Epidemiology of Endometrial Cancers and Uterine Sarcomas

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Introduction

Majority of the cancers that affect the body of the uterus originate in the endometrial lining and are endometrial carcinomas while uterine sarcomas arise in the muscle layer or supporting connective tissue of the uterus.

Globally, cancer of the body of the uterus, also known as corpus uteri cancer, is the sixth most common cancer among women. It has been estimated that in the year 2012, cancers of the corpus uteri accounted for 319,605 new cases. This accounted for 4.8 % of the total cancers among women with an age-standardized rate (ASR) of 8.3 per 100,000 women. There were an estimated 76,160 deaths due to endometrial cancers among women globally during 2012. The ASR for mortality due to endometrial cancer was 1.8 per 100,000 women accounting for 2.1 % of the total cancer deaths among women [1]. An estimated 49,560 new cases and 8,190 deaths due to cancer of the corpus uteri were expected to be diagnosed in the United States in 2013 [2].

In India, it is estimated that there were 12,325 new corpus uteri cancer cases in the year 2012. It ranked as the tenth most common cancer accounting for 2.3 % of all cancers among women with an ASR of 2.3 per 100,000 women and was responsible for an estimated 4,773 cancer deaths (1.5 % of total cancer deaths among women) [1].

Endometrial cancers are commonly diagnosed among postmenopausal women in their 60s. Several risk factors, mentioned below, have been implicated and studied in populations across the globe.

Age

The risk of endometrial cancer increases as a woman gets older. Most cases of endometrial cancers are found in women over 55 years of age. A few cases may occur before age 45 [3].

Risk Factors Related to Reproduction

Menstrual Factors

Early menarche is associated with 1.5–4-fold increased risk of endometrial cancer [4, 5]. Early menarche was identified as a risk factor for endometrial cancer among Turkish women [6] and late menarche as a protective factor in the European Prospective Investigation into Cancer and Nutrition (EPIC) [7]. Also, a reduction in endometrial cancer risk was observed in women with early menopause

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in the EPIC study [7]. Menstrual span of more than 39 years was associated with 4.2 times higher risk than one with less than 25 years [8].

Parity

Lower parity has been identified as a risk factor for endometrial cancer [6] and high parity as a protective factor [7]. Parity, age at first birth, age at last birth and time since last birth are highly correlated. It is difficult to separate their independent effects, although some studies have shown that late age at last childbirth reduces the risk of endometrial cancer [9, 10]. A study from Norway shows that the risk of endometrial carcinoma decreased significantly with increasing parity as well as with increasing age at first and last birth [11].

Pregnancy

Pregnancy acts as a protective factor [2]. Decreased risk of endometrial cancer was associated with cumulative duration of full-term pregnancy (FTP) [7].

Studies done so far report contradictory findings regarding the association between spontaneous and induced abortion with risk of endometrial cancer. In comparison with women reporting no induced abortion, the odds ratio (OR) of endometrial cancer was 0.6 in women reporting one and 0.4 in those reporting two or more induced abortion [10]. Certain conditions like Stein–Leventhal syndrome characterized by accumulation of incompletely developed follicles in the ovaries have been linked to endometrial cancer [12].

Oral Contraceptive Pills (OCPs)

Oral contraceptive use lowers the risk of endometrial cancer [7] with the lowest risk observed in women taking pills for a long time [2]. Combined oral contraception has shown to have a protective effect ranging from less than 5 years to greater than 15 years after cessation of the pills [13].

A nationwide, population-based case–control study among postmenopausal women aged 50–74 years in Sweden shows that oral contraceptives decrease the risk for endometrial cancer by 30 %, while progestin-only pills reduced the risk more markedly. Reduction in the risk was noticeable following 3 or more years of use for combined oral contraceptives and increased with duration of intake, reaching 80 % lower risk after 10 years of use. The protection remained for at least 20 years after cessation of use [14].

Intrauterine Devices

Theoretically, IUD use may decrease endometrial cancer risk through at least two mechanisms: Intrauterine devices act as protective factor through either one of the following mechanisms. IUDs may exert an intense inflammatory response leading to other lysosomal and inflammatory actions including recruitment of cells responsible for early elimination of abnormal, precancerous, hyperplastic endometrial epithelial cells. IUDs may induce changes in endometrial environment and endometrial response to hormones leading to more complete shedding of the endometrium, thereby decreasing chances of endometrial hyperplasia which is a known risk factor for endometrial carcinoma [15]. The meta-analysis by Beining RM found a protective association among women who reported ever use of an intrauterine device and risk of endometrial cancer [16].

Oestrogen-Related Risk Factors

Polycystic Ovarian Syndrome

Women with polycystic ovarian syndrome (PCOS) have a 2.7-fold increased risk for developing endometrial cancer, most of which are well-differentiated tumours with good prognosis. The link between PCOS and endometrial cancer involves prolonged endometrial exposure to unopposed oestrogen due to anovulation and endometrial progesterone resistance. This is accompanied by several gene abnormalities controlling progesterone action and cell proliferation [17].

Use of Unopposed Oestrogen Replacement Therapy

There is strong evidence suggesting oestrogen therapy unopposed by progesterone therapy is a major risk factor for endometrial cancer in women with an intact uterus, with the risk substantially increasing with current, long-duration use [18].

Many studies show that women taking combination of oestrogen–progesterone therapy exhibit a similar risk to women who do not take postmenopausal hormone therapy. However, a meta-analysis including ten case–control studies and one cohort study calculated a significant reduction of risk, with a relative risk (RR) of 0.44, 0.33 and 0.28 after 4, 8 and 12 years of combined oral contraceptive (COC) use, respectively. This was based on 33 time-dependent estimates of RR, adjusted for age, adiposity, parity and use of oestrogen replacement therapy [19].

It is now considered that risk varies with specific categories of oestrogen plus progestin usage, like the use of long duration of sequential progestins increases the risk, whereas decreased risk is observed for users of short-duration continuous progestins. Higher risk noted among thin to normal-weight women could indicate that there is an endogenous oestrogen threshold beyond which exogenous oestrogen exposures fail to increase the risk [18].

Hormone Replacement Therapy (HRT)

HRT use was identified as a risk factor for endometrial cancer among Turkish women [6]. Oestrogen-only HRT substantially increases the risk of endometrial cancer in women with a uterus [20].

Tamoxifen Therapy

Tamoxifen is one of the selective oestrogen receptor modulators (SERMs) and has primarily antioestrogenic properties in the breast tissue. However, it also has modest estrogenic activity and hence is found to be associated with endometrial carcinoma. There is an increasing risk of endometrial cancer associated with longer tamoxifen treatment, extending well beyond 5 years which does not diminish in follow-up to at least 5 years after the end of the last treatment [21].

In the Israel national breast cancer cohort, tamoxifen use was associated with elevated risks of uterine cancer incidence and mortality [22].

Endometrial Hyperplasia

A population-based study of women with endometrial hyperplasia, who remained at risk for at least 1 year, indicates that the overall progression risk for endometrial hyperplasia is three times higher than the average population risk of endometrial carcinoma. Fewer than 5 % of women with non-atypical or simple endometrial hyperplasia will experience progression to carcinoma, but 28 % of women with atypical hyperplasia will progress to carcinoma during 20 years [23].

Breast or Ovarian Cancer

Women diagnosed with breast cancer have a higher incidence of second primary cancers, particularly of endometrial cancer in women over 50 at diagnosis [24]. The granulosa–theca cell tumour of the ovary secretes oestrogen, which is uncontrolled, and this can sometimes lead to high oestrogen levels, leading to stimulation of the endometrium and resulting in endometrial cancer [2].

Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Syndrome or Lynch Syndrome

This disorder is commonly caused by a defect in either the gene *MLH1* or the gene *MSH2*. Defects in other genes can also cause HNPCC, namely, *MLH3*, *MSH6*, *TGBR2*, *PMS1* and *PMS2*, and increase the risk of endometrial cancer [2].

Lifestyle Factors and Other Non-communicable Diseases

Obesity

The risk of endometrial cancers has been recorded as high among obese women [18]. Endometrial cancer is twice as common in overweight women and more than three times as common in obese women.

Endometrial cancer is inversely related to the age at menarche and directly related to the age at menopause. Women with higher BMI tend to be younger at menarche than the ones with lower BMI, and conversely, women with higher BMI tend to be older at menopause than women with lower BMI [25]. Some studies suggest that the association between high BMI and endometrial cancer is stronger in postmenopausal women than in premenopausal women [26]. This indicates that obesity may have a continuous and cumulative effect on the development of endometrial cancer [27].

McCullough et al. in their prospective cohort found adult body mass index (BMI) as a strong predictor of risk. The use of oestrogen plus progestin postmenopausal hormone therapy modified the association. Among never users, risk was significantly linear across the entire range of BMI examined, but among ever oestrogen plus progestin users, the association was not significant. No difference in risk was observed according to the tendency for central versus peripheral fat deposition [28]. Weight gain and lack of weight stability are associated with risk of endometrial cancer [29].

Adiposity causes an increase in the frequency of anovulatory and irregular menstrual cycles, resulting in the reduction of luteal phase progesterone levels and ultimately increased exposure to unopposed oestrogen, thus explaining the increased risk of endometrial cancer in younger women [30, 31]. Obesity in postmenopausal women is associated with excess aromatization of androgen into oestrogen in the adipose tissue and lowered circulating sex hormone-binding globulin [32].

Sedentary Behaviour

Excessive sitting time is associated with an increased endometrial cancer risk, independent of the level of moderate–vigorous physical activity. Physical activity was clearly associated with reduced risk of endometrial cancer, with active women having an approximately 30–33 % lower risk than inactive women [33]. In addition, consistent overweight or obesity during adulthood was associated with greater risk of endometrial cancer than being overweight or obese only in later adult life.

High-Fat Diet

Percent energy from fat was associated with an increased risk of endometrial cancer, with saturated and monounsaturated fats being the main contributors of risk. A number of studies have concluded that diets rich in fat and poor in complex carbohydrates and fibre are associated with increased risk of endometrial cancer, while some studies have shown independent association between the two after adjusting for BMI and total energy intake [34, 35]. There was a stronger association between dietary fat and endometrial cancer among groups with higher circulating oestrogen levels [36].

Metabolic Factors

Hypertension

Hypertension was identified as a risk factor for endometrial cancer in studies conducted in women in Finland as well as in Turkey [37, 6].

Diabetes

The risk of endometrial cancer is high among women with diabetes. High glucose levels increases the risk by providing energy for proliferation of cells, generating free radicals causing damage to DNA and DNA repair enzymes [38, 39].

A meta-analysis of cohort studies suggests significant association between diabetes mellitus and increased risk of incidence of endometrial cancer but no increased risk of mortality due to endometrial cancers [40]. Another meta-analysis involving both case–control and cohort studies found diabetes to be statistically significantly associated with an increased risk of endometrial cancer with the risk estimates being somewhat stronger for case–control studies [41]. Diabetes was identified as a strong risk factor for endometrial cancer in a nationwide record-linkage study in Finland [37] and among Turkish women [6]. Diabetes was associated with a two-fold increased risk, and combination of diabetes with obesity and low physical activity was associated with a further increased risk for endometrial cancer [42].

Uterine Sarcomas

Uterine sarcomas are rare tumours that affect relatively younger women and account for less than 5 % of uterine malignancies [3, 43].

Uterine sarcomas fall under the broad category of soft tissue sarcomas and are extremely rare. They are generally considered as aggressive tumours with poor prognosis. They have further pathological subgroups with around 50 % being carcinosarcomas, arising in the endometrium [also known as malignant mixed Müllerian tumour (MMMT)]; followed by leiomyosarcoma (30 %), arising from the myometrial muscle; and the remaining comprising of endometrial stromal sarcoma (ESS) (10 %), arising in the endometrial stroma. Each group is known to harbour its own risk factors and clinical manifestations including response to treatment and prognosis [44]. Carcinosarcomas have the same risk factors as endometrial carcinomas [45].

The aetiology of uterine sarcomas has been investigated in only a few case–control studies due to the very low incidence of this disease. Overall, obesity, menopausal use of oestrogen plus progestin, oral contraceptives and tamoxifen use are associated with increased risks of uterine sarcoma, whereas cigarette smoking and parity were associated with a reduced risk [46].

Few factors that are known to change the risk of developing uterine sarcomas are as follows:

Race

The risk of uterine sarcomas is low among white or Asian women and about twice as common in African-American women. The reason for this increased risk is unknown [3].

Menarche and Menopause

Older age at menarche is inversely associated with uterine sarcoma risk (≥15 years vs. <11 years) [43]. Most of the uterine sarcomas occur after menopause [47].

Obesity

Obesity and increased body mass index (BMI) significantly increase the risk of uterine sarcomas [46].

Diabetes

History of diabetes increases the risk of uterine sarcomas [46].

Pelvic Radiation Therapy

Prior pelvic radiation therapy has been documented as an aetiologic factor in 10–25 % of uterine sarcomas. High-energy ionizing radiation used to treat some cancers can damage the cell DNA, thus increasing the risk of developing a second type of cancer. Uterine sarcomas are diagnosed from 5 to 25 years after exposure to the radiation [47].

Hormone Therapy

Estrogen–progestin therapy (EPT) was associated with an increased risk for uterine sarcomas in the nationwide cohort study on Finnish women more than 50 years of age [48]. Uterine sarcomas appear to be overrepresented among women in Israel who use tamoxifen [22]. An increased incidence of uterine sarcoma has been associated with the use of tamoxifen given either in treatment of breast cancer or to prevent breast cancer in women at increased risk [47–51]. Hence, patients on tamoxifen should have follow-up pelvic examinations and should undergo endometrial biopsy if there is any abnormal uterine bleeding [49–51].

Retinoblastoma Gene Changes

An increased risk of uterine leiomyosarcomas is noted among women born with an abnormal copy of the retinoblastoma gene [3].

In general, the endometrial stromal sarcoma and leiomyosarcoma had similar risk factor associations to those observed for all uterine sarcomas combined which are suggestive of an overlap in the biological mechanisms associated with the development of these tumours [46]. Overall, uterine sarcomas are considered a rare yet fatal uterine cancer subtype and tend to behave more aggressively having a poorer prognosis than endometrial carcinoma [43].

Conclusions

A major aetiologic pathway for endometrial cancers is exposure to oestrogen without cyclic exposure to progesterone. Most of the established risk factors for endometrial cancer appear to affect risk at least in part through this pathway. Increasing age, early menarche, larger menstrual span, lower parity, PCOS, unopposed oestrogen replacement therapy, use of tamoxifen, endometrial hyperplasia, women with breast or ovarian cancer and women with HNPCC or Lynch syndrome are at greater risk. The risk is also more among women with hypertension and diabetes. Pregnancy, use of combined oral contraceptive pills and intrauterine device act as protective factors. Physical activity is clearly associated with reduced risk of endometrial cancer. Consistent overweight or obesity during adulthood is found to harbour greater risk of endometrial cancer than being overweight or obese only in later adult life though the relation of body mass at different time periods in life and weight change over time to endometrial cancer risk are less well understood.

Key Points

1. Majority of the cancers that affect the body of the uterus initiate in the endometrial lining of the uterus and are called endometrial carcinomas.
2. Cancer of the muscle and supporting tissues of the uterus, known as uterine sarcomas, comprises less than 1 % of gynaecological malignancies and 2–5 % of all uterine malignancies.
3. The commonly identified risk factors of endometrial carcinomas are higher age, early age at menarche, late age at menopause, lower parity, polycystic ovarian syndrome, use of unopposed oestrogen replacement therapy, use of hormone replacement therapy, tamoxifen therapy, atypical endometrial hyperplasia, breast or ovarian cancer, hereditary nonpolyposis colorectal cancer (HNPCC) syndrome or Lynch syndrome, obesity, sedentary behaviours, high-fat diet and hypertension.
4. The protective factors for endometrial carcinomas are late menarche, early menopause, increased parity (Decreased risk of endometrial cancer was associated with cumulative duration of full-term pregnancy), use of oral contraceptive pills and use of intrauterine device.

5. The risk factors for uterine sarcomas are race (African-American), older age at menarche, postmenopausal status, obesity and increased BMI, prior pelvic radiation therapy, oestrogen–progestin therapy (EPT), tamoxifen therapy and women with retinoblastoma gene changes.
6. The aetiology of uterine sarcomas has been investigated in only a few case–control studies due to the very low incidence of this disease. Overall, obesity, menopausal use of oestrogen plus progestin, oral contraceptives and tamoxifen use are associated with increased risks of uterine sarcoma, whereas cigarette smoking and parity were associated with a reduced risk.

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