Relationship between change in female sex hormones and endometrial cancer: A review

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ABSTRACT: Endometrial cancer is an important disease because of its aggressive behavior. Additionally, prospective, randomized studies are either too difficult or impossible because of the small number of women affected. This review explores the differences between clear cell and endometrioid endometrial cancer. In addition, it uses available evidence to determine the best approach to management. Uterine activity is regulated by complex and mutual interactions among sex steroids, pituitary hormones and neurotransmitters. During the menopausal period, female sex hormones, especially estrogen play crucial role on cell division and apoptosis. Estrogen receptor α and p53 are transcription factors which play important roles in uterine cancer. p53 is a target of ERα and is responsible for the sensitivity of ERα-positive cancer cells to DNA damage. A number of randomized clinical studies have demonstrated that in postmenopausal women, because of insufficient estrogen levels, endometrial polyp incidence increases. So, the aim of the current paper was to investigate role of sex hormones in this phenomenon and subsequent strategies for minimize endometrial polyp occur in women.

KEYWORDS: Estrogen, Progesterone, Endometrial polyps, Women

1. INTRODUCTION

Endometrial adenocarcinoma represents 90% of tumors in the uterine body and is the fourth commonest neoplasm in Western society [1]. It is well established that a better understanding of the interplay between tumor-associated proapoptotic and antiapoptotic pathways may offer novel modalities of manipulating tumor cell growth and thereby improving the effectiveness of cancer treatment. Estrogen (17β-estradiol), apart from its role in reproduction, is also known to regulate the growth of hormone responsive tissues, eventually leading to carcinogenous progression [2]. Clinical and epidemiological studies correlate the prolonged estrogen treatment of post-menopausal women with an increase rate of cancer occurrences [3].

There are two distinct types of estrogen receptor (ER), the ERα and ERβ. Both share similar domain design, estrogen-binding affinity [4] and recognize the same DNA
sequence, the estrogen response element [5] in promoters of estrogen responsive genes [6]. The precise roles of ERα and ERβ on the proliferation and protection are still unknown.

The novel mechanism by which ERα, generally upregulated in cancer, suppresses the p53 function was discovered [7]. Various other studies have documented the delicate relationship of estrogen signaling and ERα with p53 [8-11]. Genetic support for this idea comes from the longstanding clinical observation that ERα-positive cancers express wild-type p53 whereas ERα-negative ones harbor mutant p53 [12]. These observations suggest that functional suppression of p53 is an important step in oncogenesis. In addition, to the functional regulation by protein–protein interaction, ERα and p53 regulate each other at the transcriptional level as well. p53 has been shown to be recruited to the ERα gene promoter resulting in increased transcription of ERα [13, 14]. On the other hand, ERα was reported to activate p53 transcription by binding to ERE half-sites within the promoter and knockdown of ERα decreases expression of p53 and its downstream targets [15]. Together, these observations suggest the existence of a feedback loop between ERα and p53.

2. ENDOMETRIAL CANCER FACTORS INCREASING ENDOMETRIAL CANCER INCIDENCE

Recent progress in the identification and characterization of normal and tumor stem and progenitor cells in murine and human tissue has triggered an intense effort to explore the mechanisms that regulate the balance between symmetric and asymmetric division of these cells [16]. p53 is a key tumor suppressor protein that serves as a sensor of cellular stress, and by integrating various signaling pathways, plays a central role in cellular processes such as cell cycle arrest, apoptosis, senescence, and differentiation. Since its discovery in 1970s, reports have been continuously emerging on multiple functions in normal and cancer cells. In addition to ability of p53 to initiate cell-cycle arrest and apoptosis, it has been shown to regulate metabolism, autophagy, and oxidative status of the cell [17]. Disabling p53 increases stem cell production by favoring symmetric division over asymmetric division, suggesting an important role for p53 in mammary tissue homeostasis and cancer formation [16]. In endometrial cancer, mutations of the p53 tumor suppressor gene have been found in 10 to 20% and more frequently in serous papillary and clear cell histologic types [18]. Although the use of the immunohistochemical expression of p53 as an indication of the level of p53 mutation presents problems in terms of false positivity and negativity [19], many clinical correlated studies of p53 immunostaining have reported. The abnormal expression of p53 has been associated with an advanced
stage and poor survival by several studies; although some have reported that the overexpression of p53 is not an independent prognostic factor in endometrial cancer [20].

![Diagram of p53 signaling](image)

Figure 1. A simplified model of some of the components of p53 signaling. Under normal conditions, the p53 pathway operates on ‘standby’ mode. Activation occurs in response to a variety of cellular stresses such as DNA damage and expression of activated oncogenes [21].

3. MECHANISM OF ACTION

Estrogen (17 β-estradiol), apart from its role in reproduction, is also known to regulate the growth of hormone responsive tissues, eventually leading to carcinogenous progression [22]. The ERα is a member of the nuclear receptor family of transcription factors that mediates the effect of estrogens through genomic (i.e., regulation of gene expression requiring specific co-regulator proteins) and non-genomic activities that results in the control of cell growth, survival, differentiation, apoptosis, and angiogenesis [23].

ERs are nuclear hormone receptors that act as transcription factors to regulate genes involved in growth, development, and differentiation of secondary sex characteristics, homeostasis, and metabolism and play a fundamental role in proliferation of cancer cells [24].

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It is well documented that ER and p53 have largely opposite roles in normal and cancer cells. ERα plays an important role in the onset and progression of breast cancer, whereas p53 functions as a major tumor suppressor. Previously reported that ERα binds to p53, resulting in inhibition of transcriptional regulation by p53 [7]. P53 is a target of ERα, modulates DNA damage-induced growth suppression in ER-positive cancer cells [15]. The p53 promoter is activated by estrogen, so any decrease in estrogen down regulates p53 levels.

4. RISK FACTORS FOR ENDOMETRIAL CANCER

We do not yet know what causes most cases of endometrial cancer. But we do know that certain risk factors are linked to this disease. A risk factor is anything that changes a person's chance of getting a disease such as cancer. Different cancers have different risk factors. A woman's hormone balance plays a part in most endometrial cancers, but other factors can also affect a women’s risk of this disease. Factors that increase the risk of endometrial cancer include:

- Estrogen therapy (without progesterone) to treat the symptoms of the change of life (menopause)
- Having more menstrual cycles, either from starting to have menstrual periods at an earlier age or going through menopause at a later age
- Being overweight or obese
- Ovarian tumors that make estrogen
- Polycystic ovarian syndrome
- Getting older
- Diabetes
- Having a mother or sister with endometrial cancer
- A genetic syndrome called hereditary nonpolyposis colon cancer (also known as Lynch syndrome)

5. STRATEGIES FOR TREATMENT

Endometrial cancer remains the most common genital tract malignancy in women in the worldwide. The incidence of endometrial cancer is approximately the same as the incidence of all other female genital tract malignances combined. By far, the most
The prevalent histological type is endometrioid endometrial cancer which represents over 50% of all histological types of endometrial cancer. Treatment for clear cell endometrial cancer incorporates surgery, chemotherapy, and/or radiotherapy, often in a multimodal combination. However, because of the rarity of this cancer, there are no prospective trials evaluating these treatments in a study population comprised solely of women with clear cell endometrial cancer [25]. Endometrial cancer may be treated with surgery, radiation therapy, chemotherapy or hormonal therapy. Depending on situation, treatment may recommend using a combination of treatments to treat cancer.

6. SURGERY

The grade of an endometrioid cancer is based on how much the cancer forms glands that look similar to the glands found in normal, healthy endometrium. In lower-grade cancers, more of the cancerous tissue forms glands. In higher-grade cancers, more of the cancer cells are arranged in a haphazard or disorganized way and do not form glands.

- Grade 1 tumors have 95% or more of the cancerous tissue forming glands.
- Grade 2 tumors have between 50% and 94% of the cancerous tissue forming glands.
- Grade 3 tumors have less than half of the cancerous tissue forming glands. Grade 3 cancers are called "high-grade." They tend to be aggressive and have a poorer outlook than lower grade cancers (grades 1 and 2).

The main treatment for endometrial cancer is an operation to remove the uterus and cervix (called a hysterectomy). When the uterus is removed through an incision in the abdomen, it is called a simple or total abdominal hysterectomy. If the uterus is removed through the vagina, it is known as a vaginal hysterectomy. Removing the ovaries and fallopian tubes, a bilateral salpingo-oophorectomy, is not actually part of a hysterectomy; it is a separate procedure that is often done during the same operation. In most women, however, comprehensive surgical staging is believed to be beneficial. In addition to providing prognostic information, accurate identification of metastatic uterine papillary serous carcinoma, or documentation of the lack thereof, allows for adjuvant therapy and surveillance to be appropriately tailored. Lymphadenectomy specifically may also provide a therapeutic benefit in women with high-grade endometrial cancer [26].

7. RADIOTHERAPY

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Treatment of endometrial cancer using radiotherapy alone, without surgical removal of the uterus has been reported. A retrospective review of endometrial cancer cases treated in a single large institution with radiotherapy alone was reported by Kupelian et al. [27]. Both pre- and post-surgery radiotherapy have been evaluated in the treatment of women with high risk endometrial cancer. Most of the reports in the literature regarding pre-surgery radiotherapy are single institution experiences. These studies did not find significant improvement in outcome with pre-surgery radiotherapy [28, 29]. Radiotherapy in the treatment of endometrial cancer is therefore primarily utilized in the post-operative adjuvant setting. Primary radiotherapy may be appropriate, however, in women whose medical status makes them unfit for surgery [25].

8. CHEMOTHERAPY

None of the chemotherapy studies that meet our inclusion criteria was done in a homogenous population consisting of clear cell endometrial cancer. A few retrospective studies that examined the role of chemotherapy in high risk (papillary serous and clear cell histology) endometrial cancer are available. In one such study, following surgical staging, patients with stage 1 to 4 endometrial cancer were given cisplatinum (50mg/m2), doxorubicin (50mg/m2) and cyclophosphamide (500mg/m2) [PAC] intravenously every 4 weeks for six cycles [25].

9. HORMONE THERAPY

It is well known that estrogen-based hormonal therapy increases the incidence of endometrial hyperplasia and cancer, but the addition of a synthetic progestin (estrogen-progestin therapy) prevents the development of endometrial cancer and might decrease the incidence of the risk of endometrial cancer, suggesting that progesterone is an important inducer of endometrial differentiation and an inhibitor of carcinogenesis mediated through estrogen. The advantages of hormones are that they are less toxic, less expensive, and easier to administer than parenteral chemotherapeutic agents, although chemotherapy is the standard antineoplastic treatment option for most women with advanced or recurrent endometrial cancers, based on the results of the Gynecologic Oncology Group (GOG) clinical trial 163 [30-33]. Gonadotropin releasing hormone (GnRH) agonist has been used in the management of various kinds of benign or malignant gynecological tumors [34]. It is mediated either through the direct effect of the GnRH-GnRH receptor pathway or
through down regulation of the GnRH receptor, producing a subsequent suppression of ovarian function and decrease of estrogen levels. Studies in the UK evaluated the efficacy of GnRH agonists in the management of recurrent endometrial cancer [35]. Treating the symptoms of menopause with estrogen is known as estrogen therapy or menopausal hormone therapy. Estrogen is available in many different forms such as pills, skin patches, creams, shots, and vaginal rings to treat the symptoms of menopause. Estrogen treatment can reduce hot flashes, improve vaginal dryness, and help prevent the weakening of the bones (osteoporosis) that can occur with menopause. Giving progesterone along with estrogen does not cause endometrial cancer, but it does still have risks. Studies have shown that this combination increases a woman's chance of developing breast cancer and also increases the risk of serious blood clots [36].

10. CONCLUSIONS

Abundant data from mechanistic, molecular pathological and transgenic animal studies support an important role for p53 in carcinogenesis. However, despite the convincing evidence implicating loss of function of p53 in neoplasia, mutations in the gene occur at a significantly lower frequency than in other common solid tumors. Over the past few years, knowledge of the upstream pathways regulating p53 activity has increased greatly and numerous transcriptional targets for p53 have been described.

References


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