Symposium introduction: metabolic syndrome and the onset of cancer1–4

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ABSTRACT
Diabetes, obesity, and related metabolic disorders are among the most pressing of today’s health care concerns. Recent evidence from epidemiologic and basic research studies, as well as translational, clinical, and intervention studies, supports the emerging hypothesis that metabolic syndrome may be an important etiologic factor for the onset of cancer. On March 15–16, 2006, The Harvard Medical School Division of Nutrition hosted the symposium “Metabolic Syndrome and the Onset of Cancer” as a platform to systematically evaluate the evidence in support of this hypothesis. This symposium, which gathered leaders in the fields of metabolism, nutrition, and cancer, will stimulate further research investigating the etiologic role of metabolic syndrome in cancer. Furthermore, it will help to guide the development of effective cancer prevention strategies via nutritional and lifestyle modifications to alleviate metabolic syndrome.

KEY WORDS Metabolic syndrome, cancer, obesity, nutrition, epidemiology, symposium

Metabolic syndrome, which is described as a cluster of risk factors that accelerate the onset of cardiovascular disease and type 2 diabetes, is characterized by visceral or intraabdominal obesity, glucose intolerance, hypertension, low serum HDL cholesterol, and high serum triacylglycerols. Having ≥3 of these risk factors qualifies an individual for metabolic syndrome. Gerald Reaven first described the syndrome in 1988 (1). Insulin resistance is considered to be the underlying pathophysiology, and it eventually results in the other aspects of the syndrome. Insulin resistance is a prediabetic state and is closely linked with obesity. The emerging hypothesis that metabolic syndrome is an etiologic factor for the onset of cancer is supported by limited yet promising evidence from epidemiologic and experimental studies. The prevalence of metabolic syndrome is high and still increasing, in parallel with increasing cancer incidence worldwide (2, 3). Most previous epidemiologic investigations focused on associations between obesity and cancer risk and mortality. Obesity is considered to be a major risk factor for cancer; it is significantly associated with both higher risks and higher death rates of most common cancers (3). Diabetes mellitus, a comorbidity of obesity, is associated with increased risks of total cancer and of cancer in specific sites (4, 5). In recent years, accumulating epidemiologic evidence has linked metabolic syndrome with the development or progression of cancer. Metabolic syndrome was associated with increased incidences of colorectal cancer (6, 7) and prostate cancer (8–10) and with the recurrence of breast cancer (11).

Limited experimental research has been conducted to investigate whether metabolic syndrome plays a causal role in the development or progression of cancer. Available experimental evidence has provided mechanistic plausibility that metabolic syndrome may play an important role in the development or progression of cancer. Obesity is implicated in the etiology and progression of cancer at multiple cancer sites through signaling pathways that regulate key functions, including cancer cell proliferation, apoptosis, metastasis, and angiogenesis. Most obese individuals are insulin-resistant, a condition that may result from a defect in the oxidation and storage of fatty acids in the liver and skeletal muscle. Impaired fatty acid oxidation, mitochondrial dysfunction, and altered serum concentrations of adipokines such as adiponectin, leptin, and TNF-α contribute to the development of insulin resistance and compensatory hyperinsulinemia. Elevated serum insulin concentrations then increase the bioavailability of insulin-like growth factor-I (IGF-I), which also plays a critical role in carcinogenesis and tumorigenesis.

The objectives of the 8th Postgraduate Nutrition Symposium were to expand insight into the relation between metabolic syndrome and cancer, update knowledge on leading-edge research, and explore strategies to transform the miracles of science into the rapid delivery of ever-more-effective cancer prevention and treatment. This symposium included 16 presentations, 3 general discussions, and 1 panel discussion. The speakers covered a wide range of topics encompassing different disciplines in epidemiology, basic research, and translational and clinical research.

The epidemiologic investigations on the associations between diabetes, metabolic syndrome, and breast cancer (12); between metabolic syndrome, hyperinsulinemia, and colon cancer (13);
and between obesity, metabolic syndrome, and prostate cancer (14) were presented in the first session of the symposium. Xue and Michels (12) conducted a meta-analysis to review the epidemiologic studies on the association between type 2 diabetes and the risk of breast cancer and found that the combined evidence supported a modest association between type 2 diabetes and risk of breast cancer, which appears more consistent among postmenopausal than among premenopausal women. Although some studies investigated the associations between breast cancer and some metabolic syndrome components, such as abdominal obesity, dyslipidemia, and hypertension, the relation between metabolic syndrome and breast cancer risk has not been considered in an observational study. Thus, the role of metabolic syndrome in breast carcinogenesis remains unknown.

Giovannucci (13) presented a comprehensive review of epidemiologic studies on the associations between metabolic syndrome or metabolic syndrome components and the risk of colon cancer. The review of available evidence indicated that elevated BMI, physical inactivity, and visceral adiposity were consistent risk factors for colon cancer and adenoma; that patients with type 2 diabetes had a higher risk of colon cancer; and that the serologic manifestations of the metabolic syndrome, including hypertriglyceridemia, low HDL cholesterol, and an elevated fasting or 2-h glucose concentration, were also associated with colon cancer and adenoma risk. In contrast with breast cancer, 6 studies investigated metabolic syndrome and risk of colorectal cancer or adenoma, and all found a suggestive or significantly increased risk. The epidemiologic evidence clearly supports the concept that persons with metabolic syndrome are at increased risk of colon cancer.

Hsing et al (14) reviewed the epidemiologic studies on obesity, metabolic syndrome, and prostate cancer. Most studies investigated the association between obesity and prostate cancer. Obesity was associated with an increased risk of high-grade prostate cancer, a decreased risk of low-grade prostate cancer, and a consistently increased risk of aggressiveness and mortality of prostate cancer. The authors proposed that the differential effects of obesity on subtypes of prostate cancer might be due to etiologic heterogeneity in these tumors and complex interactions between androgen metabolism and several putative risk factors, including insulin resistance, diabetes, inflammation, and genetic susceptibility. Although some studies investigated metabolic syndrome and prostate cancer risk (8–10), the data are insufficient and the roles of metabolic syndrome in prostate carcinogenesis warrant further clarification.

The second part of the symposium consisted of presentations on basic research to demonstrate possible mechanisms by which the components of the metabolic syndrome might modulate cancer development and progression. Pollak (15) described several lines of experimental evidence supporting that one of the mechanisms may be related to increased insulin and IGF-I activities. Insulin resistance and hyperinsulinemia are underlying factors for metabolic syndrome. Elevated serum insulin concentrations increase the level and bioavailability of IGF-I, which plays a critical role in the development and progression of several cancers. It was further proposed that insulin-lowering treatment, such as the use of metformin, deserves investigation as a potential adjunct in the treatment or prevention of cancer in persons with hyperinsulinemia (15).

Besides serving as a storage depot for energy in the form of triacylglycerols, adipocytes also function as endocrine cells. They secrete several adipokines, such as leptin, angiotensinogen, plasminogen activator inhibitor-1, tumor necrosis factor-α, interleukin-6, resistin, and adiponectin. Of all the adipokines, adiponectin is probably most likely to affect insulin sensitivity. Adiponectin is the most abundant adipose-specific protein and is produced exclusively in adipocytes. Unlike other adipokines, it is lowered in adiposity and raised after weight reduction. Obesity-linked down-regulation of adiponectin has been suggested to be a mechanism whereby obesity could cause insulin resistance and diabetes (16). Obesity decreases expression levels of adiponectin receptors, AdipoR1/R2, thereby reducing adiponectin sensitivity, which finally leads to insulin resistance. Adiponectin stimulates fatty acid oxidation, decreases plasma triacylglycerols, and improves glucose metabolism by increasing insulin sensitivity (17). Barb et al (18) reviewed the experimental evidence from basic research and clinical investigations that support the role of adiponectin in obesity-related malignancies, including cancers of the breast, endometrium, colon, and prostate.

The mechanism by which insulin resistance develops is not well understood. In addition to the adipokines theory, the free fatty acid (FFA) theory has been proposed. It is thought that increasing intracellular fatty acid metabolites, such as diacylglycerol, fatty acyl-CoAs, or ceramides, activates a serine-threonine kinase cascade, which leads to phosphorylation of serine-threonine sites on insulin receptor substrates. Serine-phosphorylated forms of these proteins fail to associate with or to activate phosphoinositide-3-kinase, which results in decreased activation of glucose transport and other downstream events. This change leads to the intracellular accumulation of triacylglycerols and, probably more importantly, of intracellular fatty acid metabolites in insulin-responsive tissues, which leads to acquired insulin signaling defects and insulin resistance (19). Increased plasma FFA concentrations are typically associated with many insulin-resistant states, including obesity and type 2 diabetes (20–22). Experimental work by Bergman et al (23) showed that nocturnal lipolysis increases the exposure of liver and muscle to FFAs at night, which causes insulin resistance. They suggested that nocturnal lipolysis not only is a cause of insulin resistance, but also is responsible for hyperinsulinemia. Furthermore, the resulting elevated nocturnal FFAs and elevated fasting and postprandial insulin concentrations may synergize and increase the risk of some cancers (23).

The importance of epigenetics in the etiology of disease, including cancer development and progression, is increasingly recognized. However, the relevance of epigenetics to the metabolic syndrome, and how it may affect cancer, is only beginning to capture the interest of the scientific community. The review by Ross and Milner (24) focuses on data supporting the hypothesis that, in addition to the thrifty genotype and thrifty phenotype hypotheses, diet-induced changes in epigenetic programming during fetal and postnatal development might precipitate the metabolic syndrome. The authors further proposed that epigenetics might bridge both the thrifty genotype and thrifty phenotype hypotheses, thereby providing a link between genes and the environment by demonstrating this predisposition to metabolic syndrome and its associated diseases.

Some speakers also presented their research findings on preclinical, translational, and clinical cancer prevention and intervention studies that targeted metabolic syndrome components. Previous preclinical animal studies showed that combinations of soy and tea bioactive components may significantly delay the
growth and progression of breast and prostate tumors (25, 26) in a synergistic manner associated with reduced serum IGF-I (25) or androgen (26) concentrations. These results suggest that combinations of soy and tea bioactive components may have potent cancer prevention activities in part through the prevention of metabolic abnormalities. However, whether and how soy and tea bioactive components modulate aspects of metabolic syndrome are unknown. Zhou et al (27) provided experimental results showing that the combination of soy phytochemicals and green tea reduces serum IGF-I concentrations in both male and female mice in a synergistic manner. The soy phytochemical and tea combinations also reduced serum estrogen concentrations in female mice in a synergistic manner. Soy phytochemicals and teas, alone and in combination, significantly reduced serum leptin concentrations in both male and female mice and testosterone concentrations in male mice. The results support the hypothesis that soy and tea combinations may prevent breast and prostate cancers in a synergistic manner in part by alleviating metabolic disorders. Clearly, future studies should investigate whether the induction of metabolic syndrome promotes the development and progression of breast or prostate tumors and whether certain soy and tea combination regimens effectively prevent breast or prostate cancer by averting metabolic syndrome and improving metabolic profiles.

The review of experimental evidence by Barnard (28) supported that prostate cancer is indeed another aspect of metabolic syndrome and is associated with consumption of a high-fat, refined-sugar diet combined with a lack of regular exercise. Insulin resistance and hyperinsulinemia are the cornerstone of metabolic syndrome and are also a factor for prostate cancer. Insulin could directly stimulate prostate cancer cell growth, but probably more importantly decreases sex hormone binding globulin and IGF binding protein 1 and 2 in the liver while increasing the production of IGF-I. It was thus proposed that adopting a low-fat (10–15% of energy, with balanced ratio of n-6 to n-3 fatty acids), complex-carbohydrate diet along with daily aerobic exercise (60 min/d) would control metabolic syndrome in most cases and therefore reduce the risk of prostate cancer.

Blackburn (29) reported the findings from the Women’s Intervention Study (WINS), a randomized clinical trial of 2437 women aged 48–79 y with early-stage breast cancer to test the hypothesis that dietary fat reduction would increase relapse-free survival. Analysis of a subgroup of 53 women with initial insulin resistance showed that a 2-y low-fat diet intervention lowered fasting insulin concentrations by 18 ± 34 μU/mL, whereas fasting insulin concentrations in the control group decreased by only 13.8 ± 47 μU/mL, which suggests that the dietary fat reduction may alleviate insulin resistance while reducing the risk of breast cancer relapse.

In summary, available evidence from epidemiologic investigations and experimental, translational, and clinical studies supports the emerging hypothesis that metabolic syndrome may be an important etiologic factor for the development and progression of certain types of cancer. Although much has yet to be learned about the relation between metabolic syndrome and cancer, the presentations at this year’s symposium indicate that we are effectively advancing research to treat and prevent cancer. Moreover, this symposium and future research will guide the development of effective cancer prevention strategies through nutritional and lifestyle modifications that alleviate metabolic syndrome.

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