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Research on Endometrial Cancer: Risk factors, Classification and Treatment

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Abstract. Endometrial cancer (EC) is one of the most common tumors of the female reproductive system. Its pathogenesis is complex, and the incidence tends to be younger, which seriously endangers women's health. Research has found that the calssification of EC is of great significance in clinical applications, including traditional types I (estrogen-dependent) and II (non-estrogen-dependent), as well as four molecular subtypes (POLE ultramutated, microsatellite instability hypermutated, copy number low, and copy number high). The risk factors affecting EC include genetic factors, obesity, menstrual irregularities, etc. In addition, significant progress has been made in the treatment of EC, with new breakthroughs in surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy, etc. This article discusses risk factors, traditional classification, molecular classification and treatments of EC, in order to provide reference for clinical research on EC.

Key words: Endometrial Cancer; Risk Factors; Classification; Treatments.

1. Introduction

Endometrial cancer (EC) is the 6th most commonly occurring cancer in women and the 15th most common cancer in the world. There were more than 417,000 new cases of endometrial cancer in 2020. Poland had the highest rate of endometrial cancer with 26.2 per 100,000 in women in 2020, followed by Lithuania with 25.4 per 100,000[1]. EC is a common cancer among women, usually diagnosed as postmenopausal women, and 14% of cases still occur in premenopausal women, with 5% of cases under the age of 40[2, 3]. In recent years, the incidence rate of EC has increased significantly, and the population that suffers from EC is gradually getting younger and younger.

In recent years, with the development of biomedical technology, research on EC has made great progress. Although its pathological mechanism is not yet clear, the analysis of its traditional and molecular calssification by researchers is of great clinical significance. Researches have found that multiple factors such as irregular menstruation, obesity, and genetics can all lead to the onset of EC. In addition, new breakthroughs have been made in treatment, whether it is traditional surgical treatment, radiotherapy and chemotherapy, or drug therapy. EC is very treatable with surgery includes total hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic or para-aortic lymphadenectomy as the primary treatment. More than 80% of women with endometrial cancer live for at least 5 years after their diagnosis. However, the cause of EC is unknown and there is still no effective treatment to treat recurrence and improve survival. Therefore, further research on EC is needed.

This article explores risk factors, traditional classification, molecular classification and treatment of endometrial cancer, in order to provide reference for clinical research and application of EC.

2. Risk factor

There are many factors affect the risk of developing EC, including obestity, hormone factors, menstrual cycles, ovarian tumors, endometrial hyperplasia, genetic factors, and so on(Table1).

Table 1. Risk factors associated with ECs.

Risk factors associated with ECs.
Obesity
Hormone factors
Excess estrogen exposure
Unopposed estrogen exposure
Reproductive factors including:
Menstrual cycles
Ovarian tumors
Endometrial hyperplasia
Genetic predispositions
Lynch syndrome
...

2.1 Obesity

Obesity is a strong risk factor for EC. As Body Mass Index (BMI) increases, the relative risk of EC also increases, especially when BMI is greater than 30 (Figure1). Obesity is also linked to hormone changes. Hormones are covered by adipose tissue to form estrogen, which can affect estrogen levels and increase her risk of developing EC[4]. In comparison with women who have a healthy weight, the incidence rate of EC is twice in overweight women (BMI 25 to 29.9), and more than 3 times in obese women (BMI > 30) [5].

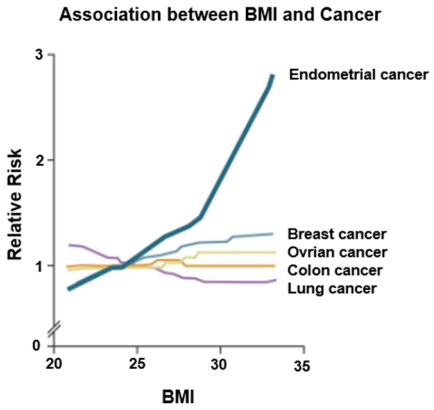

Figure 1. The association of obesity with cancer[6].

2.2 Hormone factors

Before menopause, the ovaries are the major source of the 2 main types of female hormones -- estrogen and progesterone. A shift in the balance of these two hormones toward more estrogen increases a woman's risk for EC. After menopause, the ovaries stop making these hormones, but a small amount of estrogen is still made naturally in fat tissue. Estrogen from fat tissue has a bigger impact after menopause than it does before menopause.

The placement of estrogen though the medication to control menopausal symptoms is an example of exogenous estrogen exposure. Unopposed estrogen replacement can increase the risk of developing EC by up to 20 fold, with duration of taking increasing risk. 8 This risk is significantly reduced with the concomitant use of progestoen [7].

2.3 Menstrual cycles

Having more menstrual cycles during a woman's lifetime raises her risk of EC. Starting menarche before age 12 and/or going through menopause later in life raises the risk. However, starting periods early is less a risk factor for women with early menopause. That’s mean late menopause may not lead to a higher risk in women whose menstruation began later in teensage.

2.4 Ovarian tumors

Sometimes abnormal vaginal bleeding is the first presentation symptom of EC. It may related to a certain type of ovarian tumor, the granulosa cell tumor, which often make estrogen. Estrogen made by one of these tumors isn't controlled like the hormones released by the ovaries, and it can sometimes lead to high estrogen levels. The resulting hormone imbalance can stimulate the endometrium and even lead to EC.

2.5 Endometrial hyperplasia

Endometrial hyperplasia is an increased growth of the endometrium. The most common type as mild or simple hyperplasia, has a very small risk of becoming cancer. It may go away on its own or after treatment with hormone therapy. If the hyperplasia is called “atypical,” it has a higher chance of becoming a cancer. Simple atypical hyperplasia turns into cancer in about 8% of cases if it’s not treated. Complex atypical hyperplasia (CAH) has a risk of becoming cancer in up to 29% of cases if it's not treated, and the risk of having an undetected EC is even higher.

2.6 Genetic factors

Lynch syndrome (LS; also called hereditary non polyposis colorectal cancer HNPCC): LS is an autosomal dominant syndrome and results from a defect in either the mismatch repair gene MLH1 or the gene MSH2. But at least 5 other genes can cause HNPCC: MLH3, MSH6, TGBR2, PMS1, and PMS2. An abnormal copy of any one of these genes reduces the body's ability to repair damage to its DNA or control cell growth. This results in a very high risk of colon cancer, as well as a high risk of EC. Women with this syndrome have a up to a 60% risk of developing EC at some point[4, 8]. (The risk for women in general is about 3%.)

3. Traditional classification and molecular classification

The pathogenesis of EC is unclear, and there are many factors that can induce the occurrence of EC. The classification of EC has important clinical applications and clinical significance. According to previous researches, there are many classification for EC including traditional classification and molecular classification and so on.

3.1 Traditional classification

EC has typically been categorized in to two broad classifications: type I(estrogen-dependent) and type II (non-estrogen-dependent) [9]. These two classifications are based on epidemiology, histopathology, prognosis, and treatment, as presented in[7, 10].

Type I EC takes account for the majority of diagnoses(85%), usually have lowe recurrence (20%), and an overall 5-year survival rate of 85% [10]. Type I EC is commonly in obese, younger and perimenopausal women, which typically has a good prognosis because they are low grade and often confined to the uterus at the time of diagnosis[7].Type I EC is related to the conditions that predispose to excess estrogen exposure, from either endogenous or exogenous sources. After binding with estrogen receptors, estrogen activates the transcription of cyclin related proteins for malignant transformation, or acts on metabolic related molecules or products such as insulin and insulin growth factor receptors, thereby activating signaling pathways such as PI3K/Akt or Ras/MAPK, leading to the occurrence of EC.

Another calassification as type II EC is definated as high grade and include high grade (FIGO grad 3) endometrioid tumour (20%), serouscarcinomas(10%) and clear cell carcinomas(<5%) [10, 11]. Mixed cell, undifferentiated, dedifferentiated, neuroendocrine, and carcinosarcomas (also known as malignant mixed Mullerian tumors or MMMT) also counted in to classification, but are much less common than serous and clear cell histologies. Type II EC is more aggressive and often presented in the advanced stage. So that, type II EC has a poor prognosis and have around 50% higher rates of

recurrence, with lower overall 5-year survival of 55% [10]. Generally, type II EC occurs in older women and are more common in African American women who can develop in a thin, atrophic endometrium. Type II EC is non estrogen dependent. It is not related to high estrogen levels and has no hormonal or metabolic disorders. The main causes are p53 mutations and abnormal dissemination of HER-2. The p53 gene, related to the onset of type II EC, is a tumor suppressor gene, and its wild-type causes cancer cell apoptosis, thereby preventing cancer transformation. It also has the function of helping cell genes repair defects. After the mutation of the p53 gene, it transforms from a tumor suppressor gene to an oncogene, losing its original physiological and tumor suppressor functions, and even promoting the occurrence of tumors. The HER-2 gene is a proto-oncogene that normally exhibits low levels of expression in human body, regulating cell growth and differentiation. Abnormal amplification of the HER-2 gene can lead to unrestricted tumor proliferation and malignant transformation by promoting the expression of cytokines such as IL-6, IL-8, etc .

3.2 Molecular classification

An integrated genomic analysis by The Cancer Genome Atlas (TCGA) resulted in the molecular classification of endometrioid and serous carcinomas into four distinct subgroups as POLE (ultramutated), microsatellite instability (hypermutated), copy number low (endometrioid), and copy number high (serous-like)(Table2) [12].

Table 2. Characteristics of TCGA molecular classification

Molecular Classification	Proportion	Characteristics
POLE (ultramutated)	7%	POLE exonuclease region hypermutation, high tumor mutation load, and good prognosis
microsatellite instability (hypermutated)	28%	Mismatch repair system defects, high tumor mutation load, sensitivity to immunosuppressive therapy, and average prognosis
copy number low (endometrioid)	39%	Low copy number, no special molecular features, sensitive to progesterone, and average prognosis
copy number high (serous-like)	26%	High copy number, P53 mutation as the main feature, sensitive to chemotherapy, and poor prognosis

3.2.1 POLE (ultramutated)

The copy number of POLE mutantions is stable and the supermutation rate is high, but the prognosis is great. DNA polymerase epsilon(polε) catalyzes the synthesis of leading chains during DNA replication and is involved in the regulation of cell cycle and DNA repair. POLE is the catalytic subunit of polε, which has not only DNA polymerase activity, can catalyze the formation and extension of replicated DNA strands, but also exonuclease activity, with correction function, can identify and repair mismatched base pairs [13].

3.2.2 Microsatellite instability (hypermutated)

DNA mismatch repair gene (MMR) can identify the wrong insertion or deletion in the process of DNA replication and recombination, and repair it, so the defect of MMR will lead to the instability of microsatellite. At the molecular level, microsatellite instability(MSI) also exhibits significant rates of mutation in PTEN (88%), PIK3CA (54%), PIK3R1 (40%), ARIDIA (37%), KRAS (35%) and RPL22 (33%), and there is a high level of tumor mutation load and a certain amount of tumor infiltrating lymphocyte [14]. In addition, MSI positivity occurs more frequently in high-level endometrial like endothelial cells than in low-level endothelial cells.

3.2.3 Copy number low (endometrioid)

Copy number low EC mainly corresponds to type I endometrial cancer, which is mainly caused by genome rearrangement and has a better prognosis than MSI EC. The mutation subtype exhibits significant rates of mutation in PTEN (77%), PIK3CA (53%), CTNNB1 (52%), ARIDIA (42%),

PIK3R1 (33%) and KRAS (16%). Research has shown that the most significant modules were found in low copy arrays, including CTNNB1, KRAS, and SOX17. Mutations in these three disrupted normal Wnt signal transduction, and abnormal activation of the Wnt signaling pathway can promote cell proliferation and survival without entering differentiation, leading to tumor development.

3.2.4 Copy number high (serous-like)

Copy number high EC mainly manifests as low mutation, also known as serous EC, which includes 94% EC, 62% mixed type cancer, 25% high-grade EEC, and 5% low-level EEC. The chromosome of this subtype is unstable and undergoes repeated amplification. With frequent TP53 mutations as a prominent feature, TP53 mutations have been found in up to 90% of serous cancers [15, 16]. High copy EC has many gene amplifications (or deletions), and although there is no POLE mutation and DNA MMR protein expression is normal, its prognosis is the worst among the four molecular subtypes.

4. Treatments of endometrial cancer

At present, the treatments for EC have made great progress include surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy, etc.

4.1 Surgery

The mainstay treatment for EC is surgery. The standard surgery should be included total hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic or para-aortic lymphadenectomy (LND) [17, 18]. Lymph node (LN) assessment is important because LN metastasis is one of the most important prognostic factors for EC [19, 20]. The 5-year overall survival (OS) for pelvic LN metastasis and para-aortic LN metastasis was found to be 57% and 49%, respectively.[21] The knowledge of LN status can also help the guidance of adjuvant chemotherapy and radiotherapy to reduce the risk of distant and local recurrence [21, 22]. Recent retrospective study also demonstrated that LND had no survival benefit in an intermediate-risk group [23]. A study trail known as the Endometrial Cancer Lymphadenectomy (ECLAT) Trial is evaluating the survival effects of comprehensive LND in the absence of bulky nodes in patients with EC stages IB to II (all histological subtypes) and stage IA endometrioid International Federation of Gynecology and Obstetrics (FIGO) grade 3, serous, clear cell, or carcinosarcomas, and the results are expected in 2023 [24, 25].

With the development of technology, minimally invasive surgeries, including laparoscopic and robotic surgeries, are now commonly performed. Compared to traditional surgery, minimally invasive surgery has obvious advantages such as less trauma, shorter hospital stay, less bleeding, and faster recovery.

4.2 Radiotherapy

Radiotherapy is one of the commonly used treatment methods for EC, and it is also the most common auxiliary treatment method for EC [26]. It mainly includes pelvic external irradiation and vaginal close range irradiation. According to the specific situation of the patient, preoperative radiotherapy, postoperative radiotherapy, and simple radiotherapy can be chosen. Among them, preoperative radiotherapy often uses vaginal brachytherapy, which helps reduce tumor volume, reduce intraoperative resection volume, and thus improve surgical safety. Postoperative radiation therapy is the main postoperative adjuvant treatment method for EC, which can effectively control local tumors and improve overall survival rate of patients, in which pelvic irradiation is more commin. Simple radiotherapy is generally suitable for patients with contraindications to surgery or those who have lost the opportunity for surgical treatment in the late stage. Pelvic external irradiation combined with vaginal close range irradiation is commonly used. Research has found that postoperative radiotherapy for advanced EC patients can significantly reduce their recurrence rate and improve patient survival rate [27].

4.3 Chemotherapy

Chemotherapy has gradually become one of the important treatment measures for EC, especially for advanced EC. It is also used for patients with high risk of recurrence after surgery to reduce the risk of recurrence. The main drugs include doxorubicin (A), cisplatin/carboplatin (P), paclitaxel (T), cyclophosphamide (C), etc [28]. Generally, a multi drug combination regimen is used, and commonly used chemotherapy regimens include AP (doxorubicin + cisplatin), APC (doxorubicin + cisplatin + cyclophosphamide), PT (cisplatin + paclitaxel), TC (paclitaxel + cyclophosphamide), etc. Chemotherapy drugs are often administered intravenously for systemic treatment. In addition, they can also be administered through pelvic artery, intraperitoneal perfusion, and other methods. Research has found that compared to patients with early EC treated solely by surgery, patients with early endometrial cancer who undergo combined postoperative chemotherapy have a higher disease progression free survival rate [29].

4.4 Endocrine therapy

Endocrine therapy is suitable for young non pregnant individuals with reproductive needs, patients with atypical endometrial hyperplasia, or late stage and recurrent patients with severe complications that cannot be operated on, and can prolong the survival time of patients. Endometrial hyperplasia and cancer are both associated with high estrogen levels in the body. Previous research has reported that the antagonism of progesterone combined with progesterone receptor on estrogen can be used for the treatment of endometrial cancer [30]. Therefore, the most commonly used medication for endocrine therapy is progesterone, represented by drugs such as megestrol acetate. It should be noted that long-term use of progesterone will have a certain impact on the cardiovascular system. In addition, patients with diabetes and liver and kidney dysfunction should also use it with caution.

At present, endocrine therapy has not been widely used for the treatment of endometrial cancer, and there is no unified and standardized treatment plan. It needs to be judged based on the specific situation of the patient when applying it.

4.5 Targeted therapy

Mutated genes and abnormal signaling pathways can both induce EC. Targeted therapy drugs mainly target targets that affect cell cycle, apoptosis, signal transduction, epigenetic modification, hormone receptor activation, and angiogenesis. With in-depth research on the mechanism of tumor occurrence, there are several recognized important pathways in EC, such as PI3K, mTOR, fibroblast growth factor receptor 2 (FGFR2), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), etc [31]. Targeted drugs targeting these molecular pathways can improve the prognosis of advanced or recurrent endometrial cancer. At present, the targeted drugs for EC include bevacizumab, PARP inhibitor, epidermal growth factor receptor inhibitor and trastuzumab and so on. Previous studies have found that the anti angiogenic drug bevacizumab is effective in treating EC, especially in late and recurrent stages. Adding bevacizumab to radiotherapy is beneficial for local control. As a new targeted therapeutic drug, bevacizumab has become an important adjuvant therapy for EC. Combined with chemotherapy can significantly improve patient survival and reduce the risk of tumor recurrence.

5. Discussion

Endometrial cancer is a common gynecological malignancy in women, with high incidence rate and mortality, and poor prognosis, and it cannot be prevented in advance, which poses a serious threat to women's health., Therefore, early detection, diagnosis and treatment, combined with good care, can effectively intervene in EC. The use of combined auxiliary examinations and rigorous nursing inquiry observation in clinical practice plays a crucial role in timely detection and early treatment of EC.

Surgical treatment is the main treatment method for EC. With the development of biomedical technology, surgery related to EC has evolved from traditional open surgery to minimally invasive

surgery such as laparoscopy, and even the emergence of robotic surgical systems. These new surgical methods bring new hope for the treatment of EC. Sentinel lymph node (SLN) localization is widely used in gynecological malignant tumors, especially in EC surgery. Compared with systemic lymphadenectomy, SLN has shorter surgical time, less trauma, and a lower incidence of surgical complications. However, currently SLN is mainly used for the treatment of low-level EC, while there is still controversy regarding the treatment of high-level EC. In addition to surgical treatment, combined with other auxiliary treatments can effectively improve the effectiveness of surgical treatment. Before or after surgery, corresponding adjuvant treatment methods such as endocrine therapy, radiotherapy, chemotherapy, etc. should be selected according to the specific situation of the patient. However, due to the different advantages and disadvantages of different treatment methods, multiple treatment methods can be combined to improve efficacy.

For women, they should develop healthy living habits, strengthen exercise, and reduce the incidence rate of EC by controlling obesity.

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