Interactions between Insulin, Body Fat, and Insulin-Like Growth Factor Axis Proteins

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Abstract

Background: **The etiology of hormonally related cancers, such as breast and colon, has been linked to hyperinsulinemia and insulin resistance, the insulin-like growth factor (IGF) axis, and obesity.**

Methods: **Data from 57 women (ages 30-50 years) were used to observationally examine cross-sectional and longitudinal relations between body fat (from dual-energy X-ray absorptiometry), insulin, IGF-I, and IGF-binding proteins (IGFBP-1, IGFBP-2, and IGFBP-3).**

Results: **At baseline, participants who had greater than median body fat and insulin levels, >39% and >4.5 microunits/mL, respectively, had 2.3- to 2.6-fold lower IGFBP-1 ($P < 0.004$) and 1.9- to 2.0-fold lower IGFBP-2 ($P < 0.004$) compared with other participants; IGF-I and IGFBP-3 levels did not differ by body fat or insulin levels. Over 39 weeks, a 1 microunit/mL reduction in fasting insulin was associated with a 17% increase in IGFBP-1 ($P = 0.02$) and a 24% increase in IGFBP-2 ($P = 0.02$) compared with participants who did not reduce insulin; 2.0% loss of body fat over time did not alter IGFBP-1 or IGFBP-2 levels after adjustment for insulin. IGF-I and IGFBP-3 did not change in participants who lost body fat percentage or insulin over time.**

Conclusions: **These observational associations are consistent with the hypothesis that elevated insulin and body fat are associated with decreased IGFBP-1 and IGFBP-2 levels cross-sectionally; they further imply that IGFBP-1 and IGFBP-2 levels may be altered through change in insulin over time. By contrast, no cross-sectional or longitudinal associations were noted between IGF-I and IGFBP-3 with insulin or body fat.** (Cancer Epidemiol Biomarkers Prev 2007;16(3):593–7)

Introduction

Incidence of several of the most common hormonally related cancers, breast, colorectal, and perhaps prostate and endometrial, has been linked to obesity (1-5), insulin (6-9), and the insulin-like growth factor (IGF) axis (10-15). These potential cancer biomarkers are intriguing for cancer control purposes because they may interact and be modifiable through behavioral or pharmaceutical interventions.

Recent evidence from population-based studies suggests that obesity, insulin, and the IGF axis may interact to increase cancer risk (9, 16-18). Higher levels of adipose, including visceral fat, are associated with increased blood levels of free fatty acids and serum insulin (19). Insulin independently leads to cellular growth and proliferation and has been associated with several cancers (8). The interactions between body fat and insulin with the IGF axis are less well understood, which poses a challenge in developing cancer control interventions. In extracellular fluids, IGF-I is complexed to six distinct IGF-binding proteins (IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6), which function in part to bind >95% of circulatory IGF-I and thereby modulate the availability of free IGF-I to act at its receptors (13). Circulating IGF-I and IGFBP-3 levels are determined by liver production, which is regulated by growth hormone activity and nutritional status (20). IGFBP-3 and IGF-I have long half-lives in circulation; as they are growth hormone dependent, they represent a stable index of long-term change in growth hormone availability and action (21). As reviewed by Lukanova et al. (22), with increased adiposity, physiologic growth hormone secretion is impaired and growth hormone responses to all stimuli are decreased; conversely, insulin enhances growth hormone–stimulated synthesis of IGF-I and IGFBP-3 through up-regulation of growth hormone receptors (23). Therefore, behavioral and pharmaceutical interventions may affect IGF-I and its binding proteins differentially according to factors that influence both growth hormone and nutritional status, including insulin and body composition (20). Insulin may affect IGF-I levels and activity by contributing to growth hormone stimulation of IGF-I production (13) and by increasing IGF-I bioavailability through direct inhibition of IGFBP-1 and IGFBP-2 synthesis at the liver (24-30). Associations of body fat and insulin with cancer risk may be mediated through alterations of bioavailable levels of IGF-I. Indeed, IGFBP-1 and IGFBP-2 have been associated negatively in some (14, 15), although not all (31-34), studies with cancer development.

Prior cross-sectional studies examining associations between body composition, insulin, and the IGF axis have generally used crude measures of body fatness, such as body mass index (BMI). We have dual-energy X-ray absorptiometry body composition data, in addition to fasting insulin and IGF axis data on 57 women at multiple time points over 39 weeks. We used these data to test two hypotheses. The first is that elevated body fat and fasting insulin are associated with lower levels of IGFBP-1 and IGFBP-2 but not with IGF-I or IGFBP-3. The second hypothesis is that decreases in insulin or in body fat levels are associated with increases in IGFBP-1 and IGFBP-2 levels over 39 weeks. The data for these analyses are from a previously completed randomized controlled trial of twice-weekly weight training in 57 women. We have previously reported a nonsignificant intervention effect on insulin change over 39 weeks in this group of women (35); however, there were an equal number of participants in both the intervention treatment and control groups who decreased their insulin level

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over 39 weeks. Therefore, to explore the associations between body fat, insulin, and the IGF axis, we examined the 57 participants as one group, controlling for assignment to the treatment condition, cross-sectionally at baseline and longitudinally over 39 weeks.

Materials and Methods

The weight gain prevention study was a 39-week randomized-controlled trial of twice-weekly weight training in 60 women (n = 30 intervention, n = 30 control). Details of participant recruitment and inclusion criteria have been described in detail (35, 36). Briefly, during December 1999 and January 2000, 60 women ages 30 to 50 years were recruited from female faculty, staff, and students at the University of Minnesota (Minneapolis, MN). Participants were randomized in a blinded fashion, stratified by decade of age (30-39 versus 40-50). The intervention design has been described (35, 36). Briefly, all participants were asked to avoid altering their baseline low-intensity aerobic or stretching exercises (most commonly one to two weekly walks) and dietary habits for the purpose of weight change for the study duration. The treatment group was enrolled in a 50-min strength training class held twice weekly for 15 weeks at the University of Minnesota Recreation Center. Participants did three sets each of nine common strength training exercises, lifting as much weight as they could for 8 to 10 repetitions per set. Through the first 15 weeks of the intervention, participants progressively increased the weight of a given exercise as described previously (35, 36). After 15 weeks, treatment group participants continued to exercise unsupervised for 6 months at the same exercise facility. Participants maintained exercise session logs, in which they recorded information about number of sets and the weight load for each exercise done per strength training session. The control group participated in measurements only. During the 15-week supervised intervention and the following 6 months of unsupervised exercise, 92% and 83% of prescribed exercise sessions were completed, respectively. Strength changes from baseline to 15 and 39 weeks corroborated self-reported adherence data as the treatment group showed increases of 19% and 24% for bench press and 13% and 20% for leg press over 15 and 39 weeks, respectively ($P < 0.0001$ for bench press, $P < 0.004$ for leg press when compared with the control group; refs. 35, 36). The main results of the intervention have been reported (35, 36). The study protocol was reviewed by and followed all regulations of the University of Minnesota Institutional Review Board for the protection of human subjects in research.

Dropouts and loss to follow-up: there were incomplete baseline blood samples for two participants (one each in the treatment and control groups); one treatment group participant was diagnosed with Grave's disease before study completion. Data for these three participants are excluded from analyses; baseline analyses include the remaining 57 women. Three women dropped out of the study after baseline (one treatment and two control group participants); longitudinal analyses include the 54 women who completed the study.

Measurements. Measurements were taken at baseline and 39 weeks later (study completion) at a measurement visit at the University of Minnesota General Clinical Research Center. Participants refrained from moderate intensity physical activity for 48 h before measurements. Body weight and height, body composition, and blood draws were done by clinical research nurses blinded to treatment group status between 6:30 and 9:30 a.m., after a 12-h fast, and between 5 and 11 days after the start of menstrual flow for menstruating participants. Participants wore hospital gowns for measurements.

Serum insulin levels were measured by a two-site immunoenzymatic assay at the Mayo Clinic (Rochester, MN) as described previously (33). ELISAs of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 were done at Diagnostic Systems Laboratories (Webster, TX) as described previously (36). All assays were done in duplicate, with the mean used for analysis, by technicians blinded to treatment status. For IGFBP-2, measurements from a single participant ID were done in a single assay using the same reagent batch. For all other assays, technicians matched reagent batch to measurement time point for all participant ID numbers.

Weight was measured on a digital scale and height was assessed using a mounted stadiometer, both calibrated daily (Scale-Tronix 5005 stand-on digital scale, Scale-Tronix, White Plains, NY). Waist circumference, at the level of the umbilicus, was measured in duplicate; the mean was used for analysis. Body composition was measured on the Lunar Prodigy Dual X-ray Absorptiometer software version 2.15 (Lunar Radiation Corp., Madison, WI), calibrated monthly with daily calibration checks. Body fat percentage was calculated as the proportion of non–bone tissue that was fat.

Participants completed three surveys: the Typical Weekly Physical Activity Survey (37), 4-day food records, and a demographic survey (given at the baseline measurement visit only) as described previously (35, 36).

Statistical Analysis. Statistical Analysis System version 8.2 (SAS, Cary, NC) was used for all analyses. Baseline demographic, physical activity energy expenditure, and total energy intake data were compared in the entire cohort, across baseline body fat percentage (above and below median, 39.1%), and across baseline insulin level (above and below median, 4.5 microunits/mL) using two-sided t tests for continuous and χ^2 tests for categorical variables.

Least-squares means of IGF axis proteins and body composition variables were compared across four groups of the participants. These groups were determined by baseline body fat percentage (above and below median, 39.1%) and by baseline insulin level (above and below median, 4.5 microunits/mL): group 1 (n = 20), ≥39.1% body fat and ≥4.5 microunits/mL insulin; group 2 (n = 9), ≥39.1% body fat and <4.5 microunits/mL insulin; group 3 (n = 9), <39.1% body fat and ≥4.5 microunits/mL insulin; and group 4 (n = 19), <39.1% body fat and <4.5 microunits/mL insulin. All ANOVAs used generalized linear models (Proc GLM). Potential confounders were tested, including treatment group status, baseline energy consumption and expenditure, menopausal status, and age; these variables did not alter the interpretation of the results and were therefore not included in final models.

To examine longitudinal change in mean levels of IGF axis proteins, participants were divided into groups for two separate analyses based on the following cut points: (*a*) the first analyses divided all participants into two groups based on those who experienced <1 or ≥1 microunit/mL loss of insulin over 39 weeks and (*b*) the second analyses divided all participants into two groups based on those who experienced <2.0% or ≥2.0% loss of body fat over 39 weeks. These cut points were chosen because both 2.0% loss of body fat and 1 microunit/mL insulin have been reported as levels of change attainable from exercise interventions (38, 39). In the Weight Gain Prevention Study (WGPS), there was a lack of effect of the intervention on insulin; specifically, 10 women in each intervention group decreased their insulin levels over the 39-week intervention (36). Therefore, in these analyses, we examined insulin effects independent of the intervention and included treatment group status as a covariate in the models. Additional adjustment for baseline levels of the dependent variable (insulin, IGF-I, and IGFBP-1, IGFBP-2, and IGFBP-3), hormone replacement therapy or hormonal contraception use,

Table 1. Baseline cross-sectional levels of anthropometric and hormonal values by baseline insulin and body fat percentage (mean ± SD)

	≥4.5 microunits/mL	<4.5 microunits/mL
IGF-I (mg/dL)		
≥39% body fat	222.6 ± 54.0	218.1 ± 51.7
<39% body fat	238.7 ± 66.1	233.5 ± 63.5
IGFBP-1 (mg/dL)		
≥39% body fat	26.0 ± 16.5 *a*	60.4 ± 26.5 *b*
<39% body fat	61.5 ± 40.4 *b*	66.4 ± 29.8 *b*
IGFBP-2 (mg/dL)		
≥39% body fat	334.8 ± 191.3 *a*	625.3 ± 192.2 *b*
<39% body fat	685.2 ± 352.0 *b*	636.7 ± 247.2 *b*
IGFBP-3 (mg/dL)		
≥39% body fat	3,670.2 ± 424.4	3,534.2 ± 249.1
<39% body fat	3,518.3 ± 860.6	3,718.4 ± 805.9
Insulin		
≥39% body fat	7.6 ± 3.1 *a*	3.1 ± 0.6 *b*
<39% body fat	5.4 ± 1.2 *a*	2.8 ± 0.9 *b*
Body fat %		
≥39% body fat	45.8 ± 3.6 *a*	44.2 ± 5.0 *a*
<39% body fat	35.4 ± 4.7 *b*	33.6 ± 3.4 *b*
Lean mass		
≥39% body fat	42.9 ± 5.2 *a*	39.9 ± 5.7 *ab*
<39% body fat	39.9 ± 5.6 *ab*	39.5 ± 3.7 *b*

NOTE: $n = 20$: ≥4.5 microunits/mL and ≥39% body fat; $n = 9$: ≥4.5 microunits/mL and <39% body fat; $n = 9$: <4.5 microunits/mL and ≥39% body fat; $n = 19$: <4.5 microunits/mL and <39% body fat. ANOVA tests: statistically significant different values have different letters; for example, value *a* is significantly different than value *b*.

demographic variables, age, physical activity (baseline or change), and energy intake (baseline or change) were tested but not included in final models as they did not alter the results presented. Change in insulin as a continuous variable was added to the models to examine whether insulin mediated the effect of change in body fat percentage on IGF axis proteins.

All statistical tests and corresponding P values were two sided; a P value of <0.05 is reported as statistically significant.

Results

Participants in the Weight Gain Prevention Study (WGPS) were mostly married, college educated, and Caucasian as described previously (36). There were no differences in age, race, marital status, energy intake, or energy expenditure in participants who were above versus below median body fat percentage (data not shown); by contrast, women who had <39% body fat were more likely to be college educated compared with women who had ≥39% body fat (96% versus 76%). There were no differences in age, race, marital status, education level, or energy expenditure in participants who were above median insulin level versus below; by contrast, women who had ≥4.5 microunits/mL insulin had greater energy intake at baseline compared with those with <4.5 microunits/mL insulin (2,024.3 ± 71.8 versus 1,645.0 ± 72.8, respectively).

At baseline, women ($n = 20$) who were above median body fat percentage (≥39%) and insulin level (≥4.5 microunits/mL) had 2.3- to 2.6-fold lowered IGFBP-1 ($P < 0.004$) and 1.8- to 2.0-fold lowered IGFBP-2 ($P < 0.004$) levels, respectively, compared with other participants (Table 1). IGFBP-1 and IGFBP-2 levels did not differ significantly among the other three groups. There was also a significant difference in IGFBP-1 and IGFBP-2 levels between those with higher and lower insulin among the subgroup with higher body fat, whereas there was no difference according to insulin in those with lower body fat. There were no associations between body fat percentage (≥39 versus <39), fasting insulin (≥4.5 microunits/mL versus <4.5 microunits/mL), or the interaction of the two with mean levels of IGF-I or IGFBP-3. There was a 2.8-fold difference in fasting insulin level over the four groups despite a study participation eligibility restriction of normal fasting insulin at baseline (≤10 microunits/mL; ref. 36). Body fat percentage varied 1.5-fold, although there was a nonstatistically significant 8% variation in lean mass over the groups.

Participants who lost ≥1.0 microunit/mL insulin from baseline to 39 weeks, in comparison with those who did not, had increased IGFBP-1 and IGFBP-2 levels by 17% ($P = 0.02$) and 24% ($P = 0.02$) at 39 weeks, respectively (Table 2). By contrast, loss of insulin over 39 weeks was not associated with significant change in levels of either IGF-I or IGFBP-3. We also examined whether a change in body fat percentage over 39 weeks (participants who lost ≥2.0% versus those who had <2.0% body fat change) would be associated with alterations of IGF axis proteins (data not shown). For these analyses, we observed IGFBP-1 and IGFBP-2 increased by 9% and 11% (not statistically significant), respectively, and there was no difference in IGF-I or IGFBP-3 level from 0 to 39 weeks in the group that lost ≥2.0% versus those who had <2.0% body fat change by 39 weeks. The group that lost ≥2.0% body fat experienced a 1.1 microunit/mL decrease in insulin over this time period. The addition of change in insulin over 39 weeks to the regression models attenuated the association between change in body fat on IGFBP-2.

Discussion

In this sample of 30- to 50-year-old women, there were inverse cross-sectional and longitudinal associations of insulin and body fat percentage with IGFBP-1 and IGFBP-2 but not with IGF-I or IGFBP-3. Change in IGFBP-1 and IGFBP-2 levels alters bioavailable IGF-I levels, which may then alter cancer risk. Although studies examining associations between IGFBP-1 and IGFBP-2 and cancer risk have been mixed (14, 15, 31-34), the findings from these analyses may have relevance for understanding mechanisms through which change in insulin levels and or body composition may alter cancer risk.

The results of the present cross-sectional analyses complement the findings of other studies that have examined cross-sectional associations of body fat (generally BMI) with insulin and the IGF axis. Similar to the present findings, several authors have reported that total IGF-I and IGFBP-3 are not correlated with BMI, whereas IGFBP-1 and/or IGFBP-2 are inversely correlated with BMI ($r = -0.3$ to -0.5 for IGFBP-1 and $r = -0.3$ to -0.5 for IGFBP-2; refs. 14, 21, 40-45), insulin, or C-peptide ($r = -0.21$ to -0.46 for IGFBP-1 and $r = -0.16$ to -0.26 for IGFBP-2; refs. 40, 42, 46-48). In a cross-sectional study of 400 women, Lukanova et al. (42) reported that diabetics (mean fasting insulin, 20.81 microunits/mL) had 2.4-fold lower IGFBP-1 and 1.8-fold lower IGFBP-2 compared with nondiabetics (mean fasting insulin, 8.59 microunits/mL). In contrast to our findings, some studies have observed decreased (49, 50) or increased (51, 52) total IGF-I levels in obese compared with nonobese participants. Whereas several

Table 2. Change in IGF axis proteins by change in insulin over 39 wks (mean ± SD)

	Insulin loss		P
	≥1 microunit/mL ($n = 10$)	<1 microunit/mL ($n = 44$)	
Insulin	−2.2 ± 1.02	1.2 ± 1.9	<0.0001
IGF-I	24.9 ± 51.0	20.0 ± 56.7	0.80
IGFBP-1	7.5 ± 30.8	−11.2 ± 19.8	0.02
IGFBP-2	113.3 ± 219.5	−15.2 ± 138.4	0.02
IGFBP-3	112.1 ± 901.5	371.3 ± 940.5	0.43

NOTE: Least-squares means from general linear regression models adjusted for treatment group.

studies did not examine associations between IGF-I and insulin, others have shown a positive correlation between total IGF-I and insulin (21). Additionally, nonlinear relations of IGF-I have been reported with BMI in one study of women (53) and with BMI and insulin in men but not women in another study (22). Whereas we did not observe an association between elevated body fat and IGFBP-3, Frystyk et al. (47) reported that obese nondiabetic subjects had elevated IGFBP-3 compared with lean subjects. There is a diversity in the findings about any association of body fat or insulin with IGFBP-3 (22, 41, 42, 44, 45, 47, 49-51, 54, 55). These collective findings indicate that body fat and insulin may be associated inversely with IGFBP-1 and IGFBP-2 but are less likely to be associated with total IGF-I levels and may or may not be associated with IGFBP-3.

Interactions between obesity, insulin, and the IGF axis are complex and incompletely understood. As noted above, although several authors have reported altered levels of IGFBP-1 and IGFBP-2 by body fat and/or insulin, observations have been mixed about levels of IGF-I or IGFBP-3 by body fat and/or insulin. The varied observations may be attributable in part to differences in age, sex, degree of obesity or elevated insulin, and nutritional factors in study participants. Additionally, a nonlinear relation between total IGF-I and BMI (22, 53) or insulin (22) has been observed, indicating that other factors may play a role in the regulation of IGF-I in obesity. Age is a predictor of IGFBP-3 (42); we may not have seen variation in IGFBP-3 in our study in part because participants were close in age. Obesity is associated with growth hormone hyposecretion; therefore, it may be expected that total IGF-I concentrations would be lower in obese compared with nonobese subjects (21). However, several of the studies reviewed above did not report lower IGF-I in obese compared with nonobese subjects. Obesity is also associated with hyperinsulinemia, which may increase hepatic IGF-I production, as reviewed above (22). It is also possible that the obesity and hyperinsulinemia may be associated with decreased total IGF-I levels but with increased free IGF-I levels. As reviewed above, insulin regulates IGFBP-1 and IGFBP-2 levels through inhibition of hepatic synthesis. IGFBP-1 and IGFBP-2 are regulators of IGF-I bioavailability (13); when IGFBP-1 and IGFBP-2 levels are decreased, free IGF-I levels increase (22). Our findings are consistent with the theory that insulin exerts its effects on IGF-I through alterations in IGFBP-1 and IGFBP-2. We found that relatively small cross-sectional or longitudinal variations in insulin levels altered levels of these binding proteins. The women in this study were all normoinsulinemic at baseline, which may explain why we did not observe associations cross-sectionally or longitudinally between IGF-I and IGFBP-3 if differences in insulin levels were not great enough to affect levels of these proteins. The present analyses included models, which adjusted for factors that may be associated with alterations of IGF axis variables, such as tobacco use, age, diet, and estrogens (50). However, we did not measure free IGF-I or growth hormone in this study and therefore cannot fully determine relations between body fat, insulin, and free IGF-I. That said, the observational studies that have reported associations of IGF-I and hormonally related cancers have generally used total IGF-I as the biomarker of interest, not free IGF-I (10-12, 14, 15, 32-34).

Two prior studies have examined specifically associations between change in body size or insulin, secondary to an intervention, with change in IGF axis proteins, including IGFBP-1 and IGFBP-2, over time. Hellenius et al. (1995) conducted a randomized controlled trial in 157 normoglycemic 35- to 60-year-old men to examine whether a 6-month intervention of diet, exercise, or diet and exercise combined compared with a control group would alter levels of insulin, IGF-I, and IGFBP-1 (37). At 6 months, fasting insulin levels decreased 16% to 19%, IGFBP-1 increased 15% to 26%, and IGF-I levels did not change in the intervention groups compared with control group. Increased IGFBP-1 levels at 6 months were positively correlated with decreased BMI ($r = 0.30$, $P < 0.01$), waist-to-hip ratio ($r = 0.30$, $P < 0.001$), and increased exercise ($r = 0.23$, $P < 0.05$; ref. 37). The Diet and Androgens study was a 5-month randomized controlled dietary intervention designed to alter body composition and hormonal levels in 50- to 65-year-old postmenopausal women (49 treatment, 50 control; ref. 46). The authors reported significant reductions in BMI (6%), waist circumference (5%), and C-peptide (19%), a significant increase in IGFBP-1 (12.1%) and IGFBP-2 (30.4%), and no change in IGF-I or IGFBP-3 in the intervention compared with control group (46). There was a nonsignificant 10.4% decrease compared with 5.1% increase in fasting insulin in the intervention compared with control group, respectively (46). Longitudinally, changes in IGFBP-1 and IGFBP-2 levels were negatively correlated with change in BMI in the intervention group ($r = -0.34$ and -0.17, respectively), whereas insulin was positively correlated with IGFBP-2 ($r = 0.20$) but not IGFBP-1 (46). The longitudinal findings of these two studies and the current findings collectively imply that change in insulin and possibly body fat may alter IGFBP-1 and IGFBP-2 over time.

The limitations of these analyses require discussion. This report is a post hoc analysis of a completed study. The availability of higher quality body fat measures compared with prior studies made it worthwhile to explore associations in this data set. Although we adjusted for treatment group status for the longitudinal analyses, we did not find evidence of confounding by this variable. However, it is possible that a residual effect of the intervention, or individual change in insulin, body fat, or IGF-I, may have altered the observed associations beyond what was observable statistically. For IGF-I, IGFBP-1, and IGFBP-3, baseline and follow-up assays were measured with different reagent batches; batch-to-batch variability in assays could obscure biological changes. Self-report instruments were used to measure changes in energy expenditure and intake. The limitations of such self-reports are well established.

In summary, we found that the combination of higher body fat percentage and insulin was associated with lowered levels of IGFBP-1 and IGFBP-2 at baseline and that decreased insulin levels were associated with increased IGFBP-1 and IGFBP-2 over 39 weeks. High levels of IGF-I have been associated with increased cancer risk. Because IGF-I circulates bound to high-affinity IGFBPs, changes in IGFBP levels likely affect the delivery of IGF-I to target tissues. Lowered insulin levels and increased IGFBP-1 and IGFBP-2 levels could limit the activation of the insulin and type I IGF receptor in target tissues by reducing the delivery of ligand. The interactions of these variables may play a role in the mechanisms between the observed associations between insulin resistance and hormonally related cancers.

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