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Evaluation of Tumor Markers in Endometrial Cancer Differentiation and Abnormal Uterine Bleeding: A Systematic Review and Meta-Analysis

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ABSTRACT

Endometrial Cancer (EC) is a malignancy of the uterine, causing 42,000 deaths. There are two types: Type I, which mainly affects postmenopausal women and is marked by endometrioid histology, and Type II, which lacks endometrioid histology and is not associated with hormonal risk factors. The most common symptom is abnormal uterine bleeding, seen in over 90% of patients. Molecular diagnostics like saline infusion sonohysterography and transvaginal sonography (TVS) are crucial for diagnosing EC. Currently, only a few biomarkers, such as HE4, CA125, and CA153, are available for EC detection, but relying on a single indicator can lead to inaccurate diagnoses. Early identification of noninvasive serologic diagnostic markers is crucial for improving diagnostic efficiency in EC. Combining multiple indicators like fibrinogen (FIB) and D-dimer (D2), which are linked to tumor metastasis and adverse outcomes, can enhance this process. Blood tests for surgical guidance and risk stratification in different genetic subgroups could help detect deep myometrial invasion and lymph node metastasis. Analyzing circulating tumor DNA (ctDNA), circulating tumor cells, and inflammatory markers aids in early endometrial cancer (EC) diagnosis. Circulating tumor cells correlate with tumor size, stage, survival, and non-endometrioid histology. Protein combinations like SWI/SNF and cadherin levels, especially N-cadherin, are potential prognostic indicators. TET enzymes play a role in DNA methylation. Monitoring cytokines (IL-4, IL-6, IL-8) helps track EC progression, with low IL-4 and high IL-8 indicating higher risk. Combining menopausal status with cytokines and CA125 enhances risk assessment. Early detection using multiple indicators can improve diagnostic efficiency and patient outcomes.

Keywords: Endometrial cancer, Abnormal uterine bleeding, Histology, Tumor markers

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1. Introduction

Endometrial cancer, also known as EmCa, is a type of adenocarcinoma that affects the lining of the uterus, called the endometrium. Globally, endometrial cancer diagnoses approximately 142,000 women annually, leading to an estimated 42,000 fatalities. The ability to grow independently of external signals, resistance to growth suppression, avoidance of programmed cell death, formation of new blood vessels, invasion into surrounding tissues, and spread to distant sites mark the progression of cancer. These traits are exclusive to EmCa and have resulted in the formation of two major divisions. Type I endometrial cancer, which is characterized by endometrioid histology, occurs mostly in pre- and peri-menopausal women. It is commonly preceded by a precancerous illness and is related to unopposed estrogen exposure. This type of cancer is most common in the white population and generally has a favorable prognosis. On the other hand, type II EmCa, which lacks endometrioid histology and is not linked to hormonal risk, primarily affects postmenopausal women, particularly African-American Women (AAW). This type of EmCa tends to have a more aggressive clinical course and generally has a worse prognosis **(1)**.

The majority of the time, the diagnosis of EC is based on the existence of symptoms; the most prevalent symptom, abnormal uterine bleeding, is present in over 90% of patients **(2)**.

Different categories of biological components, such as DNA, RNA, proteins, and metabolites, can serve as indicators of diseases. Among these substances, proteins have significant advantages as biomarkers. They are the final biological products that regulate both normal and abnormal physiological processes, and they are the primary focus of most existing medications **(3)**.

Numerous tumor markers have been identified for EmCa, with the primary focus on the epidemiology, treatment outcome, and classification of EmCa. This article has examined the tumor markers associated with AUB and endometrial cancer.

AUB

Approximately 33% of women tend to experience abnormal uterine bleeding at some point in their lifetime, with irregularities typically occurring during the onset of menstruation and the transition to menopause. A typical menstrual cycle occurs every 24 to 38 days and lasts for 2 to 7 days. During this time, the amount of blood loss ranges from 5 to 80 milliliters. Any changes in any of these four indicators are classified as abnormal uterine bleeding. It is advisable to replace older words like oligomenorrhea, menorrhagia, and dysfunctional uterine bleeding with simpler terms that accurately reflect aberrant uterine bleeding. The International Federation of Obstetrics and Gynecology (FIGO) initially revised and published the nomenclature in 2007, and provided subsequent changes in 2011 and 2018. The FIGO systems initially establish a clear definition for abnormal uterine bleeding, followed by an acronym for frequently encountered causes. In 2018, the committee included intermenstrual bleeding and characterized irregular bleeding as occurring beyond the 75th percentile **(4)**. We can further categorize abnormal uterine bleeding as acute or persistent. Acute Abnormal Uterine Bleeding (AUB) refers to a condition when there is an excessive amount of bleeding that necessitates prompt attention in order to prevent any additional blood loss. Acute Abnormal Uterine Bleeding (AUB) can manifest independently or be present alongside chronic AUB, which pertains to irregularities in monthly bleeding over the majority of the preceding 6 months **(5)**.

The International Federation of Obstetrics and Gynecology (FIGO) has developed the useful term PALM-COEIN to classify the primary reasons for irregular uterine bleeding. The first section, PALM, lists the structural problems (hyperplasia, adenomyosis, leiomyoma, and malignancy). Non-structural issues are covered by the second component, COEI (coagulopathy, ovulatory dysfunction, endometrial disorders, and iatrogenic). The acronym "N" identifies conditions not otherwise classified.

Certain structures in the anatomy, such as endocervical polyps, endometrial polyps, or leiomyomas, may not present any symptoms and may not be the main reason for a patient's abnormal uterine bleeding (AUB). The 2018 version of the FIGO system shifted the classification of anticoagulant-induced abnormal uterine bleeding (AUB) from the coagulopathy category to the iatrogenic category. The "not otherwise classified" category should include conditions such as pelvic inflammatory illness, chronic liver disease, and cervicitis.**(4)**

The differential diagnosis of Abnormal Uterine Bleeding (AUB) categorized by age groups is as follows:

Infant:

Withdrawal of estrogens

Prepubertal foreign body. Psychological distress is caused by a distressing event, specifically non-consensual sexual activity infection (namely vulvovaginitis, urethral prolapse, and precocious puberty). A tumor located in the ovaries or vagina is also present.

Postmenarchal refers to the period following a girl's first menstruation. Anovulation is the absence of ovulation, which is the release of an egg from the ovary. Bleeding disorders are conditions that cause abnormal or excessive bleeding. Pregnancy refers to the state of carrying a developing fetus. Infection, namely Pelvic Inflammatory Disease (PID), can also cause abnormal bleeding. PCOS stands for polycystic ovary syndrome, a hormonal problem that can affect

The age group comprises individuals who are capable of sexual reproduction.

The potential causes of anovulation include pregnancy, polyps, adenomyosis, fibroids, cancer, infection, and endocrine abnormalities such as PCOS, thyroid problems, and pituitary adenoma. Hemorrhagic conditions

Iatrogenic medications include the Oral Contraceptive Pill (OCP), Intrauterine Device (IUD), and antipsychotic medication.

Perimenopausal women may experience conditions such as anovulation, polyps, adenomyosis, fibroids, and cancer.

These conditions include menopausal atrophy, cancer, polyps, and iatrogenic conditions such as Estrogen Replacement Therapy (ERT), Hormone Replacement Therapy (HRT), Intrauterine Devices (IUDs), steroid injections, and tamoxifen.

Abbreviations: AUB refers to abnormal uterine bleeding, PID is for pelvic inflammatory disease, PCOS stands for polycystic ovarian syndrome, OCP refers to oral contraceptive pills, IUD stands for intrauterine device, ERT refers to estrogen replacement therapy, and HRT stands for hormone replacement therapy **(6)**.

Endometrial cancer

Endometrial Cancer (EC) is a malignant tumor that develops in the inner epithelial lining of the uterus. The condition has a growing prevalence and fatality rate globally **(7)**.

Types of EC

The term "EC" refers to a collection of different histological subtypes and molecular traits. Historically, we classified Endometrial Cancer (EC) into two types: Type I, associated with unopposed estrogen stimulation and consisting of low-grade cells that are more prevalent and have a positive prognosis, and Type II, not driven by estrogen and consisting of high-grade cells that are less common and have a negative prognosis. Type I Endometrial Cancers (ECs) consist mostly of grade I or grade II endometrioid adenocarcinomas. Type II ECs, on the other hand, include grade III endometrioid adenocarcinomas, serous clear cell, undifferentiated, and carcinosarcomas.

Epidemiology

In 2020, there were a total of 417,336 cases of EC reported worldwide. EC ranks as the sixth-most prevalent form of cancer among women **(8)**. The majority of cases often manifest in individuals aged between 65 and 75 **(2).** While 67% of patients initially have early-stage disease, associated with an 81% overall survival rate over a 5-year period, the 5-year overall survival rates for stage IVA and stage IVB EC are only 17% and 15%, respectively **(9)**.

A total of 417,367 women worldwide received an EC diagnosis in 2020. The regions with the highest number of cases were North America and Western Europe **(4).** A substantial prevalence of lifestyle risk factors for EC, such as obesity, linked to around 50% of EC cases, accounts for the elevated occurrence rate in North America and Western Europe **(10)**.

The death rate associated with EC has shown an average annual increase of 1.9%, according to comprehensive research from 2016 that combined data from multiple epidemiological studies conducted between 1971 and 2014 **(11)**.

Risk factors

Several significant risk factors exist for endometrial cancer:

1- Endometrial Hyperplasia (EH) is the first sign of cells growing in a way that isn't normal. This can lead to endometrioid adenocarcinoma of the Endometrium (EC), which is the most common cancer in women in developed countries. Chronic exposure to unopposed estrogen is the primary risk factor for EH development. From a histopathological perspective, we can categorize EH into two groups: benign EH without atypia and atypical EH/x (EIN). The clinical therapeutic options vary from monitoring or progestin therapy to hysterectomy, based on the likelihood of developing or coexisting endometrial cancer and the patient's preference to maintain fertility. Various studies provide evidence for the effectiveness of progestins in treating both benign and atypical endometrial hyperplasia. This review provides a comprehensive overview of the available data on the risk factors and management strategies for EH. In addition, we conducted a thorough search of the PubMed and cochrane controlled trials register databases to find studies that examined the effectiveness of progestin treatment in women with EH **(12)**. We followed the current guidelines provided by the American College of Obstetricians and Gynecologists (ACOG), which suggest that women experiencing their first episode of postmenopausal Bleeding (PMB) should undergo either an endometrial sample or Transvaginal Ultrasound (TVUS) for examination. If Transvaginal Ultrasound (TVUS) is conducted and the resulting Endometrial Thickness (ET) measurement is equal to or less than 4mm, there is no need for an endometrial sample. For women whose endometrial thickness exceeds 4mm, it is advisable to undergo endometrial tissue sampling. For women who experience recurring Postmenopausal Bleeding (PMB), it is advisable to undergo endometrial biopsy, independent of Estrogen Therapy (ET) usage **(13,14)**.

2- Multiple studies have consistently shown a strong correlation between having a Body Mass Index (BMI) greater than 30 kg/m^2 and an increased chance of developing endometrial cancer. Researchers hypothesize that food may contribute to the onset of endometrial cancer, given the significant correlation between obesity and this form of cancer **(15-17)**. Observational and MR analyses strongly link both higher BMI and larger waist circumference to an increased risk of endometrial cancer **(15,16,18)**. Therefore, a previous study linked a decrease in the proportion of carbohydrate intake and an increase in the proportion of fat intake to a higher Body Mass Index (BMI) and waist circumference **(19)**.

Examination of AUB

When examining patients who complain of Abnormal Uterine Bleeding (AUB), it is crucial to conduct a thorough medical history, including information about any inherited predisposition for uterine malignancies. Additionally, a vaginal speculum exam and a Transvaginal Ultrasound (TVS) are necessary components of the evaluation process **(20-22)**. Nevertheless, the established diagnostic criteria and the ability to reproduce Transvaginal Sonography (TVS) results are not uniform.The accuracy of TVS in diagnosing benign uterine diseases is less than optimum. The Transvaginal Ultrasound (TVS) is a useful tool for ruling out Endometrial Cancer (EC) in postmenopausal women, specifically when the thickness of the uterine lining is 4 mm or less. This method has a negative predictive value of over 99%

(21,23-25). TVS provides a thorough evaluation of the uterus and its surrounding components **(20,26)**. In comparison to Transvaginal Ultrasound (TVS), saline Infusion Sonohysterography (SIS) has a higher rate of detecting benign lesions. However, expenses, convenience, and tolerability are among the limitations **(27,28)**.

Genetics

In 2013, The Cancer Genome Atlas (TCGA) performed a comprehensive genomic analysis of Endometrial Cancer (EC). They classified 373 cases of serous and endometrioid EC into four molecular subgroups based on the presence of mutations and copy number alterations. These subgroups included cases with POLE mutations, microsatellite instability (MSI), low copy number alterations, and high copy number alterations **(29)**. The study also found that the four groups had different prognostic outcomes. The 5-year Progression-Free Survival (PFS) rate was highest in POLE-mutant Endometrial Cancers (ECs) and lowest in ECs with large copy number alterations. The predictive information obtained from genomic analysis was comparable to the prognostic value derived from histologic classification. Survival curves were found to be similar for the high copy number and serous subtypes. The other clusters and endometrioid histology were also similar. However, we can further divide the other clusters into three groups based on their prognosis. The group with the POLE mutation had the most favorable survival prognosis, while the groups with MSI and low copy numbers had an intermediate prognosis. Additionally, researchers have discovered that the endometrioid EC subtype frequently links to tumors with POLE mutations, while serous and high-grade endometrioid EC composes copy-number-high tumors **(29,30)**.

The preliminary research indicated a higher occurrence of TP53 mutations in the serous histologic subtype and high-grade endometrioid cancers, while TP53 mutations were rare and POLE mutations were more common in low-grade endometrioid histology tumors **(29)**. Further investigations into this molecular classification have demonstrated that the four categories are present in all stages, histologic types, and grades **(31)**. In addition, the molecular classification allows for the categorization of tumors in a standardized and highly reproducible manner, with consistent agreement between the initial biopsy and the final hysterectomy specimen. These advantages surpass those of the old histological classification **(32-34).**

6–9% of endometrial cancer specimens have the POLE mutation, and younger, thinner women are more likely to have it. The endometrioid histological subtype and the early stage of the disease commonly correlate with it **(29,35)**. This genetic anomaly leads to a highly mutated tumor, thereby triggering a stronger immune response against mutant cells. The presence of CD8 lymphocytes and the activity of cytotoxic T-cells have demonstrated this **(36)**. Tumors with POLE mutations frequently exhibit aggressive pathological characteristics, such as high-grade LVSI. However, they still lead to a positive prognosis, with a 96% survival rate at five years **(29)**.

A follow-up research conducted on the PORTEC cohorts reaffirmed that the prognosis is highly favorable, independent of the adjuvant therapy used **(30)**. A study examined the clinicopathological and molecular features of multiple-classifier EC. Patients with both POLE ultramutation and aberrant p53 status exhibited molecular clustering and clinical outcomes comparable to EC cases solely characterized by POLE mutation. The small number of participants constrained the study, but it did propose the hypothesis that we should categorize these EC tumors in the POLE group **(37)**. It is crucial to make a thorough decision on the pathogenicity of the POLE mutation, as not all mutations in this gene are pathogenic and could potentially result in a false conclusion. The genetic study of the PORTEC-3 group showed that people with Endometrial Cancer (EC) who had p53 that wasn't working normally did better when they got platinum-based chemotherapy along with adjuvant radiation therapy. More precisely, the 5-year Recurrence-Free Survival (RFS) rate was 59% for patients who received chemoradiation compared to 36% for those who had radiation alone (P=0.019) **(38)**.

The use of radiation in the group with aberrant p53 raises concerns **(39)**. An effective approach to treating abnormal p53 Endometrial Cancer (EC) could involve targeting HER-2 (human epidermal growth factor receptor 2) and HRD (homologous recombination deficiency). This is supported by findings from the PORTEC-3 cohort analysis, which showed a correlation between abnormal p53 tumors and HER2 status, as well as another study that found a correlation between abnormal p53 tumors and HRD **(40,41).** Unfortunately, no more research has examined transtuzumab using molecular classifiers such as aberrant p53. Nevertheless, individuals with stage III or IV serous EC are recommended to undergo IHC Her2Neu testing according to the SGO's current 2021 guidelines **(42)**. In relation to the HRD relationship, clinical studies have not yet investigated PARP inhibitors, compounds that inhibit the enzyme poly adenosine diphosphate-ribose polymerase, but future trials will include them. An exploratory analysis was conducted to compare the addition of bevacizumab with temsirolimus to standard chemotherapy in advanced EC. The analysis showed a correlation between the TP53 mutation and improved survival outcomes in the bevacizumab-treated subgroup **(43)**.

The MMR-deficient molecular group represents 20-30% of EC cases and is analogous to MSI in the initial genomic classification **(29,44)**. There are three ways that tumors with poor DNA mismatch repair (MMRd) or high microsatellite instability (MSI-high) can arise: inherited mutations in the MLH1, PMS2, MSH2, and

MSH6 genes that make DNA mismatch repair proteins (Lynch syndrome); acquired mutations in the MMR genes (Lynch-like); and complete methylation of the MLH1 gene promoter (sporadic) **(45)**. Various institutions have widely adopted Immunohistochemistry (IHC), a cost-effective method, to detect these mutations. The primary purpose of this implementation was to aid in validating the histologic diagnosis and to perform screening for Lynch syndrome, which accounts for approximately 3% of EC cases **(46)**. Detecting the MMR status of an EC tumor is useful not only for predicting outcome, but also for determining the possibility of using newer treatments such as checkpoint inhibitors **(42,47)**. An intermediate prognosis for EC has been observed to be associated with MMR status **(48)** When analyzed from a demographic perspective, MMRd showed no correlation with age group or BMI **(35)**.

The NSMP profile shows p53 wild-type status, demonstrates MMR competence, is free of POLE mutation, and correlates with 40-50% of Endometrial Cancers (ECs). The initial genomic categorization correlates with the low copy number of this molecular group, indicating its intermediate prognostic significance **(29,44)**. This group consists mostly of endometrioid Endometrial Cancers (ECs) that are positive for Estrogen a Progesterone Receptors (ER, PR) and have high response rates to hormonal therapy.**(30,49)** In a separate study, CTNNB1 mutation was associated with poorer recurrence-free survival in early-stage, low-grade endometrioid EC **(50)**. L1CAM is a transmembrane glycoprotein that allows malignant cells to migrate. It is a reliable indicator of reduced life expectancy and is associated with negative clinicopathologic features, including more than 50% myometrial invasion, Lymphovascular Space Invasion (LVSI), and lymph node involvement **(51)**. Researchers have also found that L1CAM helps to categorize patients who were previously unclassified in the conventional EC molecular subgroup classification. In addition, it has a close relationship with p53 (**52**). Both are currently involved in ongoing EC clinical trials, such as PORTEC-4 **(49)**.

The prognosis of endometrial cancer is more favorable when there is a higher level of Estrogen Receptor (ER) and Progesterone Receptor (PR), but a higher level of HER2 indicates a poorer prognosis. Hormone receptors play a critical role in determining the efficacy of hormone therapy in the treatment of endometrial cancer **(53)**.

There is a limited amount of research examining the relationship between ER, PR, p53 status, and lymph node metastasis. Goswami (2017) conducted a study that examined 34 cases of endometrial cancer. Of these, 30 cases had undergone hysterectomy with staging laparotomy to examine the relationship between ER and PR status of EC cases and the occurrence of nodal metastases. A p-value of 0.19 showed statistical insignificance of the association. Yang B et al. (2016) conducted a study in China, including 200 patients at the Shanghai Cancer Center, and found that loss of ER/PR was an independent predictor of nodal metastasis. Trovik J. et al. (2013) conducted a study with results comparable to the previous study. Iwai K. et al. (1999) found that PR IHC was a clear prognostic indicator for lymph node metastasis. In cases of endometrial cancer, there was a strong association between high levels of p53 expression and the spread of cancer cells to lymph nodes. The presence of p53 itself appeared to be a separate factor associated with nodal involvement. Patients diagnosed with endometrial cancer who previously tested negative for PR immunohistochemistry are at greater risk of developing lymph node metastases **(53)**.

Diagnose

Molecular diagnostics is a field that focuses on the accurate assessment of medical conditions, even when there are limitations in local economics and laboratory equipment. Currently, a reliable, accurate, cost-effective, and non-invasive diagnostic technique for endometrial cancer is lacking. The non-invasive nature, stability and repeatability of serum tumor markers aid in the diagnosis of the disease. Human epididymal epithelial secretory protein 4 (HE4) is a recently discovered tumor biomarker. It is predominantly found in the epithelial cells of the reproductive system, but its expression is lower in normal endometrium **(54)**.

Tumor markers

Currently, there are a limited number of accepted markers that are both sensitive and specific. Researchers have evaluated the diagnostic efficacy of several possible biomarkers, including HE4, carbohydrate antigen 125 (CA125), and CA153, in detecting endometrial cancer, but they have not yet reached the desired diagnostic capability. More specifically, the rate of misdiagnosis of endometrial cancer is higher when relying on a single indicator. However, combining multiple indicators for diagnosis can improve diagnostic efficiency **(55)**. Therefore, the discovery of suitable non-invasive serologic diagnostic markers in the early stages is of great practical importance. Malignant tumors have a strong association with thrombosis **(56)**. Extensive research has shown that the initial manifestation of malignant tumors is characterized by abnormal blood clotting. More than 90% of individuals with tumors have defective coagulation, which promotes tumor progression **(57,58)**. Fibrinogen (FIB), a protein strongly associated with tumor spread and a risk factor for poor prognosis, is the focus of this study **(59)**. D-dimer (D2), a major degradation product of fibrin, plays a critical role in the coagulation and fibrinolysis systems. It also serves as a signal for activation of the coagulation system in various types of malignancies, particularly in advanced stages **(59,60)**. A large body of data consistently demonstrates a strong association between defective blood clotting function, particularly

Fibrinogen (FIB) and D-dimer (D2), and cancer incidence, progression, and prognosis **(61-64)**.

Both clinicians and patients have a strong desire to determine a predictive biomarker from a blood sample. Is it possible to use a blood test to predict the likelihood of survival and/or recurrence? The James Lind Alliance Endometrial Cancer Priority Setting Collaboration has ranked endometrial cancer as the 5th most important research priority. This ranking is based on input and perspectives from patients, physicians, and the public **(65)**. A preoperative blood test that can accurately identify deep myometrial invasion and lymph node metastases could provide valuable information for surgical decision-making. This test could be useful for risk stratification within different molecular groups of endometrial cancer. Women whose tumors fall into the MMR-D or NSMP groups have similar survival outcomes, and some may benefit from adjuvant therapy while others may not **(66)**.

Cancer Antigen 125 (CA125)

In 1984, Niloff and colleagues discovered that serum levels of CA125 were higher in women with recurrent endometrial cancer and in women with advanced endometrial cancer **(67)**. Follow-up studies have consistently shown an association between blood levels of CA125 and negative clinicopathologic features and outcomes in endometrial cancer **(68-72)**. Jiang and colleagues conducted a study where they analyzed a group of 995 patients with endometrial cancer. They found that high levels of CA125 were strongly associated with cancer spread to the lymph nodes, myometrial invasion, and the International Federation of Gynecology and Obstetrics (FIGO) stage of the disease. However, they did not find a correlation between CA125 levels and the specific type of cancer cells. In addition, they found that higher CA125 levels may independently predict patient prognosis **(73)**. The retrospective design and selection bias limited the results, as the analysis excluded nearly 20% of patients with endometrial cancer due to lack of preoperative serum CA125 measurements **(73)**. Preoperative elevation of CA-125 may be an indicator of poor prognosis and reduced disease-free survival. Because of this, measuring CA-125 before surgery can be used as an additional way to figure out the risk in these people, along with MI or tumor size **(74)**.

Human Epididymis protein 4 (HE4)

There is compelling evidence for an association between serum HE4 levels and endometrial cancer outcomes. Dai and colleagues conducted a meta-analysis involving 4235 patients and found a strong correlation between elevated HE4 levels and worse overall, disease-free, and progression-free survival outcome **(75)**. Researchers have demonstrated an association between serum HE4 and adverse histologic features of endometrial cancer. However, the evidence is limited due to significant differences in the studies, small sample sizes, and variations in the prognostic thresholds used. Researchers have associated various blood-based metabolites with adverse clinicopathologic variables and unfavorable endometrial cancer outcomes **(76)**.

Cell-free tumour DNA

New research suggests a link between the amount of circulating cell-free tumor DNA and endometrial cancer prognosis **(77-80)**. Recent research suggests a link between the amount of circulating cell-free tumor DNA and prognosis in endometrial cancer. Cicchillitti and colleagues discovered increased amounts of cell-free DNA in grade 2 and 3 endometrial cancer compared to grade 1 disease **(79)**. The study by Vizza and colleagues, which reported a significant increase in the amount of cell-free DNA in high-grade endometrial cancer, is consistent with these findings. In addition, the ratio of long to short fragments of cell-free DNA showed greater serum DNA integrity in women with LVSI **(80)**. In contrast, Tanaka and colleagues did not observe a statistically significant change in cell-free DNA levels based on the grade or stage of endometrial cancer **(81)**. Further research is needed to validate the potential predictive value of circulating tumor DNA in endometrial cancer. Researchers have also proposed circulating tumor DNA as a potential early detection method for endometrial cancer recurrence **(77,81,82)**. In a small pilot study, Moss and his colleagues discovered that ctDNA could detect the recurrence and development of endometrial cancer earlier than imaging or clinical presentation. They determined that the median lead time for detection was 2.5 months **(77)**. Endometrial cancer prognosis has been linked to certain mutations found in the blood. Dobrzycka and her colleagues found an association between KRAS mutation status and the amount of circulating cell-free DNA p53 antibodies in people with high-grade endometrial cancer **(78)**. Bolivar and his team found a strong association between plasma ctDNA mutations (CTNNBI, KRAS, PTEN, or PIK3C) and advanced stage, deep myometrial invasion, LVSI, and primary tumor size **(83)**. Endometrial cancer prognosis has also been linked to the presence of circulating tumor cells. Lemech and colleagues conducted a feasibility study where they discovered a correlation between the presence of circulating tumor cells and certain factors such as non-endometrioid histology, tumor size, disease stage, and survival in a group of 30 patients with advanced endometrial cancer **(84)**. Bogani and colleagues studied 28 patients with grade 3 endometrial cancer in a small prospective study. It was found that there was a strong association between circulating tumor cells, deep infiltration of the myometrium, and positive lymph nodes **(85)**.

Promising predictive indicators of endometrial cancer include measures of systemic inflammation **(86)**. Chronic low-grade inflammation is a biological process that plays a fundamental role in the development of endometrial cancer. We have observed that inflammation damages DNA and enhances

mechanisms that promote cell growth and inhibit cell death, thereby contributing to the development and progression of tumors. Our previous study showed that women with elevated levels of CRP, specifically at a decision threshold of 5.5 mg/L, had a twofold increase in the likelihood of cancer-specific mortality **(87)**.

Molecular targets

In recent decades, research investigations have concentrated on molecular targets to enhance diagnostic procedures, provide novel prognostic biomarkers, and suggest therapeutic approaches. One intriguing focus is the SWI/SNF protein combination. The SWI/SNF complex is made up of different parts, such as ARID1A or ARID1B, SMARCA4, SMARCC1 and 2, SMARCD1, 2 and 3, and ACTL6A and B. It has a crucial role in modifying the structure of chromatin and is involved in various physiological processes, such as cell differentiation, DNA repair, and tumor suppression **(88)**.

The ARID1A subunit is the most commonly altered element of the SWI/SNF complex. ARID1A's C-terminal domain facilitates the connection between ARID1A and nuclear hormone receptors. Additionally, it regulates the activity of many transcription factors. ARID1A expression loss appears to occur early in endometrial cancer development. A 2024 study observed total loss of ARID1A expression in 27% of endometrioid carcinomas, and significant lack of expression in the majority of cancer cells in an additional 51%. There was a strong association between complete loss, high tumor grade, and extension to the endocervix. Korentzelos et al. have verified that 75% of 20 instances of undifferentiated endometrial cancer showed a loss of ARID1A expression, based on our research **(88)**.

BRG1/SMARCA4 functions as a catalytic component within the SWI/SNF chromatin-remodeling complex. Many enzymes responsible for modifying the shape of chromatin utilize it. Recent research has revealed that it may have a dual role, functioning both as a tumor suppressor gene and as a tumor promoter. BRG1 expression loss in non-small cell lung cancer (NSCLC) was minimal, accounting for just 4% of cases, and primarily observed in undifferentiated tumors. In 2024, a study revealed that most cases of endometrioid carcinomas had BRG1 present in the nuclei of cancer cells, with rare instances of down-regulation. Korentzelos et al. observed that BRG1 deletion was present in 20% of undifferentiated endometrial carcinomas.**(88)**

ARID1A expression is totally absent in 25% of endometrial carcinomas and partially reduced in a significant proportion of cancer cells in an additional 50% of cases. It was linked to aggressive clinical behavior to lose all histological features, like poor differentiation and expansion to the endocervix. These traits are crucial determinants of the need for post-operative radiation. However, BRG1 does not appear to have a function in the development of endometrial cancer and does not affect the clinical behavior of this type of cancer **(88)**.

Cadherin

Cadherin levels may serve as a prognostic indicator. However, there is a paucity of evidence regarding the presence of these proteins in different forms of EC, particularly for N-cadherin. In addition, there is little information on the relationship between E-cadherin and N-cadherin levels in the main tumor and the endocervix. The purpose of this study was to look at how much E-cadherin and N-cadherin were expressed in the endocervix of women with EC to see if these cadherins could be used as predictive biomarkers. In general, we observed a higher expression of N-cadherin compared to E-cadherin. We also observed a significant decrease in E-cadherin expression in more than 40% of the samples. The composition of cadherins changes as malignancies grow and metastasize to different regions of the body in response to different microenvironments. Reduced levels of E-cadherin lead to weakening of adherens junctions, which are important for cell-cell adhesion. This promotes the separation of cells from primary tumors. Conversely, studies have shown that N-cadherin promotes cell clustering and synchronized movement. Researchers propose that elevated levels of N-cadherin enhance the metastatic potential of tumor cells, overcoming the inhibitory effects of E-cadherin and allowing them to spread to distant sites. As a result, cancer cells exhibit aggressive behavior due to increased N-cadherin expression. Furthermore, the low levels of protective E-cadherin (found in 44% of cases) indicate the ongoing process of epithelial-mesenchymal transition (EMT) in the samples studied **(89)**.

TET enzymes and 5hmC epigenetic mark

A process called DNA methylation adds a methyl group to cytosine at position C5 to form 5-methylcytosine (5 mC). In cancer, DNA methylation typically inhibits the activity of tumor suppressor genes (TSGs), while demethylation increases the production of oncogenes. For a long time, DNA methylation was thought to be a permanent change. However, in 2009 it was shown that DNA methylation is a changeable process. By converting 5 mC to 5-hydroxymethylcytosine (5 hmC), the TET enzymes (TET1, TET2, and TET3) help to demethylate DNA. Thymine DNA glycosylase (TDG) oxidizes 5-hydroxymethylcytosine (5hmC) to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), which are then replaced by unmodified cytosines. Numerous studies have shown that gynecological malignancies such as Cervical (CC), Endometrial (EC), and Ovarian (OC) cancers disrupt TET protein activity and 5-hmC levels. Furthermore, we have documented the molecular pathways responsible for this perturbation and their potential utility as biomarkers in these specific cancers **(90)**.

Cytokines

To track the development and progression of endometrial cancer, women with irregular uterine bleeding can use cytokines such as IL-4, IL-8 and IL-6 as reliable indicators. Cytokine test results, including IL-8, IL-4 and IL-6 levels, have proven to be highly valuable in diagnosing endometrial cancer in individuals with abnormal uterine bleeding. Studies have shown that individuals with abnormal uterine bleeding (AUB) who have low levels of IL-4 and high levels of IL-8 are more likely to be at risk for Endometrial Cancer (EC). Incorporating IL-4, IL-8, CA125 and menopausal status improved the accuracy of endometrial cancer risk assessment. In addition, patients with Endometrial Cancer (EC) had elevated levels of IL-6 and IL-8, which were identified as independent risk factors for deep myometrial invasion. The combination of IL-6, IL-8 and monocyte counts provides a more accurate assessment of the likelihood of endometrial cancer with deep myometrial invasion. Scientists have conducted extensive research into the effects of inflammation on tumor formation and growth. This research has shed light on how inflammation can affect different stages of tumor development, including initiation, growth, progression and metastasis. They identify IL-6 and IL-8 as pro-inflammatory cytokines, while IL-4 is classified as an anti-inflammatory cytokine. IL-8 expression not only contributes to the development of EC, but also influences its progression and prognosis. Previous studies have shown a clear relationship between EC myometrial invasion and IL-8 levels. During myometrial invasion, IL-8 appears to play a role in regulating blood vessel formation in stage I uterine ECs.**(91)**.

IL-8

Illustrated the practicality of IL-8 readings as potential indicators of prognosis in type 1 EC. Regardless of other factors, the study linked higher levels of IL-8 in the blood before treatment to shorter periods of disease-free survival and overall survival. Furthermore, there is a clear correlation between elevated levels of IL-8 in the blood and the progression of diseases, including tumor growth, disease stage, and prognosis. Patients with breast, colon, ovarian, prostate, and melanoma cancers have observed this correlation **(91)**.

IL-4

IL-4, a powerful regulator of the immune response against tumors, has the ability to both promote and inhibit tumor growth. This is because IL-4 has immunosuppressive effects and can also prevent the formation of new blood vessels that support tumor growth. IL-4 is known to suppress the growth of kidney, colon and breast cancer cells. This effect also induces regression of certain tumor xenografts in mouse cancer models. Several studies have shown that IL-4 has anti-inflammatory properties and may reduce the likelihood of developing esophageal squamous cell carcinoma by suppressing inflammation. Conversely, some studies have shown a positive correlation between elevated levels of IL-4 in the bloodstream and cancer progression. However, there is a paucity of research on the function of IL-4 in EC. In addition, variations in the IL-4 gene also play a critical role in determining its intricate involvement in malignancies, thus requiring further comprehensive investigation **(91)**.

The decrease in the anti-inflammatory cytokine IL-4 and the increase in the pro-inflammatory proteins L-6 and IL-8 in EC helped to comprehend the complex connection between inflammation and cancer. Thus, these alterations could function as indicators for monitoring the development and advancement of endometrial cancer in women with abnormal uterine bleeding (AUB). Multiple studies have demonstrated the critical role of additional cytokines in EC diagnosis and treatment. The tumor is able to avoid immune responses with the help of anti-inflammatory cytokines such as IL-10, TGF-β, IL-1Ra, and IDO. They create an immunomodulatory atmosphere that efficiently inhibits the immune system. Pro-inflammatory cytokines, including IL-6, IL-8, IL-31, and IL-33, stimulate the growth of tumors and enhance their resistance to apoptosis. As a result, cytokines have become critical focal points for EC identification and management **(91)**.

EIF4G2

During the current research, we investigated the role of the non-canonical translation factor EIF4G2 in the development of endometrial cancer in both human patients and cell lines. EC cells lacking EIF4G2 were found to have reduced sensitivity to taxol and radiation, which are commonly employed therapeutic agents in the clinical treatment of EC. Also, when EIF4G2 was turned off, markers like CD133, CD44, and ALDH1A1 were found in more cells. These markers, commonly known as cancer stem cells (CSC), are associated with aggressiveness. Taking away EIF4G2 changed the transcriptome and proteome of the sorted cell population in a big way, which suggests a fundamentally different cell phenotype. Furthermore, this population exhibited notable resistance to both chemotherapy and radiotherapy. The treatment resistance is consistent with the elevated ALDH1A1 expression at both mRNA and protein levels. ALDH1A1 overexpression was found to be essential for the development of resistance to Paclitaxel in EC cells cultured as spheroids in a laboratory setting. In summary, the data indicate that a decrease in EIF4G2 expression, as shown in EC, would have a major negative impact on clinical prognosis. This study found that lower levels of the EIF4G2 protein in EC tumors are linked to a worse prognosis and higher recurrence rates, especially in people with Grade 2 tumors. This aligns with the previously documented varied correlation of EIF4G2 with different forms and phases

of cancer. Generally, we regard tumors classified as Grade 2 EC as low risk and do not require aggressive treatment. However, in certain cases, these tumors display clinical signs similar to larger Grade 3 tumors, necessitating appropriate treatment. EIF4G2 shows potential as a reliable prognostic indicator for distinguishing between less aggressive and more aggressive Grade 2 cancers **(92)**.

PRT4165

The activity of RING1A/B has only been linked to autophagy through the AMBRA1 protein. In endometrial cancer cells, PRT4165 modulates the expression of many genes involved in the autophagy pathway. PRT4165, a small molecule, inhibits the two E3 ligase paralogs RING1A and RING1B, thereby preventing H2A ubiquitination in cells.

H2A histone ubiquitination can be completely stopped by PRT4165, even when RING1 or RNF2 are the ones doing it. Our study showed that administration of PRT4165 in Ishikawa cells led to an increase in the LC3B form and a decrease in p62, both of which are commonly recognized as markers of autophagy. When a cell undergoes autophagy, it converts free LC3-I in the cytoplasm to lipidated LC3-II (LC3B), which is the active form. The amount of LC3-II can serve as an indicator of the extent of autophagy in cells. P62, a protein that binds to ubiquitin and LC3, regulates the formation of protein aggregates and is eliminated during autophagy. Both transcriptional regulation and post-transcriptional degradation regulate the intracellular concentration of p62 throughout the autophagy process. Inhibition of autophagy leads to accumulation of p62, whereas initiation of autophagy results in a decrease in p62 levels. It has been suggested that alterations in autophagy may have a significant impact on cancer. However, the precise role of autophagy in carcinogenesis is uncertain. Researchers hypothesize that autophagy not only inhibits the development of cancer cells, but also stimulates tumor growth. However, the exact role of autophagy in cancer development is uncertain. Researchers hypothesize that autophagy not only inhibits the development of cancer cells, but also stimulates tumor growth. Autophagy has the ability to induce cell death. Autophagosomal structures can serve as precise scaffolds to induce apoptosis or necroptosis. PRT4165 reduces the viability of endometrial cancer cells and Ishikawa cells are more sensitive to inhibitors. However, co-administration of PRT with either Lys05 or HCQ results in predominantly antagonistic effects. Therefore, this particular combination does not appear to be a favorable approach for anticancer therapy. The inhibitor induces changes in the expression of ATG genes and exhibits anticancer activity by inducing either autophagy or apoptosis. However, the specific effect of the inhibitor varies depending on the cell type **(93)**.

5. Conclusion

There is a significant decrease in the 5-year survival rate related to the fact that 33 percent of EC patients are misdiagnosed until the disease has progressed to advanced stages and 67 percent of patients are diagnosed with early-stage disease at initial presentation. In addition, endometrial biopsies are typically obtained through invasive procedures and rely on pathologic evaluation for diagnosis. In summary, there is a clear need to improve this diagnostic procedure to promote early detection of EC while making it less intrusive for patients and more cost-effective. Although numerous studies have attempted to develop biomarkers with potential clinical utility, none have made it to actual clinical use. There are now only a handful of accepted markers that are sensitive and specific, but lack the diagnostic power that would be ideal. It is more accurate to say that relying on a single indication increases the rate of misdiagnosis of endometrial cancer. It is possible to improve diagnostic efficiency by combining different markers for diagnosis. Serum tumor markers are helpful in diagnosing the disease because they are non-invasive, stable, and repeatable. More research is needed to better understand tumor markers, develop more accurate tumor markers, and discover ways to combine tumor markers for early diagnosis.

6. Declarations

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Ethical Considerations

None.

Authors' Contributions

Each author participated in data analysis, drafting, and revising of the manuscript, and consented to assume responsibility for all aspects of this project.

Conflict of Interest

The authors declare that they have no conflict of interest.

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