

## Mechanistic Insights into Reducing the Weight of Breast Cancer

Perspective on Jiang et al., p. 338

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The prevalence of obesity, an established epidemiologic risk factor for many cancers including breast cancer in postmenopausal women (1), has increased dramatically over the past 30 years (2). Particularly alarming are the increasing rates of obesity among children. Therefore, we can expect continuing increases in the rates of adult obesity and obesity-related cancers for many years to come unless new strategies can be developed for decreasing the harmful, carcinogenic effect of obesity. Unfortunately, the obesity-breast cancer link has not been well-studied. Research on the biological mechanisms underlying the association between obesity and postmenopausal breast cancer, as well as the potential anticancer effects of interventions to prevent or reverse obesity, is urgently needed to develop new strategies to prevent and control obesity-related breast cancers in postmenopausal women.

The primary life-style-based interventions to induce negative energy balance (the state at which the number of calories eaten is equal to the number of calories used) and prevent or reverse obesity include a dietary regimen of calorie restriction (3) and increased physical activity (4). Calorie restriction regimens are formulated so that total dietary energy intake is reduced (generally 20-40% lower than usual intake) while micronutrient levels remain constant. Calorie restriction is arguably the most potent and broad-acting dietary intervention for preventing tumors in experimental animals. Calorie restriction inhibits a variety of spontaneous neoplasias in experimental model systems, including tumors arising in several knockout and transgenic mouse models (3). Calorie restriction also suppresses the carcinogenic action of several classes of chemicals, as well as several forms of radiation, in rodents (3). Therefore, the inhibitory action of calorie restriction on carcinogenesis is effective in several species, for a variety of tumor types, and for spontaneously arising tumors as well as chemically and physically induced neoplasias. The limited data in humans and other primates suggest that a moderate calorie restriction regimen also has anticancer effects in higher organisms (5-7).

Although less studied than calorie restriction, previous studies of physical activity and mammary tumorigenesis in rodents (most involving chemically induced models) have found beneficial effects of treadmill exercise with intensities higher than 70% of maximal aerobic capacity (VO<sub>2</sub> max) for 30 minutes or more (4). This intensity level is roughly equivalent to a fairly vigorous run in a human that would burn

~400 calories (~12 metabolic equivalent task [MET] hours; ref. 8). Epidemiologic studies also support the hypothesis that increased physical activity decreases breast cancer risk (9) and improves outcomes in breast cancer patients (10).

Potential mechanisms related to physical activity–altered tumor burden have not been adequately examined. Another important knowledge gap is a lack of information on whether the two types of energy-balance–modulating interventions—reduced caloric intake (such as calorie restriction) and increased energy expenditure (such as physical activity)—have an equivalent effect on breast cancer development. It is also unclear whether calorie restriction and physical activity could combine in an additive or synergistic fashion to inhibit breast cancer. Given that over one-third of the current adult U.S. population is obese, information on these matters is urgently needed to guide recommendations to maximize the health-promoting and cancer-preventive effects of life-style modifications. Furthermore, not everyone can significantly increase their physical activity (due to physical or other limitations) or significantly decrease their caloric intake (which is almost universally difficult in our society for many reasons). Therefore, insights into the mechanisms underlying the effects of calorie restriction and physical activity will reveal new dietary or pharmacologic targets that may be used to mimic or enhance life-style-based strategies for breaking the obesity-breast cancer link.

In this issue of the journal, Jiang, Zhu, and Thompson report their results in directly comparing the effects of physical activity with those of a mild restricted energy intake regimen (equivalent to a modest 8-10% calorie restriction) in a 1-methyl-1 nitrosourea–induced rat model (11). They controlled the food intake of their physical activity and restricted energy rats such that both groups had the same net energy balance, resulting in body weights that were 92% of sedentary control rats. This approach allowed the direct comparison of physical activity with restricted energy effects without confounding from differences in net energy balance. They also used an innovative voluntary wheel running system in which the physical activity animals were given free access to an activity wheel, and their voluntary running behavior was encouraged and reinforced via a periodic food reward. This food reinforcement was administered as a predetermined amount using an automated pellet dispenser after a prescribed distance run. The goal was to administer a low-intensity, consistent, and self-determined physical activity regimen that would mimic the national recommendation of 10,000 steps, which is being promoted by several health organizations to encourage all individuals in the United States to wear a pedometer and take 10,000 steps (roughly equal to 5 miles) a day so as to improve overall fitness and help control weight (12). Developed in the Thompson laboratory, this innovative food-reward approach to voluntary wheel running has its own limitations, including

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the potential for important but currently uncharacterized differences between exercised and sedentary animals in brain neurochemistry and related effects in response to the food reward. It does overcome, however, several of the limitations of forced exercise on treadmills, which can be highly stressful (to both the animals and investigators), and of traditional voluntary wheel running regimens, which tend to be variable and often yield inadequate levels of physical activity. Indeed, an impressive average of over 7600 meters/day was achieved with the new system (12), suggesting that this novel strategy effectively encouraged the rats to maintain their voluntary running activity. This is an important contribution to the field of exercise and carcinogenesis.

Reductions in mammary cancer incidence were ~13% with the physical activity regimen and ~9% with the restricted energy regimen, relative to the sedentary controls; tumor multiplicity decreased by 28% with physical activity and 15% with restricted energy. These reductions were statistically significant only for the physical activity regimen relative to the sedentary controls. This finding is important because it suggests that physical activity exerts effects on tumor development independently of energy balance, which was the same in both physical activity and restricted energy animals. Proteins involved in cell proliferation and apoptosis also were affected. Physical activity seemed to induce a proapoptotic state because, for example, Bax protein expression and caspase 3 activity were statistically significantly higher, and levels of Bcl-2 and human X-linked inhibitor of apoptosis were significantly lower, in mammary tumor tissue from physical activity rats than from controls. Jiang and colleagues (11) also conducted an exploratory analysis using Western blots to assess the activation of energy-sensing pathways associated with cell growth, survival, and metabolism. These analyses focused on AMP-activated protein kinase (AMPK), protein kinase B (Akt), and their downstream targets. Taken together, these analyses suggest that the AMPK and Akt pathways are modulated by physical activity (and to a lesser extent by the mild restricted energy regimen), with AMPK activated and Akt down-regulated. Both of these signaling pathways converge on the mammalian target of rapamycin (mTOR), which has emerged as a critical regulator of growth, survival, and protein translation. Indeed, Jiang and colleagues (11) observed that physical activity (and to a lesser extent restricted energy) was associated with decreased phosphorylated and total levels of mTOR and several downstream targets of mTOR including p70S6 kinase and 4E-BP1.

These findings are consistent with several recent studies in the literature suggesting that energy balance can influence both the Akt and AMPK pathways of mTOR signaling, which is discussed in detail in a well-written, timely review by Fay et al. (13) in this issue of the journal. We have known for many years that the overweight and obese states are positively associated with high serum levels of growth factors, such as insulin and bioavailable insulin-like growth factor-I, and adipokines such as leptin (14). These hormones and growth factors serve as intermediate and long-term communicators of the nutritional state throughout the biosystem. We have found that obesity is associated with enhanced activation of the PI3K/Akt pathway, which is downstream of several growth factor receptors, including insulin and insulin-like growth factor-I receptors, in multiple tissues (15). We also observed that obesity-induced decreases in AMPK activation (which can be modulated by adipokines as well as by altered ATP levels) occurs in a more limited range of tissues than does obesity-induced increases in Akt activation, suggesting that energy-balance effects on AMPK may be tissue specific (15). In contrast, negative energy balance induced by calorie restriction results in reduced PI3K/Akt signaling in multiple tissues (and increased AMPK, albeit in a tissue-specific fashion; refs. 15, 16). Furthermore, genetic reduction of circulating insulin-like growth factor-I mimics the effects of calorie restriction on tumor development and PI3K/Akt signaling (17). In addition, recent literature suggests that elevated cellular amino acid, glucose, and ATP/AMP concentrations, as are present under excess energy conditions such as the obese state, each promote mTOR activation (18). Conversely, it has been shown that low glucose availability, high AMP/ATP ratios, and decreased amino acids, as is observed in response to calorie restriction, can lead to growth arrest, apoptosis, and autophagy through an AMPK-induced repression of mTOR (19). Although nutrient and growth factor availability directly regulates mTOR, no causal associations have been made between mTOR activation or repression, energy balance, and tumorigenesis. The paper by Jiang and colleagues (11) provides further support that this pathway is an important target for blocking the development of breast and possibly other tumors associated with excess body weight.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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