Risk Factors and Variations in Global Occurrence of Endometrial Cancer

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Abstract

Introduction: Endometrial cancer (EC), is one of the most common cancers but there are variations in occurrence, may be because of risk factors. It is more common in developed countries, four to five times higher in United States than in developing countries and Japan.

Objectives: Were to get information about risk factors and differences in occurrence of EC.

Materials and methods: Simple review of literature, studies, review, opinions related to risk factors and occurrence of EC was done to get the desired information.

Results: More than 3 lacs cases of EC were diagnosed in 2012 in US and EC was amongst first 5 most common cancers in women. Another study estimated nearly 44,000 new cases, 800 deaths in 2010. Annual incidence has been estimated at 10–20 per 100,000 women. It is amongst first four most common cancers, 6% of cancers in women in India. In US more than 40% cases of EC were attributed to excess body weight, lack of physical activity. Risk factors seem to be later age, nulliparity, infertility, early menarche, late menopause, obesity, diabetes, hypertension, unopposed estrogen therapy breast cancer with long-term Tamoxifen use, animal origin food, Metabolic syndrome,(obesity, hypertension, Insulin resistance, diabetes, dyslipidaemia) . Two types have been recognized Type I Adeno carcinoma, most common, sequlae of endometrial hyperplasia due to unopposed estrogenic stimulation, Type II, high risk histologic types, serous carcinoma, clear cell carcinoma, anaplastic carcinoma occurring in atrophic endometrium in older women. Gynaecological examination, transvaginal ultrasound, aspiration biopsy are recommended in mutation carriers of 30 to 35years. Reported protective factors are birth control pills, plant origin nutrients, dietary fiber, retinol, β-carotene and vitamin C, E.

Conclusion: Risk factors for occurrence of EC vary and because of such factors the occurrence varies. However risk factors may be present but do not cause cancer, many women with EC may not have any known risk factor. Even if there are risk factors, there is no way to know which factors were responsible, if et al. Research needs to continue.

Keywords: Endometrial Cancer; Variations; Risk Factors; Incidence

Introduction

There are global variations in the incidence of endometrial cancer (EC). EC has been reported four to five times less often in developing countries and Japan than United States. It was believed that EC occurred more often in developed countries, however more cases are being diagnosed in developing countries also. Because most of the cases are diagnosed in early stage, treated timely, mortality is prevented. Dobrzycka reported that 75% cases were diagnosed at early stage with the tumor confined to the uterus [1].

Objective

Objective of the review was to get information about variations in risk factors and incidence of EC.

Materials and Methods

Simple review of studies, reviews, opinions about risk factors for EC was done by available search engines like Up-to-date, PubMed, ERMED CONSORTIUM, Cochrane Library, Delnet, MedIND

Results

In its most recent report on World cancers international agency for research on cancers (IARC), reported around 76,000 estimated deaths due to EC each year, sixth cancer in women [2]. Unlike most cancers, the numbers of new cases of EC have risen in recent years, an increase of over

40% in the United Kingdom (UK) between 1993 and 2013 [3]. In the UK, 7,400 and in Europe, around 88,000 of EC have been diagnosed annually [4]. Asia saw 41% of the world's EC diagnosed in 2012, Northern Europe, Eastern Europe, and North America together contributed to 48% of cases [2]. EC was reported to be the most common gynecologic cancer in women with 49,154 new cases and 8911 deaths reported from the United States in 2012 [5]. Four to five times lower rates have been reported in low resource countries and Japan than US [6]. Arafa, et al. [7] Reported EC as the fourth most common cancer in women after breast cancer, colorectal cancer and lung cancer. Cramer and Dinkelspiel, *et al.* reported that in the US, EC was the most frequently diagnosed gynecologic cancer and the fourth most common cancer in women representing 6% of all cancers in women [8]. The US national cancer database Surveillance, Epidemiology and End Results (SEER) reported the incidence of EC 23.9 per 100,000 women between 2004 to 2008 higher in whites (24.8 per 100,000) compared to blacks (20.9 per100,000), Hispanic (18.9 per 100,000), or Asian/ Pacific Islander women (18.2 per 100,000) [9]. However, mortality was almost two fold higher in blacks than in whites (7.1 versus 3.9 per 100,000), may be due to a higher incidence of aggressive subtypes, as well as problems of access to and quality of healthcare. In some studies incidence of EC was estimated at 10–20 per 100,000 women and it was found to be increasing, making it the most common cancer of the female genital tract in the developed countries [10,11]. There are variations in the incidence, 12.9 per 100,000 women and a mortality rate of 2.4 per 100,000 women reported from developed and 5.9 per 100,000 women and mortality of 1.7 per 100,000 women from developing countries [12]. Approximately, 2–3% lifetime risk for EC has been reported [13]. Galaal, *et al.* reported that the lifetime risk of EC was 1.6% in western world, compared to 0.6% in developing countries may be due to the increase in the life span of women, or the investigative modalities or increase in risk factors [6]. The reasons seem to be much obesity in the developed countries, higher life expectancy, lower birth rates. A lot of research is needed. Stewart, Smotkin and Elshaikh reported that Northern Europe, Eastern Europe, and North America have the highest rates of EC and Africa as well as West Asia the lowest [2,14,15]. Ferlay reported that EC accounted for 4.8% of all cancers in women globally [16]. In India it has been reported to occur in 4.3 per 100,000 women, six times higher incidence in urban compared to rural women [3,16-18]. Significant increase in incidence of EC in urban registries from four metros of India has been reported, In Bangalore Registry, the Annual Percentage Change (APC) was 7.4% between 1986 and 2009 and Mumbai registry, 7.3% between 2005 and 2010 compared to 1.7% between 1982 and 2004 [19]. The increase in incidence was more in last five years than previous 22 years. EC was tenth leading cancer between1982-83, constituting 1.5% all body cancers in women with age adjusted rate of 1.9/ 100,000 women. Between 2008-2009, it became 6th most common cancer, constituting 4.2% of cancers and age adjusted rate (ARR) of 6.2/100,000 females. It accounted for 3.8% of body cancers in females in Chandigarh registry. Regional Cancer Centre (RCC), Thiruvanthanapuram reported 3.3%, in Mumbai it was 14th (1.9% of body cancers), Bangalore too 14th (2.4%), Chennai 13th (2%), Dibrugarh16[th] (1.4%) and Guwahati 14th (1.5%). Amongst all body cancers EC had the highest APC reported by Population Based Cancer Registry (PBCR) in India between 1982-83 to 2008-09 [19-20]. The population of India in general and that of the areas covered by cancer registries in particular, have displayed rapid changes in life styles, dietary practices and socio economic milieu which may be responsible for increase in EC. But more research is needed.

Types

Because of differences in risk factors, presentation, histopathology and response to therapy behavior EC cases have been divided into two types. Type IA deno carcinoma, the most common variety has been increasing, 80-85% typically occurring in association with obesity, complex endometrial hyperplasia. It has mostly low grade endometrioid histology with the cancer limited to the uterus with minimal invasion at diagnosis [21]. Type II EC is high-grade adeno carcinoma with the non-endometrioid histologies, serous carcinoma, clear cell carcinoma and anaplastic carcinoma, known to develop in the atrophic endometrium in older women. They commonly have early metastasis and most of the cases of relapses have been reported after Type II tumors [22]. There are distinctions between two groups on a molecular level too. Type I tumors commonly have PTEN, K-ras, and β- catenin mutations as well as microsatellite instability (MSI). Progesterone receptors are more likely to be found in significant numbers in these cancers. Type II cases typically have p53 mutations and HER2/neu amplification. Many risk factors have been identified for EC, early onset menstruation, obesity, nulliparity, late menopause, diabetes mellitus, hypertension, infertility, unopposed estrogen exposure and Tamoxifen.

Age

Most common risk factor for Type II cancers is later age [23]. Most cases of EC have been reported between 61-70 of years age. In India NCRP Bangalore, Delhi and Mumbai reported a significant increase in AARs between 45-54 years of age. Chennai reported an increase between 55-64 years of age [19]. However more studies are needed to know whether it is age or type of cancer. In another study Purdie reported majority of the women prior postmenopausal between 50 and 65years [24].

Women under 50 who developed EC often had risk factors such as obesity or chronic an ovulation. The average age of diagnosis in the US between 2005 to 2009 was 61 years, In another study 37.7% patients were of less than or equal to 50 years of age, range of 45 to 80 years with mean 55.5 years has been reported [6]. Yet another study revealed 13% women less than 50 years of age [6,25,26]. Bangalore registry had the mean age of EC, 56yearswith range of 30 to 80 years [27]. Colombo reported more than 90% of cases older than 50 years of age, with a median age of 63 years [24]. In UK and most of the European countries the incidence in older women (aged 60–79) increased by more than 40% between 1993 and 2007 [24]. Mean age of women with EC reported from Pakistan was 56.7 +12.4 years, Another study revealed 59.4 +10.5 years in women from Japan [28,29].

Nulliparity and Infertility

A positive association between nulliparity and EC was first recognized in the 1950s [30]. Studies since then have found nulli parous women having two to three times the risk of developing EC compared with parous women. Infertile women have been found to have 3.5 times higher risk than fertile women [31]. Risk of EC was found to have inverse relationship with parity, reduced risk with each pregnancy. One study revealed a relative risk of 0.3 for women who delivered their last child after the age of 40 [32]. There are reports of parity and infertility independently contributing to EC risk, parity being the predominant risk factor [33].

Obesity

Obesity has long been recognized as an important risk factor for EC, because of to increased exposure of the endometrium to endogenous estrogen in many ways, a 5-fold increase in the rate of peripheral conversion of estrogen precursors to active estrogen, increased 16α- hydroxylation of estrone and increased serum free estrogen due to decreased serum sex binding globulin [34].

Obese women may have lower circulating levels of sex hormone binding globulin, leading to increased steroid hormone activity, alterations in the concentration of insulin-like growth factor and its binding proteins, and insulin resistance (IR), all may contribute to the increased risk of EC. Brinton, *et al.* reported that women with a body mass index (BMI) of $32kg/m^2$ or greater were four times as likely to develop EC compared with a BMI of less than $23kg/m^2$ [35]. Women with a BMI of 35 kg/m^2 or greater had six times risk than those of normal MBI. Swanson also reported that heaviest women were at the highest risk of developing EC [36].

Researchers reported that a patient's weight and weight gain throughout adult hood were most predictive of risk of developing EC [37]. There are reports of disease at younger age, 45years with higher BMI. A meta-analysis of 19 prospective studies, including over three million women revealed that each increase in BMI of $5kg/m^2$ incurred a significantly increased risk of developing EC [38]. As a risk factor for EC, obesity has been reported to account for 17–46% of all cases [39]. A recent study found that overweight women had twice the risk of developing EC, Obese women carried four to five times the risk compared to normal-weight women [40]. The length of the time, a woman remains over weight also affected her chances of developing EC and age at disease also. Lu, *et al.* reported that patients who gained 35% or more weight in their 20s were diagnosed with EC 10years earlier than women who reported a 5% or less weight change in their 20s. In the same study, women who remained overweight throughout their adult hood were five times more likely to develop EC than their normal-weight counterparts [40].

Some authors have reported a trend towards better survival in the overweight women compared with the more slender women [41]. Others reported poorer survival in women with higher BMI [42]. There are reports of no difference too [43]. Mauland, *et al.* reported more Stage I and II cancers diagnosed in obese women with a trend towards improved prognosis in these patients [44].

Accordingly, severely obese women were more likely to present with stageI disease (77 versus 61 percent), low grade histology (44 versus 24 percent) or a less aggressive histologic subtype (endometrioid: 87 percent versus serous or clear cell: 75 percent) [45]. In a study the risk of dying from EC among those with the highest BMI (≥40 kg/m^2) was 6.25-fold higher than that of normal weight women (BMI 18.5 to 24.9 kg/m^2) [46]. It is not clear why this occurs may be due to continued stimulation of metastatic cells by endogenous estrogen or due to obesity-associated conditions, like diabetes or cardiovascular disease. Gruenigen reported that morbidly obese women had a greater risk of mortality due to causes other than their cancer [42]. Epidemiological studies revealed more than 40% of incidence attributed to excess body weight and lack of physical activity. Alterations in endogenous hormone metabolism were thought to provide the main links between risk of EC excess body weight and physical inactivity [47]. A lot of research is still needed.

Early Menarche and Late Menopause

Since decades early menarche has been reported to be associated with more chances of EC at younger age. Early menarche and late menopause contribute to long years of menstruation with possibilities of more an ovulatory cycles. This leads to longer menstruation span, (the number of years between menarche and menopause excluding pregnancy) which has been reported as risk factor because of longer lifetime exposure to endogenous estrogen due to an ovulatory cycles and deficient progesterone [48]. However some researchers have reported that it may be secondary to more accurate recall of menarche age in younger women [24]. As such late menopause has been consistently associated with increased risk of EC. MacMahon reported that women who underwent menopause around the age of 52 had twice the risk of developing EC compared to women who underwent menopause under the age of 49, others have also reported the same [30,49]. Bajracharya reported that if a woman was nulli parous, obese and reached menopause at 52 years or later, she had a 5-fold increase in the risk of EC [50].

Endogenous and / Or Exogenous Unopposed Estrogen

Clinical findings have been consistent with unopposed estrogenic stimulation without adequate opposition by a progestin. The role of unopposed estrogenic stimulation in endometrial carcinogenesis is so strong that any factor that mediates this effect is believed to be a risk factor. Many researchers have found an increased risk of EC among women receiving unopposed estrogen replacement therapy for menopausal symptoms [24,51]. The long era woman used estrogen replacement, the higher her risk of developing EC. Though it is generally thought to require 2–3 years of unopposed estrogen for increased risk of EC, some studies have found upto 40% increase in risk over baseline only after one year estrogen use. The increased risk of EC persisted after cessation of un estrogen

use, though the exact time required for the risk to decrease to the level of non estrogen users was unclear. Some authors have reported a relatively rapid decrease in risk of cancer after cessation of HRT while others have found an increased risk upto 10years after cessation of estrogen use [52]. Higher dose of estrogen increased the risk of developing EC. Common reasons for excessive endogenous estrogen are chronic an ovulation or excessive endogenous conversion of adrenal precursors to estrone and estradiol by adipose cells in obese women. Aromatase has been reported to be aberrantly expressed in endometriosis which promoted the growth of EC by increasing estrogen. Studies have revealed that a postmenopausal woman's increased risk of developing EC had linkage to higher circulating estrogen, androgen and lower sex hormone binding globulin levels, compared to unaffected controls [53]. However in such women there was preponderance of well-differentiated, localized tumor, with less chance so myometrial invasion and metastasis, and a 5-year survival rate of well over 90% [54]. This explained high mortality from EC did not increase when the incidence increased in 1960s and 1970s. This was in agreement with the theory that Type I tumors were estrogen driven with a favorable prognosis with reports of EC in hormone users less aggressive than nonusers [54]. But others have found an increased risk of metastasis [55]. The increase in relative risk of EC with conjugated estrogen has been reported in comparison to women who never used hormones. Continuous combined therapy had no risk for Type I tumors. Estrogen from fat tissue is believed to have a bigger impact after menopause than before menopause. Oestrogen producing ovarian tumours have been reported to increase the risk. Granulosa cell tumors were most likely to be associated with EC, 5-10 showed EC and 25-50% endometrial hyperplasia [56]. EC that were associated with G-stromal CT were further reported to be well differentiated and diagnosed in early stage, Beyond 40 years atypical hyperplasia was commonly observed in cases of GCT [57,58]. So researchers recommended that endometrial sampling should be performed in symptomatic women at least from 40 years of age. However endometrial sampling gives-lower yield in asymptomatic women of less than 40years.

Diabetes Mellitus and Hypertension

Given the strong association between obesity and Type 2 diabetes, and that many patients with EC were obese, the relationship between diabetes and EC was often confounding. Many researchers have since established Type 2 diabetes to be an independent risk factor for developing EC. With persistent elevated risk of developing EC when either adjusting for weight or studying non obese women [59]. Obese diabetic women have the highest risk of developing EC. Many studies have revealed a relationship between IR and EC [60]. In a study in non-diabetes women 35% cases of EC had IR. In another study 66% of patients were found to have IR at the time of diagnosis of EC and half of the women with IR did not have diabetes [61]. Observations linking blood pressure, glucose metabolism, and IR to EC came mostly from retrospective studies which provided less conclusive results because of self-reported disease history and anthropometry or an absence of adjustment for body mass. Increased association of hypertension with EC has been reported in obese women [59]. With reports of positive as well as no association also. Elisabete's did not find any effect of hypertension after adjustment for BMI. However, they did observe an effect of hypertension among obese women, compatible with the hypothesis that metabolic syndrome,(including obesity, hypertension and IR) was a risk factor for EC [62].

Breast Cancer

History of breast cancer was a risk factor for development of EC in women treated with Tamoxifen, also in part because both diseases shared some common risk factors (obesity, nulliparity). Some researchers have suggested that women with breast cancer had an increased risk of having serous EC.

Einbeigi reported that EC may also be associated with a personal or family history of breast cancer [62,63]. In a case-control study of women with EC, women with serous histology were more likely than those with endometrioid histology to have history of breast cancer (19 versus 3 percent) [64]. The real reasons of association are unclear. Serous tumors are typically not estrogen responsive in contrast with most breast cancers.

Tamoxifen

The first case of EC linked to Tamoxifen was reported in 1985 [65]. Many researchers have confirmed the relationship. The risk of developing EC increased with longer Tamoxifen use and higher cumulative dose [66]. There were conflicting data regarding the prognosis for patients who developed EC while using Tamoxifen. It has also been argued that long-term Tamoxifen sures had a poorer prognosis of EC [67]. In postmenopausal women, the increased risk of EC with Tamoxifen was established however for premenopausal women, there was lack of evidence. Further the risk of EC not only increased with increased use of Tamoxifen which persisted after discontinuation of Tamoxifen [68]. But studies on this subject have failed to show a difference in survival between Tamoxifen users and nonusers [69]. There was some evidence to suggest that long-term Tamoxifen use (generally defined as 60 months or more) was associated with high risk histologic types of EC, such as grade 3endometrioid, serous, and clear cell [70]. Though no screening for EC was recommended in patients taking Tamoxifen, a high index of suspicion has been suggested for women on Tamoxifen with complaints of abnormal vaginal bleeding.

Genes, Family History

Most cases of EC have reported to be sporadic, however accumulation of EC in families occurred in around 5% of cases [71]. Inherited genetic mutations have been linked to significant number of EC. Lynch syndrome (LS) also known as HNPCC accounted for 2-5% of all EC [72]. Up to 5% of EC is associated with Lynch syndrome Type II (Hereditary Non-polyposis Colorectal Syndrome).

Women with this syndrome have a 30-71% lifetime risk of developing EC [73]. Lynch, *et al.* reported increased EC, in LS II and was the primary basis for distinction from LS [74]. In ILS hereditary NPCC, the women were at high risk of developing EC with incidence of 3201:2000 to 1:660 [75]. Approximately 5% of EC cases can be attributed to an inherited predisposition. The majority of these cases have been reported to be secondary to LS which accounted for two to five percent of all EC. With Lynch syndrome, the lifetime risk of EC was 27-71% compared with 2.6percent in the general population. The mean age at diagnosis of EC with Lynch syndrome was 46 to 54 years, compared with a mean age of 61 years for other women [76]. The majority of LS-associated EC had endometrioid histology and presented at an early stage with low grade similar to sporadic EC I. History of colorectal or ovarian cancer in first degree relatives has been associated with an increased risk of EC especially at a younger age (55 years), although no candidate genes have been identified consistently [77]. In Cowden syndrome caused by a germ line mutation in the PTEN gene women had a 5-10% life time risk of developing EC [78]. BRCA1 mutations and EC linkage was first reported in 1999 [79]. By multinational cohort study involving 11,847 BRCA1 mutation carriers researchers reported a significant increase in the risk of EC [80]. There have been some reports of an increased risk of serous carcinoma of the endometrium in BRCA carriers.

However, data from a prospective series suggested that the risk of EC was significantly elevated only for BRCA mutation carriers taking Tamoxifen [81]. Type 1 cancers with Estrogen mediated high rates of K-ras and PTEN loss or mutation; have defects in mismatch repair (MMR) genes leading to microsatellite instability (MSI) [82]. These cancers showed aneuploidy, p5mutations, and over expression of HER-2/neu [83]. Researchers recommended gynecological examination, transvaginal ultrasound and aspiration biopsy from 30 to 35years in mutation carriers every year to diagnose early stage EC. Researchers suggested prophylactic hysterectomy with salpingo-oophorectomy after completion of child bearing or at the age of 40yrs in such women.

Dietary Factors

Higher risk of EC has been reported in those consuming Fat more and inverse by related to beta-carotene and fiber intake. Women with EC consumed milk, liver and fish less frequently than controls. No significant difference was found between cases and controls in the frequency of intake of carrots, meat, eggs, ham, and cheese. Levi reported that besides the predictable adverse effects of overeating and consequent overweight, some qualitative aspects of the habitual diet may also be associated with the risk of EC, Animal proteins and fat increased the risk and fresh fruits and vegetables, fibers decreased the risk [84]. Goodman reported that foods high in fat and cholesterol, such as red meat, margarine, and eggs, were positively associated with EC [85]. Cereals, legumes, vegetables, and fruits, particularly those high in lutein, were inversely associated. Some researchers reported no specific foods or beverages as risk factors of EC. Others have found that dietary macronutrients which have risk of EC may depend on their sources also. Intake of animal origin nutrients are linked to higher risk and plant origin nutrients are linked to lower risk. Association was also found between a high glycemic diet and EC, mostly dependent upon obesity. It is not uncertain whether alcohol increased the risk of EC though alcohol has been associated with elevated estrogen levels. No association was found between alcohol and EC in a meta-analysis of 20 studies, but subset analysis suggested that the type of beverage may be important [86]. Ganma, *et al.* found that total dairy in take was associated with a modest increased risk of EC, particularly among women who were postmenopausal and not using hormones [87]. Positive association between heme iron, total iron, and liver and EC risk has been reported [88]. No significant association was observed with other red and processed meats. Some researchers reported a positive association between a combination of foods rich in antioxidants, fibres, phytochemicals, and unsaturated fatty acids and decreased risk of EC [89]. However, others have not found any correlation. More research is needed.

Protective factors

Older age at first birth has been shown to lower the risk of developing EC with some evidence that older age at last birth also decreased the risk [90]. But others found no association between age at first birth and EC. Normal weight women with a diet low in plant and animal fats and high in complex carbohydrates were found at to be reduced risk of EC. Dietary fiber, retinol, β-carotene, vitamin C, vitamin E, supplementation may decrease the risk of EC [91]. More consumption of isoflavone-containing foods has been associated with a reduced risk of EC in non hysterectomized postmenopausal women [92]. There is increasing evidence that combined oral contraceptives decreased the risk of EC [93]. Continuous combined therapy of oral contraceptives pills lowered the risk of EC. In various studies expression of estrogen receptors (ER) and PR was found in most EC, but in amounts lower than could be identified in normal cycling endometrium [94]. Although neither ER nor PR expression correlated with stage, myometrial invasion, or lymph node metastasis, many recent reports suggested that expression of PR correlated with low tumor grade, low recurrence rate, and higher survival [94]. In patients with EC clinically confined to the uterus, the 5-year survival was 86% with ER-positive and PR-positive tumor sand only 52% in ER-positive and PR-negative tumors [95]. Therefore, PR status may be relevant in predicting prognosis as well as consideration of therapy with progestational agents in PR-positive tumors. Conversely, the absence of PR is associated with a worse prognosis. High-grade tumors such as serous and clear cell carcinoma tended to be negative, with antibodies directed towards ER and PR.

On the basis of a systematic review of the literature, the evidence for inclusion of measures of obesity, reproduction, insulin resistance, and genetic risk in such a model was discussed by Kitson, *et al.* and the strength of association between the risk factors and endometrial cancer was used to guide the development of a pragmatic risk prediction scoring system that could be implemented in the general population [96].

However the researchers said it needed refinement. And the potential risk-reducing interventions were also suggested highlighting the need for future studies in this area if the increasing tide of EC is to be stemmed.

Conclusion

Globally the EC is increasing not only in the developed world, but is also expected to rise in lower income countries as the global burden of obesity in addition to many of the risk factors is increasing. Attempts are being made to try prediction. By looking into risk factors which are many from, age to genetic to diet but everywhere more research is needed. Although certain factors increase a woman's risk for developing EC, they did not always cause the disease. Many women with one or more risk factors never developed EC. Some women with EC did not have any known risk factors. Even if a woman with EC had one or more risk factors, there was no way to know which, if any, of these factors was responsible for her cancer. It is essential to continue research.

References

1. Dobrzycka B, Terlikowski SJ (2010) Biomarkers as prognostic factors in endometrial cancer. Folia Histochem Cytobiol 48: 319-22.

2. Stewart BW, Christopher PW (2014) World Cancer Report 2014. International Agency for Research on Cancer, Switzerland.

3. Galaal K, Al Moundhri M, Bryant A, Lopes AD, Lawrie TA (2014) Adjuvant chemotherapy for advanced endometrial cancer. Cochrane Database Syst Rev 15: CD010681.

4. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, et al. (2013) Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Suppl 6: vi33-8.

5. Group UCSW (2014) United States Cancer Statistics: 1999–2011 incidence and mortality web-based report. Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute, Atlanta.

6. Balasubramaniam G, Sushama S, Rasika B, Mahantshetty U (2013) Hospital-based study of endometrial cancer survival in Mumbai, India. Asian Pac J Cancer Prev 14: 977-80.

7. Arafa M, Somja J, Dehan P, Kridelka F, Goffin F, et al. (2010) Current concepts in the pathology and epigenetics of endometrial carcinoma. Pathology 42: 613-7.

8. Dinkelspiel HE, Wright JD, Lewin SN, Herzog TJ (2013) Contemporary clinical management of endometrial cancer. Obstet Gynecol Int 2013: 583891.

9. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62: 10-29.

10. Prat J, Gallardo A, Cuatrecasas M, Catasús L (2007) Endometrial carcinoma: pathology and genetics.Pathology 39: 72-87.

11. Shu J, Fang S, Teichman P, Xing L, Huang H (2012) Endometrial carcinoma tumorigenesis and pharmacotherapy research. Minerva Endocrinol 37: 117-32.

12. Siegel R, Ward E, Brawley O, Jemal A (2011) Cancer statistics: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 61: 212-36.

13. Ma J, Ledbetter N, Glenn L (2013) Testing women with endometrial cancer for lynch syndrome: should we test all? J Adv Pract Oncol 4: 322-30.

14. Smotkin D, Nevadunsky NS, Harris K, Einstein MH, Yu Y, Goldberg GL (2012) Histopathologic differences account for racial disparity in uterine cancer survival. Gynecol Oncol 127: 616-9.

15. Elshaikh MA, Munkarah AR, Robbins JR, Laser BS, Bhatt N, et al. (2013) The impact of race on outcomes of patients with early stage uterine endometrioid carcinoma. Gynecol Oncol 128: 171-4.

16. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-86.

17. Hoskins WJ (2005) Principles and practice of gynecologic oncology. Lippincott Williams & Wilkins, USA.

18. Dey S, Hablas A, Seifeldin I, Ismail K, Ramadan M, et al. (2010) Urban–rural differences of gynaecological malignancies in Egypt (1999–2002). BJOG 117: 348-55.

19. NCRP (2013) Time trends in cancer incidence rates 1982 -2010. Indian Council of Medical Research, Bangalore, India.

20. HBCR (2011) Individual hospital based cancer registry data. NCRP, Indian Council of Medical Research, Bangalore, India.

21. Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, Mariani A, Dowdy SC (2008) Current issues in the management of endometrial cancer. Mayo Clin Proc 83: 97-112.

22. McMeekin D, Alektiar K, Sabbatini P, Zaino R (2009) Corpus: epithelial tumors. Principles and Practice of Gynecologic Oncology Philadelphia: Lipponcott: 683-732.83: 97-112.

23. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, et al. (2011) Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology 22: vi33-8.

24. Purdie DM, Green AC (2001) Epidemiology of endometrial cancer. Best Pract Res Clin Obstet Gynaecol 15: 341-54.

25. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, et al. (2018) SEER cancer statistics Review 1975–2008. National Cancer Institute. Bethesda, MD.

26. Viswanathan M, Daniel S, Shailaja M, et al. (2014) Socio demographic profile of patients with postmenopausal bleeding attending outpatient unit of a tertiary care centre. Sch J App Med Sci 2: 681-4.

27. Rathod P, Reddihalli P, Krishnappa S, Devi UK, Bafna UD (2014) A retrospective clinicopathological study of 131cases with endometrial cancers-Is it possible to define the role of retroperitoneal lymphadenectomy in low-resource settings? Indian J Cancer 51: 54-7.

28. Bhurgri Y, Nazir K, Shaheen Y, Usman A, Faridi N, et al. (2007) Patho-epidemiology of Cancer Corpus Uteri in Karachi South '1995-1997'. Asian Pac J Cancer Prev 8: 489-94.

29. Fujita M, Tase T, Kakugawa Y, Hoshi S, Nishino Y, et al. (2008) Smoking, earlier menarche and low parity as independent risk factors for gynecologic cancers in Japanese: a case-control study. Tohoku J Exp Med 216: 297-307.

30. MacMahon B (1974) Risk factors for endometrial cancer. Gynecol Oncol 2: 122-9.

31. Henderson B, Casagrande JT, Pike MC, Mack T, Rosario I (1983) The epidemiology of endometrial cancer in young women. Br J Cancer 47: 749-56.

32. Bevier M, Sundquist J, Hemminki K (2011) Does the time interval between first and last birth influence the risk of endometrial and ovarian cancer? Eur J Cancer 47: 586-91.

33. Yang H, Cook L, Weiderpass E, Adami H, Anderson K, et al. (2015) Infertility and incident endometrial cancer risk: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2). Br J Cancer 112 : 925-33.

34. Hershcopf R, Bradlow H (1987) Obesity, diet, endogenous estrogens, and the risk of hormone-sensitive cancer. Am J Clin Nutr 45: 283-9.

35. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, et al. (1992) Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol 167: 1317-25.

36. Swanson CA, Potischman N, Wilbanks GD, Twiggs LB, Mortel R, et al. (1993) Relation of endometrial cancer risk to past and contemporary body size and body fat distribution. Cancer Epidemiol Biomarkers Prev 2: 321-7.

37. Weiderpass E, Persson I, Adami H-O, Magnusson C, Lindgren A, et al. (2000) Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). Cancer Causes Control 11: 185-92.

38. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371: 569-78.

39. Boren T, Miller D (2010) An update on endometrial cancer. Texas medicine 106: 50-5.

40. Lu L, Risch H, Irwin ML, Mayne ST, Cartmel B, et al. (2011) Long-term overweight and weight gain in early adulthood in association with risk of endometrial cancer. Int J Cancer 129: 1237-43.

41. Münstedt K, Wagner M, Kullmer U, Hackethal A, Franke FE (2008) Influence of body mass index on prognosis in gynecological malignancies. Cancer Causes Control 19: 909-16.

42. Von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, et al. (2006) Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma. Cancer 107: 2786-91.

43. Jeong N-H, Lee J-M, Lee J-K, Kim JW, Cho C-H, et al. (2010) Role of body mass index as a risk and prognostic factor of endometrioid uterine cancer in Korean women. Gynecol Oncol 118: 24-8.

44. Mauland K, Trovik J, Wik E, Raeder M, Njølstad T, et al. (2011) High BMI is significantly associated with positive progesterone receptor status and clinico-pathological markers for non- aggressive disease in endometrial cancer. Br J Cancer 104: 921-6.

45. Everett E, Tamimi H, Greer B, Swisher E, Paley P, et al. (2003) The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol 90: 150-7.

46. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003) Overweight,obesity, and mortality from cancer in a prospectively studied cohort of US adults. N Engl J Med 348: 1625-38

47. Renehan AG, Zwahlen M, Egger M (2015) Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer 15: 484-98.

48. Gong TT, Wang YL, Ma XX (2015) Age at menarche and endometrial cancer risk: a dose-response meta- analysi of prospective studies. Sci Rep 11: 14051.

49. Niwa K, Imai A, Hashimoto M, Yokoyama Y, Mori H, et al. (2000) A case-control study of uterine endometrial cancer of pre-and post-menopausal women. Oncol Rep 7: 89-93.

50. Bajracharya S, Juan F (2013) Prognostic factors in endometrial cancer. J of inst med 35: 9-17.

51. Ewertz M, Schou G, Boice JD (1988) The joint effect of risk factors on endometrial cancer. Eur J Cancer Clin Oncol 24: 189-94.

52. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D (1995) Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 85: 304-13.

53. Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I, Koenig K, Shore R, et al. (2001) Postmenopausal endogenous oestrogens and risk of endometrial cancer: results of a prospective study. Br J Cancer. 84: 975.

54. Furness S, Roberts H, Marjoribanks J, Lethaby A, Hickey M, et al. (2009) Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev 15: CD000402.

55. Boren T, Miller D (2010) An update on endometrial cancer. Texas medicine 106: 50-55.

56. Schumer ST, Cannistra SA (2003) Granulosa cell tumor of the ovary. J Clin Oncol 21: 1180-9.

57. Ukah CO, Ikpeze OC, Eleje GU, Eke AC (2011) Adult granulosa cell tumor associated with endometrial carcinoma: a case report. J Med Case Rep 5: 340.

58. Ottolina J, Ferrandina G, Gadducci A, Scollo P, Lorusso D, et al (2015) Is the endometrial evaluation routinely required in patients with adult granulosa cell tumors of the ovary? Gynecol Oncol 136: 230-4.

59. Weiderpass E, Persson I, Adami H-O, Magnusson C, Lindgren A, Baron JA (2000) Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). Cancer Causes Control 11: 185-92.

60. Soliman PT, Wu D, Tortolero-Luna G, Schmeler KM, Slomovitz BM, et al. (2006) Association between adiponectin, insulin resistance, and endometrial cancer. Cancer 106: 2376-81.

61. Burzawa JK, Schmeler KM, Soliman PT, Meyer LA, Bevers MW, et al. (2011) Prospective evaluation of insulin resistance among endometrial cancer patients. Am J Obstet Gynecol 204: 355.e1-7.

62. Friedenreich CM, Biel RK, Lau DC, Csizmadi I, Courneya KS, et al. (2011) Case–control study of the metabolic syndrome and metabolic risk factors for endometrial cancer. Cancer Epidemiol Biomarkers Prev 20: 2384-95.

63. Einbeigi Z, Rosenquist R, Gardman C, Iselius L (2007) A hypothesis-generating search for new genetic breast cancer syndromes–a national study in 803 Swedish families. Hered Cancer Clin Pract 5: 17-24.

64. Liang SX, Pearl M, Liang S, Xiang L, Jia L, et al. (2011) Personal history of breast cancer as a significant risk factor for endometrial serous carcinoma in women aged 55 years old or younger. Int J Cancer 128: 763-70.

65. Killackey MA (1985) Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens. Cancer Treat Rep 69: 237-8.

66. Iqbal J, Ginsburg OM, Wijeratne TD, Howell A, Evans G, et al. (2012) Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review. Cancer treatment reviews 38: 318-28.

67. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, et al. (2000) Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet 356: 881-7.

68. EBCTCG (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 378: 771-84.

69. Swerdlow AJ, Jones ME, Group BTSCS (2005) Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case–control study. J NT Cancer Inst 97: 375-84.

70. Bland AE, Calingaert B, Secord AA, Lee PS, Valea FA, et al. (2009) Relationship between tamoxifen use and high risk endometrial cancer histologic types. Gynecol Oncol 112: 150-4.

71. Olson SH, Chen C, De Vivo I, Doherty JA, Hartmuller V, et al. (2009) Maximizing resources to study an uncommon cancer: E2C2—Epidemiology of Endometrial Cancer Consortium. Cancer Causes Control 20: 491-6.

72. Lancaster JM, Powell CB, Chen LM, et al. (2015) Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol 136: 3-7.

73. Strafford JC (2012) Genetic testing for lynch syndrome, an inherited cancer of the bowel, endometrium, and ovary. Rev Obstet Gynecol 5: 42-9.

74. Lynch HT, Watson P, Kriegler M, Lynch JF, Lanspa SJ, et al. (1988) Differential diagnosis of hereditary nonpolyposis colorectal cancer (Lynch syndrome I and Lynch syndrome II). Dis Colon Rectum 31: 372-7.

75. de la Chapelle A (2005) The incidence of Lynch syndrome. Fam Cancer 4: 233-7.

76. Lucenteforte E, Talamini R, Montella M, Dal Maso L, Pelucchi C, et al. (2009) Family history of cancer and the risk of endometrial cancer. Eur J Cancer Prev 18: 95-9.

77. Hemminki K, Granström C (2004) Familial clustering of ovarian and endometrial cancers. Eur J Cancer 40: 90-5.

78. Farooq A, Walker L, Bowling J, Audisio R (2010) Cowden syndrome. Cancer treatment reviews. 36: 577-83.

79. Thompson D, Easton DF, Consortium BCL (2002) Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 94: 1358-65.

80. Beiner ME, Finch A, Rosen B, Lubinski J, Moller P, et al. (2007) The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol 104: 7-10.

81. Hecht JL, Mutter GL (2006) Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol 24: 4783-91.

82. Doll A, Abal M, Rigau M, Monge M, Gonzalez M, et al. (2008) Novel molecular profiles of endometrial cancer-new light through old windows. J Steroid Biochem Mol Biol 108: 221-9.

83. Levi F, La Vecchia C, Franceschi S, Negri E (1993) Dietary factors and the risk of endometrial cancer. Cancer 71: 3575-81.

84. Goodman MT, Hankin JH, Wilkens LR, Lyu L-C, McDuffie K, et al. (1997) Diet, body size, physical activity,and the risk of endometrial cancer. Cancer research 57: 5077-85.

85. Sun Q, Xu L, Zhou B, Wang Y, Jing Y, et al. (2011) Alcohol consumption and the risk of endometrial cancer: a meta-analysis. Asia Pac J Clin Nutr 20: 125-323.

86. Ganmaa D, Cui X, Feskanich D, Hankinson SE, Willett WC (2012) Milk, dairy intake and risk of endometrial cancer: A 26-year follow-up. Int J Cancer 130: 2664-71.

87. Genkinger JM, Friberg E, Goldbohm RA, Wolk A (2012) Long-term dietary heme iron and red meat intake in relation to endometrial cancer risk. Am J Clin Nutr 96: 848-54.

88. Filomeno M, Bosetti C, Bidoli E, Levi F, Serraino D, et al. (2015) Mediterranean diet and risk of endometrial cancer: a pooled analysis of three italian case-control studies. Br J Cancer 112: 1816-21.

89. Wernli KJ, Ray RM, Gao DL, De Roos AJ, Checkoway H, et al. (2006) Menstrual and reproductive factors in relation to risk of endometrial cancer in Chinese women. Cancer Causes Control 17: 949-55.

90. Xu WH, Xiang YB, Ruan ZX, Zheng W, Cheng JR, et al. (2004) Menstrual and reproductive factors and endometrial cancer risk: Results from a population-based case-control study in urban Shanghai. Int J Cancer 108: 613-9

91. Ollberding NJ, Lim U, Wilkens LR, Setiawan VW, Shvetsov YB, et al. (2012) Legume, soy, tofu, and isoflavone intake and endometrial cancer risk in postmenopausal women in the multiethnic cohort study. J Natl Cancer Inst 104: 67-76.

92. Allen RH, Cwiak CA, Kaunitz AM (2013) Contraception in women over 40 years of age. Can Med Assoc J 185: 565-73.

93. Kleine W, Maier T, Geyer H, Pfleiderer A (1990) Estrogen and progesterone receptors in endometrial cancer and their prognostic relevance. Gynecol Oncol 38: 59-65.

94. Creasman WT (1993) Prognostic significance of hormone receptors in endometrial cancer. Cancer 71: 1467-70.

95. Kitson SJ, Evans DG, Crosbie EJ (2017) Identifying High-Risk Women for Endometrial Cancer Prevention Strategies: Proposal of an Endometrial Cancer Risk Prediction Model. Cancer Prev Res 10: 1-13.