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Review Article

# Endometrial cancer: Pathophysiology, diagnosis and management

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ABSTRACT

The most prevalent gynecologic disease is cancer of the endometrium, In the US, it is the fourth most prevalent malignancy in women after breast, lung, and colorectal malignancies. Despite a steady prevalence of sickness, during the past 20 years, the death rate has climbed by more than 100%. The risk factors of endometrial cancer includes unopposed estrogen therapy, early menarche, late menopause, tamoxifen therapy, nulliparity, infertility or inability to ovulate, and polycystic ovarian syndrome. Ageing, obesity, hypertension, diabetes mellitus, and genetic nonpolyposis colorectal cancer are additional risk factors.
This article presents an overview of endometrial carcinoma's epidemiology, prevention, diagnosis, therapy, and prognosis. Chemotherapy, radiation, surgery, and radiation therapy are all forms of treatment. Nonsurgical treatments can be used to treat endometrial hyperplasia with a low to moderate risk. The likelihood of survival is often determined by the disease stage and histology, with the majority of patients at stages I and II having a good prognosis. Endometrial cancer may be prevented in part by managing risk factors such obesity, diabetes, and hypertension.



## 1. Introduction

Uterine cancer can occur at the inner lining of the uterus (endometrium) or at the muscle layer of the uterus (myometrium). The two forms of uterine cancer include adenocarcinomas, which occur at the endometrium, and sarcomas, which arise from the myometrium.[1] Both forms are treated with different management options; however, adenocarcinomas are more prevalent, ranging from 70 to 80%. Endometrium cancer (EC) is a prevalent malignant condition; however, its prevalence varies by location.[2] It is the sixth most frequent type of cancer among women and the 15th most frequent cancer worldwide, usually referred to as womb or corpus uteri cancer. In 2020, there were about 417,000 brand-new instances of endometrial cancer. The majority of incidents of EC are observed in the United States, where incidences among women in the white and black populations respectively rise by 1% and 2.5% per year.[1,3]

The risk factors are less prevalent, and endometrial cancer is uncommon in undeveloped countries, yet overall mortality is considerable.[4] EC is the most prevalent in genital tract, colorectal, and breast cancers. The prevalence is 10 times greater in European countries than in less-developed nations. In the United States, EC is the most frequent gynecological cancer, and rates are still expanding, most likely as a consequence of the rising incidence of obesity.[5]

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## 2. Classification and Histopathology

Based on epidemiology, prognosis, and available treatment, the EC have been classified into two categories: type I and type II.[6] Endometrioid adenocarcinomas comprise the majority of type I tumors that are linked with unopposed oestrogen stimulation and frequently accompanied by endometrial enlargements.[7] In most cases, type II tumors are serous carcinomas that are estrogen-independent and develop from intraepithelial carcinoma. Type II cancers often have a worse prognosis than type I tumors as they are less well-differentiated. Since type I and type II EC exhibit different genetic alterations, these subtypes may have different aetiologies.[8]

Obesity and unopposed oestrogen treatment are recognized risk factors for type I EC that are linked to an alteration in the balance between oestrogen and progesterone exposures.[9] The risk of EC is diminished by using combination oral contraceptives (OCs), smoking, physical activity which are linked to progesterone-dominant states.[10] Early menarche, late menopause, and persistent anovulation, are the other contributing factors. The risk factors for type II tumors are not clearly understood, mostly because there haven't been enough cases in most epidemiologic investigations to examine these less frequent tumors independently.[5,11]

**Table 1:** A comparison between type-I and type-IIECs[9]

| Features | Type I | Type II |
|---|---|---|
| Prevalence | 80 to 90 % | 10 to 20% |
| Race | Common in White population | Common in black population |
| Major contributing factor | Unopposed estrogen | Postmenopausal women's |
| Molecular mechanism | Mutations of PTEN; K-ras up regulation; microsatellite alterations | overexpression of K-ras, p53 and HER2/neu |
| Prognosis | satisfactory | Not satisfactory |

### 2.1. FIGO Grading System

A grading system for EC was established by the International Federation of Obstetrics and Gynecology (FIGO) depending on cellular structurization and the extent of glandular differentiation.[12] According to FIGO, there are three forms of EC: Grade 1, which comprises 95% or more glandular squamous growth and up to 5% solid growth; Grade 2, characterized by 6–50% solid growth tissue; and Grade 3, which has less than half (50%) of the glandular divergence in the cancer tissue and more than 50% solid growth.[13]

Since that Grades 1 and 2 ECs have similar molecular and epidemiological characteristics, a new approach known as the "binary FIGO scheme" is currently preferred. This classification system places Grades 1 and 2 cancers in the "low-grade" group and Grade 3 tumours in the "highgrade" class. The FIGO grading system has drawbacks, as histomorphologic criteria are inadequate for figuring EC risk. The histological assessment derived from histopathological and immunochemical markers is often delayed as tumors need to be surgically removed, especially in high-grade ECs. Accurately identifying and classifying the many tumor forms is challenging.[14]

## 3. Pathogenesis

### 3.1. Genetic mutation

Genetic mutations associated to molecular signalling pathways plays important role in the aetiology of EC. This molecular pathways are hampered by circumstances including suppression of cell proliferation, apoptosis, elevation of telomere reverse transcription, and DNA synthesis abnormalities. Genetic Alteration in the phosphate and tensin homolog (PTEN), Catenin beta-1 (CTNNB1), Kirsten rat sarcoma (KRAS) viral oncogene homolog, AT-rich interaction domain 1A (ARID1A),and mismatch repair (MMR) molecular pathways have a substantial impact on ECs.

The most of carcinosarcomas, serous and high-grade endometrioid carcinomas possess mutations in human epidermal growth factor 2 (HEGF2), tumour protein p53 (TP53), cyclin-dependent kinase inhibitor 2A (CDKN2A), F-box/WD repeat-containing protein 7 (FBXW7) genes and Cyclin E1 (CCNE1). More precisely, 80–95% of ECs have altered phosphatidylinositol 3-kinase (PI3K)-PTEN–serine/threonine kinase (AKT)–mTOR pathways. PTEN mutation impairs protein function and raises AKT levels that have been phosphorylated. Alterations to PTEN frequently co-occur with phosphatidylinositol 3-kinase regulatory subunit 1 (PIK3R1) and phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) mutations.[15]

### 3.2. Hyperinsulinism

Hyperinsulinism is linked to diabetes mellitus or PCOS and plays a significant role in the development of cancer, as it amplifies mitotic activity in the glands and stroma by boosting IGF-1 activity. Excess insulin increases blood free testosterone levels by reducing the formation of the liver sex hormone-binding globulin (SHBG), enhances the production of androgens driven by LH and IGF-I, and increases serum IGF-I bioactivity by suppressing the development of IGF-binding proteins. Women with EC also have insulin binding sites expressed in their endometrial stroma. It follows that excessive insulin signalling can cause endometrial alterations that are pro-proliferative, pro-survival, and inflammatory changes similar to those caused by unopposed oestrogen.[16]

## 4. Risk Factors

The exact cause of EC is not yet clearly known. However, several contributing factors that are responsible for the predisposition to EC are discussed below.

### *4.1. Hormonal imbalance and overexposure:*

The ovaries release the two principal female hormones, oestrogen and progesterone; any alterations in the balance between these two hormones affect the health of the endometrium[17] similar to irregular ovulation patterns, a disease in which your body produces more oestrogen than progesterone might elevate the chances of developing endometrial cancer. The risk of endometrial cancer is raised with the use of only estrogen hormones after menopause.[18]

Long-term oestrogen exposure without progestin opposition is a significant predictor for type I EC. Both endogenous and exogenous oestrogen exposure are possible. Hormone replacement therapy is one form of exogenous oestrogen exposure. Obesity, estrogen-producing tumors, and persistent anovulation are all risk factors for endogenous oestrogen exposure.[19] The following are potential risk factors associated with excessive oestrogen.

### *4.2. Obesity*

Obesity is the primary risk factor for endometrial hyperplasia developing into malignant cancer. Obesity results in excessive peripheral conversion of androgens to estrone in adipose cells; this extra oestrogen promotes endometrial lining growth and frequently results in carcinogenesis. Moreover, prolonged anovulation is more prevalent in obese premenopausal women, which is also a major contributing factor for overexposure of estrogen.[18]

### *4.3. Hormone replacement therapy*

One aspect of exogenous oestrogen exposure is the replacement of oestrogen with medicine to manage menopausal symptoms. The prolonged, unopposed administration of single oestrogen increases the incidence of EC by 20 fold. However, concomitant use of progestin can lower the risk.[20]

### *4.4. Persistent anovulation*

EC risk is exacerbated by early menstruation (before age 12) and the delayed onset of menopause, which lead to an increase in the frequency of periods and thus overexposure to oestrogen.[21,22]

### *4.5. Tamoxifen therapy*

Tamoxifen therapy has been linked to an increased likelihood of developing EC even while it considerably lowers the risk of breast cancer and breast cancer recurrence. Tamoxifen is a selective oestrogen receptor modulator (SERM), which acts as an oestrogen antagonist in breast tissues but as an agonist in bone and endometrial tissues. Based on the majority of research, tamoxifen-using women had a 2-3 fold greater risk of developing EC than the general population. Tamoxifen-using women should be reminded to report any unusual vaginal symptoms; however, no additional monitoring is advised beyond standard gynecologic treatment.[23]

### *4.6. Age*

The majority of postmenopausal women who are diagnosed with EC are 60 years of age or older. Almost 85% of cases developing after the age of 50 and only 5% before the age of 40, the highest age-specific incidence occurs between the ages of 75 and 79. Juvenile premenopausal patients with EC frequently have higher body mass indices, anovulatory cycles, and/or a genetic vulnerability to the disease.[24]

### *4.7. Metabolic disorders*

The metabolic syndrome raises the risk of diabetes, heart disease, stroke, and other chronic disease conditions. Hypertension, increased triglycerides, reduced HDL cholesterol, obesity, and hyperglycemia are major contributing factors to all possible causes of the metabolic syndrome.[25] Epidemiologically, type 2 diabetes and hypertension have been linked to an increased risk of EC; however, the associated obesity is the hidden cause.[26]

### *4.8. Genetic Predisposition*

The majority of ECs are triggered by sporadic mutations; however, only around 5% of EC instances are due to genetic alterations. Lynch syndrome and Cowden syndrome are examples of genetic predispositions that result in EC.

Lynch syndrome**:** MLH1, MSH2, MSH6, or PMS2 are the four DNA mismatch repair genes. A germline mutation in any one of the four genes develops an autosomal dominant condition called Lynch syndrome. It is linked to a considerably higher lifetime risk of colorectal and ECs, as well as a higher risk of gastrointestinal, ovarian, pancreatic, ureteral, renal, biliary tract, brain, and small intestine cancers.[27]

Cowden syndrome: PTEN mutations are the defining feature of the autosomal dominant Cowden syndrome, which is associated with a 19% to 28% risk of EC after the age of 70 years.[28]

## 5. Diagnosis

Currently, there are no recognized screening tests for the rapid diagnosis of EC. Histologically, EC is typically detected in endometrial tissue. Endometrial biopsy, which is the primary and fundamental diagnostic tool for several

endometrial diseases, can be performed in a variety of ways.[29] A significant quantity and adequate quality of endometrial samples are needed for the proper diagnosis. The traditional dilation and curettage technique (D&C), Pipelle sampling, hysteroscopy, Mi-Mark cell sampler, biopsy using a Vabra Z-sampler, Gynoscann device, Isaacs cell sampler, Tao Brush, Endorette, etc. are a few of the methods used to collect endometrial samples. The preferred method presently is sampling with a small-bore endometrial biopsy outpatient device like Pipelle.[30,31]

## 6. Management of EC

### *6.1. Chemotherapy*

ECs are traditionally considered to be chemotherapy-resistant tumors that respond better to radiotherapy; however, chemotherapy does play a significant role in advanced, unresectable, metastatic cancer that has been surgically removed as well as recurring disease. Nonetheless, multimodal therapy is now advised for type II histologies since these tumors are regarded as being more malignant and having a greater prevalence of extrauterine malignancy.[32] Research into the use of chemotherapy in high-risk, initial-stage cancer is underway.Carboplatin with paclitaxel, cisplatin with doxorubicin, cisplatin, doxorubicin and paclitaxel, or carboplatin/paclitaxel/bevacizumab are examples of multiagent chemotherapy regimens that are approved. For advanced, metastatic, or recurrent EC, carboplatin plus paclitaxel is a more advantageous regimen to adopt due to its equivalent response rates and lower toxicity.[33,34]

### *6.2. Radiotherapy*

For women with a low risk of recurrence, adjuvant treatment is not advised. For women who had a high risk of recurrence, radiation treatment was typically advised for adjuvant therapy. The previous research shows that adjuvant radiation treatment reduces the incidence of recurrence in early-stage, intermediate-risk endometrial carcinoma, but it should only be used in individuals with high-intermediate-risk endometrial cancer.[35] Under the European Commission's standards of treatment, radiation is included as an adjuvant technique and comprises vaginal brachytherapy, whole pelvic diotherapy, and pelvic external beam radiotherapy (PEBRT).[36] Adjuvant radiation treatment (ART) relies heavily on risk classification. Individuals diagnosed with low-risk Stage I EC are not candidates for ART, as brachytherapy does not triumph over surgical care. While brachytherapy is advised for patients with intermediate-risk, high-risk, or high-intermediate-risk EC, the presence of lymphovascular space invasion (LVSI), which necessitates the use of external beam radiation therapy (EBRT), is particularly significant for those patients.[37]

### *6.3. Immunotherapy*

In recent times, targeted medications have been developed largely due to molecular categorization. Although extensive research is being done on the PI3K/Akt/mTOR pathway, glucose metabolism, and the angiogenesis pathway, as of now there is no approved targeted therapy for this disease beyond hormone therapy.[38] Immune system cells and ECs both exhibit a variety of immunological checkpoints and biomarkers that can be used as potential tools in diagnostic testing, targeted therapeutic management, and diagnostic accuracy. The extreme overexpression of programmed cell death 1 (PD-1) is seen in endometrial cancer.[39] The PDCD1 gene produces the cell surface protein known as PD-1, which is mostly expressed on the surface of activated B and T lymphocytes.[40] By using the PD1 pathway, a negative feedback mechanism that regulates lymphocyte cytotoxicity, lymphocytes are able to avoid autoimmune responses.[41] Its primary ligand, PD-L1, is mostly found on antigen-presenting cells, such as macrophages, dendritic cells, and B cells. It is also detected on activated T cells and in a number of cancer cells. PDL1 is regulated by a variety of inflammatory cytokines, including IFN, LPS, IL-4, and IL-10. In tumors, PD-L1 expression has been abundantly detected. The up regulation of PD-L1 is attuned by CD8 + T cells and IFN$\gamma$. PD-L1 is expressed in 92% of endometrial cancers. For treating recurrent EC, immunotherapy using a PD-1 inhibitor in combination with an antiangiogenic drug has been reported to significantly increase patient survival. A translational Phase II study with NCT03367741 found that cabozantinib-nivolumab combination massively increased PFS. Atezolizumab, an IgG1 PD-L1 inhibitor, will be added to conventional treatment in advanced or recurring EC; the findings of this Phase III randomised placebo controlled study are anticipated in 2023.[42,43]

## 7. Conclusion

EC incidence rates and mortality risk are predominantly rising as a consequence of increasing obesity rates and the associated hyperinsulinemia. Because older women are more likely to die from their disease and the surgery, risk and benefit should always be carefully assessed. Especially in the older. EC and associated health conditions become more common in younger women, and they can be treated carefully to preserve fertility. Controlling this rise in risk and mortality largely depends on changes in lifestyle. Exercise and losing weight are essential for reducing the hyperinsulinemia that contributes to the development of EC. The backbone of the management of EC is surgery, with minimally invasive outpacing open surgery. Adjuvant and targeted therapeutic approaches are significant for monitoring EC and improving its overall prognosis yet do not reduce surgical intervention. Early presentation with postmenopausal bleeding assures that the majority

of endometrial malignancies are treated by hysterectomy. Sentinel lymph node biopsy and minimally invasive surgical staging offer a lower morbidity option to conventional surgical therapy without impacting oncological results. In individuals with a high or moderate risk of recurrence, adjuvant therapy decreases loco-regional recurrence.

In order to better and facilitate the lives of those affected by EC, there is an urgent need for comprehensive management based on the most recent data. Further research is needed to provide preventive strategies to high-risk women and to maximize survivorship since obesity presents difficulties for both screening and therapy. A novel perspective will surely develop as more findings continue to emerge. Current EC treatment recommendations will be strengthened by ongoing clinical trials, which will also improve present approaches. To have a better grasp of the molecular categorization and, consequently, of the risk stratification of EC, further research must be done.

## 8. Abbreviations

EC- Endometrial Cancer, FIGO- International Federation of Obstetrics and Gynecology, PTEN - phosphate and tensin homolog, CTNNB1- Catenin beta-1, KRAS- Kirsten rat sarcoma, ARID1A - AT-rich interaction domain 1A, MMR- mismatch repair, HEGF2- human epidermal growth factor 2, TP53- tumour protein p53, SHBG- sex hormone-binding globulin.

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