Editorial

Unopposed Estrogen and Endometrial Carcinogenesis: Current Concepts

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Introduction

Endometrial carcinoma represents the sixth most frequently diagnosed malignancy affecting the female genital tract globally.[1] In 2020, approximately 417,000 new cases were identified worldwide, accompanied by an estimated 97,000 related deaths.[2] Across Europe, the burden of disease remains substantial, with projections indicating 124,874 newly diagnosed cases and 30,272 deaths in 2022.[3-5] The incidence of endometrial cancer continues to increase, largely driven by demographic aging and the rising prevalence of obesity. Over a woman's lifetime, the risk of developing endometrial cancer is estimated at around 3%, with a median age at diagnosis of 61 years.[6] Notably, the global incidence has risen by approximately 132% during the past three decades, underscoring the expanding impact of key risk factors, particularly obesity and population aging.[6]

Prevalence estimates vary substantially between countries. Although high-income countries report a greater incidence of disease, low- and middle-income countries bear a disproportionate mortality burden relative to incidence, indicating unequal access to timely diagnosis and effective treatment. Advanced age is an independent prognostic factor associated with more aggressive tumor characteristics and poorer oncologic outcomes.[7]

Bokhman proposed a dualistic model in 1983 that classifies endometrial carcinoma into two distinct clinical types, which has since formed the basis for understanding its pathogenesis.[8] This estrogen-dependent subtype (Type I endometrial carcinoma) accounts for nearly two-thirds (65%) of cases and predominantly affects obese premenopausal or perimenopausal women with prolonged unopposed estrogen exposure.[8] This subtype is often preceded by endometrial hyperplasia and is typically well to moderately differentiated (grade 1–2), with superficial myometrial invasion and a favorable prognosis, reflected by an approximate five-year survival rate of 85%.[8]

Advances in molecular pathology have rendered this dichotomous classification overly simplistic for modern clinical practice.[9] Integration of histopathological findings with molecular data indicates that the majority of tumors classified as type I are endometrioid carcinomas, typically harboring mutations in CTNNB1, PIK3CA, KRAS, and PTEN frequently exhibiting microsatellite instability.[9] Tumors categorized as type II are predominantly serous carcinomas and are characterized by TP53 mutations, loss of p16 and E-cadherin expression, amplification of c-erbB2, and marked chromosomal instability, consistent with their more aggressive biological behavior.[9] Further refinement through the molecular classification proposed by **The Cancer Genome Atlas (TCGA)** has identified four distinct molecular subgroups with different prognostic implications. Consequently, the contemporary approach to endometrial carcinoma is no longer based solely on morphology, but also incorporates the tumor's genetic profile.

Despite the ability of molecular classification to stratify risk and guide therapy, the concept of **unopposed estrogen** remains fundamental in explaining the pathogenesis of most endometrioid carcinomas. Chronic estrogen exposure without adequate progesterone

 DOI: 10.24198/obgynia.v9i1.1105

counterbalance promotes persistent endometrial proliferation, increases the likelihood of accumulating genetic mutations, and ultimately leads to malignant transformation. Therefore, this concept continues to serve as an essential foundation for prevention strategies focused on controlling of metabolic risk factors, including obesity, metabolic syndrome, and insulin resistance.

Risk Factors

The development of endometrial carcinoma is influenced by multiple factors, predominantly associated with prolonged estrogen exposure without adequate progesterone opposition. Excess estrogen exposure may arise from endogenous factors, such as a greater lifetime number of menstrual cycles and nulliparity, as well as exogenous factors, including the use of estrogen-only menopausal hormone replacement therapy and tamoxifen.[10]

Nulliparous women have an approximately 2–3 times higher risk of developing endometrial carcinoma compared with multiparous women.[11] Nulliparity increases the risk of endometrial cancer through a higher number of menstrual cycles resulting from the absence of pregnancy and lactation, leading to prolonged and uninterrupted estrogen exposure.[12] Polycystic ovary syndrome (PCOS) also plays a significant role through chronic anovulation, which results in estrogen dominance without progesterone antagonism, thereby increasing the risk of endometrial hyperplasia and malignant transformation.[13] Women with PCOS have an approximately 2,7-fold higher lifetime risk of developing endometrial cancer compared with those without PCOS.[13]

Later age at menopause further prolongs estrogen exposure to the endometrium. Menopause occurring after the age of 52 years is associated with an approximately 2.4-fold increased risk compared with menopause before the age of 49 years.[11] In addition, estrogen-only therapy in postmenopausal women increases the risk of endometrial cancer by four- to eightfold, with risk rising in proportion to the dose and duration of use.[11] The addition of progestin significantly reduces this risk. Tamoxifen, widely used as adjuvant therapy for breast cancer, is also associated with an approximately twofold increased risk of endometrial cancer, particularly with long-term use.[10,11]

Obesity represents a dominant risk factor across all age groups. Analyses from multiple studies indicate that women with a body mass index (BMI) ≥35 kg/m² have more than a 5.57-fold increased risk at <50 years of age and a 4.68-fold increased risk at ≥50 years of age compared with women with a normal BMI.[14] This association is attributed to increased aromatization of androgens to estrogens in adipose tissue and insulin resistance, both of which stimulate endometrial proliferation.[14]

Overall, biological and epidemiological evidence strongly supports the concept that estrogen dominance without progesterone antagonism is the principal pathogenic mechanism in endometrial carcinoma. The effects of multiple risk factors are cumulative; women younger than 50 years with four or more risk factors have nearly a ninefold increased risk, whereas those aged 50 years or older have an approximately fourfold increased risk. More than half of endometrial cancer cases can be explained by a combination of metabolic and reproductive factors, highlighting weight control, prevention of metabolic disorders, and reproductive health education as key strategies to reduce the rising incidence of this disease.

Table 1. The Risk Factors of Endometrial Carcinoma

Risk Factor	OR
Nulliparity	2-3
Polycystic ovary syndrome (PCOS)	2.7
Menopause after 52 years of age	2.4
Estrogen-only therapy (without progestin)	4-8
Long-term tamoxifen use	2
Obesity (BMI ≥35 kg/m²), <50 years	5.5
Obesity (BMI ≥35 kg/m²), ≥50 years	4.6

Endometrial Hyperplasia

Endometrial hyperplasia is a pathological disorder defined by abnormal proliferation of the endometrial glands and supporting stroma within the uterine cavity.[15] Most cases are caused by estrogen exposure unopposed by progesterone, resulting in sustained proliferative stimulation of the glandular epithelium.[15] This process leads to morphological changes, including an increased number and size of glands, irregular glandular architecture, and variation in gland shape.[15] Endometrial hyperplasia represents a frequent etiology of abnormal uterine bleeding (AUB) and carries a risk of progression to endometrial carcinoma when inadequately treated. Histopathological evaluation reveals endometrial hyperplasia in approximately 10% of premenopausal women presenting with AUB, while endometrial carcinoma is detected in about 6% of postmenopausal women with uterine bleeding.[16] Furthermore, data from the Gynaecological Oncology Group reported that 42.6% of cases of atypical hyperplasia undergoing hysterectomy had specimens demonstrating concurrent endometrial carcinoma.[17]

Accurate clinical assessment of endometrial hyperplasia is further complicated by the existence of multiple classification systems that are still in use. In 2000, the International Endometrial Collaborative Group introduced the Endometrial Intraepithelial Neoplasia (EIN) system, which is based on quantitative morphometric assessment and clonality.[18] EIN represents a precancerous lesion characterized by an increased gland-to-stroma ratio (glandular crowding), the presence of cytologic atypia, and a lesion size greater than 1 mm.[18] This system categorizes lesions into three groups: benign (hyperplasia without atypia), premalignant (EIN), and malignant (well-differentiated endometrial adenocarcinoma).[18] The diagnosis of EIN was developed through correlations between histopathological features, clinical data, and molecular findings as predictors of cancer risk. In 2003, the World Health Organization (WHO) accepted EIN as an alternative to the 1994 WHO classification, although its application requires specific expertise or computerized analysis.[18]

In 2014, the WHO simplified the classification into two categories: hyperplasia without atypia and atypical hyperplasia.[19] This classification is based primarily on morphological criteria, with immunohistochemistry or molecular analysis used as adjuncts in challenging cases. The sensitivity and negative predictive value of atypical hyperplasia and EIN for detecting concurrent carcinoma have been reported to be comparable.[19] Non-atypical endometrial hyperplasia, which corresponds to benign lesions in the EIN system, carries a very low risk of progression to endometrial carcinoma (<1%) compared with the general population. In contrast, atypical hyperplasia is associated with a substantially higher risk of progression to cancer, estimated at 25–33% and reported to be as high as 59% in some studies. These findings underscore that atypical hyperplasia/EIN is a strong precursor of endometrial carcinoma and requires more

aggressive management than hyperplasia without atypia.

Clinical Manifestations

Endometrial carcinoma is most commonly diagnosed at an early stage, and the most frequent presenting complaint is postmenopausal bleeding.[20] However, not all cases of postmenopausal bleeding are caused by endometrial carcinoma; only about 5–10% are associated with malignancy. The risk of an underlying malignancy increases with advancing age, remaining below 1% in women younger than 50 years, rising to approximately 3% at 55 years of age, and reaching up to 24% in women over 80 years.[7] Consequently, the National Institute for Health and Care Excellence (NICE) recommends endometrial biopsy for women older than 55 years who present with postmenopausal bleeding.[21]

The diagnosis of endometrial carcinoma is established through histopathological examination of endometrial tissue.[22] Endometrial biopsy is usually performed when abnormalities or increased endometrial thickness are detected on transvaginal ultrasonography. In postmenopausal women, an endometrial thickness of ≥5 mm has a high sensitivity (approximately 96.2%) and a negative predictive value of 99.3%, making it a reliable tool to exclude endometrial carcinoma.[23] However, due to its relatively low specificity (around 51.5%), many patients still require further diagnostic evaluation.[23] In premenopausal women, transvaginal ultrasound is less accurate because endometrial thickness varies according to the menstrual cycle.

Diagnostic hysteroscopy allows direct visualization of the uterine cavity and targeted sampling of suspicious areas, particularly in cases with localized abnormalities or recurrent symptoms. Blind endometrial biopsy is also considered effective, although approximately 11% of cases may fail due to inadequate tissue sampling.[24] A one-stop clinic approach—combining ultrasound, hysteroscopy, and biopsy in a single visit—has been shown to expedite diagnosis and reduce delays in management.[25]

Preoperative assessment may include pelvic magnetic resonance imaging (MRI) to evaluate the depth of tumor invasion into surrounding structures. This modality is particularly important in patients being considered for fertility-sparing treatment or in those with high-risk disease. In cases of high-grade malignancy, computed tomography (CT) of the chest, abdomen, and pelvis is routinely utilized to evaluate the presence of distant metastatic disease. In addition, preoperative anesthetic evaluation is essential, especially in patients with severe obesity or significant comorbidities.

Pathogenesis

The pathogenesis of endometrial cancer is closely related to estrogen exposure that is not counterbalanced by progesterone (unopposed estrogen). Under normal conditions, the endometrium consists of glands and stroma that undergo cyclical growth, maturation, and shedding in response to the menstrual cycle. When estrogen acts without the influence of progesterone, excessive glandular proliferation occurs relative to the stroma, leading to hyperplastic changes.[26] Progression from the premalignant lesion of atypical endometrial hyperplasia to carcinoma occurs through stepwise genetic alterations, including mutations in PTEN, PIK3CA, and β-catenin, as well as loss of PAX2 expression, reflecting a gradual process of malignant transformation.[27]

Classically, endometrial cancer has been divided into two major groups based on clinical and pathological features. Type I tumors are low-grade endometrioid carcinomas that typically occur in younger women, often arise from hyperplasia, tend to grow more slowly, and are associated with a more favorable prognosis. In contrast, type II tumors comprise high-grade or non-endometrioid carcinomas, are more frequently observed in older women, are not necessarily preceded by hyperplasia, and exhibit more aggressive behavior with poorer clinical outcomes.[28]

Molecular Classification of Endometrial Carcinoma

Endometrial carcinoma represents a gynecologic malignancy with considerable biological heterogeneity and diverse clinical behavior; consequently, treatment decisions are informed not only by disease stage but also by multiple prognostic variables. The European Society of Gynaecological Oncology, the European Society of Pathology, and the European Society for Radiotherapy and Oncology have developed a prognostic risk stratification system that forms the basis for adjuvant treatment recommendations.[29] This system stratifies patients into five categories: low risk, intermediate risk, high–intermediate risk, high risk, and advanced or metastatic disease.[29]

Risk stratification was initially based exclusively on conventional clinicopathological parameters, without the incorporation of molecular classification. These parameters included FIGO stage, histological subtype, tumor grade, depth of myometrial invasion, and the presence of lymphovascular space invasion (LVSI), and were used to estimate recurrence risk and guide the selection of adjuvant therapies such as radiotherapy or chemotherapy.[29]

Advances in tumor biology have led to the increasing integration of the molecular classification proposed by the The Cancer Genome Atlas into prognostic risk stratification.[30] This classification divides endometrial carcinoma into four principal molecular subgroups—POLE-mutated, mismatch repair–deficient (MMRd), no specific molecular profile (NSMP), and p53-abnormal—each demonstrating distinct biological characteristics and clinical behavior that are frequently independent of histological type and tumor grade.[30]

Integration of molecular classification into the ESGO–ESP–ESTRO system has been shown to improve prognostic accuracy compared with the use of histopathological factors alone.[29] Tumors harboring POLE mutations may have an excellent prognosis despite high-grade morphology and can be categorized as low risk. In contrast, tumors with p53 abnormalities, including those that morphologically resemble endometrioid carcinoma, tend to exhibit aggressive behavior and are assigned to the high-risk group. Thus, molecular classification enables a more individualized therapeutic approach and reduces the risk of both overtreatment and undertreatment.[29]

Despite its superior prognostic value, implementation of molecular classification in routine clinical practice requires additional investigations, such as immunohistochemistry for mismatch repair (MMR) proteins and p53, as well as POLE mutation analysis. These tests increase diagnostic costs and are not uniformly available across all healthcare facilities.[29] Consequently, ESGO–ESP–ESTRO guidelines continue to maintain a risk stratification framework that can be applied with or without molecular data, allowing adaptation according to local resource availability.

Overall, the ESGO–ESP–ESTRO prognostic risk group system provides a structured framework for estimating recurrence risk and survival outcomes in endometrial cancer and serves as a foundation for determining the need for adjuvant therapy (table 2). The integration of

clinicopathological parameters with molecular characteristics reflects a paradigm shift toward a more individualized, precision oncology–based approach to the management of endometrial carcinoma.

Table 2 ESGO–ESP–ESTRO Prognostic Risk Groups in Endometrial Cancer[29]

Risk Category	Molecular Classification Unknown	Molecular Classification Known
Low Risk	Stage IA low-grade endometrioid carcinoma with negative or focal LVSI	Stage I–II POLE-mutated tumors without residual disease; Stage IA low-grade endometrioid carcinoma (MMRd or NSMP) with negative or focal LVSI
Intermediate Risk	Stage IB low-grade endometrioid carcinoma with negative or focal LVSI; Stage IA high-grade endometrioid carcinoma with negative or focal LVSI; Stage IA non-endometrioid carcinoma (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, or mixed histology) without myometrial invasion	Stage IB low-grade endometrioid carcinoma (MMRd/NSMP) with negative or focal LVSI; Stage IA high-grade endometrioid carcinoma (MMRd/NSMP) with negative or focal LVSI; Stage IA p53-abnormal or non-endometrioid carcinoma without myometrial invasion
High–Intermediate Risk	Stage I endometrioid carcinoma with substantial LVSI regardless of grade or depth of invasion; Stage IB high-grade endometrioid carcinoma regardless of LVSI status; Stage II endometrioid carcinoma	Stage I endometrioid carcinoma (MMRd/NSMP) with substantial LVSI regardless of grade or depth of invasion; Stage IB high-grade endometrioid carcinoma (MMRd/NSMP) regardless of LVSI status; Stage II endometrioid carcinoma (MMRd/NSMP)
High Risk	Stage III–IVA endometrioid carcinoma without residual disease; Stage I–IVA non-endometrioid carcinoma with myometrial invasion and no residual disease	Stage III–IVA endometrioid carcinoma (MMRd/NSMP) without residual disease; Stage I–IVA serous, undifferentiated carcinoma, or carcinosarcoma (MMRd/NSMP) with myometrial invasion and no residual disease; Stage I–IVA p53-abnormal carcinoma with myometrial invasion and no residual disease
Advanced / Metastatic	Stage III–IVA disease with residual tumor; Stage IVB	Stage III–IVA disease with residual tumor of any molecular type; Stage IVB disease of any molecular type

Management

The mainstay of treatment for endometrial carcinoma is surgical management consisting of total hysterectomy with bilateral salpingo-oophorectomy, with consideration of sentinel lymph node mapping or lymphadenectomy.[29,31] Minimally invasive surgery—either laparoscopic or robotic—has become the standard approach because it is associated with lower morbidity compared with laparotomy, resulting in shorter hospital stays and reduced risks of infection and thromboembolism.[29,31] In addition, surgical staging should be performed, including peritoneal biopsies and peritoneal fluid cytology, to assess for extrauterine spread that may not be detected on preoperative imaging. Intraoperative tumor spillage should be avoided, including the use of

morcellation.[29,31]

When surgery is not feasible, definitive radiotherapy may be considered. A combination of external beam radiotherapy (EBRT) and brachytherapy is recommended for high-grade tumors or those with deep myometrial invasion, whereas low-grade tumors may be managed with brachytherapy alone. If patients are not suitable candidates for either modality, systemic therapy, including hormonal therapy, may be considered.[29,31]

Fertility preservation may be considered only in selected patients with atypical hyperplasia/endometrial intraepithelial neoplasia (AH/EIN) or grade 1 endometrioid carcinoma without myometrial invasion and without genetic risk factors. These patients should be referred to specialized centers, undergo endometrial biopsy—preferably via hysteroscopy—and have the diagnosis confirmed by an experienced gynecologic pathologist. Assessment of disease extent should be performed using pelvic MRI or expert-performed ultrasonography. Patients must be informed that this approach is not standard therapy and requires strict adherence to close follow-up.[29,31]

In the low-risk group, adjuvant therapy is not recommended, including for patients with stage I–II POLE-mutated tumors.[29] In intermediate-risk disease, brachytherapy may be administered to reduce the risk of vaginal recurrence, but it can be omitted, particularly in patients younger than 60 years. Cases with p53 abnormalities confined to a polyp or without myometrial invasion generally do not require adjuvant therapy.[29]

In the high–intermediate risk group with pN0 status, brachytherapy is recommended, while EBRT should be considered in cases with substantial lymphovascular space invasion or stage II disease.[29] Chemotherapy may be considered, and in selected situations, omission of adjuvant therapy may also be acceptable. In high-risk disease, combined EBRT and chemotherapy, administered either concurrently or sequentially, represents the standard of care, with chemotherapy alone as an alternative option. Carcinosarcoma is managed as a high-risk carcinoma.[29]

In stage III–IV disease, debulking surgery, including resection of bulky lymph nodes, is recommended when complete macroscopic resection is achievable.[29] Primary systemic therapy should be considered when surgery is not feasible, and systematic lymphadenectomy is not recommended except for enlarged lymph nodes.[29] Unresectable primary tumors may be managed with definitive radiotherapy or neoadjuvant chemotherapy, with image-guided brachytherapy strongly recommended. Adjuvant chemotherapy following radiotherapy may be considered. In the presence of residual nodal disease, treatment options include combined chemotherapy and EBRT or either modality alone, with pelvic and para-aortic EBRT and a boost to involved lymph nodes.[29]

Through the integration of surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy, this multidisciplinary approach enables more personalized, evidence-based management across the full spectrum of disease—from low-risk to advanced-stage endometrial cancer—aiming for optimal disease control with minimal treatment-related morbidity.

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