

Association between Metabolic Syndrome and Cancer

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Key Words

Metabolic syndrome · Cancer · Hyperlipidemia · Obesity · Hypertension

Abstract

Growing data show the association of metabolic syndrome (MetS) or its components with cancer development and cancer-related mortality. It is suggested that in MetS and cancer association, insulin resistance and insulin-like growth factor 1 system play a key role, especially adipokines secreted from visceral adipocytes, free fatty acids and aromatase activity contribute to this process. It is also reported that MetS has a link with colorectal, breast, endometrial, pancreas, primary liver and, although controversial, prostate cancer. Although every component of MetS is known to have an association with cancer development, it is still debated whether the effects of these components are additive or synergistic. On the other hand, in the association between MetS and cancer, the role of antidiabetic and antihypertensive treatments including thiazolidinedione, insulin, angiotensin receptor blockers is also suggested. The primary approach in MetS-cancer relation is to prevent risk factors. Life style changes including weight loss and a healthy diet are known to decrease cancer risk in normal population. It is postulated that an insulin-sensitizing agent, metformin, has cancer-preventing effects on

diabetic patients. This review discusses the relationship between MetS and cancer from different aspects and examines this relationship in some of the cancers suggested to be linked with MetS.

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Introduction

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors characterized with obesity, hypertension, atherogenic dyslipidemia, hyperglycemia, prothrombotic and proinflammatory states [1, 2]. Moreover, growing data show the association of MetS or its components with cancer development and cancer-related mortality.

MetS and Cancer Risk; Epidemiological Data

It is shown in cohort studies and meta-analyses that MetS increases cancer risk. In a population-based study, which recruited 16,667 individuals with an age higher than forty and assessed 45,828 person years in cases with MetS; it is reported that pancreas cancer risk has increased in men (standardized incidence rate 178 (114–266)) and

Table 1. Examples of cohorts and cancer sites according to MetS components

MetS component	Cohort	Related cancer sites	Results
Increase in WC and or BMI (Calle et al. [8], 2003)	900,000 US adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982, 16 years of follow-up BMI (35 vs. 18–24.9 kg/m ²): cancer mortality	All cancers Breast Endometrial Cervix Prostate Colorectal Pancreatic Liver Renal Esophageal Stomach Non-Hodgkin's lymphoma	RR M 1.52 (1.13, 2.05), F 1.62 (1.40, 1.87) RR F 2.12 (1.41, 3.19) RR F 6.25 (3.75, 10.42) RR F 3.20 (1.77, 5.78) RR M 1.34 (0.98, 1.83) RR M 1.84 (1.39, 2.41), F 1.46 (0.94, 2.24) RR M 1.49 (0.99, 2.22), F 2.76 (1.74, 4.36) RR M 4.52 (2.94, 6.94), F 1.68 (0.93, 3.05) RR M 1.70 (0.99, 2.92), F 4.75 (2.50, 9.04) RR M 1.63 (0.95, 2.80) RR M 1.94 (1.21, 3.13), F 1.08 (0.61, 1.89) RR M 1.49 (0.93, 2.39), F 1.95 (1.39, 2.72)
Hyperglycemia (Esposito et al. [4], 2012)	1,298,385 Koreans (829,770 M and 468,615 F) age 30–95 years, 10 years follow-up	Pancreatic cancer	M 1.91; 95% CI 1.52–2.41 F 2.05; 95% CI 1.43–2.93
Dyslipidemia (Kucharska-Newton et al. [17], 2008)	14,545 adults (6,569 M and 7,978 F), 13 years follow-up	Lung	Hazard ratio 1.45 (95% CI 1.10–1.92)
Hypertension (Grossman et al. [21], 2002)	In 13 case-control studies, including 6,964 cases of renal cell cancer and 9,181 controls	Renal cell cancer	The adjusted OR for among hypertensive patients, relative to normotensive counterparts, was 1.75 (95% CI 1.61–1.90)

colorectal cancer risk has increased in women (standardized incidence rate 133 (101–170)) [3]. In a meta-analysis that has evaluated 38,940 cancer cases, although difference demonstrated according to sex, population, MetS definitions used, the presence of MetS has been shown to be in association with liver (1.58, $p < 0.0001$), colorectal (1.25, $p < 0.001$) and bladder (1.10, $p = 0.013$) cancer in men and endometrial (1.61, $p = 0.001$), pancreas (1.58, $p < 0.0001$), postmenopausal breast (1.56, $p = 0.017$), rectal (1.52, $p = 0.005$) and colorectal (1.34, $p = 0.006$) cancer in women [4].

MetS and Cancer-Related Mortality

Cancer-related mortality is reported to be high in cases with MetS [5]. In a 14-year follow-up of 33,230 male cases (28% with MetS) aged between 20 and 88 with no known cancer at baseline, patients with MetS were associated with a 56% greater age-adjusted risk in cancer mortality. Mortality risk was 83% higher in individuals with 3 or more MetS components than those with none [6]. In the 'Risk Factors and Life Expectancy Project' study, 21,311 male and 15,991 women were followed for an av-

erage period of 7 years. Results showed that a cluster of MetS components has increased colorectal cancer mortality significantly (hazard ratio (HR) 2.96 (1.05–8.31) for male, HR 2.71 (0.59–12.50) for female, HR 2.99 (1.27–7.01) combined) [7].

MetS Components and Cancer Risk

Although every component of MetS is known to have an association with cancer development (table 1), it is still debated whether the effects of these components are additive or synergistic.

Obesity and Cancer

Being overweight and obese has been reported to be responsible for death in 14% of men and 20% of women [8]. Epidemiological studies have demonstrated that an increase in waist circumference and/or body mass index (BMI) has an association with colon, postmenopausal breast, endometrium, esophagus, liver, gallbladder, gastric (cardia) and kidney cancer development [9]. In the pathophysiology of obesity and cancer relationship, insulin resistance is found to play an essential role. Chronic

elevated insulin levels related to insulin resistance increases the bioavailability of insulin-like growth factor (IGF)-1; meanwhile, an increase in endogenous estrogen levels and bioavailability play an important role in cancer development especially in hormone-dependent cancers [10].

Hyperglycemia and Cancer

Hyperglycemia and cancer development are associated independent of BMI [11]. In a population-based study [12] in which 140,000 adults (63,585 male, 77,228 female) were followed for an average of 8.4 years, elevation of fasting plasma glucose was found to be associated with cancer development (HR 1.20; 95% CI 1.03–1.39 in male, 1.28; 95% CI 1.08–1.53 in female), and the strongest association was observed with hepatocellular cancer in men (HR 4.58; 95% CI 1.81–11.62).

In a 10-year follow-up of 1,298,385 Korean adults (829,770 male and 468,615 female), fasting glucose levels were found to be in association with increase in pancreas, liver and renal cancer and it is reported that mortality risk was increased in individuals with plasma glucose ≥ 140 mg/dl than those with plasma glucose < 90 mg/dl in all cancer types (HR 1.29; 95% CI 1.22–1.37 in males, HR 1.23; 95% CI 1.09–1.39 in females). The strongest association in both sexes were observed with pancreas cancer (HR 1.91; 95% CI 1.52–2.41 in males, HR 2.05; 95% CI 1.43–2.93 in females) [13]. It is stated that colorectal cancer risk is increased both in men and women with type 2 diabetes and this is associated with colon cell proliferation triggered by hyperinsulinemia and increase free IGF-1 levels [14, 15]. It is also shown that chronic insulin treatment is associated with increased colorectal adenoma risk in type 2 diabetic patients [16].

Dyslipidemia and Cancer

Low high density lipoprotein (HDL) cholesterol levels are reported to be in relation with an increase in lung cancer incidence, and in individuals with very low HDL cholesterol (≤ 20 mg/dl), cancer risk has increased 6.5 fold [17, 18]. High triglyceride levels are shown to be in association with prostate cancer in men [19]. Low-density lipoprotein cholesterol levels have been found to be associated with hematologic malignancy development (approximately 15-fold increase) [20].

Hypertension and Cancer

Although there is no clear data revealing a link between hypertension and cancer development, it is suggested that it is in relation with increased cancer mortality, and inhibition of apoptosis may have a role in this. In

a meta-analysis that included 10 prospective studies, the mean 9–20-year follow-up of 47,119 hypertensive cases, OR for cancer mortality was found to be 1.23 (1.11–1.36) [21].

Possible Mechanisms of MetS and Cancer Association

It is proposed that obesity, inflammation and insulin resistance are all interconnected and this is potentially as a result of adipose tissue hypoxemia. It is also stated that development of insulin resistance in obese individuals is associated with tumor necrosis factor alpha (TNF- α) secreted from adipose tissue impairing intracellular insulin signal cascade, elevation in free fatty acid levels, decrease in adiponectin levels and also inhibition of peroxisome proliferator-activated receptor gamma by TNF- α and interleukin (IL)-1 stimulated with nuclear factor kappa B (NF- κ B) [22].

Insulin resistance/hyperinsulinemia/IGF-1 system: it is accepted that hyperinsulinemia/insulin resistance is the primary mechanism responsible for many manifestations of MetS. The strongest evidence in MetS and cancer association focuses on obesity and hyperinsulinemia/insulin resistance. Insulin is a major anabolic hormone that stimulates cell proliferation and its effect on cancer cell proliferation is suggested to be with IGF-1 stimulation. Growth hormone is the primary stimulant for IGF-1 production in liver and insulin stimulates IGF-1 production in liver by upregulating growth hormone receptors. Hyperinsulinemia also increases IGF-1 bioavailability by decreasing hepatic secretion of IGF-binding protein-1 and 2 [23]. IGF receptor is overexpressed in breast and colon cancers and its activation activates the p21 ras/mitogen-activated protein kinase (MAPK) pathway and phosphatidylinositol-3 kinase/AKT pathway for cell proliferation [24].

Among the proliferative and anti-apoptotic characteristics of IGF, its angiogenetic effect (due to vascular endothelial growth factor (VEGF)) is also suggested to play an important role in colon, endometrium, breast and prostate cancer development [24, 25]. On the other hand, it is reported that hyperinsulinemia and IGF-1 inhibit sex-binding globulin synthesis in liver increasing bioavailability of sex hormones and this may have a role in hormone-dependent cancers like breast, endometrium and prostate cancer [26].

Aromatase Activity. The most important estrogen source after menopause is aromatization of androgens in

adipose tissue with cytochrome p450 enzyme complex. In obese women (especially visceral obesity), an increase of estrogen bioavailability with the effect of insulin and IGF-1 and an increase in estrogen synthesis due to aromatization in adipose tissue are considered to be the most important factors in the development of breast and endometrium cancer in postmenopausal women [27, 28].

Adipokines. Adipokines are a group of signal molecules, which play a role in appetite and energy balance, inflammation, insulin sensitivity, angiogenesis, lipid metabolism, cell proliferation and atherosclerosis [29]. Most of these functions are postulated to be in association with MetS and cancer and to have a role in the relationship between them.

Leptin. Leptin is a hormone secreted from adipocytes, causing the inhibition of appetite with metabolic signal and increase in basal metabolism. Obese individuals have hyperleptinemia due to leptin resistance and therefore, are more sensitive to MetS. It is suggested that high leptin levels are associated with prostate, colon, breast and endometrium cancer, and the cell proliferation effect of leptin via MAPK signal may have a role in this. On the other hand, it is also suggested that leptin may stimulate angiogenesis and increase the expression of matrix metalloproteinase-2 and contribute to cancer metastasis [30].

Adiponectin. Contrary to other hormones secreted from adipocytes, adiponectin levels are low in obese patients. It is known that adiponectin increases insulin sensitivity in muscle and liver with 5'-adenosine monophosphate-activated protein kinase (AMPK) pathway, decreases plasma free fatty acid concentration and have anti-inflammatory anti-atherosclerotic properties [31]. It is considered that adiponectin is inversely correlated with breast, endometrium and gastric cancer risk and this is associated with its ameliorating effect on insulin resistance and its antiproliferative, antiapoptotic and anti-inflammatory effects [32].

VEGF. Angiogenesis is a critical process for tumor development and metastasis. The secretion of VEGF, the most important proangiogenic factor secreted from adipocytes (only visceral adipose tissue), is stimulated by insulin, IGF-1, estrogen, leptin, TNF- α and hypoxia [33].

Cytokines and Prostaglandins. Cyclooxygenase-2 (COX-2) is overexpressed in many types of cancer including colon, breast, prostate and pancreas cancer. Its contribution to carcinogenesis results from its stimulating effects on the increase in prostaglandin production, conversion of procarcinogens to carcinogens, inhibition of apoptosis, stimulation of angiogenesis, modulation of inflammation and

immune function and increase in tumor cell invasion. These properties place COX-2 as a perfect target for the prevention and treatment of human cancers [34].

Proinflammatory Cytokines. After the discovery of an association between TNF- α and insulin resistance [35], more cytokines were under focus to identify similar associations, including IL-1 β , IL-6, IL-8, IL-10, macrophage inflammatory protein-1, monocyte chemoattractant protein-1. For instance, TNF- α and IL-1 β activate IKK β /NF- κ B and JNK pathways in adipocytes, hepatocytes, and associated macrophages and cause insulin resistance [36, 37]. Inflammation is related with many cancer types, including gastric, pancreas, esophagus, liver, gall bladder and colorectal cancer. El-Omar et al. showed that carriage of multiple proinflammatory polymorphisms of IL-1B, IL-1 receptor antagonist, TNF- α , and IL-10 conferred greater risk, with ORs (and 95% CIs) of 2.8 (1.6–5.1) for one, 5.4 (2.7–10.6) for 2, and 27.3 (7.4–99.8) for 3 or 4 high-risk genotypes [38]. Aforementioned cytokines also lead to cancer cachexia, thereby increasing cancer-related mortality. In a study by Mantovani et al. serum levels of IL-1 α , IL-6, and TNF α were significantly higher in cancer patients than in healthy individuals [39]. It is found that cytokines, reactive oxygen products and inflammatory pathways (NF- κ B) cause cancer by decreasing the tumor-suppression function with increasing cell cycle and stimulation of oncogene expression [40].

Examples of MetS and Cancer Association

MetS and Colorectal Cancer

Epidemiological data reveal that colorectal cancer and adenoma risk is increased in patients with MetS. In a study from Korea, it is shown that abdominal obesity causes an independent increase in precancerous lesion risk [41]. In another study consisting of 368,277 cases, a high BMI and excess weight have a positive relationship with colon cancer only in men and an increase in waist circumference has a positive relationship in both men and women [42]. In 'Physicians' Health Study' (22,046 male physicians), it is demonstrated that colorectal cancer risk is increased 1.4 fold in individuals with 2 or more MetS components than those who have none, and the highest risk increase was observed with obesity and diabetes [43].

The male gender is thought to be affected from MetS and cancer relation more than the female gender. In a study investigating the association of MetS and its com-

ponents with colorectal cancer, it is found that only in men there is a direct relation with both colon and rectum cancer as shown by Pelucchi et al. [44]. Another population-based cohort study has shown that the presence of MetS increases colorectal cancer risk only in men (RR 1.78; 95% CI 1.0–3.6) [45].

It is postulated that the increased risk of colorectal cancer in men than in women with MetS may be caused due to differences in adipose tissue distribution [46].

MetS and Breast Cancer

Growing data show the association between MetS components and insulin resistance with postmenopausal breast cancer, and the presence of MetS is considered a poor prognosis indicator [47]. Between 1983 and 2007, in 2 case-control study analyses of 3,869 postmenopausal women with breast cancer and 4,082 postmenopausal control cases, it is demonstrated that postmenopausal breast cancer is higher in women with MetS than those without (OR 1.75; 95% CI 1.37–2.22) and risk increases more in women older than 70 (OR 3.04; 95% CI 1.75–5.29) [48]. In relationship between breast cancer and MetS, the production of extra gonadal estrogen, increase in estrogen bioavailability due to low sex hormone binding globulin levels and mitogenic effect on both non-transformed and neoplastic breast epithelial cells triggered by insulin resistance and hyperinsulinemia are suggested to play key roles [49].

MetS and Prostate Cancer

Although there are prospective studies showing the association between MetS and prostate cancer, there are also other studies reporting a decrease in prostate cancer in individuals with MetS [50]. Conflicting results are also suggested regarding the link between obesity and prostate cancer. For example, in an analysis evaluating 31 cohort and 25 case-control studies, for every 5 kg/m² increase in BMI, relative risk for prostate cancer was found 1.05, and a higher risk was observed in patients with progressed diseases than localized diseases [51]. On the other hand, in a population-based case-control study, it is observed that obesity (BMI ≥30 kg/m²) is inversely related to prostate cancer [52]. Nevertheless, it is also shown that there is a positive association between obesity and advanced stage or metastatic prostate cancer and that non-metastatic advanced stage prostate cancer risk is decreased with weight loss [53]. The relationship between prostate cancer and diabetes is more complex. There are reports suggesting that prostate cancer risk is moderately low in men with diabetes [54].

Prevention

The basic approach for cancer prevention in patients with MetS is to prevent risk factors. Life style changes including weight loss and a healthy diet, especially the Mediterranean diet, are known to decrease cancer risk in normal population [55]. In cases with bariatric surgery cancer-related mortality was shown to have decreased compared to all cases and matched controls (HR 0.38 and 0.40, $p < 0.001$ respectively) [56]. Epidemiological studies have revealed that metformin therapy decreased cancer incidence and the risk of cancer-related mortality in diabetics when compared to those treated with sulfonylureas or other therapies. In patients using sulfonylureas or insulin, cancer-related mortality was found to be 1.3 and 1.9 fold higher respectively than metformin-using patients [57]. In a study investigating the cancer risk of glucose-lowering agents adjusted HR for cancer risk was found 1.36 (95% CI 1.19–1.54) in sulfonylurea monotherapy, 1.42 (95% CI 1.27–1.60) in insulin monotherapy group and 0.54 (95% CI 0.43–0.66) in insulin + metformin group [58]. These findings have given birth to the opinion that metformin treatment in patients with type 2 diabetes may have a cancer-preventive effect. Today, an insulin-sensitizing agent, metformin may have cancer-preventive effects independent of its hypoglycemic effect [59]. It is postulated that metformin suppresses in vitro and in vivo cancer cell growth and there may be potential mechanisms like liver kinase b1/AMPK pathway activation, induction of apoptosis, inhibition of protein synthesis, decrease in insulin levels, activation of immune system and eradication of cancer stem cell [60]. The benefit of metformin as an adjuvant chemotherapeutic agent and its affect as increased response to chemotherapy is still investigated. Some of the observational studies managed to prove this effect of metformin. Jiralerspong et al. showed that diabetic patients with breast cancer receiving metformin and neoadjuvant chemotherapy have a higher pathologic complete response rate than diabetics not receiving metformin [61]. Prospective studies are warranted to clarify this effect of metformin.

As conclusion, a recent pandemic, MetS and its components are found to be associated with cancer development and mortality. The only and most efficient preventive method is still life style change. Metformin is a promising agent for prevention and some studies show favoring effects of metformin on cancer treatment.

Disclosure Statement

Authors declare no conflict of interest.

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