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Editorial

Updates in Classification and Pathogenesis of Endometrial Cancer

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Endometrial Cancer (EC) is the most common malignancy of the uterus and 95% are carcinoma that arises from the glandular epithelial layer of the uterus. Uterine cancer is the fourth most common gynaecological malignancy in the affluent countries with increasing annual rate [1]. The incidence, prevalence, and mortality of EC vary from region to region across the globe. According to the GLOBCAN, there were 320,000 new cases in 2012 [2]. The American Cancer Society estimated that EC account for 7% of all cancers in women and 60,000 new cases were expected to be diagnosed and 14, 000 patients were estimated to die in 2016 [1,3]. The incidence rate of EC is; 19 - 21/100,000 in US and Canada, 12 - 18/ 100,000 in Europe, 10 - 12/ 100,000 in Australia and New Zealand, and 0.9 - 5/100,000 in Asia and Africa [4, 5]. The high incidence rate in USA, Canada, Europe and Australia but low in Asia and Africa could be explained due to high endemic obesity in these regions. In less developed countries such as African countries, cervical cancer is the most common cancer and it is related to human papilloma virus (HPV) with highest mortality rate in African continent due to the lack of vaccination to HPV, screening, appropriate resources for diagnosis and therapy and poor health seeking behaviour.

Conventionally, EC was classified by Bokhman in 1983 into endometrioid endometrial carcinoma (type I) and non-endometrioid endometrial carcinoma (type II) [6]. Type I EC is more common in Caucasians women, accounts for 80%, well differentiated, endometrioid histology and has good prognosis. Patients with type I have a better outcome about 96% of five year overall survival. On the other hand, type II is poorly differentiated, more common in black African American women, more aggressive and has poor prognosis (less than a year overall survival). But the dual classification does not tailor patients adequately as all well differentiated ECs have no good outcome and some poorly differentiated EC has good outcome. To overcome this clinical dilemma, the Cancer Genome Atlas (TCGA) recently has proposed a new molecular classification that better tailors EC patients. This classifies EC into POLE (ultramutated), MSI (hypermutated), MSS/none-specific molecular profile (NSMP) (copy number low) and serous like (copy number high). The POLE subtype has excellent prognosis, serous like has worst prognosis and MSI and MSS/NSMP have intermediate. Summary of the classification is outlined in the diagram below [7] (Figure 1).

The most common risk factors for type-I EC are obesity, diabetes, hyperlipidaemia, and hypertension (metabolic disorder syndrome), nulliparity, late onset menopause, oestrogen secreting ovarian lesions, hormone replacement therapy, and tamoxifen treatment. These factors are associated with increased oestrogenic state and unopposed estrogen is a potential factor for initiation of endometrial cancer. It is hypothesized that there is peripheral synthesis of oestrogen and this is more common in obese postmenopausal women that predispose to develop to EEC. Excess weight increases the risk of developing EC by 50% for every 5 Body Mass index (BMI) units [5]. EC is a paradigm that directly associated with obesity. For type II EC the pathogenesis is not related to obesity as it is more common in thin, old with atrophied endometrium and endometrial serous intra-neoplasia (ESIN) is a common precursor.

There are also increasing evidence obesity is associated with many cancers such as breast and ovarian cancer, the former is the most prevalent female malignancy and the latter is the common cause of mortality in women. Types of diet that we consume daily have a lot to do whether to acquire a malignancy or not. Animal fats and red meat has been reported to increase risk of developing cancer. Some types

of food are not only increasing risk of having cancer but also increase to have virulent type of cancer. It has been recently reported amino acids like glutamine could potentially promote cancer cells vigorously to proliferate, grow and survive in EC. We hypothesize foods rich in glutamine such as red meat may let cancer cells to proliferate, rescue from death, progress and develop resistance to therapy in many cancers including EC.

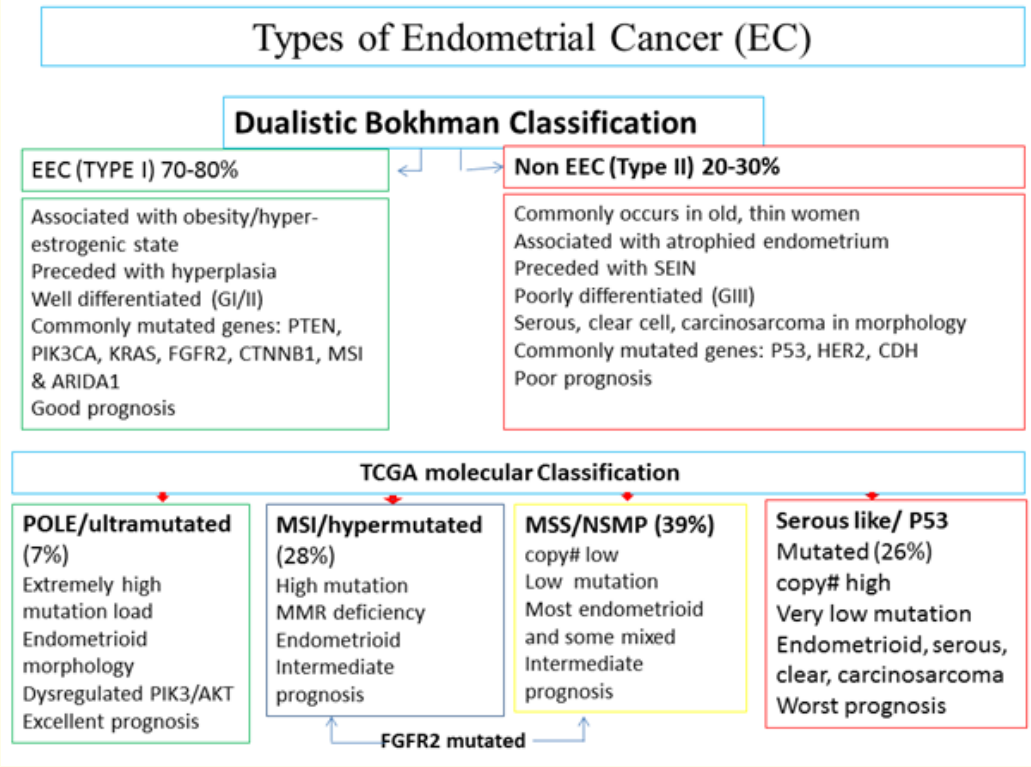

Figure 1: *Sketch showing the dualistic and molecular classification of endometrial cancer and most common genes mutated in each classification. FGFR2 fibroblast growth factor receptor-2 MSI micro-satellite instability, MSS micro-satellite stable, SEIN serous endometrial intra-neoplasia.*

In postmenopausal women, there is a peripheral synthesis of oestrogen that persistently increases blood estrogen and this is aggravated by obesity. It is not clearly understood how oestrogen attributes for the development of endometrial cancer. There is growing evidence that epithelial-stromal communication in the context of steroid hormone and growth factors and their respective receptors contribute to the proliferation of glandular epithelium of the endometrium (hyperplasia, a precursor of EEC). A number of oncogenes and suppressor genes are involved in this paradigm (Figure 1). One of the potential mechanisms is the cross-talk of epithelial- stromal network in the context of fibroblast growth factor and fibroblast growth factor receptors (FGFR) signalling. Dysregulation of FGF-FGFR signalling pathway has been reported in tumorigenesis of many gynaecological malignancies such as breast, ovary, cervical and EC [8]. FGFR2 is mutated in 10 - 16% of endometrial cancers [9]. Estrogen mediated expression of fibroblast growth factors (FGF) from stroma provoke FGF-FGFR signalling that lead to proliferation of glandular epithelium of the endometrium and this creates a fertile land for development of EC. In a rapid proliferation there is likely to occur high mutation and it has been reported PTEN mutation occurs in 60 - 80% EEC and in 20% hyperplasia. There is also increasing evidence epigenetic silencing and hypermethylation of some genes also contributing to tumorigenesis of EC. A recent investigation documented hypermethylation and silencing of Heart and Neural crest Derivatives expressed transcript 2 (HAND2), a transcription factor and progesterone contribute to EC initiation and progesterone dependent therapeutic resistance [10].

The HAND2 and progesterone regulate endometrial stromal-epithelial network through FGF-FGFR communication and control epithelial proliferation and differentiation. Unpublished data from our lab also supported this phenomenon.

In conclusion, there is increasing knowledge in understanding the molecular mechanism of carcinogenesis of endometrial cancer and this will help in planning preventing strategies, appropriate diagnosis and innovating personalized targeted therapy. An effective strategy is reducing the burden of obesity and promoting eating healthy diet and adequate exercise through public education.

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