

ENDOMETRIAL CANCER: AN OVERVIEW OF EPIDEMIOLOGY, RISK FACTORS, AND PREVENTION STRATEGIES**Karan Sahu, Rashmi Pandey*, Rupali Bharati Sao, Sandip Prasad Tiwari****Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh India (492101)***Corresponding Author's E mail: rashmi.pandey@kalingauniversity.ac.in

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ABSTRACT

Endometrial cancer, the most common malignancy of the female reproductive tract, presents a significant public health challenge worldwide. This review provides a comprehensive overview of the epidemiology, risk factors, and prevention strategies associated with endometrial cancer. Epidemiologically, endometrial cancer predominantly affects postmenopausal women, with incidence rates varying across different geographic regions and ethnic groups. The increasing prevalence is attributed to factors such as aging populations, rising obesity rates, and lifestyle changes. Key risk factors include obesity, hormone replacement therapy, reproductive history, and genetic predispositions such as Lynch syndrome. The interplay between these factors, particularly the role of excess adiposity and hormonal imbalances, underscores the complexity of endometrial carcinogenesis. Additionally, lifestyle factors such as diet, physical activity, and the use of oral contraceptives play a crucial role in modulating risk. Prevention strategies are multifaceted, focusing on modifiable risk factors and early detection. Weight management and physical activity emerge as pivotal preventive measures, given their impact on hormonal regulation and metabolic health. Pharmacological interventions, including the use of oral contraceptives and progestins, have shown efficacy in reducing risk, particularly in high-risk populations. Furthermore, advancements in genetic screening and personalized medicine offer promising avenues for targeted prevention and early intervention in genetically predisposed individuals. Public health initiatives aimed at raising awareness, promoting healthy lifestyles, and ensuring access to screening and preventive services are essential components in reducing the burden of endometrial cancer. This review underscores the need for continued research into the etiological mechanisms and effective prevention strategies to address this growing concern.

Keywords: Endometrial cancer, epidemiology, risk factors, prevention, obesity.

INTRODUCTION

Endometrial cancer, a type of cancer that originates in the lining of the uterus, known as the endometrium, is the most common malignancy of the female reproductive system. This cancer predominantly affects postmenopausal women, though it can also occur in younger women, particularly those with certain risk factors. The endometrium is responsible for the monthly preparation of the uterus for potential

pregnancy, undergoing cyclical changes under the influence of hormones, primarily estrogen and progesterone. When the delicate balance between these hormones is disrupted, it can lead to abnormal cell growth and the development of cancer. The significance of endometrial cancer extends beyond its prevalence, as it poses considerable health challenges and impacts the quality of life for those affected ¹.

The global incidence of endometrial cancer is on the rise, a trend that has been attributed to several factors, including increasing obesity rates, aging populations, and lifestyle changes. Obesity, in particular, is a major risk factor due to its influence on hormonal balance. Adipose tissue, or body fat, can convert androgens into estrogens, leading to elevated levels of estrogen that are unopposed by progesterone, a scenario conducive to the development of endometrial hyperplasia and subsequent cancer. The link between obesity and endometrial cancer underscores the importance of addressing weight management as a key component of prevention strategies.

Apart from obesity, other significant risk factors include the use of hormone replacement therapy (HRT), particularly unopposed estrogen therapy, which increases the risk of endometrial cancer. Reproductive history also plays a role; women who have never been pregnant, who have experienced late menopause, or who have polycystic ovary syndrome (PCOS) are at higher risk. Genetic predispositions, such as Lynch syndrome, a hereditary condition associated with a high risk of several cancers, including endometrial cancer, further complicate the risk landscape. This genetic link emphasizes the need for genetic counselling and regular screenings for women with a family history of Lynch syndrome or other hereditary cancer syndromes ².

The significance of endometrial cancer is highlighted by its impact on morbidity and mortality. Early-stage endometrial cancer often presents with symptoms such as abnormal uterine bleeding, which can lead to timely diagnosis and treatment. When detected early, the prognosis for endometrial cancer is generally favorable, with high survival rates. However, advanced stages of the disease, where the cancer has spread beyond the uterus, are associated with significantly poorer outcomes. This disparity in prognosis based on the stage at diagnosis underscores the importance of early detection and the implementation of effective screening programs.

Current screening methods for endometrial cancer are limited, and there is no standardized screening program akin to those for breast or cervical cancer. As a result, most cases are diagnosed based on symptomatic presentation, particularly postmenopausal bleeding. This symptom-driven approach means that women and healthcare providers must be vigilant in recognizing potential warning signs and seeking

prompt medical evaluation. Developing more effective screening methods remains a critical area of research, with the goal of identifying endometrial cancer at an earlier, more treatable stage ³.

Prevention strategies for endometrial cancer are multifaceted, focusing on both modifiable and non-modifiable risk factors. Lifestyle modifications, including maintaining a healthy weight, engaging in regular physical activity, and adhering to a balanced diet, are fundamental components of primary prevention. These measures not only reduce the risk of endometrial cancer but also contribute to overall health and well-being. Pharmacological interventions, such as the use of oral contraceptives and progestins, have shown efficacy in reducing the risk of endometrial cancer, particularly among high-risk populations. Oral contraceptives, which combine estrogen and progestin, are believed to lower the risk by regulating the hormonal balance and reducing endometrial proliferation ⁴.

In addition to lifestyle and pharmacological interventions, the role of genetic screening and personalized medicine is increasingly recognized in the prevention of endometrial cancer. For women with a genetic predisposition, such as those with Lynch syndrome, regular screenings and proactive measures, including prophylactic surgery, may be recommended to reduce the risk. Advances in genetic research and the increasing accessibility of genetic testing offer promising avenues for identifying at-risk individuals and tailoring prevention strategies accordingly.

Epidemiology of Endometrial Cancer

Endometrial cancer is the most common malignancy of the female reproductive system, with significant variations in global incidence and prevalence rates. According to GLOBOCAN 2020, there were approximately 417,367 new cases and 97,370 deaths worldwide. The incidence is notably higher in developed countries, particularly in North America and Europe, where lifestyle factors such as obesity and hormonal imbalances are prevalent. In contrast, lower rates are observed in Asia and Africa, although increasing trends in these regions are anticipated due to changing lifestyles and increased obesity rates ⁵.

The incidence of endometrial cancer has been rising steadily in many parts of the world. In the United States, the incidence increased by about 1% per year from the early 2000s to 2020. Similar upward trends have been reported in Europe, linked to the growing prevalence of obesity, an aging population, and changes in reproductive patterns such as delayed childbirth and reduced parity. These factors contribute to prolonged exposure to unopposed estrogen, a key risk factor for endometrial cancer. However, mortality trends are more variable. Some high-income countries have seen stable or slightly decreasing mortality rates, attributed to improvements in early detection and treatment. In contrast, mortality

remains high in regions with limited healthcare access, reflecting disparities in diagnosis and treatment capabilities ⁶.

Significant regional differences in the epidemiology of endometrial cancer underscore the complex interplay of genetic, environmental, and lifestyle factors. In Western countries, high obesity rates are a major risk factor, as adipose tissue increases estrogen levels, promoting endometrial proliferation. In contrast, lower incidence rates in East Asia and Africa have been attributed to lower obesity rates, different dietary habits, and higher fertility rates. However, as globalization leads to lifestyle changes, these regions may see rising incidence rates. Additionally, differences in healthcare infrastructure and access significantly impact diagnosis and treatment outcomes across different regions ⁷.

Age distribution is a critical factor in understanding the epidemiology of endometrial cancer. The disease predominantly affects postmenopausal women, with the median age at diagnosis around 60 years. Approximately 75% of cases occur in women aged 55 and older, with incidence rates peaking in those aged 70-74. However, there is a concerning increase in incidence among younger women, particularly those under 50, likely linked to rising obesity rates and the prevalence of polycystic ovary syndrome (PCOS), which causes chronic anovulation and hyperestrogenism.

Demographic factors such as race and socioeconomic status also significantly influence the epidemiology of endometrial cancer. In the United States, Caucasian women have higher incidence rates compared to African American women, but African American women are more likely to be diagnosed at an advanced stage and have poorer survival outcomes. This disparity is attributed to a combination of biological differences, socioeconomic factors, and healthcare access issues. African American women are more likely to have aggressive histological subtypes, such as high-grade endometrioid, serous, and clear cell carcinomas, which have worse prognoses.

Pathophysiology of Endometrial Carcinogenesis

The endometrium is the inner lining of the uterus, playing a crucial role in the menstrual cycle and pregnancy. It undergoes cyclic changes influenced by hormonal variations, primarily estrogen and progesterone. The endometrium consists of two main layers: the functional layer, which sheds during menstruation, and the basal layer, which remains intact to regenerate the functional layer. Histologically, the endometrium is composed of glandular epithelial cells and a supportive stroma, with blood vessels intricately supplying the tissue ⁸.

Endometrial carcinogenesis refers to the process by which normal endometrial cells transform into malignant cells, leading to endometrial cancer. This process involves multiple genetic and molecular alterations that disrupt normal cell growth and regulation. The primary mechanisms of carcinogenesis in endometrial tissue include genetic mutations, hormonal imbalances, and molecular pathway disruptions.

One of the key genetic alterations in endometrial cancer is mutations in the PTEN gene, a tumor suppressor gene that regulates cell growth and apoptosis. PTEN mutations result in uncontrolled cell proliferation. Other notable genetic mutations involve the PIK3CA, KRAS, and ARID1A genes, contributing to oncogenic signaling and cellular transformation. Microsatellite instability (MSI) and mutations in mismatch repair (MMR) genes, such as MLH1, MSH2, and MSH6, are also observed, leading to genomic instability and accumulation of mutations ⁹.

Hormonal factors play a significant role in endometrial carcinogenesis. Prolonged exposure to unopposed estrogen, either endogenous (e.g., obesity, polycystic ovary syndrome) or exogenous (e.g., hormone replacement therapy), is a well-established risk factor. Estrogen stimulates endometrial proliferation, and without the counterbalancing effect of progesterone, it can lead to hyperplasia and subsequent neoplastic transformation. This hormonal imbalance underscores the pathophysiology of type I endometrial cancer, which is typically estrogen-dependent and presents as endometrioid adenocarcinoma ¹⁰.

Molecular pathways implicated in endometrial carcinogenesis include the PI3K/AKT/mTOR pathway, the Wnt/ β -catenin pathway, and the TP53 pathway. Aberrations in the PI3K/AKT/mTOR pathway, often due to PTEN or PIK3CA mutations, result in enhanced cell survival and growth. Dysregulation of the Wnt/ β -catenin pathway, frequently associated with CTNNB1 mutations, leads to abnormal cellular adhesion and increased proliferation. Mutations in the TP53 gene, more common in type II endometrial cancers (e.g., serous carcinoma), result in loss of tumor suppressor function and genomic instability.

Molecular and genetic factors are crucial in the pathogenesis and classification of endometrial cancer. Type I endometrial cancer is associated with hormone-driven mechanisms and mutations in PTEN, PIK3CA, and KRAS, while type II endometrial cancer is characterized by more aggressive behavior, higher grade, and frequent TP53 mutations. Additionally, Lynch syndrome, an inherited condition caused by germline mutations in MMR genes, significantly increases the risk of endometrial cancer, highlighting the importance of genetic predisposition ¹¹.

Risk Factors for Endometrial Cancer

Endometrial cancer, the most common gynecological malignancy in developed countries, has several well-established risk factors. These risk factors include hormonal influences, reproductive history, obesity and metabolic syndrome, genetic predispositions, lifestyle factors, use of medications, and comorbidities ¹².

Hormonal influences play a significant role in the development of endometrial cancer. Estrogen and progesterone are the primary hormones affecting endometrial cell growth. Unopposed estrogen exposure, where estrogen is not counterbalanced by progesterone, increases the risk of endometrial hyperplasia and subsequent cancer. This can occur in conditions such as polycystic ovary syndrome (PCOS), estrogen-producing tumors, or in postmenopausal women using estrogen-only hormone replacement therapy (HRT). Conversely, progesterone has a protective effect by counteracting estrogen's proliferative action on the endometrium.

Reproductive history significantly impacts endometrial cancer risk. Nulliparity (having no children) and early menarche (beginning menstruation at a young age) increase the cumulative exposure to estrogen, thereby raising the risk. Similarly, late menopause extends the duration of estrogen exposure, further increasing the risk. Each full-term pregnancy, which involves prolonged exposure to high levels of progesterone, provides a protective effect against endometrial cancer ¹³.

Obesity and metabolic syndrome are major risk factors for endometrial cancer. Adipose tissue converts androgens to estrogens, leading to higher levels of circulating estrogen in obese women. Additionally, obesity is often associated with insulin resistance and hyperinsulinemia, which can promote endometrial cell proliferation. Metabolic syndrome, characterized by a cluster of conditions including hypertension, dyslipidemia, and central obesity, exacerbates these risks by creating a pro-inflammatory and pro-estrogenic environment.

Genetic predispositions also play a crucial role in endometrial cancer risk. Lynch syndrome, an inherited condition caused by mutations in mismatch repair (MMR) genes, significantly increases the risk of endometrial cancer. Women with Lynch syndrome have a 40-60% lifetime risk of developing endometrial cancer. Cowden syndrome, another genetic disorder associated with mutations in the PTEN gene, also elevates the risk of endometrial and other cancers ¹⁴.

Lifestyle factors such as diet, physical activity, smoking, and alcohol consumption can influence endometrial cancer risk. Diets high in fat and low in fruits and vegetables may contribute to obesity and

thus increase risk. Regular physical activity helps maintain a healthy weight and reduce insulin resistance, thereby lowering risk. Smoking has a complex relationship with endometrial cancer; it is associated with a reduced risk due to its anti-estrogenic effect, but its harmful effects on overall health outweigh this benefit. Alcohol consumption has been linked to a slight increase in endometrial cancer risk, potentially due to its role in increasing estrogen levels.

The use of certain medications can affect endometrial cancer risk. Hormone replacement therapy, particularly estrogen-only regimens, significantly increases the risk. Combined estrogen-progestin therapy has a lower risk but still poses a concern. Tamoxifen, a selective estrogen receptor modulator used in breast cancer treatment, has estrogen-like effects on the endometrium, increasing the risk of endometrial cancer ¹⁵.

Comorbidities such as diabetes and hypertension are also associated with a higher risk of endometrial cancer. Diabetes, particularly type 2, is linked to obesity and hyperinsulinemia, both of which promote endometrial proliferation. Hypertension, often associated with obesity and metabolic syndrome, further exacerbates the risk.

Clinical Presentation of Endometrial Cancer

Endometrial cancer typically presents with a variety of symptoms and signs, with abnormal uterine bleeding being the most common. Postmenopausal bleeding is a particularly concerning symptom and prompts further investigation, as it is a hallmark of endometrial cancer. Premenopausal women may experience irregular, heavy, or prolonged menstrual bleeding. Other symptoms can include pelvic pain, which may indicate advanced disease, and in rare cases, an abnormal vaginal discharge that may be watery or blood-tinged. Less commonly, weight loss, fatigue, and difficulty or pain during urination or intercourse can also be signs of advanced endometrial cancer.

The staging and classification of endometrial cancer are crucial for determining the appropriate treatment and prognosis. The International Federation of Gynecology and Obstetrics (FIGO) system is widely used for staging. The FIGO staging system classifies endometrial cancer into four stages based on the extent of the disease: ¹⁶

Stage I: Cancer is confined to the uterus. Stage IA involves invasion of less than half of the myometrium, while Stage IB involves invasion of more than half.

Stage II: Cancer has spread to the cervical stroma but not beyond the uterus.

Stage III: Cancer extends beyond the uterus but is confined to the pelvic area. This includes invasion into the serosa, adnexa, vagina, or pelvic lymph nodes.

Stage IV: Cancer has spread to the bladder or bowel mucosa (Stage IVA) or to distant organs, such as the lungs, liver, or bones (Stage IVB).

The classification of endometrial cancer also includes histological subtypes, with the most common being endometrioid adenocarcinoma. Other subtypes include serous carcinoma, clear cell carcinoma, and carcinosarcoma, each with distinct pathological features and varying prognoses ¹⁷.

Diagnostic techniques for endometrial cancer involve a combination of imaging, biopsy, and hysteroscopy. Transvaginal ultrasound (TVUS) is often the first-line imaging modality used to evaluate the endometrium in women with abnormal bleeding. TVUS can measure endometrial thickness, with a thickness greater than 4-5 mm in postmenopausal women being suggestive of pathology. Additionally, ultrasound can detect other uterine abnormalities, such as polyps or fibroids.

Endometrial biopsy is the gold standard for diagnosing endometrial cancer. It is a relatively simple and minimally invasive procedure that involves sampling endometrial tissue for histopathological examination. This procedure can be performed in an outpatient setting. If the biopsy results are inconclusive or if there is a high suspicion of cancer despite a negative biopsy, a dilation and curettage (D&C) procedure may be performed to obtain a more comprehensive tissue sample ¹⁸.

Hysteroscopy is another valuable diagnostic tool that allows direct visualization of the uterine cavity. During hysteroscopy, a thin, lighted scope is inserted through the cervix into the uterus, enabling the physician to inspect the endometrial lining and obtain targeted biopsies of any suspicious areas. Hysteroscopy can be particularly useful in evaluating focal lesions that may not be adequately sampled by blind biopsy techniques.

Additional imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT) scans, can be used to assess the extent of the disease and guide treatment planning. MRI is particularly useful for evaluating the depth of myometrial invasion and the involvement of adjacent structures, while CT scans are often employed to detect distant metastases ¹⁹.

Prevention Strategies for Endometrial Cancer

Endometrial cancer prevention encompasses a range of strategies, including primary prevention through lifestyle modification, chemoprevention, screening programs, genetic counseling and testing for high-risk individuals, and public health initiatives and awareness programs.

Primary prevention focuses on lifestyle modifications that can reduce the risk of endometrial cancer. Weight management is crucial, as obesity is a significant risk factor for this cancer. Maintaining a healthy weight through a balanced diet and regular physical activity helps reduce estrogen levels, insulin resistance, and chronic inflammation, all of which are linked to endometrial cancer. A diet rich in fruits, vegetables, and whole grains, coupled with limited intake of processed foods and sugary drinks, can aid in weight management and overall health. Regular exercise, such as 150 minutes of moderate-intensity aerobic activity per week, is recommended to achieve and maintain a healthy weight ²⁰.

Chemoprevention involves the use of medications to reduce cancer risk. Hormonal contraceptives, particularly combined oral contraceptives (COCs), play a significant role in reducing the risk of endometrial cancer. COCs contain both estrogen and progestin, which together provide a protective effect by countering the proliferative action of unopposed estrogen on the endometrial lining. Long-term use of COCs is associated with a substantial reduction in endometrial cancer risk. Metformin, a medication commonly used to treat type 2 diabetes, has also shown potential in reducing endometrial cancer risk. Metformin improves insulin sensitivity and reduces circulating insulin levels, which may help prevent the development of endometrial cancer, especially in obese and insulin-resistant women ²¹.

Screening programs aim to detect endometrial cancer at an early, more treatable stage. However, unlike cervical cancer, there are no universally recommended screening programs for endometrial cancer in asymptomatic women due to a lack of evidence demonstrating efficacy and cost-effectiveness. Current guidelines recommend that women, particularly postmenopausal women, seek medical evaluation for any abnormal uterine bleeding. While transvaginal ultrasound and endometrial biopsy are effective diagnostic tools, their use in screening asymptomatic women is not routinely advised due to the low prevalence of endometrial cancer in this population and the potential for false-positive results ^{22, 23}.

Genetic counselling and testing are crucial for individuals at high risk of endometrial cancer due to inherited genetic conditions, such as Lynch syndrome and Cowden syndrome. Women with these conditions have a significantly elevated risk of endometrial cancer and can benefit from regular surveillance and preventive measures. Genetic counselling provides these individuals with information about their risk and options for risk reduction, including prophylactic surgery (e.g., hysterectomy) and close monitoring with annual endometrial biopsies or ultrasounds²⁴.

Public health initiatives and awareness programs play an essential role in the prevention of endometrial cancer by educating the public about risk factors, symptoms, and the importance of seeking medical evaluation for abnormal uterine bleeding. Awareness campaigns can encourage lifestyle changes,

promote weight management, and highlight the benefits of hormonal contraceptives and metformin in reducing cancer risk. Public health efforts can also focus on improving access to healthcare services, especially for underserved populations, ensuring timely diagnosis and treatment ²⁵.

CONCLUSION

Endometrial cancer, a prevalent gynecological malignancy, arises from complex interactions between genetic, hormonal, and lifestyle factors. The pathophysiology involves genetic mutations, hormonal imbalances, and disruptions in molecular pathways, leading to uncontrolled cell proliferation. Key risk factors include prolonged exposure to unopposed estrogen, obesity, metabolic syndrome, and genetic predispositions like Lynch and Cowden syndromes. The clinical presentation often features abnormal uterine bleeding, with staging and classification guided by the FIGO system to inform treatment and prognosis. Diagnostic techniques such as transvaginal ultrasound, biopsy, and hysteroscopy are essential for confirming diagnosis and assessing disease extent.

Prevention strategies emphasize primary prevention through lifestyle modifications, including weight management, healthy diet, and regular physical activity. Chemoprevention with hormonal contraceptives and metformin shows promise in reducing risk. While universal screening for asymptomatic women is not recommended, targeted surveillance for high-risk individuals, supported by genetic counseling and testing, is crucial. Public health initiatives and awareness programs play a vital role in educating the population about risk factors, symptoms, and the importance of medical evaluation for abnormal bleeding. By integrating these approaches, the incidence and impact of endometrial cancer can be mitigated. A comprehensive understanding of the disease's pathophysiology, risk factors, clinical presentation, and preventive strategies is essential for improving early detection, treatment outcomes, and overall patient care. Continued research and public health efforts are vital to further refine prevention, diagnostic, and therapeutic measures, ultimately enhancing the quality of life for women at risk of or affected by endometrial cancer.

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