Women's Health & Gynecology

ISSN: 2369-307X Editorial

A Proposed Reclassification of the Endometrial Carcinomas as Luteinizing Hormone Independent and Dependent Diseases

This article was published in the following Scient Open Access Journal:
Women's Health & Gynecology
Received June 09, 2016; **Accepted** June 13, 2016; **Published** June 17, 2016;

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Endometrial carcinomas are the most common gynecologic malignancies, exceeding the incidence of ovarian and cervical cancers in Western countries [1-3]. Eighty percent of them occur in elderly (post-menopausal) women, perhaps due to increased longevities in industrialized societies [1-3]. Caucasian women are at a greater risk than black, Hispanic, Asian and Pacific Islanders, but black women are more likely to die from the disease [1-3]. The incidence of endometrial carcinomas is on the rise without a corresponding increase in survival rates during the last four decades [2,3]. According to some estimates, there were about 55,000 new cases and 10,000 died from the disease in 2015 [3]. EC costs the U.S. economy approximately $2.6 billion per year [3].

Endometrial carcinomas were classified in 1983 as type I and type 2 diseases based on a number of characteristics, including estrogen dependency [4]. Thus, while type 1 disease arises under hyperestrogenic conditions, type 2 disease is not estrogen dependent, as it primarily occurs in post-menopausal women, who have very low estrogen levels [1,2]. There are a number of other distinguishing features between these two diseases. For example, type 1 disease is a low grade adenocarcinoma, non-aggressive and the tumors contain estrogen and progesterone receptors. Type 2 disease, on the other hand, is poorly differentiated, aggressive and contain very low or no estrogen or progesterone receptors [1,2]. Pooled analysis of 14,000 cases revealed that many risk factors are similar for both types of endometrial carcinomas [5]. Since the original endometrial carcinoma classification, there have been scientific developments, which increased our understanding of the roles of hormones in the development of these two diseases.

Elderly women have elevated LH and follicle stimulating hormone (FSH) and low estradiol levels. The role of FSH in endometrial carcinomas is unknown. However, there is considerable evidence for the potential LH involvement in the development of endometrial carcinomas in elderly women. Postmenopausal women with endometrial carcinoma have hypothalamic-pituitary hyperactivity [6,7]. This hyperactivity has been associated with LH, as its levels are further elevated in post-menopausal women who have developed endometrial carcinomas than the cohorts who did not develop the disease [8]. In addition, LH receptors, which also can bind human chorionic gonadotropin (hCG), are overexpressed in endometrial carcinomas as compared with pre and post-menopausal endometria [9]. These receptor levels further increase from low to high grade tumors [9]. The LH/hCG receptor activation in primary and immortalized endometrial carcinoma cells results in an increase in cell proliferation, invasion, activation of $ß_1$ integrin receptors and increased secretion of metalloproteinase-9 in an active form [10,11]. These changes are mediated by cyclic AMP/protein kinase A signaling and requires the receptor's presence [10]. The LH actions to induce endometrial carcinomas may also involve its actions in the ovaries, adrenals, adipose tissue and pancreas [12]. The elevation of LH levels alone may not be sufficient, as not all post-menopausal women with these elevations develop the disease. Therefore, genetic, epigenetic, life style and other risk factors may also be required to collaborate with LH in EC development.

Estrogens are believed to be the culprits in type I endometrial carcinomas development because of their mitogenic actions [1,2]. These actions are antagonized by progesterone, which promote the differentiation of endometrial epithelial cells [1,2]. Thus, women who regularly ovulate and produce progesterone rarely get endometrial carcinomas [1,2]. When the cyclicity stops, as in the cases of anovulatory women, the balance tips in favor of estrogens, which then stimulate endometrial epithelial cells to

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proliferate, the hallmark feature of endometrial carcinomas [1,2]. This tipping can also happen in women who are obese or take an unopposed estrogen therapy for the control of menopausal symptoms [1-3]. Estrogens, however, cannot the culprits in type 2 endometrial carcinomas development, because their circulating levels are very low and the tumors do not contain estrogen receptors [1,2]. Similarly, LH cannot be the culprit in type I endometrial carcinomas development, because its levels are low, except during a brief periovulatory period. However, LH/hCG receptors are present in normal endometrium and they are functional in mediating the physiologic responses required for pregnancy initiation and maintenance [13]. It is only when the LH levels are chronically elevated, coupled with the receptor dysregulation, and then LH becomes relevant as in the type 2 endometrial carcinomas development.

The old endometrial carcinomas classification now requires a change. We propose reclassification of type 1 disease as LH independent disease and type 2 disease as LH dependent disease. Estrogens have different roles in both the diseases. In LH independent disease, estrogens have a causative role through their mitogenic effects [1,2]. Estrogens have a supportive role in LH dependent disease by facilitating further release of LH from the anterior pituitary gland [12]. In elderly women, estrogens come from peripheral conversion from androgen precursors, through aromatization in the fat and endometrial carcinoma tissues. The androgen precursors come from the LH stimulation of ovaries and adrenals [12]. The LH and/or insulin actions in fat and endometrial carcinoma tissues promote aromatization of androgens [12]. The LH actions in ß-cells of pancreas results in an increase in insulin secretion [14]. A decrease in sex steroid binding globulin in the obese women increases free estrogens, which are even more potent than bound estrogens in releasing bioactive LH [12].

The reclassification is important for the following reasons:

1. First, it is important for medical management of the disease. Thus, there is no rationale for the progestin therapy for LH dependent disease, as there are no progesterone receptors. Similarly, there is no basis for gonadotropin release hormone analog therapy for LH independent disease.
2. Second, the reclassification recognizes the scientific progress made since the original classification more than 30 years ago. Further research could provide a new discovery path for finding new therapeutic targets in the disease.
3. The switch from LH independent to dependent disease should be expected gradual. Thus, as LH independence of disease progressively declines, LH dependence progressively increases during women's aging. The switch may take several years during perimenopausal transition period. During these transitional years, combination therapy with progestin and GnRHa could be more effective than the therapy with either one of them alone.

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