COMMENTARY

Obesity, Breast Cancer and the Role of Adipocytokines

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Abstract

   Obesity is a worldwide problem which impacts the risk and prognosis of some of the more common forms of cancer, including breast cancer in post-menopausal women. As the basis for understanding the potential mechanisms of obesity and cancer relationship has advanced, a number of new hypotheses have emerged. The adipocytokines are a complex group of biologically active polypeptides. Leptin is a growth hormone, secreted by adipose tissue, whose levels are normally elevated in obese individuals and may have a promoting effect on carcinogenesis and metastasis of breast cancer, possibly in an autocrine manner. Leptin interferes with the insulin signaling pathway and in type 2 diabetes plasma leptin levels are found to be correlated with the degree of insulin resistance, a relationship independent of body mass. This relationship might provide a mechanistic explanation for promotion potential.

Key Words: Obesity - breast cancer - adipocytokines - leptin

Introduction

   Obesity is recognized as an important risk factor for many serious medical conditions (Somasundaram et al, 2004) including certain cancers. The predominant cancers associated with obesity have a hormonal base and include breast, prostrate, endometrium, colon, and gall bladder neoplasms (Bray, 2002). Obesity can be measured with reference to body weight, body weight relative to height or by the distribution of fat in the body. The two most widely used and clinically relevant classifications to assess the degree of obesity are body mass index (BMI), calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m^2), and the central or peripheral distribution of fat. According to WHO standards, the BMI is between 18.5 and <25 for a normal person, between 25 to <30 for an overweight person, and ≥30 for an obese person. Table 1 shows data for prevalence of cancers for overweight individuals with a BMI>25 and for those who are labeled as obese with a BMI≥30.

Breast Cancer

   Breast cancer is the most commonly occurring cancer among females in the world and is the second cause of cancer death in women, following lung cancer. (Parkin, 2004; Stewart et al, 2004). The estimated annual incidence of breast cancer worldwide is about one million cases with 200,000 cases in United States (27% of all cancers in women) and ~320,000 cases in Europe. Over the last two decades, the annual incidence rate has been increasing steadily (15% of cancer deaths, Jemal et al, 2002)). The etiology of breast cancer is still poorly understood with known breast cancer risk factors explaining only a small proportion of cases. Numerous studies have investigated the relation between indicators of body size and breast cancer incidence (IARC, 2002; Freidenreich, 2001). Despite a number of generally accepted risk factor characteristics, the association between body weight and breast cancer risk remains complex. The relation is modified by the menopausal status, with a higher weight or BMI associated with reduced risk in pre-menopausal and increased risk in post menopausal women. The case control studies have tended to report significant positive associations between weight or BMI and post

Table 1. Relative Risk with Increased Body Weight for Specific Cancers

Cancer site	Relative risk (overweight vs normal weight)	Relative risk (obese vs normal weight)
Breast (postmenopausal)	1.12	1.25
Colon	1.15	1.33
Endometrium	1.59	2.52
Prostrate	1.06	1.12
Kidney	1.36	1.84
Gallbladder	1.34	1.78

Bergstrom et al (2001). Intl J Cancer 91; 421-30.

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menopausal breast cancer risk, whereas results from cohort studies are less consistent.

Increased central obesity that primarily occurs during or after menopause may be a more specific marker of the metabolic consequences of obesity and a better indicator of risk than body weight itself (WHO., 2002; Lahmann et al., 2004). However, results on the role of fat distribution in post menopausal breast cancer risk are unambiguous. An International Agency for Research on Cancer (IARC) review concluded that central obesity assessed by measuring waist circumference or WHR is not predictive of pre-menopausal breast cancer risk (WHO., 2002). A cohort study on 73,542 pre-menopausal and 103,344 post menopausal women from nine European countries showed general obesity as a significant predictor of breast cancer in post menopausal women who did not take exogenous hormones, while abdominal fat assessed as waist-hip ratio or waist circumference was not related to excess risk when BMI was adjusted for Among pre-menopausal women, weight and BMI showed a non significant inverse association with breast cancer (Lahmann et al., 2002).

Obesity and estrogens have long been implicated in the pathogenesis of breast cancer (Lipmann., 1998). Adipose tissue serves as the site of peripheral aromatization of renal androgens to estrogens, which induce mitogenic activity in mammary tissue by binding to estrogen receptors. A strong association of obesity with insulin resistance characterized by hyper-insulinemia has also been well documented. There are studies which report that insulin as well as insulin like growth factors (IGFs) plays an important mitogenic role in the development of breast cancer (Mantzoros and Flier., 1995). Adiponectin (acrp30, adipoQ, apM1 gene product) is an adipocyte secreted protein whose decreased levels are implicated in the pathogenesis of insulin resistant states, obesity and type 2 diabetes mellitus (Stefan et al., 2002). The adiponectin levels are decreased in pre-menopausal women with endometrial carcinoma, a malignancy closely associated with obesity and insulin resistance. A recent case control study showed strong statistically significant inverse association of serum adiponectin with breast cancer in post menopausal women, whereas no such association was seen among pre-menopausal women (Mantzoros et al., 2005).

Anthropometric Indices and Breast Cancer

It is suggested that higher BMI is associated with a more advanced stage of breast cancer at diagnosis. Numerous studies have investigated the relationship between indicators of body size and breast cancer incidences. Studies on attained height in relation to breast cancer occurrence from diverse populations consistently suggest that taller women are a greater risk for breast cancer regardless of menopausal status. With the pooled data from seven prospective cohort studies (33,819 women and 4385 incident invasive breast cancer cases in total) and after adjustments for reproductive, dietary and other risk factors, the pooled relative risk of breast cancer per height increment of 5cm was 1.02 (95%

CI 0.96-1.10) in pre-menopausal women and 1.07 (1.03-1.12) in post menopausal women. These findings indicate that height is an independent risk factor for breast cancer after menopause, whereas the relationship is not as clear in pre-menopausal women. Despite a number of generally accepted risk characteristics, the association between body weight and breast cancer remains complex. Case control studies have reported significant positive associations between weight or BMI and postmenopausal breast cancer risk, whereas results of cohort studies are less consistent. Among pre-menopausal women, inverse associations with BMI have been found in most cohort studies but both inverse and direct associations have been reported in case control studies. Body mass index showed substantial inverse and positive associations with the disease in pre menopausal and post menopausal women respectively (Van den et al., 2000).

Adipocytokines and Obesity

Adipocytokines constitute a group of polypeptide growth factors and cytokines which are produced by white adipose tissue and act by endocrine, paracrine and autocrine mechanisms (Rose et al., 2004). Some adipocytokines such as TNF-α have been known for many years, while others, such as leptin and adiponectin are relatively recent discoveries. The adipocytokines circulate in the blood and normally constitute approximately 0.01% of total plasma proteins (Arita et al., 1999).

Leptin

Normal body weight is regulated by the presence of leptin, an adipocyte derived hormone that acts on the brain to regulate food intake. Leptin, a product of the obese (ob) gene, is a multifunctional hormone and a polypeptide which was first identified in 1995 (Schoeller et al., 1997). It is a neuro-endocrine protein with biological activities such as appetite regulation, bone formation, reproductive function and angiogenesis (MacDougald et al., 1995). It is largely expressed by adipocytes and is also express in relatively small amounts by a variety of other cell types including mammary epithelial cells. The major factor influencing the plasma leptin concentrations is adipose tissue mass (Somasundaram et al., 2004). The circulating leptin levels exhibit a particularly strong positive correlation with total body fat, and to a lesser degree with the body mass index (Thomas et al., 2000). Thus the serum leptin is highly elevated in obese individuals and significantly reduced in the lipodystrophic states (Kolaczynski et al., 1996). Elevation of serum leptin in obesity appears to result from both an increased fat mass and an increased leptin release from larger adipocytes (Hamilton et al., 1995). Circulating leptin levels are influenced by a variety of metabolic active factors, the most prominent of which is insulin. Insulin stimulates both leptin secretion and leptin mRNA levels (Leroy et al., 1996). The leptin levels increase after the peak insulin levels following meals and decrease during insulin deficiency.

Aging is associated with changes in fat distribution, insulin resistance and obesity. Leptin levels are elevated in aged rodents and humans, suggesting a leptin resistant stage (Sanchez-Rodriguez et al., 2000). The increase in leptin levels can partially be attributed to increased adiposity, and is often disproportionate to the increase in fat mass. The ability of leptin to inhibit food intake is decreased in aged rats, independent of food patterns, which suggests the development of leptin resistance may play a role in aging induced obesity (Gabriely et al., 2002).

Tumor Necrosis Factor-alpha

Tomor necrosis factor-α was originally identified as a polypeptide cytokine produced by macrophages during infections, injury and cancer progression. The first described TNF polypeptide is now known to be just one of a super family of ten ligands with an equal number of trans-membrane glycoprotein receptors (Gruss, 1996). A diversity of its functions such as immune responses, inflammatory reactions and neovascularization contribute to a variety of diseases such as inflammatory bowel disease, rheumatoid arthritis and cardiomyopathies. It inhibits tumor cell proliferation, promotes cellular apoptosis and stimulates oestrogen biosynthesis by way of aromatase induction and angiogenesis (Fajardo et al., 1992). Under physiological conditions, it is produced in adipose tissue in large quantities and is therefore included among adipocytokines. However, the TNF-α derived from the adipose tissue originates only in part from the adipocytes. A considerable portion may be secreted by infiltrating macrophages particularly in obesity (Weisberg et al., 2003). The TNF-α is also reported to both stimulate and inhibit leptin release (Finck and Johnson, 2000).

Interleukin-6

The interleukins are a member of a group of cytokines which are typically produced by leukocytes. They perform a variety of biological functions such as regulation of inflammatory and immune responses. Human adipocytes secrete sizeable amounts of IL-6. IL-6 has activities related to insulin resistance, angiogenesis and tumor cell biology. Like leptin and TNF-α; IL-6 can stimulate estrogen biosynthesis by the aromatase activity (Kern et al., 2001).

Heparin-binding Epidermal Growth Factor-like Growth Factor

Heparin-binding epidermal growth factor-like growth factor is one of the several polypeptides which are structurally and functionally related to EGF and bind to its receptor. It is a potent mitogen for fibroblasts and smooth muscle cells, but not endothelial cells (Raab and Klagsburn, 1997). However, it stimulates endothelial cell migration and promotes angiogenesis in vivo. The studies reported indicate the substantial expression of HB-EGF in human adipose tissue and increased mRNA levels in obese mice.

Vascular Endothelial Growth Factor and Hepatocyte Growth Factor

The growth factor has an important role in the angiogenic process. It promotes angiogenesis by inducing matrix metalloproteinase (MMP) expression and stimulates vascular endothelial cell migration (Thomas et al., 1996). It is also produced by adipose cells and maintains local vascularity and the expansion and retraction of adipose tissue mass (Hausman and Richardson, 2004). Like VEGF, HGF stimulates vascular endothelial cell proliferation and migration in vitro, induces MMP expression and stimulates angiogenesis in in vivo models (Rosen et al., 1993). The synthesis and secretion of HGF by adipocytes are elevated in obese human subjects and blood concentrations are positively correlated with BMI (Rehman et al., 2003).

Adiponectin

Adiponectin is the most abundant gene product of human adipocytes (Scherer et al., 1995). There is sufficient evidence of roles in the modulation of endothelial function, inhibition of inflammatory processes and protection against the insulin resistance syndrome (Kubota et al., 2002). This hormone suppresses the process of angiogenesis through a pathway leading to the activation of caspases (Brakenhielm et al., 2004).

Adipocytokines and Obesity

The expression of adipocytokines in human adipose tissue and the corresponding circulating concentrations are influenced by the total body mass. In six of the seven adipocytokines mentioned above, the plasma levels are positively associated with BMI and are elevated in obesity, except adiponectin which is negatively correlated. The leptin production rate in adipose tissue is directly proportional to the degree of adiposity (Klein et al., 1996). The plasma leptin concentrations in healthy men and women are positively correlated with both BMI and total body fat (Thomas et al., 2000). In obesity, elevated levels of tissue TNF-α expression correlate with similar changes in leptin, and the plasma concentrations of both TNF-α and leptin are reduced by weight loss. The plasma IL-6 and HB-EGF and serum HGF concentrations are positively correlated with BMI (Matesumoto et al., 2002). The elevated plasma and adipose tissue IL-6 levels which are present in obesity are reduced in conjunction with diet induced weight loss (Yang et al., 2001). The negative relationship between plasma leptin and adiponectin levels is actually stronger after adjustment for BMI and body fat mass. A positive correlation exists between adipocyte TNF-α expression and plasma TNF-α concentrations and BMI (Bruun et al., 2002). In obesity, elevated levels of adipose tissue TNF-α levels correlate with similar changes in leptin, and the plasma concentrations of

both TNF-α and leptin are reduced by weight loss (Considine et al., 1996). In contrast to other adipocytokines, there is an inverse relationship between plasma adiponectin concentration and body fat mass. Weight reduction in obesity produces an elevation in subnormal plasma adiponectin levels (Yang et al., 2001).

Leptin gene expression occurs in normal mammary tissue, in breast cancer cell lines and in solid tumors (Chilliard et al., 2001). Estrogens as well as other hormones and growth factors, some of which act as mediators or biological proximate effectors for leptin mitogenic activities, stimulate breast cancer. Insulin is also a mitogenic agent for breast cancer. Its capacity to stimulate leptin release and elevate circulating leptin levels provide a potential interaction between insulin and the metastatic cascade as targets for leptin bioactivity (Askari et al., 2000).

There are controversial reports over the significance of body fat distribution, as opposed to obesity defined by BMI in breast cancer. Central obesity is associated with an increased risk in post menopausal women. Most published studies use the ratio of waist to hip circumference (WHR) to assess body fat distribution and have concluded that an elevated WHR is associated with increased breast cancer risk (Harvie et al., 2003).

Breast Cancer Biology and Adipocytokines

The early focus of cancerous epithelial cells is provided with a favorable microenvironment by the surrounding adipocytes and stromal cells of breast adipose tissue. Exogenous leptin stimulates the proliferation of the breast cancer cell lines in in vitro culture experiments (Hu et al., 2002). The studies in the recent past indicated the influence of obesity on breast cancer cell behavior. There are no published studies which state whether adiponectin has an effect on breast cancer cell proliferation although there are few findings which indicate the exertion of biological functions that may modulate tumor cell behavior. A recent finding reported that adiponectin suppressed the growth of myelocyte lines and induced apoptosis in myelomonocytic leukemia lines. Macrophage induced TNF- α production have also indicated an interaction between these adipocytokines (Yokota et al., 2000).

Breast Cancer Progression and Angiogenesis

Angiogenesis is the process of the formation of a new blood vessel system from the pre-existing capillaries and it occurs physiologically during embryogenesis. It has physiological functions under normal conditions in wound

Table 2. Proteins Secreted by Adipocytes that Act as Signaling Molecules

Adiponectin	Leptin
TNF-α	IL-6
Acetylation stimulation protein (derived from adipsin, C3 and factor B)	

healing, the secretory phase of the menstrual cycle and in embryonic implantation (Liekens et al., 2001). In pathological situations, it is involved in conditions as diverse as diabetic retinopathy, solid tumor growth and metastasis. The process of angiogenesis is highly complex with a number of interrelated components including endothelial cell proliferation, production of matrix metalloproteinase family of proteolytic enzymes and cell migration (Park et al., 2001). It is an important part of tumor growth and in the transition of benign proliferative breast disease to a malignant stage. Angiogenesis is stimulated by VEGF, leptin and HGF.

Angiogenesis is now established as a biomarker of a poor prognosis in invasive breast cancer, as is the expression of vascular endothelial growth factor (VEGF, Gasparini et al., 2000). The nuclear phosphoprotein p53, normally a regulator of cell cycle and apoptosis, undergoes mutations that are among the most common genetic effects in cancer cells, leading to tumor development. A number of studies have reported the association of p53 mutations with poor prognosis of breast cancer (Hursting et al., 2001). Animal studies have also reported the role of leptin in the development of mammary carcinoma in wild type p53 deficient mice.

Leptin's role as an angiogenic factor was first reported independently by two studies which indicated that leptin stimulated angiogenesis in both in vitro and in vivo models. Leptin has been shown to increase the expression of many other genes involved in angiogenesis, such as matrix metalloproteinase -2 (MMP-2) and metalloproteinase -9 (MMP-9) products (Kume et al., 2002).

Breast Cancer Risk, Insulin Resistance Syndrome and Adipocytokines

The insulin resistance syndrome comprises type 2 diabetes with hyperinsulinaemia, dyslipidaemia and cardiovascular abnormalities arising from atherosclerotic disease. Resistance to insulin action is a primary defect and leads to the emergence of the clinical syndrome. Several of the adipocytokines contribute to the regulation of insulin action, and have been associated with the insulin resistance syndrome (Matsuzawa et al., 1999). Leptin interferes with insulin signaling. In type 2 diabetes, plasma leptin levels were found to be correlated with the degree of insulin resistance; a relationship that was independent of BMI and body fat mass (Wauters et al., 2003). The adipose tissue TNF-α expression is also positively correlated with the degree of insulin resistance independent of BMI and body fat mass (Hotamisligi et al., 1995). In abdominal obesity, high circulating TNF-α level were associated with hyper-insulinemia and insulin resistance (Miyazaki et al., 2003). Insulin resistance is also associated with human adipose tissue derived IL-6 (Kerne et al., 2001).

The adiponectin is reported to have a protective role in the maintenance of insulin sensitivity. The gene expression of adiponectin is reversibly down regulated by insulin and plasma adiponectin concentration is inversely correlated with

fasting plasma insulin levels (Fassahauer et al., 2002; Matsubara et al., 2002). Thus adiponectin increases the sensitivity of tissues to insulin and hypo-adiponectinaemia is associated with insulin resistance (Stefan et al., 2002). Type 2 diabetes is reported to be associated with a slight increase in breast cancer risk in post menopausal women (Michels et al., 2003). Thus, it is an adipocyte-derived plasma protein with insulin sensitizing, anti-inflammatory and anti-atherogenic properties. Its low levels in insulin resistance suggest that therapeutic modulation of adiponectin may provide a novel treatment for insulin resistance as well.

In conclusion, it is clear that adipocytokines exert their effect on the clinical disease. However, it is still very important to explore whether the stimulating effects of adipocytokines extend to breast cancer. It is quite evident that excessive adipose tissue may be detrimental through the secretion of cytokines. The relative contribution of adipocytokines to glucose homeostasis and insulin resistance and their relationship with the occurrence of breast cancer should be the focus of research in coming years.

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