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Obesity, Diabetes and Breast Cancer: Defining Metabolic Oncogenesis

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Summary

The American Cancer Society (ACS) has estimated 1,638,910 new cancer cases and 577,190 cancer-related deaths for 2012. Breast cancer is the second leading cause of death in women in the US. In 2012, 229,315 new cases (29% of total estimated new cancer cases) of breast cancer in women will be diagnosed and 38,552 women will die from breast cancer (14% of estimated total cancer deaths) [1]. Cardiovascular disease is the number one cause of death in women in the US. Epidemiological and antidotal data suggests that individuals who are at risk of breast cancer may also be at a previously unrecognized risk of heart disease implying that the factors underlying cardiovascular risk can also be applicable to breast and other cancers. Obesity and abnormal glucose metabolism have been implicated in the risk of cardiovascular disease and with breast cancer incidence and mortality. 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 abdominal obesity, glucose intolerance, hypertension, low serum HDL cholesterol, and high serum triacylglycerols. 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. Insulin resistance, hyperinsulinemia, and changes in the signaling of growth hormones and steroid hormones associated with diabetes and obesity may affect the risk of breast cancer. The combined epidemiological evidence supports a modest association between type 2 diabetes, obesity and metabolic syndrome and the risk of breast cancer, which appears to be more consistent among postmenopausal than among premenopausal women.

With these associations it is not surprising that women who perform mild to moderate exercise each week will have a lower risk of breast cancer. Women who have already been diagnosed with breast cancer may have better chances of survival and lower rates of recurrence with more exercise. However, the biological processes that link exercise and breast cancer are still unclear. Despite many proposed potential pathways affected by metabolic associated chronic diseases, the mechanisms underlying an association between them and breast cancer risk remain unclear, particularly because they share several risk factors, including a sedentary lifestyle, and possibly intake of saturated fat and refined carbohydrates, that may confound associations. Although metabolic syndrome is closely related to diabetes and obesity and embraces additional components that might influence risk and progression of breast cancer, the role of the metabolic syndrome in breast carcinogenesis remains unknown.

The altering of the metabolic machinery because of chronic disease status should have a profound effect of cancer incidence, and thus tailoring cancer risk based upon chronic disease status needs continued study. We have coined the phrase metabolic oncogenesis to highlight the intersection of metabolism and cancer. Metabolic dysfunction is considered an underlying contributor to many diseases. It is well established that many genetic pathways respond to nutritional and hormonal signals. Importantly, metabolic alterations can be associated with strongly enhanced tumor cell survival and proliferation. Such observations support a hypothesis that predisposition and adaptation of tumor cell energy metabolism are key contributors to carcinogenesis and tumorigenesis. Metabolic diseases create a microenvironment for cancer to emerge and progress that includes the effect on gene regulation. Here we discuss some of the mechanisms that are involved in linking obesity and type 2 diabetes (T2D) to breast cancer development and elaborate on our recent data to illustrate different mechanistic interactions of these major public health concerns.

Framing the Major Players

Obesity has been an epidemic in the US for more than two decades, and the proportion of obese adults continues to increase. The most recent obesity statistics from the National Health and Examination Survey (NHANES) captured by the Centers for Disease Control (CDC) in 2009-2010 indicate that approximately 35.7% of American adults (age 20 and over) are obese (Body Mass Index (BMI) ≥ 30) [2]. The obesity rate among adults doubled between the 1976-1980 NHANES II and the 2009-2010 NHANES. This epidemic is spreading to the younger population as well, with 17% of America's children and adolescents (ages 2-19) falling in the obese category (BMI for age ≥ 95th percentile) [2]. Most countries are experiencing similar dramatic increases in obesity [3]. Worldwide, more than 300 million adults are obese. This trend has alarming health implications, as obesity is associated with serious health conditions, including certain type of cancers, such as breast cancer [4]. Obesity has been consistently shown to increase rates of breast cancer in postmenopausal women by 30% to 50% [5]. In an ethnically diverse cohort of postmenopausal women diagnosed with breast cancer, obese women had a higher risk of all-cause and breast cancer-specific mortality relative to women with high-normal BMI (22.5–24.9 kg/m^2) [6]. Others illustrate that adiposity is associated with reduced likelihood of survival and increased likelihood of recurrence regardless of menopausal status [7,8].

Obesity often accompanies insulin resistance and high blood sugar levels, leading to T2D. Therefore, the rate of T2D has mirrored obesity [9]. As with studies of obesity, epidemiologic studies have shown that diabetes and chronically elevated insulin levels are associated with a

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variety of cancers [10-14]. Diabetes is significantly correlated with female breast cancers [14]. High levels of insulin are associated with cancer-related poorer survival of postmenopausal women with breast cancer [15] and correlates with distant recurrence of tumor and tumor-associated death in early-stage breast cancer [16], where insulin levels were significantly related to tumor stage. Larsson et al. [17] in a meta analysis reported a 24% increase in relative risk in mortality among women with diabetes.

Approximately 47 million Americans have metabolic syndrome, a constellation of chronic diseases that includes obesity, hypertension, dyslipidemia, and insulin resistance, which poses a significant therapeutic challenge for effective patient management. African Americans tend to be diagnosed with metabolic syndrome later than Caucasians and have more risk factors, conferring greater-than-additive risks. While genetic variability accounts for most of the inter-individual variation in metabolism, comprehensive characterization of genetic variability as it relates to changes in metabolic profile markers has not been fully examined, particularly as a contributor to the disparity in cancer survival. Therapeutic lifestyle changes (e.g. weight loss and increased physical activity) along with pharmacologic interventions that are recommended to prevent the complications of metabolic syndrome may similarly affect cancer survival.

Mechanisms of action

There is a large body of literature that relates obesity and abnormal carbohydrate metabolism to breast cancer. Drawing a detailed picture of mechanisms involved is necessary before taking on intervention studies. Obese women have higher circulating levels of estrone and free estradiol that may stimulate tumor cell proliferation [18,19]. Adipokines and IGF production by adipocytes are also involved [20,21]. Due to their accumulation in hypoxic condition or in high glucose or high insulin environments and their central role in activating stress-related pathways, reactive oxygen species (ROS) have been the center of attention of the research community [22-25]. Hyperglycemia or hyperinsulinemia also increases the synthesis of advanced glycated end products (AGEs), whose binding to cells enhances ROS production [26-28]. Hypoxia also increases intracellular ROS formation [24]. ROS activates stress-sensitive pathways [25] leading to change in expression of genes that control central cellular processes such as proliferation and apoptosis, which are implicated in the development of cancer. ROS accumulation may lead to toxicity and cell death, a mechanism employed by chemotherapeutic drugs to kill cancer cells. However, the ability of cancer cells to handle high concentrations of ROS results in survival and realization of protumor effects. In this case, ROS affects the expression of oncogenes and tumor suppressor genes, leading to both initiation and progression of cancer [29].

Accumulation of ROS can also induce oxidative DNA damage that results in decreased DNA methylation [30]. Oxidative damage to methyl-CpG sequences inhibits the binding of methyl-CpG-binding proteins to these sequences and impairs the activity of DNA methyl transferase [30]. ROS also inhibits production of S-adenosyl-methionine (a methyl donor that induces DNA methylation) via reduction in the activity of methionine synthase, promoting the hypomethylated state [31]. Therefore, a high glucose- or insulin-mediated increase in expression of oncogenes may be associated with alteration in methylation status of these genes. Thus, ROS-induced abnormal methylation is a plausible consequence of metabolic alteration associated with hyperglycemia or hyperinsulinemia.

Anticancer Effect of Anti-Diabetic and Weight-Loss Drugs

Metformin, an anti-diabetic drug, has been suggested by observational studies to reduce breast cancer incidence and mortality [32,33]. Thiazolidinediones (TZDs) are another class of anti-diabetes drug with reported anticancer activity [34]. TZDs are ligands for the transcription factor peroxisome proliferator-activated receptor (PPARγ) that is expressed in breast cancer. However, their anti-tumor effect does not seem linked to PPARγ activation as an increase in PPAR-γ signaling promoted breast cancer development, enhanced tumor cell proliferation, and inhibited apoptosis [35,36]. Identification of the right patient population and responsive tumors are the most critical steps in further evaluating these drugs for cancer therapy. Studying the involvement of these drugs in ROS-mediated pathways appears to be of major significance.

Dehydroepiandrosterone (DHEA), a naturally occurring steroid hormone, is a widely available over-the-counter dietary supplement used for weight loss. DHEA is reported to have anti-cancer effects [37]. Recently, we used the DMBA-induced mammary tumor model to investigate the effects of DHEA supplementation on tumor development in the obese Zucker rat model [38]. In this experiment, we randomly assigned rats to a diet of either chow as a control diet or chow with the addition of DHEA at a concentration of 6 g/kg of chow as a DHEA diet. At 50 days of age, all rats received 65 mg DMBA/kg body weight by oral gavage. Rats were weighed and palpated twice weekly for detection of mammary tumors and sacrificed 155 days post-DMBA treatment. Obese rats fed with DHEA diet gained significantly less weight than obese control diet rats ($P<0.001$). We observed that 55% of the control diet group developed mammary tumors while no tumors were detected in the DHEA diet group ($P<0.001$). These results suggested that DHEA treatment can reduce body weight gain and protect against DMBA-induced mammary tumor development [39]. DHEA is a potent inhibitor of mammalian glucose-6-phophate dehydrogenase (G6PDH), an enzyme that plays a key role in protection against ROS, as cells with reduced levels of G6PDH are especially sensitive to oxidative stress [40].

Role of glucose-6-phophate dehydrogenase

Glucose-6-phosphate dehydrogenase (G6PDH) is an enzyme that catalyzes the oxidation of glucose-6-phosphate to 6-phosphogluconolactone and the reduction of NADP+ to NADPH. Of greater quantitative importance is the production of NADPH for tissues actively engaged in biosynthesis of fatty acids and/or isoprenoids, such as the liver, mammary glands, adipose tissue, and the adrenal glands. G6PDH activity is essential for maintenance of the cell's capacity to withstand oxidative stress. The correlation between G6PDH and cancer is controversial. Previous studies revealed elevated G6PDH activities in malignant tissues in various cancers. However, a recent mortality follow up showed an association between G6PDH deficiency and non-Hodgkin's lymphomas [41]. Consistently low G6PDH activity was associated with poor prognosis and tumor recurrence of nasopharyngeal carcinoma patients [42]. G6PDH-A allele is formed by an adenine to guanine substitution at position 376 (A376G, rs1050829) and has around 80% to 85% of normal enzyme activity. This genotype has been reported in at least one breast cancer cell line, MDA-MB-468 [43]. This decrease in activity may make cells more susceptible to damaging ROS effects generated under high glucose/high insulin condition leading to more oxidative damage and probably to an increase in ROS-mediated abnormal DNA methylation.

We have shown that substitution of glucose with fructose as a carbon source in tissue culture induced an aggressive phenotype in this cell line that was associated with surface glycan profile [44]. The role of G6PDH activity levels in the phenotypic changes observed need to be further studied.

Remarks

Without an understanding of the underlying biological mechanisms, lifestyle approaches that include exercise, watching the amount and type of carbohydrate intake, being cognizant of individual body fat distribution can reduce an individual's risk of breast cancer and cancer in general. The microenvironment caused by chronic diseases like obesity and diabetes provides a soil for seeds to grow, tending to cause or give rise to tumors and their progression. We have termed this convergence of metabolism and cancer as metabolic oncogenesis. The negative impact of obesity, hyperglycemia, and high insulin levels on breast cancer incidence or progression can be explained by a wide range of mechanisms. Here, we proposed rationale for ROS-mediated abnormal DNA methylation and discussed potential ways of better understanding the response and possible intervention. Any intervention that limits ROS production or reverse abnormal methylation can be potentially considered. G6PDH activity may predict tumor cell reaction to ROS and manipulating the activity of this enzyme may also be a legitimate approach to alleviate ROS-mediated deteriorating effects. G6PD-A allele has 0.15 to 0.4 frequency in Africans with rare frequency in Caucasians [45,46] that might play a role in the well-known racial disparity among breast cancer patients.

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