REVIEW

Genetic polymorphism and current biotechnology approaches of therapeutic aspects within endometrial tumors

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Abstract

Among oncological diseases of women, gynecological diseases deserve special attention. Gynecological tumors contribute significantly to women's health throughout the world. Notably, gynecologic malignancies represent a prevalent category of cancers affecting women globally. Single nucleotide polymorphisms have emerged as a promising source of genetic information to better understand complex diseases such as cancer, in terms of etiology, interindividual differences and treatment response. In this review, we summarize some selected gene single nucleotide polymorphisms' implication in gynecological cancer susceptibility/predisposition, as well as the potential to use such genetic markers for improved diagnosis and individualized treatment of gynecological cancers. Furthermore, this review explores the advances in biotechnology that have contributed to the management of gynecological tumors, in particular endometrial tumors, with a focus on molecular diagnostics, therapeutic innovations, and personalized medicine. It is critical to investigate the single nucleotide gene polymorphisms associated with gynecologic cancer susceptibility/predisposition as some of them might be utilized as useful molecular markers for assessing gy-

necologic cancer predisposition and might be further used for diagnosis and treatment modalities in individuals with similar single nucleotide polymorphism profile. Moreover, recent advancements in biosensing technologies, particularly nano-biosensors and microfluidic biosensors, have significantly enhanced the detection of gynecological tumor markers. Taken together, the revolution in cancer research, diagnosis, and treatment has been made possible by advances in biotechnology in recent decades.

Keywords: gynecological tumors, endometrial tumors, gene, single nucleotide polymorphism, biosensing

Introduction

Among oncological diseases of women, gynecological diseases deserve special attention. Notably, gynecologic malignancies represent a prevalent category of cancers affecting women globally, characterized by their diverse nature in terms of risk factors, management approaches, and outcomes (Bray et al., 2018). Ovarian cancer stands as the primary contributor to mortality linked to gynecologic malignancies and ranks as the fifth leading cause of death among women (Arora et al., 2023). Predominantly affecting postmenopausal women, the majority of ovarian cancer cases surface in individuals aged between 50 and 75 years (Momenimovahed et al., 2019). On a parallel note, endometrial cancer (EC) holds the position of the fourth most prevalent cancer in women. Its prevalence is notably heightened in postmenopausal females, with a peak incidence occurring between ages 50 and 70 (Makker et al., 2021). The risk factors associated with endometrial cancer encompass heightened exposure to estrogen, stemming from either endogenous sources (such as obesity) or exogenous influences (such as estrogen replacement therapy). In general, among the reasons for the development of woman's tumors (both .0benign, malignant), various factors are considered, among which hormonal imbalance (Nakashidze et al., 2014), the alteration of lipid profile (Kotrikadze, et al., 2019a), alteration of gene expression and alteration of the micrRNA (Petrovic et al., 2017; Shaikh et al., 2023; Kotrikadze, et al., 2019b) (Kotrikadze, et al., 2019c) (Kotrikadze et al., 2020). Moreover, women carrying the hereditary nonpolyposis colorectal cancer syndrome, commonly (Petrović et al., 2021) known as Lynch syndrome, confront a significantly elevated lifetime risk of developing uterine cancer (Endometrial Cancer Prevention (PDQ®) - NCI, 2023). This heightened risk underscores the need for regular screening and the implementation of risk reduction strategies in this specific population. Cervical cancer, with its alarming worldwide incidence and mortality rates, poses a substantial burden of disease globally. As the fourth leading cause of cancer-related deaths worldwide, with highest fatalities concentrated in developing countries (cervical cancer, n.d.). A clear and direct causal link exists between human papillomavirus (HPV) (Fernandes et al. 2022), the precursors to cancer, and the onset of cervical cancer. Notably, the high-risk HPV serotypes 16 and 18 contribute to more than 70% of cervical cancer cases among the approximately 100 identified HPV strains (Ahmed et al., 2017). Besides of mentioned, the another factors, including age (Liu et al., 2023a, Hitchins et. al. 2023), cigarette smoking, immunosuppression, and nutritional considerations, serve as predictive indicators for the advancement of HPV infection to cervical intraepithelial neoplasia (CIN) and subsequent invasive stages (Hewavisenti et al., 2023). According to the literature, the SNP gene is associated with numerous diseases (Castellanos-Rubio & Ghosh, 2019; Leitão et al., 2023; Nakashidze & Ahmad, 2019) including oncological disorders (Nakashidze et al., 2020).

In this review article, we summarize some selected Gene SNP's implications in gynecological cancers to understand disease genetic predisposition. In particular, this review focuses on the genetic polymorphism significance in the diagnosis (including early diagnosis) and treatment of gynecological cancers, which could further introduce single nucleotide polymorphisms (SNPs) as tools to develop early intervention strategies. As gynecological tumors contribute significantly to women's health throughout the world, therefore it is important to develop new approaches. Notably, the revolution in cancer research, diagnosis, and treatment has been made possible by advances in biotechnology in recent decades. This review also explores the advances in biotechnology that have contributed to the management of gynecological tumors, with a focus on molecular diagnostics, therapeutic innovations, and personalized medicine.

Genetics and epigenetics aspects of the gynecological tumors

As is already widely recognized, the carcinogenesis of endometrial cancer is presently thought to be primarily caused by estrogen exposure (Rodriguez et al., 2019), aberrant mismatch repair (MMR) system (Ouh et al., 2024) genetic abnormalities (Marković et al., 2024), and incorrect DNA and microRNA methylation (Zmarzły et al., 2023) Based on clinicopathological features, endometrial cancer is categorized as type I or type II. Atypical endometrial hyperplasia, the mechanism by which type I endometrial cancer operates in an estrogen-dependent way, is usually more common in premenopausal or perimenopausal women.These tumors have minimal muscle invasion, well-differentiated endometrioid adenocarcinoma, reduced rates of lymph node metastases, and a generally good prognosis. They also show positive for estrogen and progesterone receptors. On the other hand, type II endometrial cancer operates independently of estrogen and typically presents in postmenopausal women. De novo carcinogenesis, or the direct development of cancer from a normal endometrium, is thought to be the cause, as opposed to endometrial hyperplasia or undetected precancerous lesions (Banno et al., 2014; Fan et al., 2021; Arciuolo et al., 2022; Galant et al., 2024). Research demonstrating variations in molecular markers based on histology supports the existence of at least two overarching classes of endometrial carcinoma (Arafa et al., 2010; Lim & Oliva, 2010; Galant et al., 2024). Numerous pathologists and gynecologists have adopted the perspective that there are at least two primary biological types of endometrial cancer, and potentially more. However, most epidemiological studies have evaluated risk factors for endometrial cancer as a whole, predominantly reflecting the risks associated with the prevalent type I tumors, particularly in predominantly Caucasian populations (Felix et al., 2010). Consistently, registry data indicates that type II cancers tend to occur more frequently in older women and those from non-white ethnic backgrounds (Lm et al., 2011; Katagiri et al., 2023; Wakkerman et al., 2024). Furthermore, certain epidemiological studies have revealed that type II cancers are less strongly associated with traditional type I risk factors, such as obesity (Wang et al., 2023), and hormonal factors (Sherman et al., 1997; Yang et al., 2013; Nees et al., 2022; Yang et al., 2024).

A steroid hormone essential to the development of the female reproductive organs (Deli et al., 2020), estrogen binds to cytoplasmic estrogen receptors (ER) to form dimers and control nuclear gene expression. In addition to ligand-independent AF-1 and ligand-dependent AF-2 transcriptional activation domains, ER has DNA-binding and ligand-binding domains. The balance of these domains varies across tissues (Metzger et al., 1995). Miyamoto et al. highlighted the significance of MMR deficiency in early-stage endometrial cancer. They found a positive correlation between blood estrogen

levels and the expression of important MMR proteins, hMLH1 and hMSH2. Higher estrogen levels corresponded to increased MMR activity, suggesting a lower likelihood of cancer in a high estrogen-exposed environment. Conversely, low estrogen levels were associated with reduced repair activity, potentially increasing the risk of genetic errors and carcinogenesis, particularly during perimenopausal conditions with sufficient estrogen but low MMR activity (McInerney & Katzenellenbogen, 1996; Miyamoto et al., 2006; Pierre et al., 2024). Various genes contribute to the development of the two types of endometrial cancer. Type I mutations involve PTEN, ß-catenin, and K-ras (Kanaya et al., 2005; Koo et al., 2022). PTEN, located on chromosome 10, serves as a tumor suppressor in several disorders and cancers, inducing apoptosis when functioning properly. Mutations in PTEN occur in 20-50% of endometrial cases, often associated with early-stage carcinogenesis (Saegusa et al., 2001; Khatami et al., 2023). B-catenin mutations (20-40% of type I cases) disrupt cell adhesion and contribute to early carcinogenesis, while K-ras mutations (10-31% of cases) play a role in both transition to cancer and invasive growth. In type II endometrial cancer, mutations in the HER-2/neu oncogene and the p53 tumor suppressor gene are prevalent. HER-2/neu mutations (present in 14-63% cases) inversely correlate with cellular differentiation. P53 mutations are found in 90% of type II cases but are less common in type I and hyperplasia. They contribute significantly to early-stage development and are associated with poorly differentiated cancer regions. Additionally, RB and c, with RB mutations associated with disease advancement and cyclin overexpression influencing cell cycle regulation and prognosis (Moreno-Bueno et al., 2003). The study analyzing 125,748 exomes from various databases confirms that MUTYH-associated genetic variants are linked to East Asian populations (Park et al., 2024). The investigation of HDR and MMR germline variants in cervical cancer has shown that MMR-related gene variants are linked to adenocarcinomas. This study suggests that targeting MMR genetics could enhance future therapeutic management (Kokemüller et al., 2025). According to another study, 308 somatic mutations were detected (56 mutations based on the analysis of 24 genes). Notably, functional mutations increase with age (Pandya et al., 2024).

Epigenetic control of gene expression involves DNA methylation, histone modification, and the activity of Polycomb group proteins. DNA methylation, crucial for genomic stability, occurs at CpG sequences during cell division (Goldberg et al., 2007). Common epigenetic changes involve DNA methylation and histone acetylation. MMR gene methylation is vital, impacting genes such as PTEN, TGF-BR2, IGF2R, and BAX, leading to microsatellite instability (MSI) and cancer development (The Epigenomics of Cancer - PMC, n.d.). In endometrial cancer, genes affected by DNA methylation include hMLH1, SPRY2, RASSF1A, RSK4, APC, CHFR, p73, CASP8, GPR54, CD1, HOXA11, and COMT. Aberrant methylation of these genes influences various cellular processes, such as cell adhesion, apoptosis, and DNA repair, contributing to cancer progression (Gu et al., 2022) . The CpG island methylator phenotype (CIMP) classification system identifies genome-wide methylation patterns, with CIMP-positive endometrial cancer associated with early carcinogenesis (Weisenberger et al., 2006; Yi et al., 2011). Understanding these epigenetic changes offers potential for targeted therapeutic interventions and prognostic markers (Zhang et al., 2011). Epimutation refers to alterations in germ cells' epigenetic patterns that either suppress the transcription of typically active genes, or activate genes which are usually suppressed (Ruiz De La Cruz et al., 2021). Epimutation can serve as the initial stage or a direct trigger for carcinogenesis, with endometrial cancer development possibly linked to epimutation in MMR genes like hMLH1 and hMSH2 (Banno et al., 2014).

Based on the above, the involvement of genetic/epigenetic factors highlights the need for tailored screening and therapeutic approaches that will enable the correct detection of important risk factors

(genetic, hormonal, etc.) in the population. Ultimately, the treatment strategy for patients with endometrial cancer will be significantly improved.

Selected single nucleotide gene polymorphisms in gynecological tumors

The clinical implications of eNOS within cervical cancer (CA) carcinogenesis, clinicopathological features, and patient survival were the main topics of a Taiwanese investigation. Patients with cervical cancer who had genotypes TC/CC in eNOS SNP rs2070744 showed a decreased risk of parametrium invasion (OR = 0.16, 95% CI = 0.02-0.75, p = 0.009), pelvic lymph node metastasis (OR = 0.12, 95% CI = 0.01-0.89, p = 0.016), and advanced stage [odds ratios (OR) = 0.30, 95% confidence interval (CI) = 0.09-0.97, p = 0.036]. In summary, among cervical cancer patients, those with genotypes TC/CC in rs2070744, especially in Taiwan, showed a lower incidence of advanced stage, parametrium invasion, and pelvic lymph node metastases (Hung et al., 2019).

Significantly, patients with grade > 2 (p = 0.03) and those with positive cervical invasion (p = 0.042) had a higher distribution of A/A (rs4693608). Patients with T/C (rs4364254), on the other hand, showed a lower tumor grade. According to this study, a robust correlation between the HPSE SNP rs4693608 and susceptibility to endometrial cancer, indicating that HPSE SNPs could potentially serve as biomarkers for prognostic evaluation in endometrial cancer (Cao et al., 2020).

Examining the SNPs (rs389209) of CYP2D6 and (rs2031920, rs6413432, rs6413420) of CYP2E1, a noteworthy finding was made in a case control study evaluating the risk of genetic polymorphisms of CYP2D6 and CYP2E1 in cervical cancer: the variant allele A of CYP2E16 showed a significant increase in cervical cancer cases (OR=4.81; 95% CI: 1.57–14.77; p=0.005). The findings of this study support the hypothesis that among the Indian rural women under investigation, the rs6413432 SNP of CYP2E1*6 increases the risk of cervical cancer (Datkhile et al., 2022).

Examining the Eastern UP population in India retrospectively, the study focused on genetic variations in the upstream region of the transcription start site of BRN3A, acknowledged for its involvement in promoting an anti-apoptotic cellular environment and facilitating epitheliotropic transformations in HPV-mediated cervical cancers. The allele frequency was 1.32 times higher in cancer cases than in control subjects ($\chi 2 = 6.315$, p = 0.012). After removing heterozygous conditions, the odds ratio (OR) analysis showed a significant correlation between cancer risk and the SNP in homozygous (GG) conditions (OR = 2.60, p ≤ 0.004). The findings suggest the potential utility of this genetic variation in the non-coding region for predicting, diagnosing, or anticipating the progression of the disease (Prakash et al., 2022).

It is suggested that the FOKI and TaqI polymorphisms are associated with CIN2+ (cervical intraepithelial neoplasia (CIN)2+) risk (Li et al., 2022). The study, which concentrated on women from Bangladesh, found that the genotypes A/A and C/A + A/A together are linked to a higher risk of cervical cancer. The purpose of the study was to investigate the relationship between Bangladeshi females' risk of developing cervical cancer and the -160C/A genetic polymorphism in CDH1. The results of the comparative analysis showed that the variant A/A genotype and the combined (C/A + A/A) or 'any A' genotypes showed a 3.80-fold (95% CI=1.150-12.561, P=0.029) and 1.93-fold (95% CI=1.126-3.323, P=0.017) higher risk of developing cervical cancer, respectively, compared to the normal C/C genotype. Additionally, a positive correlation between the incidence of cervical cancer and the -160C allele was found, increasing the risk by 1.81 times (OR= 1.814, 95% CI=1.152-2.857,

p=0.01). Interestingly, it was discovered that women with an early marital history (less than 18 years) and the homozygosity of the -160A/A variant were more likely to develop cervical cancer ($\chi 2$ =6.605, p=0.037) (Rahman et al., 2023). A meta-analysis study revealed the significance of 42 SNPs in cervical cancer development.

There was a universal observation of a wild-type phenotype in FGFR3 rs121913483 in the female population of southwest China. There was a significant rise in the rs25487 mutation found in the cervical cancer population. A 2-locus SNP-SNP interaction pattern involving rs25487 and rs1042522 showed a significant correlation with the risk of cervical cancer (OR = 4.63, 95% CI = 1.83-11.75; cases vs. elderly group: OR = 17.61, 95% CI = 4.34-71.50). In the female population of southwest China, this study represents the first time that a novel interaction between the XRCC1 and TP53 genes has been found. This interaction is strongly linked to susceptibility to cervical cancer risk (Liu et al., 2019).

The four SNPs for the EXOC1 (rs13117307), BCL2 (rs2279115), CCAT2 (rs6983267), and CARD8 (rs7248320) genes associated with CC. The same study suggests that the SNPs rs13117307, rs2279115, rs6983267 correlate also with some clinical characteristics in CC (Feng et al., 2022). Notably, the robust correlation between ANPGTL4 and the predisposition to CA was established, signifying its potential implication in cervical neoplasia. The ANPGTL4 polymorphism exhibited an association with an elevated risk of developing cervical neoplasia, as evidenced by the dominant model (OR = 12.48, CI = 4.9-31.82, $p < 0.0001$) and the additive model (OR = 30.54, CI = 7.35-126.89, $p < 0.0001$) (Rahmani et al., 2020). According to this study, there is an association between IL6 rs2069837, TGFB1 rs1800469, TLR9 rs187084, MMP7 rs11568818 and CCa ($p < 0.05$) (Wang et al., 2015). Also some immune and inflammatory genes, including the IL1B, IL6, IL10, IL18, TGFB1, CCR5, CD40, TLR9, and MMP7, are associated with CCa (Das et al., 2022).

The study suggests that CYP17A1 gene rs743572 SNP, (CC genotype ($p \leq 0.001$), C allele frequency ($p \leq 0.001$)) also CYP19A1 rs10046 SNP (CT genotype ($p = 0.023$), T allele frequency ($p = 0.015$)) are associated with ovarian cancer. Moreover, the rs743572 and rs10046 SNPs were associated with some clinical characteristics of ovarian cancer. In particular, CYP19A1 rs10046 associated to post-menopausal ovarian cancer. Authors suggest that genes CYP17A1 and CYP19A1 SNPs increase the risk for ovarian cancer development within South Indian Women (Kumar et al., 2022). Ovarian cancer risk is also substantially correlated with H19 rs2107425, miR-146a rs2910164, and miR-196a rs11614913 SNPs (H. Liu et al., 2023). The study found a relationship between the incidence of uterine fibroids (UF) in Caucasian women and the VDR polymorphisms rs731236, rs1544410, and rs2228570. (Uterine Fibroid Incidence and vitamin D Receptor Gene Polymorphisms in Caucasian Women, n.d.).

Thus, the importance of SNP in developing gynaecological tumours within several populations is confirmed. Notably, eNOS genotypes are associated with a reduced risk of advanced stages and metastasis. Additionally, SNPs HPSE, CYP2D6, and CYP2E1 are linked to increased cancer development risk and are suggesting their potential as biomarkers for early detection, etc. These findings suggest further exploration of genetic variations to enhance personalized approaches/ strategies for treating the gynaecological tumour.

Selected gene single nucleotide polymorphisms in endometrial tumors

Endometrial cancer (EC) ranks among the three prominent malignant tumors affecting female reproductive organs, predominantly affecting postmenopausal women (Mahdy et al., 2022). Recent

clinical data indicate a global rise in EC incidence, with a noticeable uptick in diagnoses among younger women (Williams et al., 2024).

An elevated risk of EC has been linked to various reproductive factors in women, including late age at menopause, younger age at menarche, nulliparity, infertility, age of birth of the first child, and prolonged use of unopposed estrogens in hormone replacement therapy (Ignatov & Ortmann, 2020). Identifying oncogenes or tumor suppressor genes capable of predicting the malignant potential of EC, holds promise for advancing early clinical detection, treatment strategies, and prognostic assessments.

A study was done to investigate the relationship between the single nucleotide polymorphism (SNP) DACH1 gene and the susceptibility of people who have EC. Compared to T allele carriers, carriers of the C allele at the DACH1 gene rs9529895 locus showed a significantly lower risk for EC (odds ratio = 0.56, 95% confidence interval: 0.38–0.84, P<0.01). The impact of the DACH1 gene rs9529895 locus SNP on the risk for EC was found to be influenced by factors such as age, body mass index, smoking, alcohol consumption, and diabetes. In conclusion, there is a substantial association between the risk for EC and EC patients' progression-free survival (PFS). The underlying mechanism is presumed to involve the modulation of DACH1 expression levels by the DACH1 gene rs9529895 locus SNP (Xu et al., 2020).

A study focused on the impact of resistin gene polymorphisms, specifically 420C > G and 62G > A, on the susceptibility to endometrial cancer (EC), revealed that within the EC group, 420 GC (47.9%) emerged as the predominant gene polymorphism among Resistin 420 profiles. Notably, the investigation into Resistin 62 gene polymorphisms indicated a significantly higher prevalence of the 62GC polymorphism in the EC group ($p < 0.01$). In contrast, the control group exhibited a higher frequency of 62 AG (52.9%), associated with a diminished risk of EC ($p < 0.01$, Odds Ratio: 0.37). Moreover, the alleles 420G+ and 62A+ were notably more prevalent in the EC and control groups, respectively (p: 0.02 and p< 0.01). The presence of the 420G+ allele increased the risk of EC by 1.99 times, while the presence of the 62A+ allele was linked to a reduced risk of EC (p< 0.01, Odds Ratio: 0.038). This study, for the first time, provides evidence that Resistin 420G > C and 62G > A gene polymorphisms play a role in the development of endometrial cancer (Ozgor et al., 2019).

A study examining both codominant and recessive models revealed that HPSE SNP rs4693608 exhibiting GG genotype demonstrated a protective effect against endometrial cancer (adjusted OR = 0.41, 95%CI = 0.21-0.81, p = .026 and adjusted OR = 0.43, 95%CI = 0.22-0.82, p =0.0076, respectively) (Cao et al., 2020).

A significant correlation was found in a Norwegian population study between women who carry the APOBEC3A/B deletion variant and a lower risk of endometrial cancer (OR = 0.75; 95% CI = 0.62-0.91; p = 0.003; dominant model). Within the subgroup of patients with endometrioid endometrial cancer, this correlation held true (OR = 0.64; 95% CI = 0.51-0.79; p = 3.6 × 10-5; dominant model). Those between the ages of 50 and 60 showed the greatest reduction in risk (OR = 0.51; 95% CI = 0.33-0.78; p = 0.002; dominant model). All of these results point to a potential association between the Norwegian population's APOBEC3A/B deletion polymorphism and a lower risk of endometrial cancer (Sofiyeva et al., 2023).

Especially in those with the SNP309T genotype, the MDM2 SNP55T-allele may be associated with a lower risk of endometrial cancer. The minor SNP55T-allele was associated with a lower risk of endometrial cancer in those with the SNP309TT genotype (dominant model: OR = 0.63; CI = 0.45-0.88; p = 0.01). Furthermore, the SNP55T-allele showed a correlation with a lower risk of endometrial

cancer before the age of 50 (dominant model: OR = 0.56; CI = 0.34-0.90; p = 0.02), independent of the genotype in nearby SNPs (Helwa et al., 2021).

In Hainan Chinese Han women, the association between IL6 gene polymorphisms and an elevated susceptibility to endometrial cancer was highlighted in this study. Cai et al. (2019) found that rs1524107 (IL6) (T/C, OR = 1.61, 95% CI = 1.09-2.37, p = 1.55 × 10-2) and rs2066992 (IL6) (OR = 3.09, 95% CI = 2.11-4.53, p = 3.13 × 10-9) significantly increased the risk of endometrial cancer. Globally, the fourth most prevalent female cancer is uterine cervix cancer, representing a leading cause of mortality in women. Approximately 6.6% of gynecological cancer cases worldwide are attributed to it, with 85% of these instances occurring predominantly in developing countries (Bray et al., 2018).

Table 1. Some selected gene SNP in gynecological tumors.

Gene Abbreviation	Gene Full Name	Category	Cytogenetic location (Genomic coordinates (GRCh38)
CYP2D6	Cytochrome P450 Family 2 Subfamily D Member 6	Protein Coding	22q13.2 (22:42,126,499-42,130,810)
CYP2E1	Cytochrome P450 Family 2 Subfamily E Member 1	Protein Coding	10q26.3 (10:133,527,363-133,539,123)
DACH1	Dachshund Family Transcription Factor 1	Protein Coding	13q21.33 (13:71,437,966-71,867,204)
eNOS	Endothelial Nitric Oxide Synthase	Protein Coding	7q36.1 (7:150,991,017-151,014,588)
FGFR3	Fibroblast Growth Factor Receptor 3	Protein Coding	4p16.3 (4:1,793,293-1,808,867)
HPSE	Heparanase	Protein Coding	4q21.23 (4:83,292,461-83,335,153)
MDM2	MDM2 Proto-Oncogene	Protein Coding	12q15 (12:68,808,172-68,850,686)

VDR (Vitamin D Receptor Protein coding gene) ApaI SNP decreases the risk of UI by around 80% (p = 0.044 respectively). Notably, carriers of the VDR gene TaqI Tt, tt genotypes associated with the risk of UI by 4.26-fold (p = 0.001). Also, the carrier of the BB in BsmI increases the risk by 3.47-fold (p = 0.005) for unexplained infertility (UI) (Isbilen et al., 2020). Fok1 rs2228570 significantly increases the risk for OC development (Hu et al., 2023). Thus, numerous genes (Table 1) SNP affect the predisposition and progression of gynecological tumors. The SNP rs4938723, located in the promoter region of pri-miR-34b/c is associated with cervical cancer in the Chinese Han population. Specifically, the C allele revealed a risk factor for developing cervical cancer. Additionally, the CT genotype has been found to correlate with advanced clinical staging and poorer prognosis of patients (Xiong et al., 2014).

Endometrial cancer (EC) is a widespread tumor among the reproductive system's organ tumours, particularly affecting postmenopausal women. Among risk factors is the genetic predisposition regarding the specific single nucleotide gene potential for genetic markers to enhance early detection and inform treatment strategies for endometrial cancer, emphasizing the need for further research. Gene SNP's implication clarity improving early detection/treatment strategies/prognostic

assessments, etc. Therefore, it opens new opportunities for the development of potential biomarkers for susceptibility/ disease progression within EC patients.

Molecular diagnostics/biomarkers, therapeutic advances and personalized medicine

Molecular biomarkers play a crucial role in the early detection and management of gynecological tumors, particularly in ovarian and uterine cancers. Commonly used biomarkers include cancer antigen 125 (CA125), which is widely recognized for ovarian cancer detection, although it has limitations in specificity (R. Zhang et al., 2022). Other significant biomarkers include human epididymis secretory protein 4 (HE4), P53, K-RAS, and estrogen and progesterone receptors, which are utilized for both early detection and therapeutic targeting in uterine cancer (Priya et al., 2024). Liquid biopsy is significantly transforming the detection and monitoring of gynecological tumors by providing a non-invasive method to analyze circulating tumor components in bodily fluids. By utilizing biomarkers like circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and extracellular vesicles, liquid biopsy enhances the ability to track tumor progression and response to therapies(C. Zhang et al., 2024; H. Wang et al., 2024). Moreover, advancements in genomic technologies, including next-generation sequencing, facilitate the identification of actionable mutations, thereby guiding treatment decisions (Ho et al., 2024).

The development of biotechnology has also contributed to the advancement of treatment for gynecological tumors. In recent years, targeted therapies have become one of the most important innovations. Drugs like PARP inhibitors have significantly transformed the therapeutic landscape for ovarian cancer, particularly for patients with BRCA mutations. These agents exploit the concept of synthetic lethality, targeting the DNA repair mechanisms that are compromised in BRCA-mutated tumors, thereby enhancing cancer cell death (Hirschl et al., 2024). The introduction of PARP inhibitors like olaparib, niraparib, and rucaparib has provided new treatment options that extend progression-free survival (PFS) and improve overall survival (OS) in these patients (Guduri et al., 2024). Immunotherapies, including immune checkpoint inhibitors like pembrolizumab, have also made significant advances in treating certain types of gynecological malignancies, like advanced or recurrent cervical cancer. As a result of inhibiting the PD-1/PD-L1 axis, these therapies enable the immune system to recognize and destroy cancer cells (Parvez et al., 2023).

Personalized medicine, leveraging genomics and proteomics, significantly enhances treatment outcomes for patients with gynecological tumors by tailoring therapies to individual molecular profiles. Genomic profiling, particularly through next-generation sequencing (NGS), allows for the identification of specific mutations and homologous recombination deficiency (HRD), which are crucial for determining the efficacy of platinum-based chemotherapy and PARP inhibitors (Hrytsay et al., 2024). Additionally, proteomics aids in discovering novel biomarkers that can improve diagnostic accuracy and therapeutic targeting, although challenges remain in translating these findings into clinical practice(Kaur Jawanda et al., 2024). Artificial intelligence (AI) and machine learning (ML) are revolutionizing personalized treatment strategies for gynecological tumors by integrating complex datasets to enhance diagnosis and treatment efficacy. AI-driven frameworks utilize multi-omics data, electronic health records, and advanced machine learning models, such as Convolutional

Neural Networks (CNNs) and Generative Adversarial Networks (GANs), to tailor treatment plans based on individual genetic and clinical characteristics (Vegesna, 2024).

Biotechnology is poised to significantly enhance the diagnosis and treatment of gynecological cancers through various innovative approaches. Nanotechnology, particularly the use of nanoparticles, is being explored to improve the sensitivity and specificity of cancer detection, enabling earlier diagnosis and more effective imaging techniques (Keyvani et al., 2024). Additionally, advancements in next-generation sequencing (NGS) facilitate genome-directed precision medicine, allowing for the identification of molecular biomarkers that guide targeted therapies, thereby improving treatment efficacy and reducing overtreatment.

Thus, advancing molecular biomarkers/ technologies (liquid biopsies/ genomic profiling, etc.) has significantly improved the early detection/ treatment of gynecological tumors. New Innovations (PARP inhibitors, immunotherapies etc.) are changing the treatment approaches/ landscape. Biotechnology approaches continue to develop/improve. Their ongoing achievements ultimately lead to further enhanced diagnostic accuracy and, finally, improving patients' diagnostic/treatment outcomes.

Clinical implications of single nucleotide polymorphisms

There are currently several limitations to determine the translational role of SNPs in determining. Even though there have been well-validated SNPs' correlation to endometrial cancers, single SNPs alone are known not to have a high contribution in cancer risk. Reliable SNPs, when validated for their medical usage, could serve for accurate diagnosis and prognosis of endometrial cancer, as well as prediction of drug response (Baker-Ran & Kitson, 2024).

The NINJ2 SNP rs118050317 revealed increased risk for the development of the EC; Notably, the carrier of mutant allele C/CC genotype revealed the elevated leves of the CEA, CA125/AFP compared to the control group (Cheng et al., 2021). For SNPs which have been identified as causal of endometrial cancer, SNP-directed RNAi drugs are a promising option for treatment purposes, especially for untreatable cancers, by specifically targeting the transcripts of oncogenes, which provide the survival advantages for cancer cells (Gebert et al., 2020). SNPs can also serve in clinical settings for therapeutic decisions, as better tools compared to family history (Srinivasan et al., 2015). The identification of relevant genetic variants is crucial for proper disease management; early detection of sensitive variants increases the likelihood of successful treatment.

Biosensing technology and its role in early detection and diagnosis

Biosensing technology refers to sophisticated analytical devices that integrate biological components with electronic systems to detect and quantify biological or chemical reactions. These devices utilize biorecognition elements such as enzymes, antibodies, or nucleic acids to selectively bind to specific analytes, converting biological signals into measurable electrical signals (Abena, 2023). Biosensing technology has emerged as a powerful tool in the early detection, diagnosis, and monitoring of gynecological tumors, including ovarian, cervical, and endometrial cancers. As biosensing continues to evolve, it holds immense potential to enhance patient outcomes through more timely and accurate diagnostics in gynecological oncology.

Biosensors significantly enhance the early detection of gynecological tumors, including ovarian, cervical, and endometrial cancers, through their ability to identify specific biomarkers in biological samples. Current research confirmed that the biosensors have revealed significant capability to detect breast cancer metastasis (Deng et al., 2023). Research is actively progressing in developing electrochemical biosensing techniques aimed at identifying precise and rapid biomarkers for the detection of breast cancer. Current studies indicate the need for affordable and efficient diagnostic biosensor technologies to enhance diagnostic capabilities and improve patient treatment options (Kiani et al., 2024). Biosensors have emerged as innovative tools for the detection of key biomarkers associated with gynecological cancers, significantly enhancing diagnostic capabilities. For ovarian cancer, biomarkers such as human epididymis protein 4 (HE4), alpha-fetoprotein (AFP), and cancer antigen 125 (CA-125) are commonly detected using advanced biosensor technologies, including electrochemical and photoelectrochemical immunosensors, which offer rapid and sensitive detection (Kovarova et al., 2023). In cervical cancer diagnostics, p16 is a notable biomarker identified through label-free electrochemical immunosensors (Kuntamung et al., 2024). Biosensors play a crucial role in detecting circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) in gynecological cancers through liquid biopsy techniques. These non-invasive methods allow for the collection of tumor-specific material from blood samples, facilitating real-time monitoring of cancer progression and treatment response. Recent advancements in electrochemical biosensing tools have enhanced the sensitivity and specificity of ctDNA detection, enabling the quantification of tumor-derived DNA in plasma samples (Sahin & Yıldırım Tirgil, 2024). The integration of biosensors with liquid biopsy techniques has shown promise in identifying genomic alterations and assessing cancer burden, which is vital for guiding therapy selection and predicting relapse (X. Wang et al., 2024).

Technological developments in biosensing

Recent advancements in biosensing technologies, particularly nano-biosensors and microfluidic biosensors, have significantly enhanced the detection of gynecological tumor markers. Nanomaterial-based biosensors have improved sensitivity and selectivity, enabling the detection of low concentrations of cancer biomarkers in complex biological samples, which is crucial for early diagnosis of gynecological cancers (Shahazi et al., 2024). Electrochemical immunosensors, leveraging nanotechnology, provide rapid and simplified detection of biomarkers, facilitating timely diagnosis and personalized healthcare (Kokilavani et al., 2024). Additionally, innovative methods such as nanopore sensing have been developed to identify specific ovarian cancer marker peptides in urine, showcasing the potential for non-invasive testing (Rockett et al., 2024). Electrochemical and optical biosensors are increasingly being employed in gynecological oncology to monitor specific biomarkers such as CA-125, HE4, and SCC-Ag, enhancing early detection and diagnosis. Electrochemical immunosensors, utilizing nanocomposites like CuCo-ONSs@AuNPs and molecularly imprinted polymers, have demonstrated high sensitivity and low limits of detection for CA-125, with ranges from 0.01 U/mL to 80 U/mL and LODs as low as 0.0089 U/mL (Wu et al., 2024). Additionally, multiplex biosensors have been developed for simultaneous detection of multiple biomarkers, including CA-125 and HE4, achieving linear detection ranges suitable for early-stage disease identification (Kumar et al., 2023).

Biosensors play a crucial role in ensuring complete tumor removal during gynecological surgery by enhancing the detection of malignant tissues. For instance, intraoperative near-infrared fluorescence imaging using agents like pafolacianine and OTL38 allows surgeons to visualize cancerous lesions that are otherwise difficult to detect, significantly improving the completeness of cytoreductive surgery (Dindere et al., 2022). Additionally, techniques such as attenuated total reflection Fourier-transform infrared (ATR-FTIR) spectroscopy provide rapid classification of fresh tissue samples, distinguishing between malignant and benign tumors with high accuracy, thus aiding in real-time decision-making (Malonek et al., 2020).

Biosensing technologies are poised to revolutionize gynecological tumor screening and diagnosis, particularly in low-resource settings, by providing cost-effective, portable, and efficient solutions. The development of lab-on-chip (LoC) technologies enables multiplex detection of various biomarkers, enhancing diagnostic reliability for gynecological cancers, including cervical and ovarian cancers (Nujhat et al., 2023).

Thus, the evolution of biosensing technologies has the potential to revolutionize diagnostics/ treatment in gynecological oncology. In particular, they have the ability to provide timely and accurate diagnostics that significantly improve the method for personalized therapy. It can be said that biosensing technology provides innovative/ effective methods for early detection/monitoring/ surgical assistance/enables personalized treatment strategies, etc. Taken together, the integration of biosensing technology into gynecological oncology may hold remarkable potential/new opportunities for transforming/improving the patient care aspects, including the following: early diagnostics/ ensuring timely intervention/facilitating personalized treatment approaches, etc.

Conclusions

It is critical to investigate the single nucleotide gene polymorphisms associated with gynecologic cancer susceptibility/predisposition as some of them might be utilized as useful molecular markers for assessing gynecologic cancer predisposition and might be further used for diagnosis and treatment modalities in individuals with a similar SNP profile. Moreover, recent advancements in biosensing technologies, particularly nano-biosensors and microfluidic biosensors, have significantly enhanced the detection of gynecological tumor markers.

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Conflict of interest

The authors must declare any conflict of interest.

Data availability statement

It is not required.

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Abbreviations

APC: Adenomatous Polyposis Coli; **BAX:** BCL-2 Associated X protein; **CIMP:** CpG Island Methylator Phenotype; **CHFR:** Checkpoint with Forkhead-Associated and Ring Finger Domains; **CASP8:** Caspase 8; **CD1**: Cluster of Differentiation 1; **COMT**: Catechol-O-Methyltransferase; **CIN**: Cervical Intraepithelial Neoplasia; **DACH1**: Dachshund family transcription factor; **GPR54**: G Protein-Coupled Receptor 54; **MLH1**: MutL Homolog 1; **HPSE**: Heparanase; **HOXA11**: Homeobox A 11; **IGF2R:** Insulin-like Growth Factor 2 Receptor; **EC**: Endometrial Cancer; **ER**: Estrogen Receptors; **HPV**: Human Papilloma Virus; **MMR**: Mismatch Repair; **MSI**: Micro-satellite Instability; **PTEN**: Phosphatase and tension homolog deleted on chromosome 10; **P73**: Tumor Protein P73; **RASSF1A**: Ras Association Domain Family Member 1A; **RSK4**: Ribosomal S6 Kinase 4; **SNP**: Single Nucleotide Polymorphism; **SPRY2**: Sprouty Homolog 2; **TGFBR2**: Transforming Growth Factor Beta Receptor 2

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