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Obesity, Oxidative Stress and Breast Cancer Risk

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For over two decades, the US has experienced a continuing obesity epidemic with a rise in the proportion of overweight and obese adult population. Overweight and obesity has been associated in carcinogenesis and to mortality from various types of cancer [1]. Women with the highest body mass index (BMI) (40 kg/m^2) had mortality rates from all types of cancer combined that were 62% higher (with a relative risk of death of 1.62) than the rates of women of normal weight. These authors also reported a significant trend demonstrating that individuals with a higher BMI exhibited an increased risk of succumbing to cancers of the breast, uterus, cervix, and ovary. Breast cancer is the most common cancer among women, and of all cancers, it is the second leading cause of mortality in women in the US. Estimates for 2013 predicted that 232,340 women were likely to be diagnosed with invasive breast cancer and that 39,620 women were likely to succumb to this disease [2]. Most countries are experiencing similar dramatic increases in obesity [3]. Obesity has been consistently shown to increase rates of breast cancer in postmenopausal women by 30% to 50% [4]. 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 kg/m^2–24.9 kg/m^2) [5]. Other studies illustrate that adiposity is associated with reduced likelihood of survival and increased likelihood of recurrence regardless of menopausal status [6,7]. We have used female obese Zucker rat as model for human obesity to investigate the effects of obesity on breast cancer development. 7,12-Dimethylbenz(a) anthracene (DMBA) has been used for past fifty years to induce mammary tumor in different rat models [8,9].

We used for the first time female obese Zucker rat as model of obesity to induce mammary tumors and showed that obesity increases the susceptibility to "DMBA-induced mammary tumor development using obese Zucker rat as model" [10]. Also, we used obese ovarictomized rats as model for postmenopausal women and reported that obesity increases the rate of DMBA-induced mammary tumor development in intact and ovariectomized Zucker rats [11]. Recently, we used dehydroepiandrosterone (DHEA), a naturally occurring steroid hormone, which is a widely available over-the-counter dietary supplement used for weight loss. DHEA is reported to have anti-cancer effects [12]. We used the DMBA-induced mammary tumor model to investigate the effects of DHEA supplementation on tumor development in the obese Zucker rat model. We found that DHEA-fed obese rats gained significantly lower 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 lower body weight gain and can protect against DMBA-induced mammary tumor development [13].

The combination of obesity and diabetes mellitus also plays very important, provocative role in the development of breast cancer. The obesity-induced chronic inflammation promoted by adipose tissue dysfunction is a key feature, which is thought to be an important link between obesity and cancer. Chronic inflammation induces an increase in free radicals generation and subsequently promotes oxidative stress, which may create a microenvironment favorable to the tumor development in obese person [14].

Reactive oxygen species (ROS) are normally produced under physiological conditions by aerobic cells. Their production is dramatically increased under conditions of excessive external exposure (UV light, radiation) or after cell injury. Low (physiological level) of ROS is crucial to maintain intracellular signaling pathways including adaptive responses and compensatory up regulations of antioxidant system what makes it essential for cell survival [15]. ROS are well recognized and accepted in both clinical and research communities for playing this double role: positive in regulation of physiological reactions and negative creating an oxidative stress and leading to alterations those reactions, and generation of variety of chronic diseases, including cancer [16]. Additionally, molecular epidemiological studies supported these experimental findings and additionally proved the links of oxidative stress with the pathogenesis of human disease and in particular carcinogenesis [17].

The redox environment has an incredibly regulatory power in regulation of capacity to control the growth behavior, spread, and differentiation of cells. Neoplastic cells express highly adaptive properties to a wide variety of environmental conditions, including persistent oxidative stress and genomic instability by shifting their redox environment to more reductive conditions, which in its turn triggers upregulation of various redox sensitive prosurvival pathways [18]. Oxidative stress creates (in both compartments intracellular and extracellular) alteration a conditions that lead to lipids, proteins, carbohydrates, and DNA damage effected biological systems function and cell structure. Breast cancer cells are subjected to a high level of oxidative stress, both intracellular and extracellular. To ensure survival, cancer cells must acquire special adaptive mechanisms that counteract the toxic effects of free radicals exposure. These mechanisms may involve the activation of redox-sensitive transcription factors andthe increased expression of antioxidant enzymes and antiapoptotic proteins. Moreover, recent data revealed that different breast cancer cell types show different intracellular antioxidant capacities that may determine their ability to resist radiotherapy and chemotherapy [19]. Oxidative stress one of the leading causes of DNA damage with the

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formation of modified bases and mutations of tumor suppressor genes that are critical initial events in not only breast cancer but also in variety of organs and tissue and considered one of the most potent factor in carcinogenesis [20].

A considerable body of evidence supports role of mitochondria-generated oxidative stress in breast carcinogenesis. Playing a central role in energy production via oxidative phosphorylation, the mitochondria at the same time are a major source of production of reactive oxygen species, which may damage nuclear and mitochondrial DNA. The mitochondrial genome may be particularly susceptible to oxidative damage leading to mitochondrial dysfunction. Genetic polymorphism in mitochondrial DNA and nuclear DNA may also contribute to mitochondrial dysfunction and in etiology of breast cancer. Several studies have shown a relatively high frequency of mitochondrial DNA mutations in breast tumor tissue in comparison with mutations in normal breast tissue [21].

In generation of neoplastic transformation of normal cells, pro-oxidative environment are accompanied with overproduction of hydrogen peroxide, which induces the generation of subsequent sets of activated fibroblasts and tumorigenic alterations in epithelial cells and breast cancer generation and progression [22]. Hormone-dependent breast cancers that are characterized by overexpression of the ligand-binding nuclear transcription factor and estrogen receptor represent the most common form of breast epithelial malignancy. Exposure of breast epithelial cells to a redox-cycling and a quinone induces mitogen-activated protein kinase phosphorylation of the cytoskeletal filament protein, cytokeratin-8, along with thiolarylation of H3 nuclear histones. Exogenous or endogenous quinones can also induce ligand-independent nuclear translocation and phosphorylation of estrogen receptor [23]. The involvement of estrogens in the pathogenesis of breast cancer is underlined by oxidative catabolism of estrogen, mediated by various cytochrome P450 enzymes and generation of reactive free radicals that can cause oxidative damage. Several environmental chemicals (xenobiotes) activate the same catabolic pathway as estrogens. Xenobiotic chemicals may also express their pathological effects through generation of reactive free radicals. Breast tissue can be a target of several xenobiotic agents. DNA-reactive metabolites of different xenobiotic compounds have been detected in breast tissue [24].

In summary, more than 300 million adults worldwide 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 [1,25]. Oxidative stress plays extremely important role in breast cancer progression and needs to be taken into consideration in preventive activities and in treatment of affected patients.

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