenvironment | LPA is elevated in the blood, tumor tissue, and ascites. LPA also influences tumor-associated macrophages, which can be used as a therapeutic target | Metanalysis from several studies mostly based on the immunoassay-based determination of markers | [22] |
| CART analysis: CA-125, OVX1, LASA, CA 15-3, CA 72-4) | MUC16, ovx1, MUC1 | Serum | Circulatory markers as well as tumor microenvironment components | CART analysis (classification and regression tree analysis), uses the sequential analysis of marker concentrations with 5 markers (CA-125, OVX1, LASA, CA 15-3, CA 72-4) to yield a sensitivity of 90.6% and a specificity of 93.2% | Initial discovery-based studies using radioimmunoassay. Multiple marker analysis performed on ANN based machine learning algorithms | [23][24][25] |
| A three-panel marker: Apolipoprotein I TransthyretinInter-α-trypsin inhibitor heavy chain H4 (cleavage fragment) | APOA1, TTR, ITIH4 | Serum | Components of the circulatory biofluids | Useful for detection of early-stage patients, exhibits higher sensitivity (74%) over CA125 alone (52%) | The study employed SELDI-TOF technology with the ProteinChip Biomarker System (Ciphergen Biosystems) | [25][26] |

| Marker(s) | Gene ID (If Applicable) | Source | Type (Circulatory/Tumor-Specific | Utility (Early/Late-Stage Pre/Post-Menopausal) | Platform & Study Design | Reference |
|---|---|---|---|---|---|---|
| CT45 | CT45A1, CT45A | Tumor tissue (FFPE blocks) | Tumor marker | Reported to be an independent prognostic factor that is associated with a doubling of disease-free survival in advanced-stage HGSCs | Quantitative proteomics on FFPE tumor samples derived from 25 chemotherapy-naive patients with advanced-stage HGSCs | [27] |
| MUCIN-16, SPINT1, TACSTD2, CLEC6A, ICOSLG, MSMB, PROK1, CDH3, WFDC2, KRT19, and FR-alpha | MUCIN-16, SPINT1, TACSTD2, CLEC6A, ICOSLG, MSMB, PROK1, CDH3, WFDC2, KRT19, and FOLR | Plasma | Circulatory markers | Potentially useful for improved diagnosis of adnexal ovarian mass and identification of potential cases for specialized referrals | PEA was implemented utilizing oligonucleotide antibody probes to measure protein abundance | [17] |

CA-125 = cancer antigen 125; HE4 = homo sapiens epididymis specific 4; MCSF = macrophage colony-stimulating factor; LPA = lysophosphatidic acids; ANN = artificial neural networking; SELDI-TOF = surface-enhanced laser desorption/ionization-time of flight; HGSC = high-grade serous ovarian carcinomas; PEA = proximity extension assay.

Proteomic characterization of tumor tissue specimens has also revealed molecular aberrations that contribute to the onset and progression of OC [28][29]. Immunohistochemistry-based examination of tumor specimens using members of the cytokeratin family (CK7 and CK20) helps in distinguishing serous OC from other gastrointestinal malignancies [30]. In-depth analysis of genetic and histopathological signatures has also led to categorizing OCs into two types, Type I (Low grade) and Type II (High grade). While Type I tumors have a high frequency of KRAS and BRAF mutation, Type II tumors have a high frequency of TP53 mutations [31][32][33][34]. Other biospecimens such as effusions, pap smear fluids, and cervicovaginal are also valuable for understanding OC pathobiology and represent sources of markers that can predict clinical outcomes [35][36]. For example, a 9-biomarker panel in ovarian cyst fluids has been shown to discriminate between type 1 and type 2 tumors [37]. Moreover, a pilot study has depicted the utility of vaginal lysophosphatidic acid (LPA) levels as a non-invasive diagnostic marker for OC in post-menopausal women [38]. Another study investigating OC effusions revealed prominent involvement of cell-cell adhesion molecules like FAK, Erk, and P-Cadherin [39]. The study also suggested that cell adhesion molecules can comprise a prognostic signature that can be utilized to predict tumor aggressiveness as well as patient segregation. Cell adhesion protein expression, when correlated with clinicopathological parameters, has also been used to identify patient cohorts for clinical trials with small molecule inhibitors of FAK and other upstream effectors [40][41][42]. While these markers have yielded insights into OC development and the molecular pathways associated with it, they are still in the early stages of investigation and are yet to be implemented for disease management.

The emergence of ‘liquid biopsies’ has indeed ushered in a new era in diagnostics [43]. There is now tremendous potential for identifying biomarkers for improved OC diagnosis by mining such liquid biopsies with state-of-the-art (prote)-omics technologies [44][45]. Mostly the liquid biopsies are probed for circulating tumor DNA, tumor cells, exosomes, or tumor microRNA. In OCs, circulating tumor cells (CTC) are often present and useful as surrogate markers of minimal residual disease. In a study by Zhang et al., wherein nearly 100 patients were screened and subjected to CA125 measurements; CTCs were detected in nearly 90% of the newly diagnosed patients. The number of CTC also correlated with the stage of the OC. However, the ratio of CTC in comparison to other components in plasma is low and the choice of detection technique influences the number of CTCs identified. Although major strides have been made through the implementation of liquid biopsies for several cancers, more research is required to assess the full utility of CTC determination for OC, which primarily metastasizes directly through the abdominal cavity [46][47][48][49][50].

With recent advances in high-throughput omics technology and automated handling of large sample cohorts, the scope of establishing multi-marker panels has increased considerably. An ideal scenario for the effective clinical management of OCs would implement an integrated approach where blood-based markers and imaging analysis are collectively used for diagnosis and guiding clinical decisions on surgery and choice of therapy.

## 4. Conclusions

Circulating protein biomarkers display great potential to discriminate between patients with benign and malignant ovarian cysts, while also guiding treatment decisions [8][51]. In recent years, proteomics characterization of plasma, effusions, and solid tumors has uncovered molecular mechanisms and a plethora of candidate biomarkers for OC, although these still need to be validated to show clinical utility. We foresee a wealth of studies in the coming years validating these candidate markers, while also identifying additional markers. We also anticipate that basic OC research will focus on the single-cell resolved analysis of tumor protein and PTMs. The integrated analysis of tumor specimens with matched blood samples is particularly interesting and has the potential to reveal accessible surrogate blood-based biomarkers that reflect tumor biology and can be used in personalized treatment.

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