J Mammary Gland Biol Neoplasia (2008) 13:371–379
DOI 10.1007/s10911-008-9100-x

The Role of Endocrine Insulin-Like Growth Factor-I and Insulin in Breast Cancer

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Received: 5 October 2008 / Accepted: 30 October 2008 / Published online: 22 November 2008

Abstract Epidemiologic studies demonstrate that breast cancer is the most common type of cancer diagnosed in women and is a significant cause of morbidity and mortality. While there are many risk factors known to be associated with increased breast cancer risk, this review will focus specifically on circulating IGF-I, hyperinsulinemia, and type 2 diabetes. Their effects on promoting breast cancer development, progression, and adverse outcomes have been demonstrated in both animal and human studies, suggesting that the IGF system is a potential target for breast cancer therapy. In addition, in the clinical setting, emphasizing metabolic risk modifications to patients including weight loss, dietary changes, and diabetes control may also play an important role in breast cancer risk reduction.

Keywords Insulin-like growth factor · IGF-I · Insulin · Hyperinsulinemia · Insulin resistance · Diabetes · Breast cancer

Abbreviations

IGF	insulin-like growth factor
IGFBP	insulin-like growth factor binding protein
BMI	body mass index
IGF-IR	insulin-like growth factor-I receptor
IR	insulin receptor
IRS	insulin receptor substrate
PI3K	phosphatidylinositol 3-kinase
MAPK	mitogen-activated protein kinase
ER	estrogen receptor
TEB	terminal end bud
GH	growth hormone
GHRH	growth hormone releasing hormone
JAK	janus kinase
STAT	signal transducer and activator of transcription
ALS	acid labile subunit
MMTV	mouse mammary tumor virus
SDR	spontaneous dwarf rat
LID	Liver IGF-I Deficient
DMBA	7,12-dimethylbenz(a)anthracene
SV40-LTA	SV40 large T antigen
SHBG	sex hormone binding globulin
MCK	muscle creatine kinase
PyVmT	polyoma virus middle T antigen

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Introduction

Insulin-like growth factor-I (IGF-I) is a polypeptide that possesses characteristics of both a circulating hormone and as a tissue growth factor. Most circulating or endocrine IGF-I is produced by the liver, which is regulated by growth hormone secreted by the anterior pituitary gland, and also by insulin and nutritional factors. However, it has also been shown that IGF-I is produced directly at the tissue level, whereby it possesses paracrine and/or autocrine functions. IGF-I belongs to a complex system of related peptides, which includes insulin and insulin-like growth factor-II (IGF-II). IGF-I plays an important role in post-natal growth and development. However, elevated IGF-I

levels have been implicated in promoting tumor growth and metastatic disease and epidemiologic studies indicate that high circulating IGF-I levels are associated with increased incidence of many common cancers, including breast cancer [1]. Insulin is an anabolic hormone that mediates its metabolic effects at the level of hepatic, muscle, and adipose tissues. Insulin is primarily involved in glucose metabolism, but it can also exhibit proliferative, anti-apoptotic, and mitogenic effects. In fact, there have been a number of epidemiologic studies linking breast cancer with conditions associated with hyperinsulinemia and insulin resistance, most important being type 2 diabetes and obesity [2]. This review will explore the effect of circulating IGF-I and insulin on breast cancer development and progression.

Epidemiology and Risk Factors

Breast cancer is the most common type of cancer diagnosed in women, excluding skin cancer. Each year, one in eight women are diagnosed with breast cancer, and approximately 40,000 women die from metastatic disease [3]. Risk factors include female sex, race (Caucasian and African American), age greater than 50, family history, genetics (germline mutations such as BRCA1, BRCA2, PTEN), long menstrual history, nulliparous state, obesity, and postmenopausal use of hormone therapy [4]. Most of the hereditary types of breast cancer occur in premenopausal women and the sporadic cases occur in postmenopausal women.

It has been established that there is heterogeneity among individual patients with regard to serum or circulating IGF-I and its major binding protein insulin-like growth factor binding protein-3 (IGFBP-3) [5]. However, it has been suggested previously that elevated levels of IGF-I, and in some studies IGFBP-3, are associated with an increased risk of breast cancer development, especially in premenopausal women [6–10]. The EPIC cohort supports the same relationship in postmenopausal women [11]. However, the role of circulating IGF-I and IGFBP-3 in breast cancer has proved to be controversial as more recent evidence demonstrates that this association seems less clear and shows conflicting results [12–14]. In fact, the Nurses' Health Study II found no significant association between breast cancer risk and serum IGF-I or IGFBP-3 levels in a large cohort of premenopausal women [12]. Renehan et al. suggest that these observations may be a result of lack of standardization of assays, variations in study design, and variability in IGFBP-3 proteolysis in serum samples [14].

Obesity is typically classified by the measure of body mass index (BMI) greater than 30 kg/m^2 and along with type 2 diabetes, both have become a worldwide epidemics. Obesity is an established risk factor for breast cancer in postmenopausal populations [15]. In addition regardless of menopausal status, obese women are more likely to present with more aggressive breast cancer and have more ominous prognoses [16, 17].

Many previous epidemiologic studies have linked type 2 diabetes with an increased risk of developing breast cancer and higher mortality rates [2, 18–20]. This association was not only seen in overt type 2 diabetes. Other studies have documented that elevated fasting plasma glucose and hyperinsulinemia (without clinical type 2 diabetes) have also been linked to the development of breast cancer in with both premenopausal and postmenopausal women [21–23]. Interestingly, there has been no associated risk of breast cancer associated with type 1 diabetes [24], further suggesting that it is the hyperinsulinemia and/or insulin resistance of type 2 diabetes that leads to the increased risk of breast cancer and associated increased mortality.

IGF-I and Insulin Receptors and Signaling Cascades

The IGF-I signaling cascade has been demonstrated to play a role in cellular proliferation and also in the inhibition of apoptosis. The IGF system is complex and is comprised of the ligands IGF-I and IGF-II, their corresponding receptors, IGF binding proteins 1–6 (IGFBPs), and the signaling molecules and pathways distal to the IGF-I receptor (IGF-IR) and insulin receptor (IR) including insulin receptor substrate-1 (IRS-1) and the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways. Insulin is structurally related to IGF-I and the insulin receptor (IR) exhibits homology to the IGF-IR. Both the IR and the IGF-IR are heterotetrameric structures containing two extracellular alpha subunits containing the ligand binding domain and two transmembrane beta subunits containing the tyrosine kinase domain, which are bound by disulfide bridges [25]. IR and IGF-IR also share common signaling pathways. However, during evolution, mammalian IR and IGF-IR developed different functions. IR began to be preferentially expressed in adipose, liver, and muscle tissues and became involved in glucose metabolism and homeostasis. On the other hand, IGF-IR remained expressed in all tissues and became mainly involved in postnatal linear growth. Moreover, insulin and IGF-I are able to possess different roles by activating and preferentially recruiting certain docking proteins and signaling molecules over others [26].

There are two isoforms of IR; IR-A, which exhibits mitogenic activity and IR-B, which primarily mediates the metabolic effects of insulin. IR-A is a fetal expressed isoform that is a splice variant created by the exclusion of exon 11, which encodes for a 12 amino acid residue; IR-B

is the adult isoform that contains this 12 amino acid residue at the C terminus of the alpha subunit [27, 28]. IR and IGF-IR have the ability to form hybrid receptors. Insulin and IGF-I have the highest affinity to their cognate receptors. Moreover, due to the high degree of homology between insulin and IGF-I, they also have binding affinity for each other's receptors and hybrid receptors as well [29].

IR and IGF-IR Over-expression in Breast Cancer

Previous researchers have shown that there is over-expression of both IGF-IR and IR in breast cancer cells and tissue specimens [30–32]. Despite the presence of IGF-IR in breast cancer specimens, conflicting data exists about its clinical significance. Shimizu et al. examined 210 primary breast tumors for IGF-IR expression utilizing immunohistochemistry. They discovered that while 43.8% of these specimens demonstrated IGF-IR over-expression, this did not correlate with tumor size, nodal status, hormone receptor status, histiological grade, or prognosis [33]. On the other hand, Railo et al. studied 126 primary breast tumors and found a significant correlation between IGF-IR expression and estrogen receptor (ER) positivity. Their data also suggest that patients with IGF-IR positive, ER negative breast tumors had a worse prognosis compared to those patients with IGF-IR negative, ER negative breast tumors [34]. An additional study demonstrated that IGF-IR expression in breast tumors was correlated with lower grade and hormone receptor positivity [35].

Previous research by Papa et al. has shown that when analyzed by ELISA, 80% of breast cancers have increased IR expression, some up to 10-fold higher compared to mean levels observed in normal breast tissue [36]. Further immunohistochemical analysis revealed that IR was in fact predominately located in neoplastic cells not in surrounding stroma or inflammatory cells. While not specific to breast cancer, it has been suggested that the presence of IR in human breast cancer specimens can be helpful in assessing prognosis [37]. In this study by Mathieu et al., 584 node negative breast tumor specimens were analyzed for IR expression by immunohistochemistry. Breast cancer patients with tumors undetectable for IR demonstrated a decreased 5-year disease free survival compared to those patients with tumors with detectable IR. However, a small subset of patients (n=62) with tumors expressing high content of IR had a much shorter disease free survival rates compared to those patients with tumors with moderate expression of IR.

As stated above, there are two known isoforms of IR; IR-A is predominantly expressed in fetal tissue, and that IR-B is primarily expressed in adult tissues [26]. The IR-A isoform possesses mitogenic activity and is known to be present in malignant tissues. It has been also demonstrated that IR-A is over-expressed in breast tumors [38]. The IGF-IR also has the ability to form hybrid receptors with the IR-A receptor, namely IGF-I/IR-A receptor. In addition, IR-A has a 2-fold increase in affinity for insulin binding compared to IR-B [39, 40]. Of particular interest is the relative high degree of affinity that insulin has with IGF-I/IR-A hybrid receptors [29]. In addition, IGF-II has a high affinity for IR-A, but not IR-B [36]. It has been demonstrated in the MDA-MB-157 human breast cancer cell line, which are known to express more IR than IGF-IR, that autocrine IGF-II stimulates cell proliferation via IR activation [38].

Circulating IGF-I and Normal Mammary Gland Development

The normal mammary gland structure consists of both epithelial and stromal compartments. During pubertal mammary gland development ductal morphogenesis occurs as terminal end buds (TEB), which are located at the leading ends of immature ducts, extend into the mammary fat pad. While it is known that the estrogen surge marking the initiation of puberty plays an important role in mammary gland development, it has been shown that estrogen does not act alone. It is now realized that growth hormone/insulin-like growth factor-I (GH/IGF-I) axis acts synergistically with estrogen during pubertal mammary gland development which has been exemplified by the research of Kleinberg. For example, hypophysectomized, oophrectomized prepubertal rats were implanted with estradiol capsules, then one mammary fat pad was implanted with growth hormone (GH) pellets the other mammary fat pad was implanted with a BSA pellet. This research group detected mammary gland development only in the fat pad containing the GH pellet [41]. The same research group demonstrated that GH administration to hypophysectomized, oophrectomized prepubertal rats resulted in increased IGF-I mRNA levels in mammary glands. In addition, this effect was potentiated by concommitent GH and estradiol administration [42]. It was further demonstrated that administration of des (1,3) IGF-I (an IGF-I analog with decreased affinity to IGFBPs) alone was able to partially induce TEB and mammary gland development. However, full development required both des(1,3) IGF-I and estradiol [42]. Similar evidence provided by Ruan and Kleinberg shows that six week old IGF(−/−) null mice require administration of des(1,3) IGF-I in addition to their own endogenous estradiol to achieve ductal morphogenesis [43]. Taken together, these data indicate that GH stimulates IGF-I production, which then acts synergistically to induce TEB formation and normal mammary gland development.

Circulating IGF-I and Breast Cancer Development

As stated previously, IGF-I possesses characteristics of both a tissue growth factor and as an endocrine or circulating hormone. It is well established that source of most circulating or endocrine IGF-I is the liver. The hypothalamus secretes growth hormone releasing hormone (GHRH), which then acts on the anterior pituitary gland initiating the release of GH, which then binds to GH receptors in the liver leading to activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling cascades and finally induces the release of IGF-I, IGFBP-3, and acid-labile subunit (ALS) into circulation [44]. This section will focus on the effects of systemic IGF-I on breast cancer development and progression.

It has been demonstrated in previous in vitro studies that breast cancer cell lines respond to IGF-I [45, 46] and that blocking the IGF-IR binding domain inhibits the effect of IGF-I induced growth in human breast cancer cell lines [47]. The WAP-DES transgenic mouse model exhibits targeted over-expression of des(1-3)hIGF-I in the mammary gland [48]. This transgenic mouse model demonstrates that increased des(1-3)hIGF-I leads to increased frequency of mammary intraepithelial neoplasia and mammary tumor development via autocrine/paracrine mechanisms [49]. In addition, transgenic mice expressing constitutively activated IGF-IR under the mouse mammary tumor virus (MMTV) promoter exhibit mammary and salivary adenocarcinomas as early as eight weeks of age [50].

It has been documented in the literature that GH levels are elevated in individuals with breast cancer [51]. Additionally, older studies document that hypophysectomy had a significant palliative effect in advanced, metastatic breast cancer patients [52–54]. Previous in vitro studies with mouse mammary carcinoma cell lines have demonstrated that GH acts on these cell lines in an autocrine manner leading to increased cell proliferation and a more invasive phenotype [55]. In vivo experiments have described that transgenic mice that over-express human GH develop mammary adenocarcinomas [56, 57].

The effect of decreased GH levels and/or circulating IGF-I on breast tumorigenesis has been further characterized utilizing animal models. To address the issue of the effects of GH on circulating IGF-I levels and mammary tumorigenesis, the lit/lit mouse model will be described. The *lit* mutation knocks out the GHRH receptor in the pituitary thereby inhibiting GH release. This mutation leads to a defect in signal transduction and a decrease in both GH and thus circulating IGF-I levels that are approximately 10% of normal levels [58, 59]. Yang et al. utilized this mouse model to determine if disrupting the GH/IGF-I axis leads to a reduction in the growth of breast tumors [60]. In this study, the mammary fat pads of lit/lit mice and control mice were orthotopically injected with human MCF-7 breast cancer cells. At 39 days, the orthotopic mammary tumors were significantly smaller compared to control animals. Sera from lit/lit and control mice were also extracted and utilized for in vitro proliferation studies. These studies demonstrated less MCF-7 cell proliferation in lit/lit sera compared to control sera. However, this difference was eliminated when IGF-I was added to the sera samples.

Dwarf rodent models have also been utilized to study the effects of reduced circulating GH and IGF-I on mammary carcinogenesis. The Spontaneous Dwarf Rat (SDR) is a Sprague–Dawley rat that exhibits GH deficiency and as a result decreased IGF-I levels secondary to a point mutation in the *gh* gene [61]. These GH deficient rats have been shown to be resistant to chemically induced mammary carcinogenesis [62]. In another study, SDR rodents were given hormonal treatments and followed for their effects on tumorigenesis [63]. When treated with GH replacement, mammary tumor incidence increased from 4.8% in controls to 100% in treated animals. When treated with IGF-I, the increase in tumor incidence was not as striking (4.8 to 62.5%). The authors suggest that in the IGF-I treated animals there is likely a high turnover of IGF-I because it is not being stabilized by the IGFBP-3/ALS complex, as GH is required for the synthesis of these binding proteins. They also suggest that mammary tumorigenesis may be dependent on the effects of both GH and IGF-I, not just IGF-I alone.

The Snell dwarf mouse model possesses a dysfunctional Pit1 transcription factor, which leads to deficiencies in GH, prolactin, and thyroid stimulating hormone [64]. It has been documented that Snell mice are also resistant to chemically induced carcinogenesis [65]. In a study by Alderman et al., these mice were allowed to age and were examined at death for naturally occurring tumors [66]. At death, 18% of Snell mice developed tumors compared to 82% of control mice. Neoplasms were identified by histology and included mammary adenocarcinoma, as well as histiocytic sarcomas, lymphomas, fibrosarcomas, leiomyosarcomas, hepatocellular carcinomas, hemangiosarcomas, and myelogenous leukemia. Interestingly, Pit1 over-expression has been documented in human breast adenocarcinomas, which has been shown to increase GH secretion, and cell growth and proliferation [67]. In contrast, Ames dwarf mice have a defect in the Prop1 transcription factor and also exhibit the same hormonal deficiencies as the Snell mice, but demonstrate a higher tumor incidence at time of death [68]. Alderman et al. suggest that the mechanisms for these differences in tumor incidences may be related to other metabolic and neuroendocrine factors [66].

Another mouse model used to assess the role of endocrine IGF-I on mammary tumorigenesis is the Liver IGF-I-Deficient (LID) model. In this model, the Cre/lox P

system is utilized to selectively knock out the *igf-1* gene in the liver leading to a 75% reduction in circulating IGF-I levels and consequently elevated levels of GH [69]. However, mRNA levels of IGF-I are preserved in other tissues. The LID mouse model has been utilized to study the effects of reduced circulating IGF-I on mammary tumorigenesis in two ways [70]. First, LID and control animals were exposed to the carcinogen 7,12-dimethylbenz (a)anthracene (DMBA) daily for seven weeks. In this model of chemically induced carcinogenesis, by 24 weeks of age 56% of control animals developed one or more mammary tumors, whereas significantly less of the LID animals (26%) developed breast tumors. In addition, the latency of tumor onset was significantly delayed in the LID mice compared to controls (59.5±1.1 days vs. 74±1.2 days). Histopathologic differences in late stage tumors were also observed. The DMBA control mice had mammary tumors with extensive squamous metaplasia whereas the tumors from the LID animals demonstrated hyperplasia but no metaplasia. Similar results were observed in the second model where LID mice were crossed with the C3(1)/SV40 large T antigen (SV40-LTA) transgenic mouse model of breast cancer. Latency of tumor onset was delayed in the LID/SV40-LTA mice compared to controls carrying the SV40-LTA transgene (30.17±1.71 weeks vs. 24.1± 1.1 weeks). The frequency of multiple breast tumors that developed was also significantly less in the LID/SV40-LTA mice compared to control SV40-LTA mice whereby 30% of LID animals developed more than one tumor compared to 60% of the controls.

Taken together, these data indicate that circulating or endocrine IGF-I is important for the onset, progression, and aggressiveness of mammary tumorigenesis. They also suggest that the GH/IGF-I axis can be utilized as a therapeutic target in breast cancer.

Hyperinsulinemia, Type 2 Diabetes and Breast Cancer

As discussed above, obesity, hyperinsulinemia and type 2 diabetes have been associated with increased risk of breast cancer. It is well established that obesity is associated with increased breast cancer risk, especially in postmenopausal women. Supporting this evidence, researchers have shown that ovariectomized obese mice show enhanced tumor growth in an orthotopic mammary tumor model [71]. In another animal model, this study demonstrated that obese female Zucker rats were more susceptible to DMBA induced mammary tumors than the lean controls [72]. Even though obesity is associated with elevated insulin levels and insulin resistance, there are other associated factors related to the metabolic syndrome that can mediate the increased risk of breast cancer including elevated inflammatory cytokines, decreased adiponectin, elevated leptin, dyslipidemia, and increased bioavailable estrogen [73]. However, there is epidemiologic evidence supporting an increased risk of breast cancer development in type 2 diabetic patients independent of obesity [74]. Population studies have shown that women with a new diagnosis of type 2 diabetes have a significantly greater likelihood of having been diagnosed with breast cancer in the past [75]. This association supports the hypothesis that the elevated insulin levels experienced during the pre-diabetes phase are promoting breast cancer development and progression. It has also been demonstrated that breast tumors over-express IR and increased IR expression has been associated with decreased disease-free survival. Moreover, previous researchers have shown that insulin is able to increase ER expression in a breast cancer cell line and that insulin and estradiol synergistically accelerate breast cancer cell proliferation [76].

Insulin can also have indirect effects on breast cancer progression. For example, insulin has the ability to stimulate aromatase activity thereby increasing the levels of bioavailable estradiol [77]. In addition, hyperinsulinemia has been demonstrated to decrease the levels of sex hormone binding globulin (SHBG) also resulting in an excess of free, bioavailable estradiol [78].

The bioavailability of IGF-I in circulation depends on the six IGF binding proteins (IGFBPs). As stated above, most IGF-I is bound to IGFBP-3 which is a large protein produced by the liver. However, IGFBP-1 is a smaller binding protein that has been implicated in the regulation of bioavailable IGF-I in relation to nutrient stores and supplies [79]. There is an inverse relationship between insulin and IGFBP-1 levels. Hyperinsulinemia, the hallmark of type 2 diabetes, can lead to the repression of IGFBP-1 hepatic production and therefore decreased release into circulation [80, 81]. This effect has also been observed in patients with obesity, which are known to be prone to the development of type 2 diabetes [82, 83].

In addition to insulin resistance and hyperinsulinemia, impaired glucose homeostasis and hyperglycemia are other characteristics of type 2 diabetes. In 1924, Warburg first described the phenomenon of increased glucose uptake and consumption by tumor tissue promoting tumor growth and survival; Warburg then summarized his hypothesis in his *Science* paper in 1956 [84]. Supporting this phenomenon, a prospective case-control study linked elevated fasting plasma glucose with breast cancer risk in pre-menopausal women and overweight post-menopausal women [21].

A fatless mouse model of type 2 diabetes has been generated called the A-ZIP/F-1 mouse. These transgenic mice lack white fat, have reduced brown fat and are diabetic with elevated serum glucose, insulin, free fatty acids, and triglycerides; they also exhibit increased levels of some inflammatory cytokines [85]. When the A-ZIP/F-1

mice were crossed with the C3(1)/T-Ag transgenic mouse model of breast cancer, the double transgenic mice had a higher incidence of mammary tumor formation, larger tumors, decreased latency of tumor onset, and multiple neoplastic foci [86].

Our lab has been exploring the hypothesis that hyperinsulinemia promotes breast cancer onset and progression independent of obesity [87]. We have developed the MKR mouse model of type 2 diabetes [88]. In this transgenic mouse model, dominant-negative IGF-I receptors are expressed specifically in skeletal muscle under the control of the muscle creatine kinase (MCK) promoter. These nonfunctional IGF-IRs have the ability to form hybrid receptors with IGF-IR and/or IR thereby abrogating normal signaling leading to insulin resistance at the level of the skeletal muscle. By three weeks of age, female MKR mice hyperinsulinemic, glucose intolerant, but are not obese. In pre-pubertal mammary glands of female MKR mice, the phenotype of the gland leads to accelerated mammary development. When the mammary fat pads of female MKR mice are orthotopically injected with mouse mammary breast carcinoma cells, breast tumors are increased in size compared with control orthotopic tumors. Moreover, when MKR mice are crossed with the Polyoma virus middle T antigen (PyVmT) transgenic mouse model of breast cancer, the double transgenic mice exhibit multiple neoplastic foci at early stages and more invasive tumors at later stages compared to control animals.

Taken together, both epidemiologic and animal studies support the hypothesis that hyperinsulinemia and type 2 diabetes promote breast tumor development. The mechanisms whereby this phenomenon occurs may include both direct and indirect factors as discussed above.

Clinical Implications and Therapeutic Targets

The IGF system is composed of ligands (insulin, IGF-I, IGF-II), tyrosine kinase receptors (IR-A and IR-B, IGF-IR and hybrid receptors) and their respective signaling cascades. In vivo and in vitro research and epidemiologic studies have implicated the IGF system in promoting tumor growth, survival and progression. Thus, this suggests that the components of the IGF system could be utilized as targets for breast cancer therapy. Some examples include: growth hormone releasing hormone antagonists, antibodies against IGF-I and IGF-II, soluble IGF-IR, small molecule inhibitors of the IGF-IR and antibodies against the IGF-IR [89]. However, an in depth discussion of the various methods that can be used is beyond the scope of this review and will be covered elsewhere in this issue. Furthermore, given the evidence that obese and type 2 diabetic patients have increased risk of developing breast cancer and also have poorer prognoses, efforts should be taken to educate patients about the importance of weight loss and metabolic risk factor reduction for primary prevention of breast cancer.

Summary

Epidemiologic studies demonstrate that breast cancer is the most common type of cancer diagnosed in women and is the second leading cause of death for women in the United States [15]. While there are many risk factors known to be associated with increased breast cancer risk, this review focused specifically on circulating IGF-I, hyperinsulinemia, and type 2 diabetes. As discussed above, their effects on promoting breast cancer development, progression, and adverse outcomes have been demonstrated in both animal and human studies. Thus, suggesting that the IGF system is a potential target for breast cancer therapy. In addition, in the clinical setting, emphasizing metabolic risk modifications to patients including weight loss, dietary changes, and diabetes control may also play an important role in breast cancer risk reduction.

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