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Review Article

Molecular Approaches to Gynecological Cancers: Biomarkers and Targeted Therapeutic Pathways

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Abstract

Gynecological cancers, including ovarian, endometrial, and cervical malignancies, represent a heterogeneous group of tumors characterized by distinct clinical behaviors and complex molecular properties. Advances in molecular oncology have substantially reshaped the understanding of gynecological carcinogenesis, revealing that dysregulation of tumor suppressor genes, DNA damage repair pathways, oncogenic signaling cascades, and virus-driven mechanisms critically influence disease initiation, progression, and therapeutic response. In ovarian cancer, alterations in homologous recombination repair, TP53 mutations, and aberrant activation of MAPK and PI3K/AKT signaling pathways have enabled molecular stratification and the successful implementation of targeted therapies. Endometrial cancer exemplifies the transition toward molecular classification, with POLE exonuclease domain mutations, mismatch repair deficiency, and copy number alterations defining biologically and clinically distinct subgroups with divergent prognostic outcomes. Cervical cancer represents a unique virus associated malignancy in which persistent high risk human papillomavirus infection drives oncogenesis through disruption of cell cycle regulatory pathways, providing a robust biological basis for molecular diagnostics and prevention strategies.

This review comprehensively summarizes the current knowledge of key molecular biomarkers and signaling pathways involved in gynecological cancers, including CA-125, mismatch repair deficiency, TP53, HER2, BRCA-associated DNA repair mechanisms, POLE mutations, WNT/β-catenin signaling, and HPV-related molecular alterations. Furthermore, the clinical implications of these molecular insights for diagnosis, prognosis, risk stratification, and personalized therapeutic approaches are discussed. In conclusion, integration of molecular profiling into clinical practice represents a critical step toward precision medicine in gynecological oncology, offering the potential to improve patient outcomes through biomarker-driven diagnosis and targeted treatment strategies.

Key Words: *Cervical cancer, Endometrial cancer, Gynecological cancers, Molecular biomarkers, Ovarian cancer, Targeted therapy*

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Introduction

Gynecological cancers, including ovarian, endometrial, and cervical malignancies, represent a major global health burden and remain leading causes of cancer-related morbidity and mortality among women worldwide (1). Despite significant advances in surgical techniques, systemic therapies, and screening programs, outcomes for many patients particularly those with advanced or recurrent disease remain suboptimal. The biological and clinical heterogeneity of gynecological cancers poses substantial challenges for early diagnosis, accurate prognostic assessment, and effective therapeutic decision-making.

Recent advances in molecular oncology have fundamentally transformed our understanding of gynecological tumorigenesis, revealing that these malignancies are driven by complex and distinct patterns of genetic, epigenetic, and signaling pathway alterations. Dysregulation of tumor suppressor genes, defects in DNA damage repair mechanisms, aberrant activation of oncogenic signaling cascades, and virus mediated oncogenesis collectively contribute to cancer initiation, progression, and treatment resistance (2). Large-scale genomic studies, including The Cancer Genome Atlas (TCGA), have enabled the molecular classification of gynecological cancers, providing a framework for biomarker-driven risk stratification and precision medicine.

In ovarian cancer, alterations in homologous recombination repair pathways, particularly involving BRCA1 and BRCA2, along with mutations in TP53 and components of the MAPK and PI3K/AKT pathways, define distinct molecular subtypes with important prognostic and therapeutic implications (3). Endometrial cancer exhibits a diverse molecular landscape characterized by mismatch repair deficiency, POLE exonuclease domain mutations, aberrations in WNT/β-catenin and PI3K signaling, and copy number alterations, enabling refined classification beyond traditional histopathological criteria (4). In cervical cancer, persistent infection with high risk human papillomavirus (HPV) serves as the primary oncogenic driver, leading to disruption of key cell cycle regulatory pathways and the emergence of molecular biomarkers such as p16INK4A, CCNA1 methylation, and circulating tumor markers (5).

The integration of molecular biomarkers including serum markers, genomic alterations, epigenetic signatures, and viral oncogene associated changes into clinical practice has significantly improved diagnostic accuracy, prognostic evaluation,

and therapeutic monitoring across gynecological cancers. Furthermore, the development of targeted therapies and immunotherapeutic approaches, such as PARP inhibitors in homologous recombination deficient tumors and immune checkpoint inhibitors in mismatch repair deficient cancers, underscores the clinical relevance of molecular profiling in guiding personalized treatment strategies (1).

In this context, the present review aims to provide a comprehensive overview of the molecular approaches underlying the pathogenesis, diagnosis, and management of ovarian, endometrial, and cervical cancers. By highlighting key molecular pathways, biomarkers, and clinically actionable alterations, this work seeks to emphasize the pivotal role of precision oncology in improving patient outcomes and shaping future therapeutic paradigms in gynecological oncology.

Molecular Pathways Driving Ovarian Cancer Progression

Ovarian cancer represents a highly heterogeneous disease, exhibiting diverse biological behaviors at both clinical and molecular levels (6). Although more than 90% of ovarian malignancies are of epithelial origin, approximately 10% arise from germ cells or granulosa theca cells (3). Advances in molecular oncology have revealed that dysregulation of tumor suppressor genes, DNA repair pathways, and oncogenic signaling cascades plays a central role in ovarian carcinogenesis, disease progression, and therapeutic response. Accordingly, a detailed understanding of key biomarkers and molecular pathways, including CA-125, mismatch repair deficiency, MAPK signaling, TP53, HER2, and BRCA-associated DNA repair mechanisms, is essential for improved risk stratification, prognostic evaluation, and the development of personalized treatment strategies in ovarian cancer.

In this context, cancer antigen 125 (CA-125) represents one of the most extensively investigated and clinically established biomarkers in ovarian cancer. CA-125 is a high molecular weight membrane associated glycoprotein encoded by the MUC16 gene and predominantly expressed by Müllerian and coelomic epithelial tissue derivatives (7). It is synthesized and secreted by several epithelial cell types, including bronchial, endometrial, ovarian, and corneal epithelial cells. CA-125 is released from tumor tissues and has long been recognized as one of the most important biomarkers in ovarian cancer (8). Clinically, elevated serum CA-125 levels are detected in approximately 80% of

patients with epithelial ovarian cancer, underscoring its established value in disease prognosis and monitoring (9). However, CA-125 levels may also increase under various physiological and non-malignant conditions, such as pregnancy, smoking, obesity, and following hysterectomy, which substantially limits its sensitivity and specificity for early cancer diagnosis (7). Consequently, CA-125 is not recommended as a standalone diagnostic marker but is widely used for monitoring disease progression, treatment response, and recurrence during and after chemotherapy. To improve diagnostic accuracy, multi-marker approaches have been developed, and in 2016, the U.S. Food and Drug Administration (FDA) approved the OVERA diagnostic test for ovarian cancer, which combines CA125-II with additional biomarkers, including human epididymis protein 4 (HE4), apolipoprotein A-1, follicle-stimulating hormone, and transferrin (9, 10).

Beyond circulating biomarkers, growing attention has been directed toward the molecular mechanisms that underlie genomic instability in ovarian cancer. Among these, defects in the DNA mismatch repair (MMR) system arising from germline or somatic mutations in MMR related genes lead to microsatellite instability (MSI), a molecular hallmark of impaired genomic fidelity (11). Pathogenic alterations in MMR genes are the underlying cause of Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), an autosomal dominant cancer predisposition syndrome (12). To date, seven MMR-associated genes have been identified, including MLH1, MSH2, MSH6, PMS2, PMS1, MLH3, and EXO1, all of which play critical roles in correcting base-base mismatches and insertion-deletion loops during DNA replication (11). MSI testing is a routinely applied, direct, and reliable method for assessing MMR deficiency and is widely used in clinical practice. In addition to colorectal and endometrial cancers, ovarian cancer represents a significant extracolonic malignancy associated with Lynch syndrome (13, 14) . Epidemiological studies have demonstrated that approximately 10-15% of individuals with Lynch syndrome develop ovarian cancer, often at a younger age and with distinct clinicopathological features compared with sporadic cases (15). Importantly, MMR deficient ovarian cancers frequently exhibit unique molecular characteristics, which may influence tumor behavior, prognosis, and therapeutic responsiveness, highlighting the clinical relevance of MSI/MMR status in the risk assessment, surveillance, and personalized management of ovarian cancer patients (16, 17).

In addition to defects in DNA repair mechanisms, aberrant activation of oncogenic signaling pathways represents another critical driver of ovarian tumorigenesis. Among these, the RAS/RAF/MEK signaling pathway, also referred to as the mitogen-activated protein kinase (MAPK) cascade, plays a central role in the regulation of cell proliferation, differentiation, survival, and tumorigenesis (18). Activation of this pathway is initiated by extracellular growth factor binding to receptor tyrosine kinases, leading to sequential activation of RAS, RAF (including B-RAF), MEK, and ERK kinases, which ultimately modulate transcriptional programs involved in cellular growth and oncogenic transformation (19). In ovarian cancer, genetic alterations affecting key components of the RAS/RAF/MEK pathway show distinct histopathological associations (20). While mutations in KRAS and B-RAF are rarely detected in high grade serous carcinomas, they are frequently observed in low-grade invasive serous carcinomas and serous borderline tumors (21). Specifically, mutations involving KRAS codons 12 and 13 or BRAF codon 599 have been identified in approximately 68% of low-grade invasive serous carcinomas and 61% of serous borderline tumors (22). Clinically, assessment of KRAS and BRAF mutational status has emerging relevance for patient stratification, disease monitoring, and therapeutic decision making, particularly in the context of targeted therapies aimed at the MAPK pathway. Moreover, the relative molecular stability of low grade serous tumors underscores the potential utility of MAPK pathway alterations as biomarkers for disease progression and longitudinal follow-up in ovarian cancer (23).

Taken together, these findings illustrate how both genomic stability and signaling pathway dynamics contribute to ovarian tumor biology. Within this broader molecular framework, disruption of critical tumor suppressor genes represents another major determinant of disease pathogenesis. In particular, tumor protein 53 (TP53) is a sequence-specific transcription factor encoded by a tumor suppressor gene located on chromosome 17p13.1 and plays a pivotal role in maintaining genomic integrity (24). TP53 regulates a wide spectrum of cellular processes, including the DNA damage response, oxidative stress signaling, telomere maintenance, cell cycle arrest, and apoptosis (25). Mutations in TP53 are among the most frequent genetic alterations in human malignancies, occurring in approximately 50% of all cancer types (26). Germline mutations in TP53 give rise to Li-Fraumeni syndrome, a rare autosomal dominant hereditary cancer predisposition

disorder (27). In ovarian cancer, TP53 mutations are particularly characteristic of high-grade serous carcinoma (HGSC), where they are detected at very high frequencies, ranging from 50% to 80%, and are considered a defining molecular feature of this histological subtype (28). In contrast, TP53 mutations are infrequently observed in serous borderline tumors and low-grade serous carcinomas, whereas a higher prevalence has been reported in serous tubal intraepithelial carcinomas (STICs), supporting the fallopian tube origin hypothesis for HGSC (29). Clinically, TP53 mutations in ovarian cancer have been associated with adverse outcomes, including reduced overall survival, early disease recurrence, and decreased sensitivity to chemotherapy and radiotherapy (27). Accordingly, accumulating evidence suggests that TP53 may serve as a valuable prognostic and predictive biomarker, particularly in type II ovarian cancers, highlighting its potential utility in risk stratification and disease management (26).

Complementing the role of tumor suppressor alterations, dysregulation of growth factor receptor-mediated signaling also contributes substantially to ovarian cancer pathobiology. In this context, human epidermal growth factor receptor 2 (HER2/neu), also known as ERBB2, is a transmembrane receptor tyrosine kinase belong to the epidermal growth factor receptor (EGFR) family and plays a critical role in cell proliferation, survival, and oncogenic signaling (30). Aberrant HER2 activation, most commonly through gene amplification or protein overexpression, has been implicated in the pathogenesis of several solid tumors. In ovarian cancer, HER2 overexpression has been reported in approximately 20-30% of high grade serous carcinomas, whereas its expression is considerably lower in low grade serous carcinomas and serous borderline tumors (31, 32).

In parallel with receptor tyrosine kinase driven oncogenic signaling, inherited defects in DNA repair pathways represent another critical dimension of ovarian cancer biology. In this regard, the breast cancer susceptibility genes BRCA1 and BRCA2, located on chromosomes 17q21 and 13q12-13, respectively, function as key tumor suppressors essential for the maintenance of genomic stability (33). These genes are critically involved in homologous recombination mediated DNA repair, regulation of gene transcription, and control of cell cycle progression (34, 35). To date, more than 250 pathogenic variants have been identified in BRCA1 and BRCA2, the majority of which (~80%) consist of frameshift or nonsense mutations that result

in truncated, nonfunctional proteins (34). Germline mutations in BRCA1 and BRCA2 are strongly associated with hereditary ovarian cancer, with lifetime ovarian cancer risks estimated at approximately 40-50% for BRCA1 mutation carriers and 20-30% for BRCA2 mutation carriers (36). In addition to BRCA1/2, next-generation sequencing analyses of patients with primary ovarian, peritoneal, and fallopian tube carcinomas have identified multiple other tumor suppressor and DNA repair genes implicated in hereditary ovarian cancer predisposition (37). These include RAD51C, RAD51D, BRIP1, BARD1, CHEK2, MRE11A, NBN, PALB2, RAD50, as well as mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) and TP53 (38). BRCA mutations have significant therapeutic implications, particularly through the use of PARP inhibitors, which have become standard of care in BRCA mutated and homologous recombination deficient ovarian cancer (39). Collectively, these findings highlight the central role of defects in DNA damage repair pathways in ovarian carcinogenesis and underscore the clinical importance of genetic testing for risk assessment, surveillance, and personalized therapeutic strategies in ovarian cancer. Together, these molecular alterations underscore the biological complexity of ovarian cancer and provide a robust framework for biomarker driven diagnosis, prognostic stratification, and the development of targeted therapeutic strategies (Fig.1).

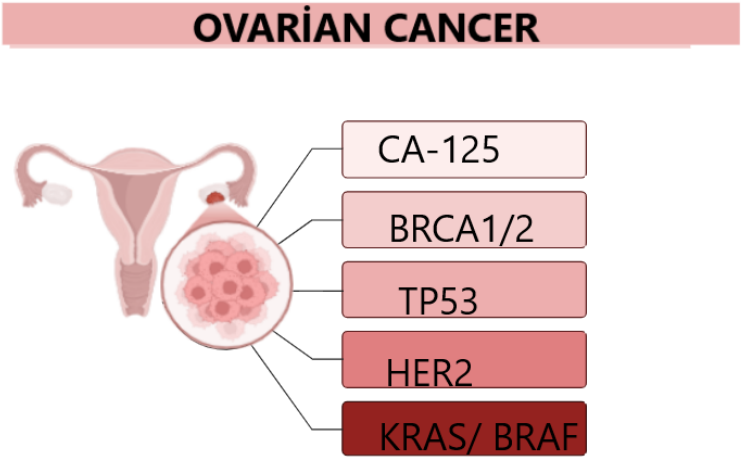

Figure 1. Molecular markers associated with ovarian cancer. Schematic representation of key molecular biomarkers involved in ovarian cancer pathogenesis and diagnosis. Important markers include CA-125, commonly used for clinical monitoring, as well as genetic alterations such as BRCA1/2, TP53, HER2, and KRAS/BRAF, which contribute to tumor development, progression, and therapeutic targeting. These molecular alterations highlight the heterogeneity and complexity of ovarian cancer biology.

Key Molecular Pathways in Endometrial Cancer Progression

Endometrial cancer (EC) originates from the endometrium, the inner epithelial lining of the uterus (40). Excess body weight and elevated estrogen levels unopposed by progesterone are well-established major risk factors for the development of EC (40, 41). Based on their molecular profiles, endometrial cancers are classified into four principal subtypes: the polymerase epsilon (POLE) ultramutated subtype, the microsatellite instability (MSI) associated subtype, the copy number low subtype, and the copy number high subtype (42). Each molecular subtype exhibits distinct biological characteristics and clinical courses, thereby resulting in distinct prognostic profiles.

Approximately 10% of endometrial cancers arise in the context of hereditary cancer syndromes and are frequently associated with a familial predisposition to breast and ovarian cancers, Lynch syndrome, and germline mutations in the BRCA1 and BRCA2 genes (26, 43). Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant cancer predisposition disorder caused by pathogenic variants in DNA mismatch repair (MMR) genes, including MLH1, MLH3, MSH2, MSH6, and PMS2 (44, 45). Molecular characterization of endometrial cancer, particularly the assessment of MMR deficiency and microsatellite instability (MSI), has become an integral component of diagnostic evaluation, enabling the identification of Lynch syndrome associated tumors (17, 44). Lynch syndrome accounts for approximately 2-6% of all endometrial cancer cases, and mutation carriers face a markedly elevated lifetime risk of endometrial cancer, estimated at 20-70% (16, 46) .

At the same time, somatic activation of key signaling pathways also shapes tumor behavior; for example, activating mutations in KRAS, a central component of the RAS/RAF/MEK cascade, are commonly observed in endometrial cancer and correlate with distinct histopathological patterns (47). KRAS mutations have been reported in approximately 60% of mucinous endometrial carcinomas, 5-16% of clear cell carcinomas, and 4-5% of low grade endometrioid tumors, and have been identified as an independent molecular factor associated with poor prognosis (47). In contrast, KRAS mutations are less commonly detected in serous and high grade clear cell carcinomas (48, 49). Alterations in BRAF, another critical component of the MAPK pathway, appear to be rare in endometrial cancer, with mutations reported in approximately 2% of

cases, while several studies have failed to detect BRAF mutations altogether (19). Consequently, the clinical and biological significance of BRAF mutations in endometrial cancer remains unclear.

Alongside these MAPK or RAS/RAF/MEK pathways aberrations, dysregulation of receptor tyrosine kinases also contributes to tumor development (50). Overexpression of the HER2/neu oncogene (ERBB2), a transmembrane receptor tyrosine kinase and a key component of the epidermal growth factor receptor (EGFR) signaling pathway, has been reported in approximately 10-15% of endometrioid endometrial carcinomas and 9-30% of serous endometrial cancers (51).

Moreover, inactivation of the tumor suppressor gene PTEN, whether through mutations or genomic deletions, leads to aberrant activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, promoting uncontrolled cellular proliferation and survival (52). PTEN alterations are detected in approximately 21% of type I (endometrioid) endometrial carcinomas, with the frequency increasing to nearly 46% when loss of heterozygosity (LOH) at the 10q23 locus is considered (53). In contrast, TP53 mutations are infrequent in clear cell endometrial carcinomas, whereas mutations in ARID1A and PIK3CA are more commonly observed in this subtype (54, 55). In addition, alterations in CTNNB1, ARID1A, and PIK3CA occur at higher rates in endometrial cancer compared with many other malignancies and have been associated with aggressive tumor behavior, rapid disease progression, and increased metastatic potential (50, 54).

Building on these key molecular alterations, dysregulation of the WNT signaling pathway represents a particularly influential oncogenic event in endometrial cancer, driving tumor progression through its effects on cell proliferation, differentiation, and adhesion. Aberrant activation of this pathway promotes cytoplasmic accumulation and nuclear translocation of β-catenin, which acts as a transcriptional coactivator for genes that regulate these critical cellular processes (56). Mutations in CTNNB1, which encodes β-catenin, are detected in approximately one-third of type I (endometrioid) endometrial carcinomas and define a distinct molecular subgroup characterized by increased tumor aggressiveness and an elevated risk of recurrence, despite otherwise favorable clinicopathological features (57). In parallel, dysregulation of the transforming growth factor-β (TGF-β) signaling pathway plays a critical role in endometrial carcinogenesis, particularly in non

endometrioid and high risk histological subtypes (58). Notably, mutations affecting components of the TGF-β pathway have been reported in up to 66% of clear cell endometrial carcinomas, underscoring their association with poor prognosis and advanced disease behavior (59).

Complementing these signaling abnormalities, defects in DNA replication fidelity further shape the molecular landscape of endometrial cancer. DNA polymerase epsilon (POLE), which possesses an exonuclease proofreading domain, is essential for correcting base misincorporation errors during DNA replication and maintaining genomic stability (60). Pathogenic mutations affecting the POLE exonuclease domain define a distinct molecular subtype of endometrial cancer characterized by an ultramutated genomic profile (61). In a cohort of 452 patients with endometrial cancer, POLE exonuclease domain mutations were identified in approximately 5% of cases, and disease recurrence occurred in only 17% of mutation-positive tumors (60). Importantly, the presence of POLE mutations has been consistently associated with an excellent prognosis, establishing POLE status as a robust prognostic biomarker and a key component of molecular risk stratification in endometrial cancer (Fig.2).

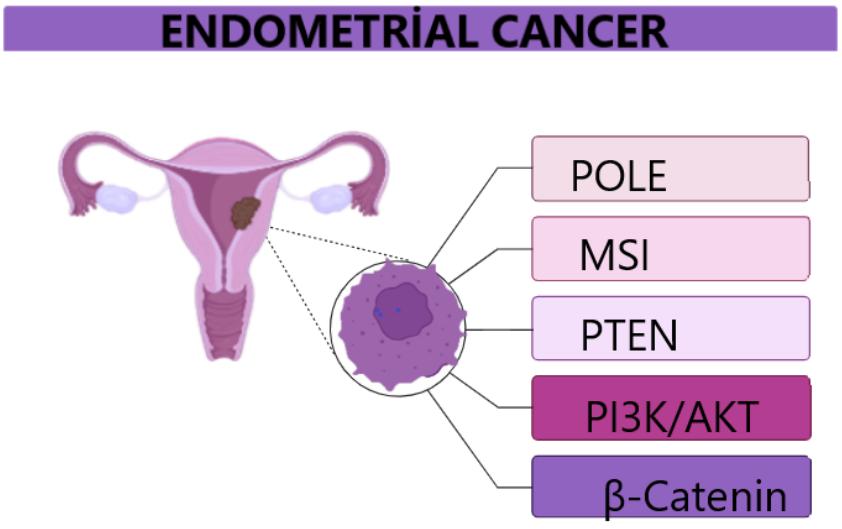

Figure 2. The molecular classification of endometrial cancer. Endometrial cancer demonstrates distinct molecular landscapes characterized by specific genomic alterations and signal pathway disregulation. These molecular features underpin tumor heterogeneity and guide risk stratification and targeted therapeutic approaches.

Critical Molecular Pathways in Cervical Cancer Progression

Cervical cancer accounts for approximately 12% of all malignancies in women and represents the second most common gynecological cancer worldwide (62). Persistent infection with human papillomavirus (HPV) has been unequivocally established as the primary etiological factor in cervical carcinogenesis and is also implicated in the development of other anogenital malignancies, including vulvar, vaginal, penile, and anal cancers (63). HPV is a small, nonenveloped, double-stranded DNA virus with an icosahedral capsid composed of 72 capsomeres and a diameter of approximately 50-55 nm (64). The viral genome is organized into three functional regions: the early (E) region, encoding proteins (E1-E8) involved in viral replication and oncogenic transformation; the late (L) region, comprising L1 and L2 genes responsible for capsid protein synthesis; and the long control region (LCR), which regulates viral transcription and replication (65).

The oncogenic potential of high risk HPV types is primarily mediated through the viral oncoproteins E6 and E7, which promote malignant transformation by functionally inactivating key tumor suppressor pathways (66). E6 facilitates the degradation of p53 and inhibits apoptosis through the suppression of pro-apoptotic proteins such as BAK, while E7 disrupts the retinoblastoma (pRB) pathway, leading to dysregulated cell cycle progression and compensatory overexpression of the cyclin dependent kinase inhibitor p16 (63). To date, more than 200 HPV genotypes have been identified and are classified into low risk and high risk groups based on their oncogenic potential (67). Among high risk HPV genotypes, HPV-16 and HPV-18 are the most prevalent and together account for approximately 70% of cervical cancer cases worldwide (68). Cervical cancer prevention and early detection rely on cytological screening and colposcopic evaluation, with the incorporation of HPV DNA testing alongside cytology significantly reducing cervical cancer incidence through improved identification of high risk lesions.

Similarly, promoter hypermethylation of cyclin A1 (CCNA1), likely triggered by human papillomavirus (HPV) infection, is frequently detected in cervical cancer, and the resulting downregulation of gene expression is specifically associated with the invasive phenotype (69). These findings suggest that CCNA1 may represent a potential biomarker for the early detection of invasive cervical cancer.

Alongside epigenetic changes like CCNA1 methylation, circulating protein fragments

such as CYFRA 21.1 a soluble portion of cytokeratin 19 released during epithelial turnover and tumor-associated cytoskeletal breakdown offer a clinically valuable biomarker for the detection and monitoring of squamous cell carcinomas (70). Squamous cell carcinoma antigen (SCC-Ag) is a glycoprotein belonging to the serine protease inhibitor (serpin) family and contributes to cervical cancer pathogenesis by inhibiting apoptosis and promoting tumor cell survival (70). Serum SCC-Ag levels are elevated in approximately 70% of patients with cervical cancer; however, its limited specificity restricts its utility as a diagnostic marker (71). Despite these limitations, both CYFRA 21.1 and SCC-Ag have demonstrated clinical relevance in the follow up of cervical cancer patients, particularly for monitoring treatment response and detecting disease recurrence.

A key molecular hallmark of cervical cancer is the dysregulation of cell cycle control, in which p16^INK4A serves as a crucial regulator. This cyclin-dependent kinase inhibitor exerts its tumor-suppressive function by controlling the G1/S phase transition through inhibition of CDK4 and CDK6, thereby preventing phosphorylation of the retinoblastoma (pRB) protein. (72). In cervical carcinogenesis, persistent infection with high risk human papillomavirus (HPV) leads to functional inactivation of pRB by the viral E7 oncoprotein, resulting in a overexpression of p16INK4A (72-74). In clinical practice, p16INK4A immunohistochemistry is routinely employed in the diagnosis of cervical intraepithelial neoplasia and invasive cervical cancer, particularly in both squamous and glandular lesions (73). Its expression aids in distinguishing high grade precancerous lesions from benign mimickers and low grade abnormalities, thereby improving diagnostic accuracy and interobserver reproducibility. Furthermore, p16INK4A has emerged as a valuable adjunct marker in risk stratification, prognostic assessment, and the molecular characterization of HPV-associated cervical neoplasms (Fig.3).

The DNA damage response (DDR) promotes programmed cell death in reproductive cells in the presence of extensive DNA damage by arresting cell cycle progression (75). This arrest enables efficient repair of DNA lesions, thereby limiting mutagenesis and maintaining genomic stability (76). In cervical cancer, localized activation of the DDR has been observed at HPV replication centers. Furthermore, growing evidence suggests that the HPV E7 oncoprotein and HPV genomic integration contribute to the upregulation of DDR-related proteins (77, 78).

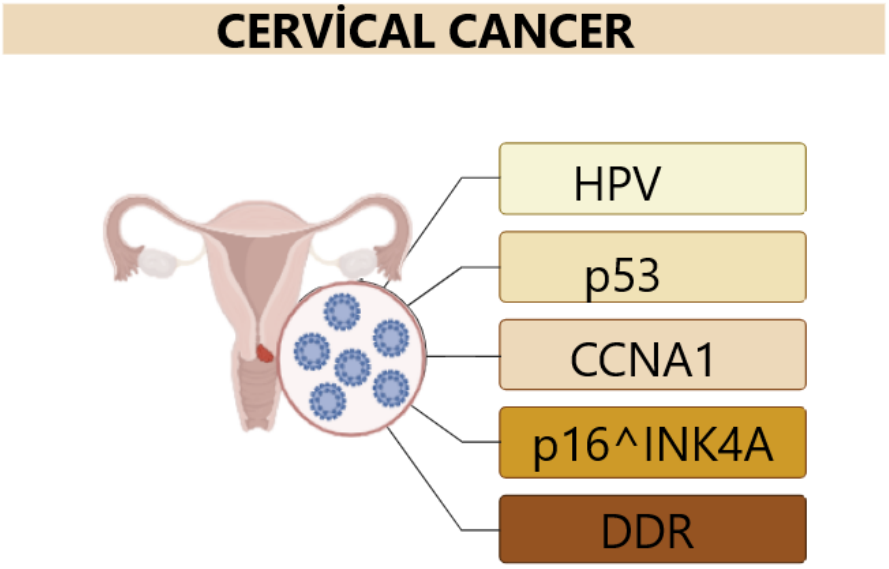

Figure 3. Key molecular factors involved in cervical cancer. Human papillomavirus (HPV) infection, tumor suppressor p53, cell cycle regulator CCNA1, p16^INK4A, and DNA damage response (DDR) pathways contribute to cervical carcinogenesis.

Conclusion

Gynecological cancers constitute a biologically diverse group of malignancies driven by distinct yet overlapping molecular mechanisms that critically influence tumor behavior, clinical outcomes, and therapeutic responsiveness. Accumulating evidence demonstrates that traditional histopathological classification alone is insufficient to capture the complexity of ovarian, endometrial, and cervical cancers, underscoring the necessity of molecularly informed approaches for accurate diagnosis, prognostication, and treatment planning.

In ovarian cancer, alterations in DNA damage repair pathways particularly involving BRCA1/2 and homologous recombination deficiency along with TP53 mutations and dysregulation of MAPK and PI3K/AKT signaling, define clinically relevant molecular subtypes and have enabled the successful integration of targeted therapies such as PARP inhibitors into standard care. Endometrial cancer exemplifies the paradigm shift toward molecular classification, where distinct subgroups defined by POLE mutations, mismatch repair deficiency, and copy number alterations exhibit markedly different prognostic profiles and therapeutic

vulnerabilities. Similarly, cervical cancer represents a unique model of virus driven oncogenesis, in which persistent high risk HPV infection orchestrates malignant transformation through disruption of cell cycle regulatory pathways, providing a strong biological rationale for molecular biomarkers and preventive strategies.

The identification and clinical implementation of molecular biomarkers including serum markers, genomic and epigenetic alterations, and pathway specific signatures have substantially improved risk stratification, disease monitoring, and treatment selection across gynecological malignancies. Moreover, advances in next-generation sequencing technologies and integrative molecular profiling have facilitated the emergence of precision oncology, enabling individualized therapeutic strategies tailored to the molecular landscape of each tumor.

Despite these advances, several challenges remain, including intratumoral heterogeneity, mechanisms of therapeutic resistance, and the need for robust, clinically validated biomarkers applicable across diverse patient populations. Future research should focus on integrating multi-omics data, refining molecular classification systems, and translating emerging biomarkers into routine clinical practice through well-designed prospective studies.

In conclusion, a comprehensive understanding of the molecular underpinnings of gynecological cancers is essential for advancing personalized medicine and improving patient outcomes. Continued integration of molecular insights into clinical decision making holds promise for the development of more effective, targeted, and durable therapeutic strategies, ultimately shaping the future landscape of gynecological oncology.

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Author Contribution

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Conflict of Interest

The authors declare that they have no conflict of interest.

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