Obesity-associated endometrial and cervical cancers

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1. ABSTRACT

Epidemiological studies have indicated that obesity (body mass index-BMI>30) and overweight (BMI>25) directly associated with risk of many cancers. The association of obesity with cancer risks may be explained by the alterations in the metabolism of endogenous hormones, production of specific proteins and cytokines, adipose related inflammatory reactions, and genetic factors. This review aims to illustrate the link between obesity and occurrence and prognosis of endometrial and cervical cancers. Convincing scientific evidence shows that nutrition and lifestyle factors initiate the development of obesity with excessive adipose tissues, which trigger production of hormones, cytokines and other factors to promote growth of cancer cells. Obese women with either endometrial or cervical cancer, especially in postmenopausal period, have shown a significantly higher mortality. This is mainly due to that the obese women are more vulnerable in cancer occurrence and they are more likely to miss routine cancer screening, putting them at a greater risk for delayed diagnosis of these cancers and deteriorate prognosis. Thus, healthcare providers should pay particular attention to this more vulnerable group of women.

2. INTRODUCTION

Positive energy imbalance leads to obesity, which is a serious health problem on the rise worldwide (1-5). Obesity is a major risk factor of many chronic diseases, including Type 2 diabetes, liver and cardiovascular diseases, etc. Recently, there is a parallel increase in cancer cases and obesity epidemic in the world. Mounting evidence exists that excessive adipose tissue triggers the production of many hormones, cytokines and other factors that stimulate development of many types of cancers, including the incidence of endometrial, breast and ovarian cancers (6-12). In terms of endometrial cancer, excessive estrogen locally produced by adipose tissues may contribute to the development of multiple cancers. Although available data are less compelling in ovarian and cervical cancers, obesity modestly increases the incidence of premenopausal ovarian cancers and potentially increases cervical cancer incidences. Perhaps as a result of the decreased screening compliance (13-16), obese women with cancer have a decreased survival rate; this may be disease-specific as the result of co-morbid illnesses, or response to some anti-cancer treatments (13). Obese women are at higher risk for multiple cancers, including endometrial cancer, cervical cancer, breast cancer, and

perhaps ovarian cancer (17). In Canada, cancers of the endometrium, ovaries, vulva, vagina, placenta and adnexa account for 11% of all malignant neoplasms in women and 81% of all genital cancers (18). Both endometrium and ovarian cancers are important public health problems. Obesity is one of the many proven risk factors associated with some gynecologic cancers including ovarian, vulvar and vaginal cancers, which may be caused by HPV infection (18). In this short review, we describe the associations of obesity with endometrial and cervical cancers and discuss the pathogenic mechanism of the two cancers associated with obesity.

3. Obesity (diabetes) and endometrial cancer

Endometrial cancer (cancer of the uterine lining) is the most commonly diagnosed cancer in gynecological reproductive tract and 4th most common cancer for women. Increasing evidence suggests that the majority of cases can be divided into two different types of endometrial cancer (Type 1 and Type 2) based on clinicopathological and molecular characteristics. More than 85% of all endometrial cancers are Type I endometrioid endometrial carcinoma, associating with an endocrine milieu of estrogen predominance (19). These tumors are of endometroid histology and develop from endometrial hyperplasia. They have good prognosis and are sensitive to endocrine treatment. Type II endometrial cancers are not associated with a history of unopposed estrogens and develop from the atrophic endometrium of elderly women. Mainly, they are of serous papillary or clear cell morphology, have a poor prognosis and do not react to endocrine treatment. The transition from normal endometrium to a malignant endometrial tumor is thought to involve a stepwise accumulation of alterations in cellular and molecular mechanisms leading to dysfunctional cell growth (20). Obesity and diabetes mellitus profoundly increase the incidence of endometrial cancer, predominantly through the effects of unopposed estrogen and are the main risk factors for type 1 endometrial cancers (6) (21) (22). In the following section, we describe our current knowledge of obesity associated with development and mortality of the type 1 endometrial cancers and the pathogenic mechanisms.

3.1. Links between obesity and endometrial cancers

Endometrial cancer was the first cancer identified as being obesity-related (23). Twombly *et al.* (1961) proposed an association of obesity with endometrial cancer in women, which was supported by many studies from 1970s (24-26). MacDonald *et al.* (1978) examined the link of obesity to endometrial cancer in women in 50 postmenopausal women, of whom 25 had adenocarcinoma of the endometrium and 25 had no endometrial disease. The mean weight of the patients with endometrial cancer was 234 ± 16 pounds, of the women with no endometrial disease was 194 ± 12 pounds, revealing that overweight which frequently results in obesity in postmenopausal women is linked to the endometrial cancer (24). Endometrial cancer risk increased significantly in proportion to excess body mass index (BMI) (21). Recent epidemiological studies have further shown that over 40% of the endometrial cancer incidences can be attributed to

excess body weight (27). Any increase in BMI in the female population will increase endometrial cancer incidences (28). Cases of endometrial cancers had a significantly higher BMI than controls and the obese subjects had a 2.65-fold increased risk for endometrial cancer (29). A strong linear positive correlation of BMI with endometrial cancer risk and a strongly increased risk among women with diabetes have been reported (28) (30). From 1995 to 1997, a case control study was carried out in Mexico City. Eighty-five histologically confirmed cases were compared with 668 population-based controls obtained through frequency matching. Results showed that an interaction between obesity and diabetes that significantly increases the risk of endometrial cancer (31). This, in turn, may explain the growing number of new endometrial cancer cases recently observed in developing countries. Thus, the relationship between BMI, diabetes and endometrial cancer is well-established.

Morbid obesity markedly affects survival in endometrial carcinoma (32). Obese women with cancer have decreased survival; this may be disease-specific, consequence of co-morbid illnesses (obesity and cancer), or response to anti-cancer treatment (21). History of obesity and diabetes may increase risk of mortality after endometrial cancer diagnosis; control of these metabolic conditions may improve survival after endometrial cancer diagnosis (33). The work also suggests that obesity and less-activity of endometrial cancer survivors contribute to poorer quality of life. This population could benefit from life-style interventions incorporating physical activity and controlled energy-uptake (34). Thus, a practical and effective preventive measure against endometrial cancer is to avoid overweight and obesity (25). The impact of obesity on racial disparities in endometrial cancer survival remains unclear, which should be evaluated (35).

In summary, the published epidemical studies have shown a strong link between obesity and endometrial cancer incidence. But more research is necessary to improve our understanding of the link between the two diseases, which might provide primary therapeutic targets of endometrial cancer by preventing overweight and obesity.

3.2. Mechanisms of obesity-associated endometrial cancer

Researchers have investigated the pathogenic mechanisms that may be responsible for promotion of endometrial cancer in individuals with obesity. Although the molecular mechanisms underlying the association of obesity with endometrial cancers are not completely understood, the published studies on endogenous hormone metabolism, specific proteins and cytokine production, and genetic factors may shed some lights on the epidemiological evidence.

Abnormal endogenous hormone metabolism: Endogenous hormones appear to play an important role in the development of endometrial cancer (36). Alterations in endogenous hormone metabolism (insulin, Insulin-like growth factor 1 (IGF1), sex steroids) may provide the main

links between obesity and endometrial cancer risk (21). Estrogen stimulation of the endometrium unopposed by progesterone, namely, unopposed estrogen stimulation, is thought to be involved in the etiology of endometrial cancer (37). Frequent intake of animal fat, obesity and histories of diabetes mellitus are all considered to increase unopposed estrogen stimulation and have been reported to be risk factors for endometrial cancers (37). In a previous case-control study, different risk factors were evaluated for endometrial cancer in 173 histologically proven endometrial cancers and 347 controls. Histological differentiation was positively correlated both to oestrogen usage and level of overweight; supporting a specific role of oestrogens in the development of endometrial cancer (38). Serum estrone and estradiol were statistically correlated with the BMI among control subjects (r = 0.37 and 0.40 for estrone and estradiol, respectively) (13). After the menopause, progesterone synthesis ceases, but elevated plasma levels of androgen precursors and increased estrogen levels through the aromatization of androgens in adipose tissue may continue result in risk of excessive weight (36). Both elevated endogenous estrogen and insulin resistance are recognized to be the major factors that link obesity and cancer development (39). Epidemiological studies have shown increased endometrial cancer risks among pre- and postmenopausal women who have elevated plasma androstenedione and testosterone, and among postmenopausal women who have increased levels of estrone and estradiol (36). Androstenedione is the common precursor of male and female sex hormones. Some androstenedione is also secreted into the plasma, and may be converted in peripheral tissues to testosterone and estrogens. Furthermore, chronic hyperinsulinemia is also a risk factor for the development of endometrial cancer. Insulin is well known to increase incidence of many cancers and results in poorer prognosis (40, 41).These relationships can all be interpreted as the "unopposed estrogen" hypothesis, which proposes that endometrial cancer may develop as a result of the mitogenic effect of estrogens. In addition, development of ovarian hyperandrogenism may also be a central mechanism relating nutritional lifestyle factors to endometrial cancer risk when the produced estrogen is insufficiently counterbalanced by progesterone (36).

Specific proteins and cytokines: It is clear that adipocyte-secreted adipocytokines are a key player in progression of endometrial cancer with obesity. Adipose tissue was previously considered an energy storage depot and mechanical barrier. In 1994, Zhang *et al.* discovered that leptin, an adipocyte-derived pleiotropic hormone, is essential to appetite and weight regulation as well as regulating reproduction, endocrine, and immunity (42). Since then, over 20 adipocyte-secreted adipocytokines have been detected with strong regulation on metabolic balances, and are particularly involved in insulin sensitivity and resistance (43). Leptin and adiponectin are the two major adipocytokines, which have been explored for their potential roles in carcinogenesis (11, 44-48). Various signaling pathways have been proposed to mediate their effects. Leptin is predominantly produced in subcutaneous white adipose tissue and is also synthesized in other types of fat and many organs, such as the liver and stomach (49). Leptin promotes cell growth in many tissues and is elevated in obesity as expected with excessive adipose tissues. Elevated serum leptin levels are observed in patients with obesity associated with postmenopausal endometrial cancers (50). The reason is that higher leptin concentrations in patients with endometrial and portio tumours were related to an increase in tissue estrogen receptor (ER) and progesterone receptor (PGR) and to an increase in circulating estradiol in the postmenopause (50). In-vitro studies demonstrate promotion of cancer cell proliferation by leptin in several cancer cell lineages (51). Leptin not only promotes carcinogenesis, but also is an important determinant factor of tumor behavior and prognosis in patients with obesity. Adiponectin, 30 kDa complement C1-q related protein, plays a role in glucose regulation and fatty acid catabolism (52). Decreased serum adiponectin levels have been reported in patients with obesity with increased risk of endometrial cancer (53). Adiponectin is an insulin-sensitizer and circulating adiponectin levels are reduced in patients with obesity and insulin resistance (54). Recently, the relationship between ratio of leptin-to-adiponectin (L/A ratio) and endometrial cancer risk in postmenopausal female subjects has been investigated. The L/A ratio was associated with an increased risk for endometrial cancer development (39). In addition, proteins secreted by adipose tissue (adipokines) also contribute to the regulation of immune response (leptin), inflammatory response (tumor necrosis factor-alpha (TNF-), interleukin-6 (IL-6), serum amyloid A), vasculature and stromal interactions and angiogenesis (vascular endothelial growth factor 1), as well as extracellular matrix components (type-VI collagen) (45, 55). Another metabolic regulatory hormone, ghrelin, and its specific receptor have been identified in endometrial tissue with expression levels closely correlated to menstrual cycles (56). This local ghrelin and receptor system has recently been reported to contribute to the development of endometrial cancers (57). Further study is warranted to clarify effect of local ghrelin on endometrial cancers.

Obesity, particularly central obesity, is considered as a systemic inflammatory condition and is related strongly to insulin resistance. Adipose tissue is now recognized as an immune organ that secretes numerous immunomodulatory factors (cytokines) and seems to be a significant source of inflammatory signals known to cause insulin resistance (58). Therefore, obese patients have the systemic inflammatory responses, which are associated with increases in serum levels of C reactive protein (CRP) and different cytokines including several interleukins (IL-6, IL-8 and IL-11) and TNF- (59-63). CRP is the most recognized biologic marker of chronic systematic inflammation, and it is conceivable that the CRP gene may work together with obesity in the development of endometrial cancer (64). Previous work suggests that human serous papillary endometrial adenocarcinoma (SPEC) and human endometrial adenocarcinoma (HEC) cells expressed steady-state IL-8-specific mRNA transcript and secreted IL-8 protein (65). The levels of IL-8 mRNA in SPEC-2 cells from stage IV serous papillary adenocarcinoma were three-fold higher as compared to

endometrial adenocarcinoma cells, HEC-1 A, from stage IA endometrial cancer (65). Higher levels of IL-8 mRNA and protein expression were associated with metastatic potentials. Treatments of IL-1 beta and TNF- induced IL-8 expression in endometrial cancer cells (65). These data demonstrate that constitutive and induced expression of IL-8 in endometrial carcinoma cells might be very important for tumor growth and metastasis (65). IL-11 is produced by human endometrium and endometrial cancer tissue. It has roles in endometrial epithelial cell adhesion and trophoblast cell invasion, two important processes in cancer progression. IL-11 is significantly upregulated in uterine lavage and endometrial cancer cells in women with endometrial carcinoma (66). IL-11, along with its specific receptor, IL11R , and downstream signaling molecules, STAT3 and SOCS3, are likely to play a role in the progression of endometrial carcinoma. IL-11 in uterine washings may be useful as a diagnostic marker for endometrial cancer at early stage (66). Recent study suggests that Lipocalin-2 (Lin-2) may play a role in the development of endometrial cancer (67). Lin-2 is an acute-phase protein that has been implicated in diverse physiological processes. Lin-2 reduced cell apoptosis, changed the cell proliferation and up-regulated secretion of cytokines, including: IL-8, IL-6, monocyte chemotatic protein-1 and growth-related oncogene in human endometrial carcinoma cells (RL95-2). Lin-2-induced cytokine production enhances endometrial carcinoma cell survival and migration (67).

Genetic Factors: Genetic variation that is associated with obesity and diabetes may provide clues to the molecular pathways mediating endometrial carcinogenesis (68). A genome-wide association study (GWAS) of BMI identified a 47 kb region on chromosome 16 encompassing FTO gene intron1-exon2-intron2 that is marked by tag SNP rs8050136 (and the correlated SNP rs9939609 (r2 =1)) to be associated with BMI (69). Another GWAS of type II diabetes identified HHEX gene region on chromosome 10 marked by rs1111875 also to be associated with BMI (70). A recent published work, however, suggests that polymorphisms in FTO and HHEX may have only weak effects on endometrial cancer risk (68). Several independent GWASs identified two common polymorphisms, FTO rs9939609 and MC4R rs17782313, that are linked to increased body weight and obesity (71). Both FTO rs9939609 and MC4R rs17782313 are associated with endometrial cancer risk in a pooled analysis of nine case-control studies within the epidemiology of Endometrial Cancer Consortium (E2C2) (71). Unconditional logistic regression models reveal that both the FTO rs9939609 A and MC4R rs17782313 C alleles were associated with a 16% increased risk of being overweight among control women, indicating that FTO rs9939609 and MC4R rs17782313 genotypes are associated with the risk of endometrial cancer (71). FTO rs9939609 is also a susceptible marker for white non-Hispanic women at higher risk of endometrial cancer. Furthermore, carriers of the FTO rs9939609 AA genotype were at increased risk of endometrial carcinoma compared to women with the TT genotype. The anti-proliferative effect of progesterone requires the progesterone receptor (PR), which exists in two isoforms, PR-A and -B. Although PR-A and B share many important structural domains, they are in fact two functionally distinct transcription factors, mediating their own response genes and physiological effects with little overlap (72). PR-B contributes to, rather than inhibits, epithelial cell proliferation both in response to estrogen alone and in the presence of progesterone and estrogen. It is suggested that in the uterus, the PR-A isoform is necessary to oppose estrogen-induced as well as PR-B-dependent proliferation. The variants in the PR gene may predispose to endometrial cancer. Six variable sites, including four polymorphisms in the hPR gene and five common haplotypes have been identified (73). One promoter region polymorphism, 331GA, creates a unique transcription start site to increases transcription of the PR gene, favoring production of human PR-B in an endometrial cancer cell line. Statistically, the 331GA polymorphism is significantly associated with the risk of endometrial cancer, which was even greater in overweight women carriers. Therefore, the 331GA hPR gene polymorphism may contribute to endometrial cancer risk by increasing expression of the hPR-B isoform (73).

In addition, aromatase is an enzyme that is responsible for a key step in the biosynthesis of estrogens. This enzyme converts rostenedione to estrone and testosterone to estradiol. After menopause, the primary source of estrogens is via peripheral conversion of androgens in adipose tissue catalyzed by aromatase. Aromatase is encoded by CYP19A1. Setiawan *et al* (2009) examined the genetic variation of CYP19A1 in a large pooled analysis of 4,998 endometrial cancer cases and 8,285 controls from 10 studies in the Epidemiology of Endometrial Cancer Consortium. They concluded that genetic variation of CYP19A1 will influence susceptibility to endometrial cancer, particularly among older and obese women (74). Previous studies have evaluated associations between various CYP19A1 polymorphisms and endometrial cancer risk (75-78). It has been reported that common variants in CYP19A1 (the A alleles of rs749292 and rs727479) are associated with a 10% to 20% increase in circulating estrogen levels in postmenopausal women (74). Given the key role of aromatase in estrogen biosynthesis, it is possible that polymorphisms in CYP19A1 that alter estrogen production could be involved in endometrial carcinogenesis.

4. Obesity and HPV-caused gynecological cancers

Human papillomaviruses (HPVs) are non-enveloped, epitheliotropic, circular double-stranded DNA viruses. Infections with HPVs are the major cause of cervical cancer and other gynecological cancers such as vaginal and vulvar cancers. Cervical cancer that attacks the cervix caused by HPV is the second biggest cause of female cancer mortality worldwide with 288,000 deaths yearly. About 510,000 cases of cervical cancer are reported each year with nearly 80% in developing countries: 68,000 in Africa, 77,000 in Latin America, and 245,000 in Asia (http://www.who.int). This cancer can spread to other organs in the body of the patient when it enters the later stages. Obese or diabetic patients are related to the HPV-caused cancers (79). Obese women

have higher mortality rates for cervical cancer compared with thinner women. Thus, this section will describe the association of obesity with the HPV-caused cancers, particularly cervical cancer, even though the published studies on this topic are very limited.

4.1. Links between diabetes (obesity) and HPV-caused cancers

Patients with type 1 diabetes are more likely to develop cervical and stomach cancers (80). In 1991, it was firstly reported that a 28-year-old woman with diabetes mellitus and alcoholic hepatitis presented a rare case of Buschke Lowenstein tumor, or giant condyloma of vulva. *In situ* hybridization of HPV DNA revealed that the tumor harboured HPV 6b DNA, which distributed in the nucleus of the squamous epithelium showing koilocytosis (81). In 2003, a 34-year-old, nonsmoking nulliparous woman was diagnosed to be an insulin-dependent diabetes mellitus type I patient (82). Another patient developed insulin-dependent diabetes mellitus at 14 years old. This patient who complained of vulvar pruritus and "burning" was further diagnosed to have an intraepithelial neoplasia grade III. HPV typing analysis proved that she was infected by multiple types of HPVs. She was positive for both low- (6, 11, 42, 43, 44) and high-risk types (16, 18, 31, 33, 35, 39, 45) in the vulvar smear (83). When the patient was 36 years old, after induction therapy with antithymocyte serum, simultaneous renal and pancreatic segment transplantation was performed from a cadaver using immunosuppression with azathioprine, prednisolone, and cyclosporine. 22 months after transplantation, an abnormal cervical smear was detected, the cervix of the uterus were excised, leading to detection of cervical intraepithelial neoplasia (CIN I and II) (84). This female pancreas plus kidney transplant patient developed multiple genital malignancies within 6 years. The genome of HPV 16 was detected in malignant lesions obtained from surgical procedure. It appears that immunosuppressed allograft recipients who have diabetes mellitus are at high risk of HPV-related de novo malignancies (84). Recently, Matei M *et al.* (2008) evaluated the risk factors for 105 women who were diagnosed with breast cancer, ovarian cancer, endometrial cancer and cervical cancer in north-eastern region of Romania. They found that both obesity and HPV infections were the mains factors correlated with multiple types of neoplasia, indirectly revealing that obesity was associated with HPV caused- cancers (85). Briefly, the published studies indicate that obesity potentially increases cervical cancer incidences although the increase of obesity paralleled with the cervical cancers is not highly compelling yet.

Pregnancy is an immunosuppressive state to protect foetus. In pregnant diabetics, both abnormalities in cell-mediated immunity and the immunologic modifications concurrently affect immunologic status (86). If the diminished immune responsiveness does depress resistance in diabetic mothers, more frequent infections including latent viral infections may reactivate more readily. Thus, the pregnant diabetics might have an increased risk for HPV infection because of possible immunosuppression (86). However, prevalence studies of

HPV in pregnant women have produced contradictory results, showing either an increase in the frequency of HPV infections (87) or no change (88). Between October 1987-May 1988, Smith EM *et al.* compared 69 pregnant patients with 54 age matched non-pregnant patients at the University of Iowa Medical School Hospital in Iowa City to examine the effect of pregnancy on the prevalence of HPV infection. Almost all cases and controls were white women. They found that pregnant women had more risks for cervical dysplasia and cancer than non-pregnant patients. This is because of activation of latent HPV infection or increased HPV plasmid replication during pregnancy. The researchers hypothesized that high progesterone levels may activate transcriptional HPV replication or change the immune response. Szepietowska *et al.* investigated cervical smears obtained from 50 pregnant patients for the presence of HPV DNA. Four of 50 patients (8%) were detected with HPV DNA. In all cases high-risk types of HPV were found. One patient had a mixed infection with both low- and high-risk types of HPV. According to this study, the diabetic patients seem to be more vulnerable to HPV infection during pregnancy (88). Hietanen *et al.* used exfoliated cells from the uterine cervix, vagina, and posterior commissure of the vulva for HPV infection analysis by means of dot blot hybridization with a probe cocktail of HPV types 11, 16, and 18 under low stringency and by means of consensus primer—mediated PCR targeted to the HPV L1 and E1 regions. Samples from 31 pregnant diabetics whose glucose levels had been reasonably well controlled were analysed. Only one of the pregnant diabetics was positive for HPV L1 DNA for both trimester samples, which were found to represent HPV 61 (86). They claimed that pregnant diabetics do not have an increased risk of developing HPV infection (86). But it is unclear whether the pregnant diabetics had an increased risk for HPV infection if their glucose levels were out of control.

4.2. Lifestyle factors, obesity and HPV-caused cancers

Obesity may modestly increase the incidence of premenopausal ovarian cancer and might potentially increase cervical cancer incidence (13). A considerable body of literature supports that lifestyle factors such as tobacco use, nutrition and physical activity can be risk factors for obese patients who will develop cervical cancers (89, 90). In addition, Eifel, *et al.* (2002) reviewed 3,489 patients treated with radiation therapy for International Federation of Gynecology and Obstetrics stage I or II carcinoma of the cervix for the information about patient characteristics, treatment details, and outcomes (91). These studies state that smoking habits and infrequent intake of vegetables and fruits may be related to the increased risk of cervical cancer by supporting persistent infection of HPV through impaired immunological function (90, 91). High animal fat and energy intakes also increase risk of gynaecological cancers including cervical cancer (89). Childbearing increases the risk of cervical cancer, but is protective against ovarian, endometrial and breast cancer (89). An increased intake of fruit and vegetables can therefore be beneficial for patients with type 2 diabetes since this group of patients is documented to have raised oxidative stress and inflammation. Fruit and vegetable

intake may decrease oxidative stress and inflammation in type 2 diabetes patients. Plasma -carotene and -carotene can be used as biomarkers for fruit and vegetable intake (90). Compared to normal-weight controls, overweight and obese women were significantly less likely to have undergone cervical cancer screening (79, 92-95). Thus, the potential link of obesity to cervical cancer incidences might be a result of the impact on glandular cancers or decreased screening compliance. Women with a BMI>40 have a 60% higher risk of dying from all cancers including cervical cancers than women of normal weight (89). Other studies report further that obesity is associated with higher cervical cancer mortality (96) as obese women are easily experiencing a substantial degree of psychological distress (93). Thus, obese women should be targeted for increased screening (79, 94).

4.3. Mechanisms of obesity-associated with HPV-caused cancers

To date, it is clear that certain types of cancers are associated with HPV infection. Both HPV-16 and HPV-18 types are the causative agent for virtually over 95% of cervical cancer cases (97, 98). The pathogenic mechanisms of cancers caused by HPV infection are well elucidated (99). In high-risk HPV-infected cells, expression of viral oncoproteins (E6 and E7) results in chromosomal instability and in accumulation of mutational events. These "endogenous" events lead to the pathogenesis of premalignant lesions and tumour or cancer progression (99). Although the pathogenic mechanisms of HPV-caused cancers are well elucidated, it remains unclear how obese women develop cervical cancers and what are the pathogenic mechanisms of obesity associated cervical cancers that are caused by HPV infection. The vast majority of cervical cancers are squamous cell cancers. However, approximately 15% are adenocarcinomas, and there have been data supporting an increased incidence of cervical adenocarcinoma (100) . Cervical adenocarcinoma may represent a more hormonally responsive cancer and, potentially, there could be a mitogenic effect of increased estrogen on glandular cervical cancers (100). Based on a 15-years study in S. Anna Hospital, Turin, and the Piedmont and Aosta Valley areas in Italy respectively, more than 30% of adenocarcinoma patients in the 66-80 age group (i.e. over the usual age of 56 to 60) had significantly higher frequency of infertility and delayed menopause. Diabetes, obesity and hypertension are pathogenetically linked to the adenocarcinoma of the endometrium and not to casual associations (101). Thus, it appears that endogenous hormone metabolism plays an important role in association of obesity with this type of cervical cancer.

5. CONCLUSION

In this short review, we have discussed the association of obesity with the incidences of both endometrial and cervical cancers. Based on the epidemiological studies, the increase of obesity is paralleled with the increased incidences of the two cancers although the data on the link of obesity to the cervical cancers is not highly compelling yet. Published studies on

the molecular mechanisms have shown that alterations in the endogenous hormone profiles, production of specific adipose proteins, cytokines and inflammation, and intrinsic genetic factors play a key role in the development and progression of endometrial cancers and cervical adenocarcinoma in obese patients. Mounting evidence shows that nutrition and lifestyle factors favour the development of obesity with excessive adipose tissue. The adipose tissue triggers the production of hormones, cytokines, inflammation and other factors that stimulate the growth of endometrial and other cancer cells. It is clear that obese women with either endometrial or cervical cancer, especially in postmenopausal period, have significantly a higher mortality. The main reason is that the obese women with a higher BMI are more vulnerable to cancer and they are more likely to delay or miss routine cancer screening, which puts them at a greater risk deteriorated prognosis from the endometrial and cervical cancers. It is therefore strongly recommended that healthcare providers pay a particular attention to the screening need of these more vulnerable women.

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Abbreviations: BMI: body mass index; CIN: cervical intraepithelial neoplasia; CRP: C reactive protein; ER: estrogen receptor; GWAS: genome-wide association study; HEC: human endometrial adenocarcinoma; HPVs: Human Papillomaviruses; IGF-1: Insulin-like growth factor 1; IL: interleukins; L/A ratio: leptin-to-adiponectin ratio; Lin-2: Lipocalin-2; PGR: progesterone receptor; PR: progesterone receptor; SPEC: serous papillary endometrial adenocarcinoma; TNF- : tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor.

Key Words: Obesity, Endometrial cancer, Cervical cancer

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