Associations between metabolic syndrome and gynecologic cancer

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Metabolic syndrome (MetS) is a group of risk factors that causes cardiovascular and diabetic morbidity and mortality, which is diagnosed by central obesity, dyslipidemia, hyperglycemia, and hypertension. Increasing epidemiological data and experimental results indicate that the presence of MetS increases the incidence of common malignancies and related mortality. Epidemiological studies have previously reported an association of endometrial cancer occurrence with MetS. Aromatization of androstenedione to estrogen, insulin resistance, and diabetes can cause increased levels of free estrogen, and the detrimental effect of elevated estrogen as a carcinogen is well studied in endometrial cancer. Medications used to manage MetS such as metformin and statins are suggested to reduce endometrial cancer risk and improve survival. Some large population-based epidemiological studies have suggested that the MetS is related to an increased risk of cervical carcinoma. MetS may contribute to viral-host interactions, which lead to persistent human papilloma virus (HPV) infection, although limited epidemiological data are available. Specific effects of obesity and diabetes on the occurrence of ovarian cancer have been suggested. However, the direct correlation between MetS and ovarian cancer is still lacking. Previous retrospective studies reported that the use of metformin, statins, and beta-blockers could be associated with cancer prevention or better prognosis. Proper diagnosis and management of the MetS should be a part of the strategies undertaken to prevent and treat gynecologic cancer. So far, only limited data is available on this subject, and further clinical and fundamental research is required to further clarify the effect of these therapies on gynecologic cancer treatment.

Keywords: Metabolic syndrome; Endometrial cancer; Cervical cancer; Ovarian cancer

Introduction

Incidence of metabolic syndrome (MetS) is increasing worldwide and is becoming an important clinical problem and public health concern in many countries. Economic development, sedentary lifestyle, and westernized dietary patterns are factors affecting the prevalence of MetS. This environment contributes to obesity as seen in many developing and developed countries. MetS is a group of risk factors for cardiovascular complications and diabetes having insulin resistance as the major principal feature. In addition, chronic proinflammatory status is the accompanying underlying characteristic [1]. The diagnostic criteria define MetS as expressing 3 or more of the 5 risk factors: 1) central obesity defined by waist circumference, 2) hyperglycemia, 3) high triglyceride level, 4) low high-density lipoprotein cholesterol level, and 5) hypertension. The World Health Organization (WHO) suggested a clinical definition for MetS in 1998. Since then, several modified definitions have been proposed for the diagnosis of MetS. Among them, the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATP III) definition has been widely accepted. According to this criteria, MetS is diagnosed as follows: 1) waist circumference: ≥102 cm in men and ≥88 cm in women (≥90 cm in men and...
Metabolic syndrome components and risk of cancer in women

The pathophysiological mechanisms through which obesity, dyslipidemia, and hyperglycemia contribute to carcinogenesis are clearer than the mechanism correlating hypertension to carcinogenesis. The effects of these components on the development of cancer, especially on the gynecologic cancer are briefly described in the following paragraphs.

1. Obesity and cancer

Central obesity, defined by increased waist circumference or increased body mass index (BMI), has been related to a higher incidence of many kinds of malignancies as well as to higher morbidity and mortality in those cancers [4].

In addition to energy storage, the adipose tissue functions as an endocrine organ that regulates the hormones and cytokines such as sex steroids, leptin, adipokines, tumor necrosis factor (TNF)-alpha, and plasminogen activator inhibitor-1 [5]. Disarrangements in the regulation of these substances and lack of capacity to store the extra free fatty acids in fatty cells leads to chronic inflammation and related carcinogenesis [6].

An association between obesity and increased cancer incidence has been reported for female-specific cancers including ovarian, endometrial, and breast cancer. For example, a recent prospective cohort study involving 1.2 million UK women showed that higher BMI was associated with an increased incidence of endometrial cancer (relative risk [RR] per 10 units, 2.89, 95% confidence interval [CI], 2.62–3.18), ovarian cancer (RR, 1.14; 95% CI, 1.03–1.27), and breast cancer in postmenopausal women (RR, 1.40; 95% CI, 1.31–1.49) [7]. When considering the menopausal status, there was an increased risk of endometrial and breast cancer in women with menopause.

The mechanism by which adiposity contributes to the development of these cancers in women can be deduced as follows: in postmenopausal women, adipose tissue becomes the major organ synthesizing estrogens [8]. Accordingly, compared with normal postmenopausal women, obese postmenopausal women show increased total and free serum estrogen levels. In addition, increased central adiposity contributes to a reduction in hepatic synthesis and blood concentrations of sex hormone-binding globulin (SHBG) which results in an increased fraction of bioavailable estradiol. Estrogens contribute to either tumor development and progression by induction of cellular proliferation and inhibition of cell apoptosis through the estrogen receptor-α. Estrogens also stimulate angiogenesis through vascular endothelial growth factor secretion [9]. Moreover, carcinogenesis can be induced by the mutagenic effects of estrogen through genotoxic metabolites [10]. Epidemiological studies suggested that this increased concentration of circulating sex steroids could elucidate the correlations between anthropometric parameters reflecting obesity and the occurrence of endometrial cancer (both in pre and postmenopausal women) and breast cancer (only in postmenopausal women) [11,12].

Increased adiposity in cancer patients may also have detrimental effects on treatment outcomes and mortality. For ex-
ample, obesity has been reported to be a negative prognostic factor for breast cancer [13].

2. Hyperinsulinemia, hyperglycemia, and cancer

Insulin resistance is considered as the most important mechanism involved in the relationship between obesity, hyperglycemia, and carcinogenesis. Chronic hyperinsulinemia is reported to be correlated with various types of cancer including endometrial and breast cancer [14].

Hyperinsulinemia caused by insulin resistance and subsequent hyperglycemia triggers carcinogenesis indirectly by increasing circulating levels of free insulin-like growth factor (IGF)-1. Receptors for insulin and IGF-1 are observed in most types of cancer tissues. The insulin receptor can activate signaling pathways that stimulate cancer cell proliferation, protect cancer cells from apoptotic stimulation, and promote invasion and metastasis of cancer cells. These receptors also stimulate normal cells including vascular smooth muscle cells to proliferate and migrate, and these processes can promote cancer progression [15].

Along with this process, impaired glucose management and hyperglycemia can promote cancer cell proliferation. This theory is supported by the increased glucose transporting proteins such as glucose transporter-1 (GLUT-1) in the cancer cells to support high glucose demands for cancer growth [16].

High levels of glucose promote cancer cell invasion and metastasis through stimulation of epithelial-mesenchymal transition (EMT) which acts as a crucial pathway for the acquisition of migration, invasion, and pluripotent stem cell-like phenotype [17]. A recent study proposed that the EMT phenotype and the expression of cancer stem cell markers in basal luminal breast cancer are induced by hyperglycemic status. These environments lead to a reduced generation of reactive oxygen species (ROS) and increased tumor cell survival. Hyperglycemia also acts as an important factor to support the rapid proliferation of cancer tissue [18]. Aggressively growing cancer tissues often are characterized by an increased expression of GLUT-1 resulting in elevated glucose uptake, a metabolic shift to anaerobe glycolysis and contributing to increased lactate production.

3. Dyslipidemia and cancer

Elevated triglyceride and suppressed HDL-cholesterol also act as risk factors for cancer. The mechanism by which hypertriglyceridermia stimulates cancer cell proliferation and promotes anti-apoptotic capacity is through the activation of ROS synthesis and DNA damage caused by this detrimental stress [3]. Several studies reported that hypertriglyceridermia has been associated with a higher prevalence of cervical cancer [19,20] and postmenopausal breast cancer [21].

Epidemiological evidence supports the association of decreased HDL-cholesterol with certain types of cancer development. One large-scale population-based epidemiological study reported the correlation of cervical carcinoma with a low serum HDL-cholesterol level [22]. Low HDL-cholesterol serum levels were reported to be a risk factor for increased breast cancer in pre- and postmenopausal women. This status might imply an unfavorable hormonal status with particularly elevated estrogen levels especially in obese women [23].

Endometrial cancer

1. Epidemiological correlation between metabolic syndrome and endometrial cancer

Epidemiologic studies have reported correlations of endometrial cancer risk with each component of the MetS, including obesity, diabetes, and hypertension. Recently, Esposito et al. [24], meta-analyzed the existing studies to clarify the epidemiologic relationship. This analysis included 3,132 endometrial cancer patients, and MetS was correlated with a significantly increased risk of endometrial cancer in all studies (RR, 1.89; 95% CI, 1.34–2.67). Among the components of MetS, obesity (measured by waist circumference) was a major component that was significantly correlated with endometrial cancer than other components (e.g. diabetes or hypertension), and the effect of obesity alone was more pronounced than the entire metabolic syndrome. Besides, diabetes, hypertension and high serum level of triglycerides were significantly correlated with a higher risk for endometrial cancer. However, no significant correlation between low HDL-cholesterol and endometrial cancer was observed.

Trabert et al. [25], conducted a large population-based case-control study including 16,323 cases and 100,751 controls. This study reaffirmed the existing results; endometrial cancer risk was correlated with MetS with RR, 1.39 (95% CI, 1.32–1.47). Among the MetS components, overweight or obesity (RR, 1.95; 95% CI, 1.80–2.11), elevated fasting glucose (RR, 1.36; 95% CI, 1.30–1.43), high blood pressure (RR, 1.31; 95% CI, 1.25–1.36), and elevated serum triglycerides
(RR, 1.13; 95% CI, 1.08–1.18) were significantly related with increased incidence of endometrial cancer.

In addition, the effects of MetS components on the treatment of endometrial cancer were investigated, and Ko et al. [26], reported that diabetes was related to an elevated incidence of recurrence and worse overall survival in women treated for type I endometrial cancer.

2. Effects of metabolic syndrome on the pathophysiology of endometrial cancer

Aromatization from androstenedione to estrogen is processed in adipose cells, and elevated free estrogen with decreased serum levels of SHBG are accompanied by obesity [27]. Diabetes and Insulin resistance are also correlated with decreased serum SHBG [28], which can promote increased levels of free estrogen. The pathophysiologic evidence for elevated free estrogen as a carcinogen is well described, especially in endometrial cancer. Constant mitogenic stimulation of the endometrium through chronic estrogen stimulation is thought to be a major factor. Moreover, the elevated IGF-1 in obesity and hyperinsulinemia has been related to cell proliferation and may play a role in the development of hyperplasia and neoplastic transformation of endometrial tissue. Endometrial tumor tissues are reported to express elevated levels of IGF-I and insulin receptors [29].

3. Management of metabolic syndrome and prognosis of endometrial cancer

Several epidemiologic studies have suggested that medications generally prescribed to patients with MetS have a positive effect on outcomes in endometrial cancer patients besides the hypoglycemic effect [30]. Clinical studies have shown that treatment with metformin was related to a decreased risk of mortality in patients with endometrial cancer [31,32]. One of the mechanisms of action is the activation of 5’-adenosine monophosphate-activated protein kinase (AMPK) and concurrent inhibition of the mammalian target of rapamycin (mTOR) cascade which may contribute to antiproliferative effects of metformin [33,34]. Besides, several plausible mechanisms have been reported for the effects of metformin to restrain cancer growth. These potential mechanisms include liver kinase b1/AMPK pathway activation, inhibition of protein synthesis, induction of cell cycle arrest and apoptosis, decrease in serum insulin concentrations, activation of the immune system, and suppression of cancer stem cells [35]. Some authors reported that the treatment with metformin was correlated with favorable outcomes after chemotherapy by potentiating these pathways [36].

Statins are prescribed to decrease cholesterol levels in dyslipidemia patients to manage and prevent cardiovascular diseases. These agents inhibit the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase and blocks protein prenylation through the suppression of the mevalonate pathway. These result in the suppression of the downstream cholesterol biosynthesis pathway and inhibited production of many types of isoprenoid metabolites including farnesyl pyrophosphate and geranyl pyrophosphate. Isoprenoid biosynthesis is essential for a variety of cancer cell growth-related cellular processes and for the initiation of cancer cell metastasis. As a result, statins block these pathways which contribute to the anticancer activity [37]. Other mechanisms include the induction of tumor cell apoptosis [38], suppression of RhoA and other guanosine triphosphatase binding proteins which is upregulated in several human malignancies [39]. Based on these theoretical bases, Lavie et al. [40], reported that statins are associated with decreased cancer risk and improved survival in endometrial cancer. The risk reduction effect was observed when statins were administrated for more than 1 year before diagnosis.

Cervical cancer

1. Epidemiological correlation between metabolic syndrome and cervical cancer

Cervical cancer is the second most common malignancy among women all over the world with a majority of the cases observed in the developing countries. Previous epidemiological studies have shown correlations between different types of metabolic syndrome components and the incidence of cervical cancer [19,41]. However, there is not enough information about the correlation between MetS and cervical cancer compared to endometrial cancer. Though some epidemiological studies do suggest that the MetS is correlated with an elevated risk of cervical cancer.

Penaranda et al. [22] reported the outcome of a case-control study using data from the U.S. population survey analysis. Among 26,393,229 women, 585,924 (2.3%) of this cohort (cases) declared a history of cervical cancer. Among them, 48.6% of individuals met the MetS criteria compared
to 33.2% of controls (P=0.0768). Logistic regression analysis reported that cervical cancer patients had higher odds of MetS in both unadjusted (odds ratio [OR], 1.91; 95% CI, 1.06–3.42), and covariates adjusted patients, including multiple lifetime sexual partners, higher parity, hormonal contraceptive use, and history of smoking (adjusted OR, 1.82; 95% CI, 1.02–3.26; P=0.0428). When each component of the MetS was analyzed separately, none of the specific components were significantly correlated with cervical cancer. Ulmer et al. [42], reported the results of a prospective cohort during mean follow up duration of 11 years. Among 288,834 cohort population, 425 cases of invasive cervical cancer were diagnosed. According to Cox proportional hazards regression model analysis, the MetS score was correlated with 26% elevated corrected risk of cervical cancer. Triglyceride levels revealed higher association with squamous cell cervical carcinoma (hazard ratio [HR], 1.48; 95% CI, 1.20–1.83) than with adenocarcinoma (HR, 0.92; 95% CI, 0.54–1.56). Compared with the results of Penaranda et al. [22], individual MetS components of obesity, higher blood pressure, and serum triglycerides respectively were correlated with increased incidence of cervical cancer.

According to these results, women with MetS would have an increased risk of experiencing cervical cancer compared to women without MetS. In the pathophysiological aspect, estrogen, adipokine, and cytokine have been reported to be correlated with cervical cancer suggesting metabolic syndrome components could act as cofactors in the carcinogenesis of cervical carcinoma [43,44]. These preceding associations support the growing body of evidence that there is a pathophysiological correlation between metabolic disarrangements observed in MetS and carcinogenesis of cervical cancer.

**2. Effects of metabolic syndrome on the development of cervical cancer through the human papilloma virus**

Previous epidemiologic studies suggested that MetS may play a role in virus and host interactions which is essential for persistent human papilloma virus (HPV) infection. This interaction is a fundamental factor in the development of cervical cancer. The causal correlation between infection with the HPV and the progress of cervical cancer has been established through decades of accumulated evidence.

Recent studies explored the influence of MetS on HPV infection among women. Huang et al., reported that the morbidity of MetS increased the risk of HPV infection in females (RR, 1.25; 95% CI, 1.09–1.46) [45]. Molokwu et al. [46], studied a male cohort that could serve as mediators of both the HPV and the female population. In this report, MetS was reported to be significantly correlated with an elevated risk of HPV 6, 11, 16, or 18 infection in the total cohort (RR, 1.24; 95% CI, 1.03–1.48) and in the female cohort (RR, 1.26; 95% CI, 1.02–1.56) [46]. However, some controversy also exists, as Liu et al. [47] reported there was no significant relationship between MetS and HPV infection among females. In a study examining the risk factors of cytological progression in Korean women infected with HPV 16, women with BMI ≥25 showed a relative risk of 1.71 compared to women with BMI <25, but there was no statistical significance (95% CI, 0.45–6.47) [48]. The study was based on fewer than 100 subjects, so larger studies will be needed to obtain clearer conclusions.

There are some pathophysiological evidence indicating that MetS components could promote carcinogenesis. An increase of adipokines (e.g., resistin), inflammatory markers (e.g., soluble Fas), and cytokines (e.g. interleukin [IL]-6, TNF-α) has been observed in women with persistent HPV infection [44,49]. These reports suggest that obesity is correlated with persistent HPV infection. Pathophysiological mechanisms through which hypertension increases the risk for HPV infection include hypertension-induced hypoxia, which in turn promotes angiogenesis through activation of hypoxia-inducible factor-1 [50]. This activation of angiogenesis has been described as a crucial pathway for the persistent infection and progression of the HPV lesions by supporting increased requirements of growing HPV lesions for nutrients and oxygen [51]. Insulin and IGFs stimulate invasive potential and proliferation of cervical cancer cells and were reported to be correlated with HPV infection [52]. Animal model from mouse reveals that estrogen and its nuclear receptor contribute to the initiation of cervical carcinogenesis by synergistic effect with the HPV oncogene [43].

**3. Effects of metabolic syndrome on the prognosis of cervical cancer treatment**

To investigate the effect of MetS on prognosis of cervical cancer after treatment, Ahn et al. [53], reported the correlation between MetS and recurrence-free survival (RFS) in patients with early-stage cervical cancer through a retro-
perspective study which assessed the patients diagnosed with the International Federation of Gynecology and Obstetrics (FIGO) stage I–II cervical cancer [53]. According to the study, RFS was not significantly different based on the presence of MetS. Among the components of MetS, hypertriglyceridemia (HR, 3.67; 95% CI, 1.18–11.43) and higher fasting glucose (HR, 4.30; 95% CI, 1.23–15.03) were suggested as independent risk factors for decreased RFS after adjustment for possible compounding factors. However, there is little epidemiological data available so far, and prospective validation in large populations is warranted.

**Ovarian cancer**

1. Epidemiological correlation between metabolic syndrome and ovarian cancer

Compared to other gynecologic cancers, there are relatively few studies that have directly analyzed the correlation between MetS and incidence of ovarian cancer. Although, there are some reports that analyzed the correlation between specific components of MetS and ovarian cancer.

Obesity has been reported to be correlated with the occurrence of ovarian cancer. The Collaborative Group on Epidemiological Studies of Ovarian Cancer performed a meta-analysis of 47 studies including 25,157 cases of ovarian cancer and reported a 10% increase in ovarian cancer risk per 5 kg/m² [54]. A prospective cohort study on 70,258 Chinese women addressed that women with a BMI of 30 or above had a 2-fold increased risk of ovarian cancer [55]. On the other hand, there is some controversy. Olsen et al. [56], analyzed studies from medical centers in the Ovarian Cancer Association Consortium and reported that elevated BMI was not correlated with high grade serous ovarian cancer.

Moreover, there are studies proposing that obesity may also be correlated with decreased overall survival in ovarian cancer patients. The meta-analysis of 14 studies analyzed by Protani et al. [57], presented a slightly decreased survival rate among obese women than in non-obese women (pooled HR, 1.17; 95% CI, 1.03–1.34). High leptin to adiponectin ratio was associated with decreased survival rate as observed in colorectal, breast, gastric and renal cancers [58]. Pavelka et al. [59], reported that in patients with advanced stages of ovarian cancer, obesity was independently associated with both shorter time to recurrence and lower overall survival. However, the effects of MetS on the prognosis of ovarian cancer are controversial. There are also studies reporting that obese women had a better prognosis after treatment for ovarian cancer [60]. According to a previous study showing higher rates of residual disease after debulking surgery in women with low BMI [61], factors other than MetS metabolic components may affect the prognosis after cancer treatment.

There is relatively little information analyzing the effects of diabetes on ovarian cancer incidence and prognosis. Shah et al. [62], analyzed 367 patients with epithelial ovarian cancer in the U.S. and reported that diabetes was correlated with an elevated risk of recurrence and mortality in women with ovarian cancer.

As described, the respective effects of obesity and diabetes on ovarian cancer risk have been analyzed, and it could be expected that MetS would increase the incidence of ovarian cancer. Although, there is still insufficient evidence on the effects of MetS on ovarian cancer risk and whether it is more obvious than the individual effects of obesity and diabetes.

The process of revealing this relationship through population-based analysis is required for the future.

2. Effects of metabolic syndrome on the progression and metastasis of ovarian cancer

The etiological association between obesity, diabetes, and ovarian cancer is not clear, however, the available data provide some clues. According to a previous study, direct interactions between adipocytes and cancer cells have been suggested to stimulate tumor growth. For example, omental tissue is the most common site of ovarian cancer metastasis and secretion of cytokines such as IL-6 and IL-8 produced by adipocytes in the omentum has been reported to promote homing, migration, and invasion of ovarian cancer cells [63]. Moreover, secretion of free fatty acids originated from elevated lipolysis in omental adipocytes has been suggested as an energy source for proliferating ovarian cancer metastasis.

As described above, insulin resistance is associated with decreased serum SHBG and elevated free estrogen. A recent experimental study on the murine model suggested that elevated estrogen may play a role in promoting ovarian cancer growth [64].

3. Management of metabolic syndrome and prognosis of ovarian cancer

Preceding retrospective studies reported that the use of met-
formin, statins, and beta-blockers is correlated with better prognosis in ovarian cancer treatment.

A meta-analysis of existing observational studies reported that metformin may decrease the incidence of ovarian cancer in diabetic patients with an odds ratio of 0.57 (95% CI, 0.16–1.99) [65]. The studies analyzing the effects on survival rates reported that metformin may improve overall, disease-specific, and progression-free survival after ovarian cancer treatment [65]. In vitro study suggested that metformin significantly suppresses the growth of ovarian cancer cell lineages and potentiates the therapeutic effect of cisplatin through its anti-proliferative property [66]. These findings suggest the possible therapeutic effects of metformin on the prevention and prognosis of ovarian cancer. Although, most of the existing evidence was retrospective observational studies with small subjects.

As discussed in endometrial cancer, statins block the pathways related to carcinogenesis and may contribute to the anticancer activity. Lavie et al. [40], reported that the treatment with statins possibly reduces the incidence of ovarian malignancies and improves the survival rate.

Stress hormones may stimulate ovarian cancer progression through multiple mechanisms including autonomic nervous system mediators such as epinephrine and norepinephrine [67,68]. These signals significantly elevate vascular endothelial growth factor and matrix metalloproteinase production which contribute to carcinogenesis and cancer progression. Beta-blockers used to manage hypertension, inhibit the production of these unfavorable adrenergic hormones, and are proved to be correlated with better survival in several cancers [69,70]. Based on this background, Diaz et al. [71], performed a retrospective study and reported that the use of beta-blockers correlated with decreased risk of recurrence and overall survival in women with ovarian cancer.

Conclusions

Preceding epidemiological data have reported a correlation between MetS or its diagnostic components and gynecologic cancer development and prognosis. Each component of MetS and associated metabolic disarrangements are proved to have a correlation with cancer development through experimental studies. However, it is still being debated whether the effects of each component are additive or synergistic. In this situation, further epidemiological and experimental studies are essential to clarify these findings.

Several clinical studies postulated that medications used to manage MetS have a preventive effect on cancer development. In addition, some clinical and experimental studies suggested the favorable effect of these medications on the prognosis, morbidity, and mortality of cancer treatment.

In view of these existing findings, addressing and managing MetS should be a part of the strategies undertaken to prevent and treat gynecologic cancer. So far, only limited data is available, and further clinical and fundamental research is required for robust conclusions.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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