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Targeting the adiponectin:leptin ratio for postmenopausal breast cancer prevention

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1. ABSTRACT

Obesity is a risk factor for postmenopausal breast cancer. Elevated estrogen levels are thought to be a growth factor associated with this relationship. However, there is increasing evidence that factors produced directly in adipose tissue, adipokines, specifically adiponectin and leptin, impact breast cancer development. Serum adiponectin levels are reduced in women diagnosed with breast cancer and *in vitro* studies using human breast cancer cell lines have shown antiproliferative action of adiponectin. In contrast, elevated serum leptin levels were associated with breast cancer in some studies. In mice which lack the leptin receptor or are leptin deficient oncogene-induced mammary tumors were not detected while leptin enhanced proliferation of breast cancer cell lines, particularly those that express estrogen receptors. Of particular interest, one recent study reported that the adiponectin:leptin ratio was reduced in women with breast cancer. Here we speculate that the ratio of these adipokines may be more important in breast cancer than their absolute concentrations. Additionally, we propose strategies to alter this ratio and thus provide protection against the development of breast cancer.

2. INTRODUCTION

Female breast cancer is the most common malignancy among women worldwide including the United States (1, 2). Interestingly, breast cancer occurs more frequently in postmenopausal compared to premenopausal women (3, 4). Obesity is associated with an increased risk of postmenopausal breast cancer (5). The increase in breast cancer risk with elevated body weight among postmenopausal women is associated with an increase in circulating estrogens, particularly bioavailable estradiol (6). After menopause, circulating estrogens mainly originate from the conversion of adrenal androgens by aromatase present in adipose tissue. Additionally, local production of estrogens by breast tissue aromatase may be an important event for cancer progression. A number of factors can stimulate aromatase activity, e.g., insulin, insulin-like growth factor-I (IGF-I), interleukin-1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-alpha) and leptin. Some of these factors have been termed adipocytokines/adipokines, a group of cytokine-like proteins produced and/or secreted by adipocytes.

Obesity is associated with poorer outcomes following breast cancer diagnosis compared to leanness. In

both premenopausal and postmenopausal women, obesity can adversely affect breast cancer prognostic factors and decrease survival (7). Interestingly, a conflicting relationship exists between obesity and breast cancer prognosis. Several investigators have reported an increased risk for the development of estrogen receptor (ER)-positive tumors among postmenopausal obese women (8). Generally, ER-positive breast cancer has a better prognosis (9), but apparently not when accompanied by obesity. Therefore, some important factors other than estrogens must be crucial in the mechanism(s) by which obesity influences breast cancer prognosis (10). Evidence is accumulating, which indicates the potential role of insulin, IGF-I and leptin in this complicated pathological situation (10).

Obese postmenopausal women are at high risk to develop hyperinsulinemia and insulin resistance and elevated insulin levels have been associated with an increased risk for breast cancer (11, 12). One aspect of insulin resistance is to produce a state of systemic chronic inflammation (13). Furthermore, insulin resistance is linked with metabolic syndrome, oxidative stress and leptin resistance (14). This complex pathological condition is influenced by several factors like peroxisome proliferator-activated receptors (PPAR), steroid hormones, and adipokines released from adipocytes (15, 16). In particular studies have indicated that the adipokine, leptin, potentiates the growth of cancer cells, while a second adipokine, adiponectin, appears to have the opposite effect (17). In this review article, we will assess the significance of adiponectin and leptin in the pathological course of breast cancer and will present a discussion of ways to modulate these two adipokines which may provide strategies for preventive oncology.

3. ADIPONECTIN: AN OVERVIEW

Adiponectin (also called gelatin-binding protein-28 (GBP28), AdipoQ, Acrp30 or apM1) is an adipokine secreted from adipose tissue in the molecular weight range of 30kDa. Adiponectin plays important roles in many physiological processes exhibiting antiatherogenic, antidiabetic, anti-inflammatory and antitumorigenic actions (17-22). Specifically, adiponectin is negatively correlated with obesity, insulin resistance and type 2 diabetes in humans and rodents (21, 23). High serum adiponectin levels are also associated with anti-inflammatory and anti-angiogenic effects (24, 25). In addition, association of higher serum adiponectin levels with decreased levels of triglycerides, increased insulin sensitivity and increased high-density lipoprotein-cholesterol levels have been reported (26, 27).

There are several different forms of adiponectin in serum. Full length adiponectin exists either as a trimer known as the low molecular weight form or as two larger multimers classified as middle molecular weight and high molecular weight forms (28). Adiponectin can also be cleaved to form trimers of smaller molecules known as globular adiponectin (gAcrp30) (29). Adiponectin functions by binding to its receptors with varying affinity. There are two forms of adiponectin receptors: Adiponectin Receptor-1 (AdipoR1) and Adiponectin Receptor-2 (AdipoR2) (30). Full length adiponectin binds with highest affinity to AdipoR2 which is most abundant in liver (30). The gAcrp30 binds with highest affinity to AdipoR1 which has previously been shown to be expressed by a number of different tissues (30). Although the high molecular weight form is thought to be the main active form of adiponectin (31), it was reported that total and high molecular weight adiponectin had similar effects on breast cancer development (22). In general, most publications do not specify which form(s) of adiponectin is/are being used but a recent study from our lab indicated that gAcrp30 inhibited ER-alpha transfected MDA-MB-231 cells to a greater scale than it did ER-negative wild type cells (32).

3.1. Adiponectin effects in *in-vivo* (human and animals studies)

Serum adiponectin levels have been reported to be related to breast cancer (22, 33-35). In general, serum adiponectin levels are in the range of 2-30 μg/ml (22, 33, 34, 36-39) and higher serum adiponectin concentrations have been correlated with up to a 65% reduced breast cancer risk (22) primarily in postmenopausal women (33, 38). In addition, lower serum adiponectin levels were associated with higher tumor grade (34). A summary of the published studies reporting serum/plasma levels of adiponectin in association with diagnosis of breast cancer is presented in Table 1.

Expression of adiponectin and its receptors in breast tumor tissue has also been studied (22, 36, 40). For example, adiponectin mRNA expression level was significantly higher in mammary tissue adjacent to breast tumors compared to either breast tumor tissue or to control tissue obtained from subjects without breast cancer (22). But, AdipoR1 mRNA expression level in mammary tissue adjacent to the breast tumor was similar to the tumor itself. However, AdipoR1 level in breast tumors was higher than in control mammary tissue from an individual without breast cancer while there were no differences in AdipoR2 expression levels among control, adjacent and tumor tissues (22). In another recent study, adiponectin level was significantly higher in mammary tissue obtained from breast cancer patients than in that of healthy controls although there was no association between tumor stage and tumor size (40).

In MMTV-TGF-α transgenic mice that develop mammary tumors in the second year of life, we have recently found that protein expression levels of AdipoR1 and adiponectin were significantly lower in mammary tumors compared to control mammary tissue obtained from 74 week old mice, while expression levels of AdipoR2 were similar in mammary tumor and control tissues (Dogan, S. & Cleary, MP unpublished data). In agreement, Takahata *et al.* reported that AdipoR1 but not AdipoR2 was expressed in breast stromal cells which led to the suggestion that adiponectin signals primarily through AdipoR1 in mammary tissue (36).

There are recent findings which lead to speculation that adiponectin could be used therapeutically (41, 42). For example, local and intraperitoneal injections of adiponectin inhibited growth of gastric cancer cells

Table 1. Reports of plasma/serum adiponectin concentrations (μg/ml) in women in association with breast cancer[1]

Subjects Pre/post/combined	Breast Cancer	Controls	Comments	Reference #
Combined	7.57±0.31 (n=102)	8.83±0.38 (n=100)	Adiponectin significantly lower in breast cancer.	(34)
Pre-menopausal	14.5±1.1 (n=49)	13±1.0 (n=44)	Differences not significant but inverse association of adiponectin in postmenopausal women.	(38)
Postmenopausal	17.6±0.9 (n=125)	19.0±1.1 (n=123)	Differences not significant but inverse association of adiponectin in postmenopausal women.	(38)
Combined	10.24±0.58 (n=100)	19.17±1.24 (n=100)	Significantly decreased in breast cancer.	(33)
Combined	6.9±0.5 (n=44)	7.6±0.5 (n=43)	No significant effect	(142)
Pre-menopausal	9.31±0.36 (n=43)	10.06±0.56 (n=26)	No significant effect	(65)
Postmenopausal	7.74±0.55 (n=37)	10.43±0.57 (n=24)	Significantly low in postmenopausal and combined groups.	(65)
Combined	(n=2643)	(n=3771)	Among postmenopausal women, adiponectin appeared strongly and inversely associated in women who never used postmenopausal hormone and women with low circulating estradiol levels	(35)
Pre-menopausal ≤ 13.3.7 > 13.3.7	(n=141) 78.7% 21.3%	(n=141) 75.2% 24.8%	No difference for premenopausal women in % high vs low adiponectin.	(143)
Postmenopausal ≤ 15.6.9 > 15.6.9	(n=103). 87.4% 12.6.%	(n=103) 75.5% 24.5.%	Postmenopausal women in the high level of adiponectin had a significantly decreased risk for breast cancer vs low level.	(143)
Combined	9.1 (n=74)	11.3 (n=76)	Adiponectin significantly lower in breast cancer	(22)

[1] All studies are case-control protocols and data presented are means ± sem where information was available.

inoculated subcutaneously into BALB/c nude female mice (41). In a different approach human breast cancer MDA-MB-231 cells were either pretreated with adiponectin prior to implantation into nude mice or the cells were implanted and the mice were then injected with recombinant adenovirus that expressed adiponectin resulting in significantly reduced tumor size (42).

3.2. Adiponectin effects *in vitro*

Studies using human breast cancer cell lines indicate that both AdipoR1 and AdipoR2 are expressed in MCF-7, MDA-MB-231, T47-D, and SKBR3 cells (22, 36, 43, 44). A recent study from our laboratory has shown that MCF-7, MDA-MB-231, MDA-MB-361, T47-D, and SKBR3 cells not only express AdipoR1 and AdipoR2 but also adiponectin itself (44). Of further interest, addition of adiponectin inhibited proliferation of a number of different human breast cancer cell lines (22, 42-44). In addition, Grossmann *et al.* reported that adiponectin inhibited the proliferation of the ER-negative SK-BR-3 breast cancer cell line at a higher concentration than it inhibited ER-positive MCF-7 and T47-D breast cancer cell lines (44). This suggests an estrogen and adiponectin interaction. Although the exact mechanisms as to how adiponectin inhibits cell proliferation and tumor growth are not known, involvement of mitogenic growth factors (43, 45), vascular endothelial growth factor (19), AMP kinase (43, 46, 47), p42/44 MAP kinase (22, 43), TNF-alpha (48) and JNK2 (44) in adiponectin signaling have all been reported. Adiponectin may also enhance aspects of apoptosis signaling (19, 43, 44, 48), although one study showed no role of apoptosis in inhibitory effect of adiponectin on T47-D cell proliferation (22).

4. LEPTIN: AN OVERVIEW.

Leptin is 16 kDa cytokine discovered in 1994 by positional cloning of the *ob* gene (49). It is a regulator of body weight, food intake and energy balance acting in the hypothalamus, but can also affect fetal development, sexual maturation, lactation, hematopoiesis and immune responses (50). It is produced by preadipocytes, adipocytes (51), mammary epithelial cells (52), as well as other tissues (53).

Leptin exerts its function through specific transmembrane leptin receptors (ObR) (54). A number of isoforms of ObR have been identified but the long isoform (Ob-Rl/Rb) contains an active intracellular signaling domain and has the ability to activate the intracellular JAK2/STAT, Ras/ERK-1/2 and PI3-K/Akt/GSK3 pathways (55). Short isoforms (Ob-Rs/Ra) lack major domains and mainly activate MAPK and have little effect on STAT activation although Ob-Rs/Ra may be involved in intra- and transcellular transport (55, 56).

Circulating leptin levels are usually proportional to total adipose tissue mass, i.e. increased in obese and decreased in lean subjects (57). Interestingly, serum leptin levels are significantly higher in women than men even when adjusted for age and body mass index (58) or total body fat mass (59). Postmenopausal weight gain and hormonal changes increase leptin levels (60). Considering that this adipokine can act as a growth factor in normal and malignant mammary epithelial cells (61) leptin is a good target to study the development and prevention of postmenopausal breast cancer.

4.1. Leptin in human breast cancer

Several epidemiological studies have evaluated serum leptin levels in women with breast cancer, but with conflicting results (Table 2). In five studies, which included combined results for pre- and postmenopausal women, serum leptin levels were higher in breast cancer patients then in controls (healthy women or patients with benign breast disease) (33, 62-65). When menopausal status was clearly separated two studies reported that both pre- and postmenopausal breast patients had significantly higher serum leptin concentrations (63, 66) than did control subjects and in a more recent study the difference in serum leptin levels between breast cancer patients and controls was significant in postmenopausal women (65). However, in a number studies (38, 67-71) serum leptin levels were not increased in subjects with breast cancer compared to controls although these studies sometimes included only premenopausal women or combined menopausal status. In one study (69) there was a significant inverse correlation of

Table 2. Reports of plasma/serum leptin concentrations (ng/ml) in women in association with breast cancer risk[1]

Subjects Pre/post/combined	Breast Cancer Subjects	Control Subjects	Comments	Reference #
Pre-menopausal	13.69±1.27 (n=83)	16.03±1.74 (n=69)	Leptin not associated with an increase the risk of pre-menopausal breast cancer	(71)
Pre-menopausal	14.7±2.0 (n=14)	23.9±4.1 (n=15)	Significant inverse association in pre-menopausal	(69)
Postmenopausal	25.6±2.1 (n=61)	24.6±2.8 (n=60)	No association in postmenopausal breast cancer	(69)
Combined	10.4±1.4 (n=23)	2.3±0.5 (n=8)	Higher in breast cancer and increases by stage	(62)
Pre-menopausal	26.81±6.25 (n=15)	17.65±0.97 (n=58)	Significantly higher in breast cancer. No difference between pre-and postmenopausal. No difference between early and late stages.	(66)
Postmenopausal	27.06±2.98 (n=43)	17.65±0.97 (n=58)	Significantly higher in breast cancer. No difference between pre-and postmenopausal. No difference between early and late stages.	(66)
Combined	38.1±2.6 (n=55) (non-metastatic) 39.6±3.0 (n=30) (metastatic)	35.6±2.8 (n=25)	No association of leptin with breast cancer	(67)
Pre-menopausal	12.8±2.2 (n=19)	3.1±0.3 (n=6)	Significantly higher in breast cancer. By stage higher values only seen for pre-menopausal.	(63)
Postmenopausal	10.5±0.6 (n=30)	2.7±0.1 (n=6)	Significantly higher in breast cancer.	(63)
Pre-menopausal	18.7±1.8 (n=49)	22.0±2.2 (n=44)	No association	(38)
Postmenopausal	26.6±1.4 (n=125)	24.9±1.8 (n=123)	No association	(38)
Postmenopausal	16.7 (n=149)	17.1 (n=258)	No association	(70)
Combined	13.57±0.66 (n=90)	9.46±0.60 (n=103) 10.87±1.09 (n=40) (benign breast disease)	Significantly higher in breast cancer. Correlation between leptin and BMI	(64)
Combined	13.63±1.18 (n=100)	10.07±0.5 5 (n=100)	Significantly higher in breast cancer.	(33)
Pre-menopausal	10.98±1.19 (n=30)	7.79±0.75 (n=26)	No association in pre- and postmenopausal No difference between early and late stages	(68)
Postmenopausal	18.29±4.63 (n=15)	12.59±1.97 (n=19)	No association in pre- and postmenopausal No difference between early and late stages.	(68)
Pre-menopausal	1.02±0.06 (n=43)	0.92±0.04 (n=26)	No association	(65)
Postmenopausal	1.56±0.07 (n=37)	1.27±0.0 (n=24)	Significantly higher in postmenopausal groups.	(65)

[1] Data presented are means ± sem where information was available.

serum leptin concentration with pre-menopausal breast cancer risk. These inconsistent findings can partially be explained by differences in serum preparation and study designs. In future studies attempts should be made to use prospective designs, larger number of women and standardized techniques. Additionally, based on *in vitro* studies and those with animals (see below), characteristics of the tumor itself are probably an important determinant of how or whether leptin impacts breast cancer development.

Another consideration is that breast carcinogenesis may be induced and/or enhanced by overabundance of locally produced leptin rather then systemic leptin. Analyses of tissue biopsies revealed that, similar to the leptin receptor, leptin is overexpressed in breast tumor tissue compared to non-cancer breast epithelium. Additionally, the expression of leptin was found to be positively correlated with expression of the leptin receptor, suggesting that leptin acts on mammary tumor cells via an autocrine pathway (72). In addition the leptin/leptin receptor axis can be induced by high levels estrogen, insulin and IGF-I, which are all increased in obese women (73).

4.2. Leptin and breast cancer (experimental animals)

As indicated above obesity is a risk factor for breast cancer in postmenopausal women particularly for hormone-dependent tumors (74). In support of this diet-induced obesity increased the tumorigenic potential of ER-positive tumors in MMTV-TGF-alpha mice (75), but not ER-negative tumors in obese MMTV-neu mice (76). We have proposed that one link between obesity and breast cancer is leptin. This is supported by reports that genetically obese leptin-deficient ($Lep^{ob}Lep^{ob}$) (77) and leptin receptor-deficient ($Lepr^{db}Lepr^{db}$) (78) mice did not develop oncogene-induced mammary tumors. When genetically obese Zucker rats which also have a leptin receptor defect were administered the chemical carcinogen methylnitrosurea, palpable mammary tumors developed at similar rate in the lean and obese rats but only a small percentage of those were carcinomas in the obese rats (79). Additionally we did not detect mammary tumors in obese Zucker rats that were administered another chemical carcinogen 7,12-dimethylbenz[alpha]anthracene (Cleary, MP and Morton, R., unpublished data). However, Hakkak and coworkers have reported that obese Zucker rats had greater susceptibility to this carcinogen than did lean rats (80). These different results may be attributable to substrains of the Zucker rats with different degrees of leptin receptor defects or other unknown factors.

In MMTV-TGF-alpha mice leptin receptor, ObRl/Rb, expression in mammary fat pad and mammary tumors has been reported (81). While obesity per se did not affect expression levels of the receptor (81) intermittent calorie restricted reduced both total leptin receptor expression, ObR, as well as expression of the signaling form, ObRl/Rb, in mammary fat pads compared to chronic caloric restriction and ad libitum fed mice (82). In a transplanted mammary tumor model it has been reported that leptin signaling was associated with tumor growth and increased expression of VEGF and VEGF-R2 and treatment by a leptin receptor agonist decreased serum

VEGF levels, tumor growth and VEGF/VEGF-R2 expression in tumors (83).

4.3. Leptin and breast cancer (*in vitro*)

There have been a number of studies evaluating leptin's effects on human breast cancer cell lines. Both ObRl/Rb and Ob-R were detected in human breast cancer cell lines (84), as well as in a nonmalignant line (61). ER-positive MCF-7 and T47-D cells express high levels of ObRl/Rb while the shorter forms are present in ER-negative MDA-MB-231 and MDA-MB-435 cell lines (85). In addition, ObR and ER-alpha are co-expressed in breast cancer cell lines (84).

In ER-positive breast cancer cell lines, MCF-7, T47-D and ZR-75-1, leptin stimulated proliferation through multiple signaling cascades, including JAK/STAT, ERK1/2, Akt/GSK3, and PKC-alpha pathways (84). In T47-D breast cancer cells, leptin also induced cellular transformation (anchorage-independent growth); this activity was not shown in normal breast epithelial cells (61).

Leptin induced breast cancer cell proliferation is accompanied by increased AP-1 activation (61) via aromatase expression by AP-1-dependent mechanism (86), upregulation of cdk2 and cyclin D1 levels, hyperphosphorylation/inactivation of pRb (85, 87), induced expression of c-myc (88) and increased the expression of VEGF and VEGF-R2 (83). It has been found that leptin modulates estrogen synthesis and ER-alpha activity by upregulation of the aromatase gene expression and aromatase activity in MCF-7 cells leading to increased estrogen synthesis (86). While the response of ER-positive breast cancer cell lines to leptin are in general in agreement, results for ER-negative breast cancer cell lines tend to be conflicting (89).

5. IMPORTANCE OF ADIPONECTIN:LEPTIN RATIO

Recent studies have suggested that the adiponectin:leptin ratio might be an important factor in different physiological conditions. For example, the adiponectin:leptin ratio has been inversely correlated with increased levels of C-reactive protein (90, 91), an indicator of low grade inflammation, thought to influence several diseases including cancer. Inflammation is associated with lower isoprostane levels, an indicator of oxidative stress, reduced adiponectin and elevated leptin levels (91). Oxidative stress in turn can result in a proinflammatory state as well as DNA mutations, tumor formation and tumor progression in breast cancer (92). The ratio of adiponectin:leptin may be a better indicator of insulin resistance than either adiponectin or leptin alone and may also be more sensitive and reliable than the use of fasting plasma glucose levels or homeostasis model assessment (93). A recent study from our laboratory has reported that adiponectin:leptin ratio was significantly lower in mice made obese with goldthioglucose injections compared to lean mice (94).

There is only one study that specifically reported the adiponectin:letpin ratio in women with breast cancer (33). Specifically, women diagnosed with breast cancer had an elevated ratio of leptin:adiponectin (conversely a decreased adiponectin: leptin ratio). There was however no correlation between serum adiponectin level and tumor size whereas, there was a significant positive correlation between the leptin:adiponectin ratio and tumor size or conversely a negative correlation of the adiponectin: leptin ratio (33). The authors suggested that this ratio may indicate the aggressiveness of breast cancer independent of body mass index. In another human study, although the adiponectin:leptin ratio was not calculated for individual subjects, when this ratio was calculated using average adiponectin and leptin values, the ito was 15 % higher in age-matched controls than in postmenopausal breast cancer subjects, whereas, the average adiponectin:leptin ratio was 30 % lower in age-matched controls than premenapousal breast cancer subjects (38).

In an in vitro study, we observed that proliferation of both ER-positive and ER-negative breast cancer cell lines was significantly inhibited when the adiponectin:leptin ratio was higher, similar to the physiological range of a lean person. On the other hand, when the adiponectin:leptin ratio level was lower, to mimic the range of an obese person, there was no reduction in cell proliferation, in fact, there was an increase in cell proliferation (32). Integration of these results suggests that the balance of adiponectin to leptin in individuals rather than the adiponectin or leptin levels alone may play important roles in physiological changes like development of cancer.

6. APPROACHES FOR ALTERING THE ADIPONECTIN:LEPTIN RATIO

The data and results presented lead to the speculation that a possible approach for prevention of postmenopausal breast cancer associated with obesity would be to change the adiponectin:leptin ratio. Here we will discuss three possible approaches citing available research supporting their potential to alter the adiponectin:leptin ratio. A summary of the supporting publications is presented in Table 3.

The first approach that can alter the adiponectin:leptin ratio is weight loss. It has been repeatedly reported that weight loss decreases serum leptin (95-99) and increases serum adiponectin (100-103) levels. Some studies also indicate that the adiponectin:leptin ratio can be altered by dietary weight loss (100-102, 104). Various gastric bypass surgeries can result in drastic weight loss accompanied by increased serum adiponectin and decreased leptin levels (105-108). Interestingly, a recent report indicated that breast cancer incidence was reduced by 85% following bypass surgery (109). However, the side effects of this intervention are serious and thus it does not warrant use solely for breast cancer prevention.

A novel option that may be more effective for breast cancer inhibition than traditional chronic caloric restriction for weight loss may be multiple periods of intermittent caloric restriction. Intermittent restriction

Table 3. Reports of potential mechanisms for altering serum adiponectin and leptin levels

Mechanism	Type of Study	Changes in Adiponectin	Changes in Leptin	Comments	Reference #
Intermittent Caloric Restriction	Human	n/d*	Decreased	Alternate days 20% or ad lib	(110)
Intermittent Caloric Restriction	Human	Increased	Decreased	20 hour fast every other day	(113)
High Glycemic Diet	Human	Decreased	n/d		(117)
Low Fat Diet	Human	Increased	Decreased	Changes seen after 3 days	(118)
Fish Oil Consumption	Human	Increased	n/d	1.8.g daily for 3 months	(126)
Fish Oil Consumption	Mouse	Increased	No Change		(129)
Fish Oil Consumption	Mouse	Increased	No Change		(130)
Rosiglitazone Treatment	Human	Increased	No Change	14 day treatment	(132)
Rosiglitazone Treatment	Human	Increased	No Change	21 day treatment	(133)
Rosiglitazone Treatment	Mouse	Increased	No Change		(135)
Pioglitazone Treatment	Human	Increased	No Change	14 day treatment	(134)
Rimonabant Treatment	Human	Increased	Decreased	Partially independent of weight loss	(136)
Rimonabant Treatment	Rat	Increased	n/d		(138)
Rimonabant Treatment	Mouse	Increased	Decreased		(139)
Hormone Replacement Therapy	Human	Decreased	n/d	Long-term study	(140)
Hormone Replacement Therapy	Human	No Change	n/d	Short-term study	(141)

*n/d = not determined.

protocols such as alternate day fasting have shown the potential for high compliance (110) and may prove more effective for some individuals as compared to chronic caloric restriction. Whether intermittent caloric restriction in humans will reduce breast cancer incidence is unknown. Interestingly, women diagnosed with anorexia nervosa were reported to have an overall 53% reduction in breast cancer incidence compared to the general population (111). Female anorexia nervosa patients who regained weight had decreased adiponectin and increased leptin compared to their levels prior to treatment (112). Assuming that women with anorexia nervosa experience periods of intermittent caloric restriction this would support a protective effect in humans. However, the extreme calorie restriction characteristic of anorexia nervosa is certainly not ideal for breast cancer prevention. Therefore, the specific details of how intermittent caloric restriction would be best implemented for alteration of the adiponectin:leptin ratio and weight reduction are under active investigation. For example, overweight subjects who used alternate day calorie restriction consuming less than 20% of their normal diet alternating with ad libitum intake lost an average of 8% of their initial body weight in 8 weeks and had decreased levels of leptin (110) but unfortunately adiponectin was not measured. In another study, healthy young men (average body mass index of 25.7) who were subjected to intermittent fasting every second day for 20 hours for 15 days had increased adiponectin levels compared to their pre-intervention levels while leptin was decreased thus increasing the average adiponectin:leptin ratio (113). These studies suggest the need for further investigation into the effects of intermittent caloric restriction on serum adiponectin and leptin levels in humans.

Direct comparison of intermittent to chronic caloric restriction in rodents supports that intermittent caloric restriction provides greater prevention than chronic caloric restriction for spontaneous and transgenic mammary tumor development (82, 114-116). In particular our laboratory reported that intermittent caloric restriction of MMTV-TGF-alpha mice with 20% lower caloric intake compared to *ad libitum*-fed mice had either a 96% (115) or 85% (82) reduction in oncogene-induced mammary tumor incidence while chronic caloric restricted mice with a similar degree of calorie restriction had only a 40% and 64% decreases respectively. The age of mammary tumor detection was also significantly earlier in the ad libitum-fed mice compared to the intermittent caloric restricted mice while mammary tumor weight was higher in the ad libitum-fed mice compared to the intermittent caloric restricted mice. How adiponectin, leptin and adiponectin:leptin ratio are impacted by these two interventions is currently under investigation.

A second approach to alter the adiponectin:leptin ratio is by dietary composition changes. Only a few studies have directly addressed how specific dietary factors may alter adiponectin, leptin, and/or the adiponectin:leptin ratio. In one report, men who consumed a carbohydrate rich diet with a high glycemic load had serum adiponectin levels that were significantly inversely correlated to glycemic load (117). However, leptin levels were not reported. Another report found that a low fat diet reduced leptin and increased adiponectin levels resulting in an increase in the adiponectin:leptin ratio (118). In addition, the types and amounts of fatty acids in serum have been reported to correlate with serum adiponectin levels. Higher serum levels of palmitic acid, correlated with lower serum adiponectin while eicosanoic acid correlated with higher adiponectin levels independently of age, body mass index, wais:hip ratio and other fatty acids (119). The lack of information on how these specific nutrients affect the adiponectin:leptin ratio is an area that is in need of additional research.

One nutritional component associated with breast cancer prevention is consumption of fish oil. The inverse relationship between high fish consumption and breast cancer was first noted over 30 years ago (120, 121). Fish such as wild salmon, sardines and mackerel are all high in omega-3 long chain polyunsaturated fatty acids (LC-PUFAs). It has been proposed that the relative proportions of omega-3 and omega-6 LC-PUFAs are important (122). Three case control studies found an inverse relationship between breast cancer and the ratio of omega -3 LC-PUFAs and omega -6 LC-PUFAs in mammary adipose tissue (123-125). To date there are no reports integrating human breast cancer, fish oil, adiponectin and leptin measurements.

However, human subjects given 1.8. grams of fish oil daily for three months had increases in plasma adiponectin levels (126).

Several animal studies support the idea that fish oil consumption influences the development of breast cancer. For example, MMTV-HER-2/neu transgenic mice fed fish oil (25% of energy) had mammary tumor incidence of 57% compared to 87% for mice fed corn oil (127). In addition, when mice with MDA-MB-435 breast cancer cell xenografts were fed a diet of 18% fish oil and 5% corn oil they had significantly slower tumor growth and fewer metastases than mice fed 5% fish oil and 18% corn oil (128). Mice have been reported to have increased serum adiponectin levels following fish oil consumption and adiponectin:leptin ratios were increased compared to mice consuming diets with fat derived from non fish oil sources (129, 130). Integration of these findings led us to the hypothesis that one mechanism of action of fish oil is through up regulation of adiponectin and alteration of the adiponectin:leptin ratio.

A third potential approach to alter the adiponectin:leptin ratio is through pharmacological intervention. There are several drugs that have been shown to directly or indirectly affect the adiponectin:leptin ratio. In addition, adiponectin appears to have potent insulin-sensitizing effects and as such drugs with this effect may act through their ability to up regulate adiponectin (131). We will summarize the evidence that implicates specific drugs in adiponectin regulation as well as the potential for adiponectin to act as a critical mediator of PPAR-gamma-agonist improvements in the adiponectin:leptin ratio.

Thiazolidinediones function as agonists of PPAR-gamma and are used to treat type 2 diabetes. In a clinical study of nondiabetic individuals 14 day treatment the thiazolidinedione, rosiglitazone, increased serum adiponectin by 130% compared to placebo (132) although leptin was not measured. In a second study also using rosiglitazone, 16 healthy males were evaluated in a double-blind, randomized, placebo-controlled parallel-group study in which adiponectin increased but leptin did not significantly change (133). In an additional study men given pioglitazone for 14 days had increased serum adiponectin levels from baseline after 3 days that continued to increase throughout the study while leptin slightly decreased resulting in an increased adiponectin:leptin ratio (134). In obese diabetic KKAy mice, rosiglitazone increased serum adiponectin concentrations but did not significantly alter leptin levels resulting in an increase in the adiponectin:leptin ratio (135). Interestingly, one potential mechanism for the increase in adiponectin seen following fish oil consumption is through activation of PPAR-gamma. As mentioned above mice fed a fish oil diet had increases in adiponectin and a decrease in leptin (129), and the effect was blocked by the PPAR-gamma inhibitor bisphenol-A-diglycidyl ether. PPAR-gamma null mice did not have an increase in adiponectin after being fed fish oil (129) further supporting the role of PPAR-gamma activation in regulation of the adiponectin:leptin ratio.

Endogenous endocannabinoids can activate the cannabinoid-1 receptor and influence appetite. In humans an antagonist to this receptor, rimonabant, increased adiponectin levels partially independently of weight loss and leptin levels were decreased resulting in an increase in the adiponectin:leptin ratio (136). Rimonabant increased adiponectin mRNA in rat adipose tissue (137) and increased serum adiponectin in rats (138) and mice (139). These studies suggest that receptor blockade may be able to not only help with weight loss but also able to alter the adiponectin:leptin ratio.

Interestingly, hormone replacement therapy may impact adiponectin levels. This may be very important both as a theoretical mechanism for understanding how these drugs impact the human body and from a practical stand point in providing women with information when contemplating hormone replacement therapy. One study found that women who received estrogen plus progesterone therapy for at least 5 years had lower serum adiponectin levels compared a control group of women who had not received hormone replacement (140). However another study reported no effect of short-term hormone replacement on plasma adiponectin levels (141). This area is relatively new and these studies have not been particularly large. Therefore, this may be an important area for future research.

7. CONCLUSION

There is consistent evidence that obesity is a risk factor for postmenopausal breast cancer. In addition to estrogen being an associated growth factor, there is increasing data indicating that leptin which circulates at higher levels in obese compared to lean women may promote breast cancer development and progression. In contrast, another factor also made in adipose tissue, adiponectin, is lower in obese women and also in women with breast cancer. This adipokine appears to prevent proliferation of breast cancer cell lines. There is emerging evidence that the adiponectin:leptin ratio may be of more important than either protein alone in regulating breast cancer growth. Thus strategies which promote high adiponectin levels relative to leptin may provide an unique approach for breast cancer prevention.

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