Epidemiology and Molecular Mechanisms Tying Obesity, Diabetes, and the Metabolic Syndrome With Cancer

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It is well recognized that the world is witnessing an epidemic of obesity and type 2 diabetes (T2D). Numerous studies have shown that both obesity and T2D are associated with an increased risk for developing many of the common epithelial cancers as well as an increased risk of cancer-related mortality. There are many factors that are commonly associated with obesity, T2D, and the metabolic syndrome; these include lifestyle factors such as diet and physical inactivity and biological factors such as abdominal obesity, increased inflammation, dyslipidemia, hyperglycemia, and altered hormone and adipokine levels. Human, animal, and in vitro cell studies have examined the potential contribution of many of these factors to the development and growth of multiple cancers. In this review, we will present the epidemiological evidence for this association and then discuss the multiple factors that may play a role in the increased cancer risk and mortality in individuals with obesity, T2D, and the metabolic syndrome.

Epidemiological association between obesity, diabetes, the metabolic syndrome, and cancer

Obesity and cancer

The World Health Organization classifies weight in adults based on BMI, and many studies examine the link between obesity and cancer using BMI as a measure of obesity. The Cancer Prevention Study II (CPS II) examined the risk of cancer mortality in obese men and women in the U.S. They reported that obesity is associated with a significant increase in mortality from multiple cancers, including esophageal, colorectal, liver, gallbladder, pancreatic, breast, endometrial, cervical, ovarian, renal, brain, kidney, and prostate cancer; non-Hodgkin lymphoma; and multiple myeloma (1). A subsequent meta-analysis of 221 datasets revealed an increased incidence of many similar tumors associated with increased BMI, as well as thyroid cancer in both men and women and malignant melanoma in men (2). It has been estimated that overall overweight and obesity cause ~20% of all cancer cases (3). The highest association is between obesity and endometrial cancer: the International Agency for Research on Cancer has reported that obesity causes 39% of endometrial cancer cases (3). While obesity is generally associated with increased overall cancer, lung cancer is a notable exception. Studies have consistently shown that obesity is inversely associated with lung cancer incidence and survival; this inverse association is thought to be due to the strong association between smoking and lung cancer (1,4,5). The association between obesity and prostate cancer is also complicated: the U.S. Health Professionals study found that obese men had a lower risk of developing prostate cancer if they were <60 years of age and had a positive family history (6). However, a meta-analysis of prospective cohort studies has reported an increase in cancer mortality (7). The inverse association between prostate cancer risk and obesity in men is hypothesized to be related to lower androgen levels; however, as many later-stage prostate cancers become androgen independent, the higher mortality may be due to other contributing factors associated with obesity.

People of different ethnic backgrounds are known to have greater or lesser susceptibility to the adverse metabolic consequences of obesity. Compared with people of European descent, individuals of South Asian and Aboriginal descent have a higher prevalence of dyslipidemia, hyperglycemia, and insulin resistance, as well as lower adiponectin and higher leptin levels for a given BMI or waist circumference (8–10). Therefore, in these populations, the risk of developing cancer may be higher even when they have a "normal" BMI or waist circumference, due to greater metabolic abnormalities that occur at a lower BMI and waist circumference. In the meta-analysis performed by Renehan, Roberts, and Dive (2), they specifically examined the association between BMI and overall cancer incidence in different populations: North American, Northern European, and Australian compared with Asian Pacific. They found that the magnitude of associations between increased BMI and cancer were particularly strong in breast cancer in the Asian Pacific population compared with other population groups (2). Other studies have used the data from the Asia-Pacific Cohort Collaboration to specifically examine the association of cancer mortality with BMI. They reported a significant increase in the risk of mortality from colon, rectal, postmenopausal breast, ovarian, cervical, and prostate cancer and leukemia in overweight and obese individuals from this population (11).

With the prevalence of childhood obesity increasing dramatically worldwide, an important question is whether

obesity in childhood leads to an increased risk of developing cancer as an adult. A recent systematic review of the epidemiological studies reported that of three studies examining the association between childhood obesity and all cancers, one study found an increased risk of cancer incidence and mortality associated with the highest quintile of BMI-SD score at ages 2–14 years, one reported an increased risk of cancer mortality in women who had a BMI >85th percentile in the reference range when aged between 14 and 19 years, and the third reported no association in men between BMI at age 18 years and cancer mortality at ages 18–49 years (12). The results were variable for breast cancer with some studies showing no association between BMI and risk and others showing an inverse risk. An increased risk of colon cancer mortality and kidney cancer was associated with increased BMI during adolescence. In women, a BMI >85th percentile at ages 14–19 years was associated with relative risk (RR) of 1.9 of developing cervical cancer, and being overweight or obese at the same age was associated with a RR of 1.56 of developing ovarian cancer compared with those with a normal BMI (12).

Diabetes and cancer

Type 2 diabetes. Type 2 diabetes has also been linked to an increased risk of developing and dying from cancer in multiple studies. Early studies found an association between diabetes and cancer of the pancreas and liver. More recent studies reported an increased incidence of endometrial, breast, colorectal, bladder, and kidney cancers, as well as non-Hodgkin lymphoma (13). The CPS II study examined the association between diabetes and cancer mortality in 467,922 men and 588,321 women in the U.S. After 16 years of follow-up, they found a significantly increased risk of mortality from bladder, colon, pancreatic, and liver cancer in men and from pancreatic, colon, and breast cancer in women with diabetes (14). The 26-year follow-up data from the CPS II study have recently been published (15). After 26 years of follow-up, in addition to finding an increased risk of mortality from bladder, pancreatic, breast, liver, and colon cancers, they reported that diabetes was associated with an increased risk of oral and pharyngeal cancer, breast cancer in men, and endometrial cancer in women (15). The association of diabetes and cancer in these studies is

independent of BMI (14,15). In the CPS II study, an inverse association was found between diabetes and prostate cancer mortality. Other studies have demonstrated that men with diabetes were more likely to present with high-grade prostate cancer (16). The inverse association between T2D and prostate cancer has previously been reported, and the reasons for it are not well understood, but it may be related to changes in hormone levels, differences in prostate-specific antigen screening, or circulating levels in those with diabetes, an effect of diabetes medications or vascular changes in the prostate.

In addition to an increase in incidence and mortality, diabetes is associated with an increase in distant metastases in breast cancer patients, as well as a greater chance of cancer recurrence in breast, lung, and colorectal cancer patients (17–19). Studies have demonstrated that those with diabetes who develop cancer have higher all-cause mortality. Whether diabetes truly increases cancer-specific mortality or whether the increase in mortality observed in those with cancer and diabetes is due to the increased overall mortality associated with diabetes remains uncertain (15,16,20). Furthermore, there may be differences in health care–seeking behavior and health screening in individuals with diabetes affecting the incidence rates of cancer and the stage of cancer at the time of diagnosis in those with diabetes. There may be differences in cancer treatment choices made by physicians and patients with diabetes that may affect their prognosis. There may also be an effect of diabetes medications on cancer progression that could positively or negatively affect outcome.

Type 1 diabetes. There are fewer studies on the links between type 1 diabetes and cancer. Many of these epidemiological studies use age cutoffs or insulin use to define type 1 diabetes. The age cutoffs vary between diabetes diagnosed under the age of 18 years and diabetes diagnosed under the age of 40 years. Therefore, many of these studies are likely to also include individuals with T2D. The results of these studies are very mixed depending on the study design (cohort vs. case control), with some studies reporting an increase in pancreatic, liver, mouth and pharyngeal, stomach, skin, and ovarian cancer and leukemia. But many other studies report no association, and individual studies with positive results report different findings. Therefore, it remains unclear whether type 1 diabetes is associated

with any increase in cancer incidence or mortality (21).

Metabolic syndrome and cancer

The metabolic syndrome is found in the continuum between obesity and type 2 diabetes. It has many different definitions, but most definitions include increased waist circumference, dyslipidemia (high triglycerides and low HDL cholesterol), hypertension, and impaired fasting glucose in their criteria for diagnosis (10). A number of studies have recently been published from the Metabolic Syndrome and Cancer Project (Me-Can) cohort in Austria, Sweden, and Norway, examining the association between the metabolic syndrome as a whole and its individual components on the risk of cancer (22). From this cohort, the investigators have reported that higher glucose levels were associated with an increased risk of liver, gallbladder, respiratory, and thyroid cancer and multiple myeloma in men, and pancreas, bladder, endometrial, cervical, and stomach cancer in women (23). Additionally, they have reported an increased risk of bladder cancer in men and postmenopausal breast cancer in women with a higher composite metabolic syndrome score (24,25). They have reported that triglycerides are associated with an increased risk of colon, respiratory tract, kidney, and thyroid cancers and melanoma in men and respiratory, cervical, and nonmelanoma skin cancers in women (26). Hypertension was also associated with an increased risk of multiple cancers in men and women in this cohort (27). The metabolic syndrome is a syndrome associated with many physiological changes including insulin resistance and hyperinsulinemia, visceral adiposity, increased estrogen levels, increased inflammatory cytokines such as interleukin (IL)-6, and tumor necrosis factor (TNF)-α, as well as altered levels of circulating adipokines. These factors may contribute to the development of hypertension, dyslipidemia, and hyperglycemia, as well as cancer. Therefore, the association between elements of the metabolic syndrome and cancer may reflect common underlying etiologies between these conditions.

Potential mechanisms linking diabetes, obesity, and the metabolic syndrome with cancer

Insulin and IGF-1

Insulin resistance is common in obese individuals and is believed to be a key

factor in the pathogenesis of the metabolic syndrome. Insulin resistance in metabolic tissues leads to β-cell compensation, which causes hyperinsulinemia. Insulin is synthesized as proinsulin. C-peptide is cleaved from the proinsulin molecule to form mature insulin. C-peptide is commonly used as a biomarker for insulin secretion. Increased insulin secretion from the pancreas into the portal circulation may lead to increased hepatic growth hormone–mediated synthesis of IGF-1. High-normal levels of insulin, C-peptide, and IGF-1 have been associated with an increased risk of certain cancers in epidemiological studies.

In women with early-stage breast cancer, those with insulin levels in the highest quartile of the normal range had the poorest survival, and among patients with type 2 diabetes fasting C-peptide has been associated with increased breast cancer mortality (28,29). The European Prospective Investigation into Cancer and Nutrition (EPIC) investigators reported an increased risk of colorectal cancer in those with C-peptide levels in the highest versus lowest quartile (30). An analysis of 12 prospective studies reported that men with serum IGF-1 levels in the highest quintile of the population range had an odds ratio of 1.38 for developing prostate cancer, compared with men with the lowest IGF-1 levels (31). Other meta-analyses have reported a similar increase in prostate cancer risk as well as colorectal cancer and premenopausal breast cancer in those with IGF-1 levels in the highest quartile of the population range (32,33). Studies have not found any association between IGF-1 levels and lung cancer (32), and not all studies have reported positive findings. In a nested case-control study of mostly premenopausal women from the Nurses' Health Study II cohort, no association was found between insulin or C-peptide levels and breast cancer (34).

Animal and in vitro studies have examined the role of insulin and IGF-1 as well as their respective receptors and signaling pathways in tumor growth and metastasis in isolation from other factors that may contribute to cancer risk. In vitro, both IGF-1 and insulin stimulate the proliferation of tumor cells lines. In vivo animal studies have demonstrated that endogenous hyperinsulinemia increases the growth and metastasis of mammary tumors (35,36), while increased circulating IGF-1 levels increased the growth and metastases of colon cancers

in mice (37). Much of the initial work focused on the role of IGF-1 and the IGF-1 receptor (IGF-1R) in increasing growth and metastasis. Subsequently, inhibitors of IGF-1 and the IGF-1R were developed to treat tumors that lack targeted therapies, such as triple-negative breast cancers and hormone therapy–resistant breast cancers. These tumors have been shown to express high levels of the IGF-1R (38). However, the results of clinical trials targeting IGF-1 and the IGF-1R have been disappointing. Recent evidence suggests that the insulin receptor (IR) is capable of conferring resistance to IGF-1R–targeted therapy in tumor cells and therefore may also be an important target (39). Many tumors are known to overexpress the IR, and some studies have reported that higher expression of the IR is associated with a worse prognosis (40). The IR has two isoforms: one that is predominantly present in fetal tissues and conveys the mitogenic actions of insulin (IR-A), while the isoform IR-B is predominant in liver and skeletal muscle and is responsible for insulin's metabolic actions. With recent developments in technology and the ability to extract and amplify RNA from formalin-fixed tissues, two studies have demonstrated that the ratio of IR-A to IR-B is higher in more aggressive breast cancers (41,42). Therefore, in insulin-resistant, hyperinsulinemic individuals insulin may be signaling through the IR-A and thus lead to increased tumor growth.

Glucose and hyperglycemia
Glucose is known to be a critical nutrient for proliferating cells. Many years ago, Otto Warburg proposed that cancer cells develop an increased ability to utilize glucose for anaerobic glycolysis—a phenomenon that is exploited today in detecting tumors by fluorodeoxyglucose-labeled positron emission tomography imaging for cancers (43,44). Many tumors overexpress the glucose transporters GLUT1, GLUT3, and GLUT4, the expression of which is regulated by many tumor suppressor genes. The upregulation of anaerobic glycolysis shunts glycolytic intermediates into the pentose phosphate pathway, leading to the production of precursors for fatty acids, amino acids, and nucleic acids (45). In a mouse model of hyperglycemia, more aggressive skin and mammary tumors are found compared with the normoglycemic mouse (46). These mice also have hyperinsulinemia and increased inflammatory

markers; therefore, the hyperglycemia alone may not be driving tumor growth. In another animal model with alloxan-induced hyperglycemia and insulin deficiency, no increase in carcinogen-induced mammary tumors was observed (47). Therefore, once tumor cells have adequate glucose to meet their demands, it is unclear that hyperglycemia alone will further stimulate their growth.

Some epidemiological studies including the Vasterbotten Intervention Project of northern Sweden have reported an increased risk of pancreatic, endometrial, and urinary cancers in those with the highest quartile versus the bottom quartile of fasting glucose levels (48). In the Me-Can project, significant increases (RR 1.15 in men and 1.21 in women) in risk of fatal cancer were found per 1 mmol/L (18 mg/dL) incremental increase in blood glucose (23). However, reducing hyperglycemia in individuals with type 2 diabetes has not been clearly associated with a decreased risk of developing cancer (49,50). Therefore, in obesity, diabetes, and the metabolic syndrome glucose may be playing a role in concert with hyperinsulinemia, inflammation, adipokines, and altered estrogen levels.

Estrogen and estrogen signaling
Endometrial cancer was one of the first cancers associated with obesity and is strongly dependent on estrogen stimulation. Similarly, increased endogenous estrogen levels have been reported to increase the risk of postmenopausal breast cancer twofold (51). Obesity has long been known to be associated with increased circulating estrogen levels, due to increased aromatase activity in adipose tissue. In addition, insulin-resistant women have suppressed hepatic production of sex hormone–binding globulin, leading to increased levels of free estrogen (52). More recent studies have also demonstrated that obese women express increased levels of aromatase in breast stromal tissues, the expression of which is increased by inflammatory mediators including TNF-α, IL-1β, prostaglandin E2, and cyclooxygenase-2 (COX-2) and is inhibited by AMP-activated protein kinase (AMPK) (53,54). AMPK is an important nutrient-sensing molecule in cells and is a negative regulator of insulin-stimulated signaling pathways. These mechanisms are thought to tie together the increased estrogen-stimulated breast cancer growth that occurs in obesity.

The estrogen receptor (ER) and IGF-1R are known to have significant cross-talk in the normal mammary gland and breast cancer. IGF-1R signaling can lead to ERα phosphorylation and thereby potentiate ERα signaling (55). Additionally, in ER-positive human breast cancer cells IGF-1R has been shown to mediate resistance to antiestrogen therapies (56). Therefore, clinical trials have been designed to reduce IGF-1R signaling in addition to targeting ER signaling. In one such study, despite the successful lowering of IGF-1 levels, using the somatostatin analog octreotide, no improvement in survival was found in the octreotide- and tamoxifen-treated group compared with tamoxifen treatment alone (57). As hormone-resistant tumors have been shown to express higher levels of the IR, particularly IR-A, blocking both the IR and IGF-1R using a tyrosine kinase inhibitor may be beneficial in treating tamoxifen-resistant breast cancers (58). Some cross-talk between the ER and IR also occur. However, there is still much to be learned about the interactions between insulin, aromatase, and estrogen in cancer development and growth.

Dyslipidemia

Two of the defining criteria for the metabolic syndrome are low HDL cholesterol and increased triglycerides; these lipid abnormalities are commonly seen in insulin-resistant patients and those with type 2 diabetes. The Me-Can study has reported that men and women with elevated triglycerides have an increased risk of overall cancer (RR 1.16 for men and 1.15 for women) (26). In a U.S. study, high baseline ($\geq$240 mg/dL) cholesterol was found to be associated with a higher risk of overall and advanced prostate cancer than lower cholesterol levels (<200 mg/dL), while higher HDL cholesterol appears to decrease the risk of prostate cancer (59). Low HDL cholesterol has also been associated with an increased risk of breast cancer. Women with a high LDL–to–HDL cholesterol ratio have higher free estradiol levels, which may be a mechanism through which this lipid profile increases the risk of breast cancer (60). Some studies suggest that statins may reduce the risk of developing cancer. In a study conducted on the CPS II Nutrition cohort, the use of cholesterol-lowering agents for $\geq$5 years was not associated with a decreased incidence of overall cancer or prostate, breast, colorectal, lung, bladder, renal cell, or pancreatic cancer.

However, they did report a decrease in the risk of melanoma, endometrial cancer, and non-Hodgkin lymphoma (61).

The mechanisms that may link cholesterol to cancer growth have been most extensively studied in prostate cancer. Prostate cells are capable of synthesizing cholesterol, while most of the cholesterol located in the cell membrane is derived from circulating cholesterol (62). Studies have reported that the cholesterol content of tumor cells is higher than in normal cells owing to increased absorption of cholesterol from the circulation and de novo lipogenesis in cancer cells. This increase in lipid accumulation has been shown to promote proliferation and protect cancer cells from apoptosis (63). Lipid accumulation in prostate cancer cells is promoted by androgens (64). Additionally, animal studies have shown that circulating cholesterol levels increase the synthesis of androgens from cholesterol in tumor cells by increasing the expression of the enzyme CYP17A (65). Recent animal studies have shown that hypercholesterolemia, independent of hyperglycemia and hyperinsulinemia, increases mammary tumor growth and metastases (66,67). This effect was found to be related to increased activation of the phosphatidylinositol 3-kinase/Akt signaling pathway (66). Hydroxylated derivatives of cholesterol, including 25-hydroxycholesterol, have recently been shown to have estrogenic activity in breast and ovarian cancer cells (68). By these mechanisms, cholesterol may have direct effects on tumor cells and may interact with androgen and estrogen signaling in tumors.

Cytokines and adipokines

Obesity is considered a state of chronic inflammation. In obesity, adipocytes increase in size and have a greater number of macrophages. Adipose tissue macrophages secrete a number of inflammatory molecules including IL-6 and TNF-α. Cytokines interfere with IR signaling and are important in the pathogenesis of insulin resistance. In the setting of insulin resistance, IL-6 levels are increased. Increased IL-6 levels have been implicated in the pathogenesis of hepatocellular carcinoma and ovarian, prostate, and breast cancer (69). IL-6 has been associated with resistance to androgen deprivation therapy in prostate cancer and more aggressive prostate cancer (70). IL-6 has also been implicated in the development of breast cancer metastases by inducing

changes in cells that lead them to have greater invasive and migration properties: a phenomenon known as epithelial-mesenchymal transition (71). TNF-α has also been seen to play a role in tumor promotion. TNF-α is associated with increased colon tumor growth in animal models and with more aggressive prostate cancer and in breast adipose tissue has been shown to increase the expression of aromatase (72–74). Inflammatory cytokines may therefore have direct and indirect effects on tumor cell growth and spread. Studies have demonstrated cross-talk between IL-6 and epidermal growth factor receptor signaling in epidermal growth factor receptor–driven breast cancer (75). Autocrine production of IL-6 in breast cancer cells leads to methylation of the ERα promoter and decreased ERα expression. By this mechanism, IL-6 may drive the basal-like (hormone receptor negative) breast cancer phenotype (76). Investigators have begun to examine the effect of knocking down IL-6 in tumor cells and found a decrease in lymph node metastases from prostate cancer cells with decreased IL-6 expression. Knocking down IL-6 was also associated with a decrease in the number of tumor-associated macrophages. Tumor-associated macrophages are a source for cytokines and TNF-α and may contribute to tumor growth and metastases (77).

Leptin and adiponectin are adipokines produced by adipocytes. In the setting of obesity, the metabolic syndrome, and type 2 diabetes, circulating leptin levels increase as a result of hypothalamic leptin resistance, and adiponectin levels decrease. Low adiponectin levels and high leptin have been associated with an increased risk of colorectal cancers in a cohort study nested within the Women's Health Initiative cohort (78). However, in this cohort only leptin was associated with an increased risk, independent of insulin. Advanced breast cancer stage has been associated with increased leptin in one epidemiological study from Italy (79); however, in the Nurses' Health Study, leptin levels were inversely associated with breast cancer risk (80). In the Physicians' Health Study, no association was found between leptin and prostate cancer (81). In colorectal, esophageal, breast, and prostate cancer cells, leptin has been seen to stimulate proliferation in vitro. Leptin is also a proangiogenic factor and increases the expression of matrix metalloproteases (MMP-2 and

MMP-9) that are important for cell invasion (82). Recent studies have also shown that leptin promotes aromatase expression in breast tissue, which may also promote growth of ER-positive breast cancers (74). Adiponectin, in contrast, is considered to have anticancer effects. Epidemiological studies have reported an inverse association between serum adiponectin levels and breast cancer in postmenopausal women, independent of BMI, leptin, and IGF-1 levels. Additionally, low adiponectin levels have been associated with an increased risk of endometrial cancer, colorectal cancer, and prostate cancer (83). Adiponectin decreases cellular proliferation and increases apoptosis (84,85). The exact mechanism through which adiponectin inhibits proliferation is not entirely understood. It is an activator of AMPK, and it also impairs de novo fatty acid synthesis by decreasing the expression of SREBP1c. It has also been reported to prevent the interaction of certain growth factors (e.g., platelet-derived growth factor-BB, heparin-binding epidermal growth factor, and basic fibroblast growth factor) with their receptors. Adiponectin also has anti-inflammatory properties that may also account for its tumor suppressing properties; it decreases the production of many inflammatory cytokines including IL-6 and TNF-α (82).

Summary and future directions

—The epidemiological data support the association of increased cancer risk and increased cancer-related mortality in obesity and type 2 diabetes. New studies and meta-analyses continue to be published from various countries and generally support these findings from different racial and ethnic groups. While the studies have looked at various known factors involved in the pathophysiology of obesity, metabolic syndrome, and type 2 diabetes, the strongest association that consistently appears is endogenous hyperinsulinemia, though less is known about biological factors involved in inflammation.

Important studies are also ongoing in preclinical models to identify real causality between the clinical disorders and cancer risk. These include hyperglycemia, hyperinsulinemia, hypertriglyceridemia, inflammatory cytokines, adipocytokines, and IGF-1, to name some of the known factors. The results of these studies may be useful in considering therapeutic interventions. Additionally, studies are addressing differences in cancer screening and treatment choices in those with diabetes to determine whether differences in these factors may be influencing cancer incidence and prognosis.

Finally, the potential effects of anti-diabetes medications on cancer risk have recently become an important subject of discussion, especially for practicing health care professionals and patients. While the signals are small and unclear, more studies need to be performed and vigilance is required.

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