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Artificial intelligence in ovarian cancers- from diagnosis to treatment; a literature review

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ABSTRACT

Ovarian cancer remains the most lethal gynecological malignancy due to challenges in early detection stemming from a lack of reliable biomarkers. Despite this, various laboratory tests are commonly employed in clinical practice, some showing diagnostic and prognostic promise for ovarian cancer. This review aims to synthesize current literature to delineate the role of artificial intelligence (AI) in both the diagnosis—from laboratory tests to imaging—and treatment of ovarian cancers. Thus, the epidemiology, risk factors, pathology, screening methods, as well as the integration of AI in the diagnosis of ovarian cancer (AI based on both blood biomarkers and imaging-based ovarian cancer detection) are presented. AI and biomarkers show considerable potential in improving ovarian cancer management, but ongoing research efforts are necessary to refine these technologies and integrate them effectively into clinical practice. This approach aims to enhance diagnostic accuracy, predict patient outcomes, and ultimately improve treatment strategies for ovarian cancer patients.

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Introduction

Epithelial ovarian cancer originates from the malignant transformation of the ovarian surface epithelium, which is continuous with the peritoneal epithelium [1]. It ranks as the sixth most prevalent cancer among women worldwide [2]. Diagnosis frequently occurs at an advanced stage, leading to poor prognoses with existing treatments. However, advancements in chemotherapy and an enhanced understanding of genetic risk factors and molecular pathogenesis offer new treatment avenues. This overview explores the clinical and molecular features of epithelial ovarian cancer and discusses potential future advancements.

The highest incidence rates of epithelial ovarian cancer are observed in Europe, the USA, and Israel, with lower rates in Japan and developing countries [2]. The median age at diagnosis is typically 60 years, and the average lifetime risk for women in developed nations approximates one in 70 [2]. A notable risk factor is a strong family history of ovarian or breast cancer, though detectable genetic predispositions, such as germline BRCA1/BRCA2 mutations, are present in only 10-15% of cases [3,4]. Women with a BRCA1 mutation face a 39-46% risk of developing epithelial ovarian cancer, whereas those with BRCA2 mutations have a 12-20% risk. Other risk factors include nulliparity, early menarche, late menopause, and

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advancing age. Conversely, factors like oral contraceptive use, pregnancy, lactation, and tubal ligation are associated with reduced risks [5,6].

Research indicates a declining incidence of epithelial ovarian cancer in developed nations across various age groups and ethnicities since 1985 [7-9]. Median survival in advanced-stage cases has also improved over the past three decades. The shift in incidence between Western and Southern/Eastern Europe and the USA may be linked to increased oral contraceptive use and reduced fecundity, respectively [10].

Several interrelated theories aim to explain these epidemiological observations [11]. The incessant ovulation hypothesis posits that repeated injury to the ovarian surface epithelium during post-ovulatory repair, coupled with subsequent cell proliferation, results in the accumulation of genomic abnormalities. This process gives rise to ovarian epithelial inclusion cysts, potentially increasing carcinogenic risk by trapping cells in an environment characterized by abnormal autocrine or paracrine stimulation by growth factors such as hormones, phospholipids, and VEGF. These factors activate intracellular pathways like kinase signaling. The gonadotropin theory suggests that surges in pituitary gonadotropins during ovulation and elevated concentrations post-menopause stimulate surface epithelial cells, fostering genetic changes and carcinogenesis. Lastly, inflammation and alterations in redox potential during ovulation and epithelial repair may explain the heightened risk of epithelial ovarian cancer associated with exposures like talc or asbestos, endometriosis, and pelvic inflammatory disease [12]. Regardless of the initiating stimulus, defective BRCA1 and BRCA2 function diminishes genomic damage repair, escalating cancer risk. Given the inflammatory-like context of ovulation, COX2-dependent chemoprevention strategies warrant exploration [13].

Discussions

Epithelial ovarian cancers are categorized based on histopathological grade (1–3) and subtype, with serous being the most common, followed by mucinous, endometrioid, and less frequently, clear cell, transitional, squamous, mixed, and undifferentiated subtypes. Additionally, cancers resembling epithelial ovarian cancers morphologically and clinically may arise from the fallopian tubes or primary peritoneum, owing to their shared embryonic precursor with ovarian surface epithelium. Evidence suggests that some ovarian cancers may originate specifically from the distal fallopian tubes (fimbria) [14]. Studies involving over 8000 cases have indicated that mucinous and endometrioid carcinomas generally carry a favorable prognosis, whereas serous carcinomas have a less favorable outlook, and undifferentiated carcinoma is considered the most aggressive subtype [15]. Clear-cell carcinoma prognosis findings have been inconsistent. Histopathological grade consistently correlates with prognosis [15].

Causes and Pathogenesis

Epithelial ovarian cancer subtypes exhibit distinct molecular aberrations and transcriptional profiles, despite sharing morphological characteristics similar to specialized epithelia derived from Müllerian ducts. Research suggests that these subtypes may originate from a single precursor cell of the surface epithelium, with differentiation guided by embryonic pathways involving HOX genes [16-18]. Normally absent in ovarian surface epithelium, HOX gene expression in tumorigenic mice transforms these cells into various Müllerian lineage tumors resembling serous, endometrioid, and mucinous ovarian tumors, respectively [16-18]. HOXA7 influences differentiation extent and tumor grade. Prolonged exposure to sex steroids during the menstrual cycle may inappropriately activate HOX genes in adult women, potentially within the context of epithelial inclusion cysts and excessive autocrine or paracrine stimulation, leading to proliferation and genomic instability.

Genomic mutations play a pivotal role in the pathogenesis of many cancers, including epithelial ovarian cancer. High-prevalence somatic mutations (occurring in over 5% of cases) are identified in a few genes in a subtype- and grade-specific manner, suggesting their involvement in ovarian carcinogenesis. These genes include TP53, CTNNB1, PTEN (all inactivated), and KRAS, PIK3CA, AKT1 (all activated) [19-21]. Epithelial ovarian cancers associated with hereditary BRCA1 and BRCA2 mutations often present at a younger age and are predominantly high-grade serous tumors with P53 dysfunction [22].

Like many solid tumors, epithelial ovarian cancers frequently exhibit high chromosomal instability levels (gene copy number amplifications and deletions), with total and regional instability correlating with tumor grade and patient outcomes [23]. While these unstable regions often encompass numerous genes, only a few are considered critical cancer process drivers, serving as vital markers and potential therapeutic targets. As protein function inhibition is typically more feasible than restoration, current research focuses on identifying potential therapy targets within chromosomal gains (amplicons). Some of these genes are currently the subject of novel agent testing in preclinical or early clinical trials. Additionally, rearrangements, epigenetic changes, and imprinting influence cellular function and highlight potential markers and therapeutic targets [24].

A model of ovarian carcinogenesis categorizes epithelial ovarian cancers into two types: type I and type II tumors, representing two primary pathways of tumorigenesis. Type I tumors develop gradually from borderline tumors and encompass low-grade serous

carcinomas, mucinous, endometrioid, and clear-cell carcinomas. Conversely, type II tumors arise sporadically and encompass high-grade serous carcinoma, malignant mixed mesodermal tumors, and undifferentiated carcinomas. Type II tumors are characterized by frequent TP53 mutations, genomic instability, and sometimes BRCA mutations. This model elucidates the relationship between borderline tumors and invasive carcinoma, providing a morphological and molecular framework for studying epithelial ovarian cancer pathogenesis [16].

Screening

The potential for early detection to significantly improve survival hinges on whether metastatic disease arises from the progression of clinically detectable early lesions and if cancers remain localized long enough for cost-effective screening [25]. Given the prevalence of epithelial ovarian cancer, early detection strategies require high sensitivity (over 75%) and exceptional specificity (99.6%) to achieve a positive predictive value of 10% or more. Serum CA125 concentration alone lacks the necessary sensitivity and specificity for effective screening. Combining CA125 measurement with transvaginal ultrasonography (TVS) or monitoring CA125 levels over time can enhance specificity. Risk assessment tools such as BRCAPRO, integrating a patient's personal and family history, can estimate the likelihood of identifying germline BRCA1 or BRCA2 mutations [26,27].

Women with germline BRCA1 or BRCA2 mutations, known to face significantly increased ovarian cancer risks, are advised periodic screening with CA125 and TVS beginning between ages 30 and 35, or 5–10 years before the youngest first ovarian cancer diagnosis in their families [28,29]. High-risk women confirmed to have a BRCA1 or BRCA2 mutation, older than 40, or finished with childbearing are recommended to reduce their ovarian cancer (and breast cancer) risk through bilateral salpingo-oophorectomy (BSO) [28-30]. Nonetheless, such patients may continue to face persistent primary peritoneal carcinoma risks.

AI in Diagnosis

AI Based on Blood Biomarkers

Enhancing long-term outcomes for patients with epithelial ovarian cancer (EOC) requires identifying reliable stratification indicators that characterize the disease and predict outcomes before initial treatment [31]. Traditionally, clinical factors such as age and tumor grade have been used for prognosis assessment, but their predictive value is limited [32,33]. Recent studies have highlighted circulating tumor cells (CTCs) in the blood as potential prognostic markers for overall survival in various cancers, including ovarian cancer, although findings remain inconsistent [34,35].

In the realm of precision medicine, there is a growing need for robust risk stratification models specifically tailored for ovarian cancer. Oncologists are increasingly turning to machine learning to construct predictive models that enhance clinical decision-making [36]. Using advanced artificial intelligence (AI) technology, computers can identify patterns from extensive historical databases [37].

A study conducted in Shanghai [38] established a significant correlation between circulating tumor cell count and factors such as FIGO stage, tumor size, and CA-125 levels. Interestingly, there were no significant differences in CTC counts concerning age, BMI index, tumor size, pathological grade, histological type, neutrophil count, lymphocyte count, platelet count, albumin level, CA-199 level, AFP level, CEA level, or HE4 level. Kawakami et al. [39] introduced an ovarian cancer-specific predictive framework for clinical staging using machine learning methods based on multiple biomarkers, excluding CTCs, achieving an AUC of 0.760. However, the relatively lower significance could partly be attributed to the limited sample size of 156 patients, highlighting the necessity for future studies with larger datasets to refine models.

Previous research has demonstrated the prognostic significance of blood biomarkers, including systemic inflammatory response indicators, in EOC patients. A recent meta-analysis involving 2,919 patients highlighted a significant association between elevated neutrophil-to-lymphocyte ratio and disease progression as well as survival in EOC patients [40]. Inflammatory markers may contribute to tumor progression by producing cytokines (such as VEGF, interleukin, and tumor necrosis factor-α), which play critical roles in the tumor microenvironment [41]. Additionally, coagulation factors can promote cancer proliferation and angiogenesis through interactions with VEGF and fibroblast growth factor-2 (FGF-2) [42]. Studies have reported that elevated preoperative plasma fibrinogen, CRP, and albumin levels predict unfavorable EOC prognosis [43,44].

Apart from inflammatory and coagulation-related biomarkers, a review from Shanghai [38] identified CTC count as an independent prognostic factor for ovarian cancer, with an AUC value of 0.841 (95% CI, 0.802–0.880). Among "liquid biopsy" alternatives for predicting solid tumors, CTCs have shown significant potential in prostate cancer, breast cancer, and hepatocellular carcinoma [45-47]. However, the relationship between CTC characteristics and prognosis in EOC remains controversial [48]. Poveda et al. [49] concluded that elevated CTCs detected using the CellSearch system were an independent risk factor for ovarian cancer prognosis.

Recent studies indicated that CTCs can spread to distant sites through epithelial-mesenchymal transition (EMT), allowing them to change phenotype and penetrate blood vessels [50]. The Shanghai study [38] categorized CTCs into three subtypes—epithelial, epithelial/mesenchymal hybrids, and mesenchymal—using the advanced CanPatrol CTC-enrichment technique. They demonstrated that the

percentage of mesenchymal CTCs (M-CTCs) had significant predictive value for ovarian cancer prognosis, with an AUC of 0.859 (95% CI, 0.818–0.903). Consistent with these findings, previous research also indicated the prognostic value of both M-CTC percentage (AUC 0.74; 95% CI 0.64–0.84) and CTCs (AUC 0.75; 95% CI 0.66–0.84) in hepatocellular carcinoma [51]. In ovarian cancer, researchers have shown that tumor cells undergoing EMT exhibit cancer stem cell (CSC) characteristics and can promote tumor growth in vivo [52], which may partly explain the critical association between high M-CTC percentages and poor prognosis.

However, there were limitations to this study. The prospective study had a relatively small sample size of 156 patients from a single institution, potentially causing selection bias and limiting the precision of the results. Additionally, detection efficiency might be biased since the CanPatrol system is a filtration-based system, allowing small CTCs to pass through the barrier easily.

AI in Image-Based Ovarian Cancer Identification

Accurate preoperative differentiation between benign and malignant ovarian masses is crucial for determining appropriate treatment strategies and enhancing postoperative quality of life [53]. Imaging is a vital tool in medical science, frequently used in clinical practice to aid in diagnosis, staging, and treatment decisions [54,55]. Ultrasound (US) is commonly employed to detect ovarian masses and distinguish between benign and malignant lesions [56]. Magnetic resonance imaging (MRI) is essential for characterizing ovarian tumors due to its high soft-tissue resolution and is recommended for assessing the need for surgery for an adnexal mass [57]. Computed tomography (CT) can evaluate the extent of hematogenous, peritoneal, and lymphatic spread of ovarian cancer, assessing areas such as the liver, paraaortic region, omentum, and mesentery [58]. Although PET CT's utility in diagnosing ovarian tumors is noted, its cost-effectiveness remains unproven. Currently, US and MRI are the most widely used imaging modalities for diagnosing and characterizing ovarian tumors [59].

Traditionally, the diagnosis of ovarian cancer has relied on the subjective assessment of radiologists or gynecologists, who use their clinical experience to evaluate imaging features and examine ovarian tumors with high heterogeneity [60,61]. The complexity arising from inadequate or absent radiology in resource-poor regions, coupled with the variability in human rater expertise, makes precise and timely diagnosis from medical imaging challenging [62,63].

Advancements in artificial intelligence (AI) offer the potential to bridge the gap between the high demand for diagnostic imaging and the limited healthcare resources [64]. Radiomics, a promising research area, involves a 'data-driven' approach to extracting large sets of quantitative signatures from radiological images [65]. These data can then be analyzed using conventional biostatistics or AI methods [66]. Through sophisticated image processing techniques, all medical images are converted into mineable high-throughput image features, which can be used to correlate these features with pathology diagnoses or treatment responses [67]. Radiomics models and AI algorithms have shown promise in integrating medical images for the detection of ovarian cancer (OC) [68]. For example, Aramendía-Vidaurreta et al. [69] reported that a machine learning (ML) algorithm based on US images achieved a diagnostic accuracy of 98% in 145 patients. Furthermore, a deep learning (DL) model was used to automatically discriminate between benign and malignant ovarian tumor images, achieving an accuracy of 87.6% [70]. Researchers continue to explore various strategies, including improving image quality, expanding sample sizes, and optimizing algorithms, to further enhance diagnostic accuracy [71].

In a study conducted in Shenyang, China [72], AI algorithms demonstrated high diagnostic accuracy for ovarian cancer (OC) using medical imaging. The sub-analysis provided insights into the performance of different AI algorithms and imaging modalities:

- Machine Learning (ML) vs. Deep Learning (DL): ML algorithms had a pooled sensitivity (SE) of 89% and specificity (SP) of 88%, meaning they correctly identified 89% of true positives and correctly ruled out 88% of true negatives. DL algorithms had slightly lower SE at 88% and SP at 84%.
- Imaging Modalities:
  - *Ultrasound (US):* US studies showed high accuracy with an SE of 91%, SP of 87%, and an Area Under the Curve (AUC) of 0.95, indicating strong overall performance.
  - *Magnetic Resonance Imaging (MRI):* MRI studies had an SE of 83%, SP of 84%, and an AUC of 0.90, showing good but slightly lower performance compared to US.
  - *Computed Tomography (CT):* CT studies had the lowest performance with an SE of 75%, SP of 75%, and an AUC of 0.82.
- AI vs. Human Clinicians: AI algorithms outperformed human clinicians, with AI showing higher SE (82% vs. 77%), SP (86% vs. 80%), and AUC (0.91 vs. 0.85).
- Sample Size Effect: Studies with sample sizes ≤ 300 had lower SE (85%) and SP (82%) compared to those with sample sizes > 300, which had an SE of 93% and SP of 91%. Larger sample sizes also had a higher AUC (0.97 vs. 0.90).
- Publication Date: Studies published before 2020 had slightly higher SE (89%) and SP (89%) compared to those published after 2020 (SE of 88%, SP of 83%). The AUC was also higher for studies before 2020 (0.95 vs. 0.92).
- Geographic Distribution: Studies conducted in Asia had an SE of 87% and SP of 83%, while those outside Asia had

higher SE (90%) and SP (89%). The AUC was higher for studies outside Asia (0.95 vs. 0.92).

Despite these promising results, significant heterogeneity was observed among the studies. However, no publication bias was detected (p = 0.83).

AI shows substantial potential in improving ovarian cancer (OC) diagnostics through medical imaging, often matching or surpassing human clinicians' performance [64]. Radiomics, a 'data-driven' approach for extracting large sets of quantitative features from radiological images [65], can be analyzed using conventional biostatistics or AI methods to correlate these features with pathology diagnoses or treatment responses [67]. AI and radiomics models have demonstrated success in detecting OC, with some achieving high diagnostic accuracy. For instance, a machine learning (ML) algorithm based on ultrasound images achieved a diagnostic accuracy of 98% in a study involving 145 patients [69]. Additionally, a deep learning (DL) model used to differentiate between benign and malignant ovarian tumor images achieved an accuracy of 87.6% [70].

However, challenges remain. ML strategies often require manual extraction and selection of features, which is essential for predicting and correlating results. They also struggle with imbalanced datasets [73]. DL, while advantageous due to its use of various neural network layers enhancing computational power, is prone to overfitting and requires large datasets to be effective [74-76]. The quality of AI research is critical, and the QUADAS-AI instrument, designed specifically for AI diagnostic test studies, provides a framework for assessing study quality and bias [77]. Many studies lack standardized metrics and large, diverse image databases necessary for training robust AI models [78].

International collaborations, such as The Cancer Imaging Archive, aim to build large, labeled datasets to address these issues [79-82]. These datasets must be curated to ensure quality and avoid unwanted variance due to differences in data acquisition standards and imaging protocols. Additionally, AI research should consider non-imaging-based patient characteristics (cancer history, demographics, and genetic data) to enhance diagnostic models [83].

Most reviewed studies were retrospective (hospital records) and conducted in single centers with limited data availability. This underscores the need for rigorous external validation and multicentric studies with interoperable standards and uniform protocols to ensure generalizability and reduce the risk of overestimation [83-85].

Key points of AI in Enhancing Ovarian Cancer (OC) Diagnostics and Prognostics

Importance of Biomarkers and AI in Prognosis and Prediction

Circulating Tumor Cells (CTCs): CTCs are emerging as potential prognostic indicators in ovarian cancer, though consistent findings are still being established [34,35]. Advanced techniques like CanPatrol allow for the classification of CTCs into subtypes, such as mesenchymal-CTCs, highlighting their prognostic value [38,50].

Inflammatory and Coagulation Biomarkers: Markers such as the neutrophil-to-lymphocyte ratio and plasma fibrinogen levels are linked to ovarian cancer progression and survival outcomes [40,42]. These biomarkers reflect systemic inflammatory responses and their interactions with tumor microenvironments [41].

Role of AI in Medical Imaging for OC Diagnosis

Advantages of AI: AI and radiomics models demonstrate high diagnostic accuracy in distinguishing between benign and malignant ovarian tumors using imaging modalities like ultrasound, MRI, and CT [69,70]. AI algorithms often outperform human clinicians in terms of sensitivity, specificity, and overall diagnostic performance [72].

Challenges and Considerations: Despite promising results, developing AI models faces challenges such as the need for large and diverse datasets, standardized metrics, and robust validation across different populations and healthcare settings [73-78].

Future Directions and Recommendations

Enhanced Study Design: Future research should aim to improve study designs, including larger sample sizes and multicentric studies to validate AI models and biomarker findings [72,84,85].

Standardization and Collaboration: International collaborations are essential for creating high-quality datasets and standardized protocols in AI research, ensuring reproducibility and generalizability of findings [79-82].

Integration of Non-Imaging Data: Incorporating non-imaging patient characteristics such as demographics, genetic data, and cancer history can further enhance the diagnostic accuracy and predictive capabilities of AI models [83].

Conclusions

AI holds significant promise in revolutionizing OC diagnosis and prognostication through advanced imaging analysis and biomarker integration. However, addressing methodological limitations and ensuring rigorous validation are critical steps toward its widespread clinical adoption [55,86].

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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