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Energy balance, insulin-resistance biomarkers and breast cancer risk

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Abstract

Background—American women are five times more likely to be at risk for breast cancer than women from Asian countries. Epidemiologic studies have linked energy balance to an increased risk of breast cancer, yet few studies have investigated potential mediators of this association with Chinese women. We examined the above association by blood levels of insulin-like growth factors, binding proteins, and C-peptide in the Shanghai Breast Cancer Study (SBCS), a case-control study conducted among 1459 breast cancer cases and 1556 healthy Chinese women from 1996 and 1998.

Methods—In-person surveys were used to collect data on energy intake, anthropometric measures, exercise/sport activity, and occupational activity. The present analyses consisted of 397 cases and 397 controls whose blood samples were measured for levels of insulin-like growth factors (IGFs), insulin growth-factor binding protein 3, (IGFBP-3) C-peptide and the relationship with physical activity status, total energy intake, and body fat distribution.

Results—Body mass index [BMI] and waist-to-hip ratio [WHR] were significantly positively correlated with IGFBP-3 and C-peptide. Adult exercise/sport activity was significantly negatively correlated with insulin-like growth factor 1(IGF-I). C-peptide levels increased with increasing quartiles of WHR (p for trend <0.01). Additional analyses were performed to evaluate whether the association of energy balance measures with breast cancer risk changed after adjustment for IGFs, IGFBP-3 and C-peptide biomarkers. The associations attenuated, but none of them changed substantially.

Conclusions—Insulin resistance biomarkers may partially explain the association between positive energy balance and breast cancer risk, but future studies are needed to identify the underlying complex biological mechanisms of action for breast cancer prevention.

Authors key words

energy balance; insulin-like growth factors; c-peptide; breast cancer risk

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Introduction

In a recent study of women from Shanghai, China (the Shanghai Breast Cancer Study, SBCS) we had convincing evidence that positive energy balance [i.e., less exercise/sport activity, high body mass index (BMI), or high energy intake] was associated with an increased breast cancer risk, particularly among postmenopausal women [1]. However, few studies have investigated potential mediators of a positive energy balance and breast cancer risk [1–7] and fewer studies have been conducted in Chinese women that have a traditionally low prevalence of obesity and breast cancer compared to their American counterparts[1–2].

Previously we had found in the same Chinese study population that a high level of either C-peptide, , There was a statistically significant increased risk of breast carcinoma for women in the highest quartile of C-peptide, a biomarker of insulin exposure [8], or insulin like growth factor-1 (IGF-I) or insulin-like growth factor binding protein-3 (IGFBP-3) [9]compared with women in the lowest quartiles. Women with high levels of both C-peptide and IGF-1 or IGFBP-3 also were found to have a substantially higher risk of breast carcinoma than those women with a high level of only one of these molecules.[10].

The insulin like growth factor (IGF) family includes the polypeptide ligands IGF-I and IGF-II, their cognate receptors and six binding proteins (i.e., IGFBP-1 to IGFBP-6). A large number of *in vitro* studies have shown that IGFs are strong mitogens for a variety of cancer cells including many breast cancer cell lines [11]. IGFs also inhibit the cell apoptotic pathway to facilitate cell proliferation [12,13]. The combination of these mitogenic and anti-apoptotic effects has a profound impact on tumor growth [14–16]. IGF-I and IGF-II are present in the circulation where a majority (over 90%) are bound to IGFBP3 [14,17–18]. IGFBPs can inhibit or enhance the action of IGFs resulting in either suppression or stimulation of cell proliferation depending on the binding proteins concentration, phosphorylation status, and proteolytic fragmentation [14,19–20].

A recent area of interest is the synergistic interplay between insulin resistance and insulin-like growth factors in relation to breast cancer risk. Insulin resistance is often measured using blood C-peptide, a 31- amino acid peptide that is a byproduct of insulin production [21]. The link between the insulin resistance hormones, IGF-I, IGFBP-3 and C-peptide, a positive energy balance, and breast cancer risk is that higher levels of visceral fat result in a compensatory response of resistance to the insulin-stimulated glucose uptake in the peripheral tissues. The overabundance of insulin, called hyperinsulemia, amplifies the bioavailability of IGF-I. IGF-I and insulin together have been shown to stimulate motility in human breast cancer cell lines, an effect that could enhance migration and invasion [19,22]. Conversely, there is good evidence that a negative energy balance is associated with a hormonal and/or metabolic milieu that would be predicted to reduce breast cancer risk [23–24]. For example, restricted energy intake has been associated with reduced insulin, and bioavailable IGF-1 (e.g., IGF-1/IGF binding protein-3 ratio).

Previously, we have investigated the effect of energy balance and insulin-resistance hormones separately on the risk of breast cancer. In the present study, we investigated whether breast cancer risk may be interpreted by the relationship of energy balance and plasma biomarkers of insulin resistance in combination.

Materials and Methods

The Shanghai Breast Cancer Study was designed to recruit women aged 25–64 who were newly diagnosed with breast cancer between August 1996 and March 1998, and a group of community controls for a population-based case-control study. All study subjects were permanent residents of urban Shanghai. They had no prior history of cancer and were alive at the time of interview.

Through a rapid case-ascertainment system, supplemented by the population-based Shanghai Cancer Registry, 1,602 eligible breast cancer cases were identified during the study period. The controls were randomly selected from female residents in urban Shanghai, using the population-based Shanghai Resident Registry and frequency-matched to cases by age (5-year intervals).

An individually matched case-control sub-study was built into the Shanghai Breast Cancer Study to increase the comparability of cases and controls in studying quantitative biomarkers. For each case whose samples were collected before any cancer treatment, a control was selected from the pool of subjects who completed the study. Controls were individually matched to the index case by age (± 3 yrs), menopausal status, and date of sample collection (± 30 days). Successful matches were completed for 400 case-control pairs for the present study.

To eliminate between-assay variability in case-control comparisons, samples from a matched case-control pair were included in the same batch in the assays of blood IGFs and C-peptide. Three case-control pairs were excluded from all analyses because of lab failure in biomarker assays.

Written informed consent was obtained by trained interviewers from the research subjects who participated in this research study during 1996–1998, in Shanghai, China. The trained interviewers then measured each eligible subject for her weight, circumference of waist and hips, sitting and standing heights and conducted an in-person interview according to a standard protocol. A structured questionnaire was used to elicit detailed information on demographic factors, menstrual and reproductive history, hormone use, dietary habits, prior disease history, physical activity, tobacco and alcohol use, weight, and family history of cancer. In-person interviews were completed for 1,459 (91.1%) of the eligible cases and 1,556 (90.3%) of the 1,724 eligible controls identified. Blood samples were collected from about 83% of the study participants.

Information on usual adult dietary intake was collected using a comprehensive quantitative food frequency questionnaire (FFQ) that covers over 85% of foods consumed in Shanghai. A physical activity questionnaire (PAQ) assessed exercise /sport activity and occupational activity levels. Women could report up to five exercises or sport activities during adolescence (13 to 19 years) and adulthood (last 10 years). Quantitative exercise/sport data were summarized in terms of intensity (metabolic equivalents (METs)), duration (hours/week), years of participation, and average energy expenditure during the period (MET-hours/week/year) using standard methods [25]. Women also reported their occupational physical activity levels for jobs they held for at least 3 years during their lifetime. For each occupation, participants reported the average time spent in ‘standing or walking’ and classified the physical exertion of the job according to three activity categories (i.e. heavy, medium, or non-physical work). Summary measures were calculated by multiplying the years spent in each occupation by the specific activity variable, and then summing the results over all jobs.

Plasma concentrations of IGF-I, IGF-II, and IGFBP-3 were determined with the use of commercially available ELISA kits (Diagnostic System Laboratory Inc., Webster, TX). These methods were used in most of the previous epidemiological studies [9]. The calibrators used in the assays ranged between 4.5–640 ng/ml for IGF-I, 500–2000 ng/ml for IGF-II, and 2.5-100 ng/ml for IGFBP-3. For IGFBP-3 measurement, plasma samples were diluted at 1:100 in an assay buffer. The intra- and interassay precisions are 1.5–3.4 and 1.5–8.5% expressed as coefficients of variation (CV) respectively, for IGF-I, 4.2–7.2 and 6.3–10.7% of CV for IGF-II and 0.5–1.9 and 1.8–3.9% of CV for IGFBP-3. Each assay has no cross-reaction with other members of the IGF family. Serum C-peptide was measured using an enzymatically amplified one-step sandwich-type ELISA assay kit from Diagnostic System Laboratory, (Webster, TX)

and the ELISA assay was performed according to the manufacture's instruction. Sample aliquots of 20 μl were pipetted into microtiter wells coated with anti-C-peptide antibodies and incubated with 200μl of a buffered solution of anti-C-peptide antibody conjugated to horseradish peroxidase. Plasma samples were measured in duplicate to improve reliability.

Geometric means and 95% confidence intervals were used to compare plasma concentrations of insulin-like growth factors (IGF-I and IGF-II) and IGFBP-3, C-peptide between cases and controls. Both parametric and non-parametric methods were used to analyze the data collected from this study. Pearson correlation coefficients were calculated to evaluate the correlation between energy balance (intake of total energy, physical activity and body size measures) and biomarkers (IGFs, IGFBP-3, C-peptide). Because the distributions for most plasma concentrations of biomarkers were positively skewed, log-transformation was used in generalized linear models to further examine the associations between energy balance and biomarkers after adjustment for potential confounding factors (age and menopausal status) and trend for linear association. Odds ratios (OR) and 95% confidence intervals (CI) for the upper three quartile groups were derived using conditional logistic regression, compared to the lowest quartile group. Multivariate analyses were performed to adjust for potential confounding variables.

Results

Comparisons of selected demographic and risk factors between breast cancer patients and their matched controls are shown in Table 1. . Although, older cases had a higher proportion of family history, younger age at menarche, an older age at menopause and consumed more energy and fat, the differences were not statistically significant. Cases were less physically active, had a higher BMI, an older age of first live birth, consumed more meat and had significantly higher plasma levels of IGF-I, IGF-II, IGFBP-3, C-peptide than controls.

Pearson correlation coefficients related body size measurements, dietary/lifestyle measures and physical activity measures to the biomarkers among controls are shown in Table 2. BMI was significantly positively correlated with IGFBP-3 and C-peptide. WHR was positively correlated with C-peptide. Adult exercise/sports activity (MET hrs/d/yr) and occupational activity were negatively correlated with IGF-I (Table 2).

Medians (25^{th}, 75^{th}) of C-peptide, IGFs and IGFBP-3 by quartile distribution of energy intake, expenditure, and body size among controls are shown in Tables 3. There was a significant trend of increasing C-peptide levels with increasing quartiles of BMI (Table 3). C-peptide levels increased with increasing quartiles of WHR (p for trend <0.01). Levels of IGFBP-3 significantly decreased with increasing quartiles of adolescent exercise/sports activity.

Additional analyses were performed to evaluate whether the association of energy balance measures with breast cancer risk changed after adjustment for IGFs, IGFBP-3 and C-peptide biomarkers. The associations attenuated after adjustment for each of the above biomarkers singly and in combination. None of them, however, changed substantially.

Discussion

In this study, we found that BMI and WHR were significantly positively correlated with IGFBP-3 and C-peptide while adult exercise/sports activity and occupational activity were significantly negatively correlated with IGF-I. These findings suggest that the association between positive energy balance and breast cancer may be partially explained by the high concentrations of these biomarkers. These results are supported by previous epidemiologic studies. Holmes et al., found a higher BMI was positively associated with higher IGFBP-3 levels (p for trend = 0.01) [26]. Allen found that obese women (BMI 30+ kg/m^2) had a

significantly higher IGFBP-3 (p for trend =0.004) concentration compared with lean women (BMI <20 kg/m^2) [6].

We found a negative association between adult exercise, occupational activity and blood IGF-I. The proposed mechanism for the effect of physical activity on incidence of breast cancer is mediated by an increased capacity for glucose transport into the muscle and adipose tissue in response to insulin stimulation. Exercise training also results in increased insulin sensitivity and decreased insulin concentrations [27]. Similar to our findings, results from the Chadan study (1999) showed that moderate level intensity exercise in postmenopausal women modulated the availability of IGF-I through elevated IGFBP-3 levels [28]. Elevated IGFBP-3 potentiated a decrease in IGF-I levels and clearance from the plasma due to higher levels of IGFBP-3.

Our report of lower levels of IGFBP-3 with increased adult exercise is conflicting with previous evidence by Holmes et al., where a moderate level exercise bout resulted in significant ($p< 0.05$) increases in IGFBP-3 immediately following activity and remained elevated 48% above baseline following the activity [26]. Irwin et al., observed higher IGF-I (p for trend = 0.0037) and IGF-binding protein-3 (p for trend = 0.055) levels with higher levels of physical activity [4].

The association of IGFBP-3 with breast cancer risk in the Chinese population contradicts findings from studies in Caucasian populations [29]. Unlike previous studies on the Caucasian population where a high/low ratio of IGF-I levels relative to IGFBP-3 levels exhibits a protective relationship versus breast cancer, we found that high levels of IGFPB-3 adjusting for IGF-I are positively associated with breast cancer risk [9,10].

The conflicting results from the previous epidemiologic studies on physical activity, IGF-I and IGFBP-3 [4,26] are not unexpected, given the dual roles of the IGFBP-3 protein regulating the biological actions of IGF-I. In actuality, blood levels of IGFBP-3 may not reflect the level of this protein in the target tissues and most epidemiologic studies have limited access to normal target tissue samples to evaluate the association of this protein with cancer risk.

Congruent with current epidemiologic findings, our study results showed obesity as positively correlated to plasma concentrations of C-peptide, a measurement of insulin resistance [2–6]. Allen found that obese women (BMI 30+ kg/m^2) had a significantly higher C-peptide (p for trend =0.018). Obesity leads to a state of insulin resistance and hyperinsulinemia, which induces an increase in bioavailable IGF-I involved in mammary tissue development and tumor promotion.

This study has several strengths. One major strength of this study is that blood samples were collected prior to any cancer treatment and the majority of breast carcinoma patients were diagnosed at the early stages of disease, which eliminates the possibility that serum hormone concentrations were altered by the presence of a large tumor. Lifestyle changes in such a short interval should not be appreciable, particularly for those patients with early-stage breast carcinoma cases. Additionally, this was a population-based case-control study that included incident cases and that obtained detailed information about traditional breast cancer risk factors that allowed for full adjustment for possible confounding factors. Participation rates were high (>90%) for both cases and controls, suggesting that the potential for selection bias in this study is low. The primary instruments used to obtain physical activity and dietary information in this study have been tested for reliability and validity in a population of women from Shanghai, and both were found to be reliable and valid instruments for stratifying women by physical activity and energy intake levels [30–31]. Another strength, distinct from other epidemiologic studies is that BMI was calculated from measured rather than self-reported weight and height,

within days of cancer diagnosis, thus reducing measurement errors and some of the effects of therapy on body weight.

In summary, an increase in breast cancer risk with increasing energy balance may be in part attributed to increases in insulin resistance related biomarkers, IGF-I, IGFBP-3, and C-peptide. Identifying the factors that affect these insulin resistance biomarkers is of particular interest as subjects at increased breast cancer risk could benefit from lifestyle changes and/or chemoprevention intervention. Further studies are warranted to investigate other underlying mediators for this energy balance and breast cancer association.

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Table 1

Comparison of cases and controls on demographics and selected breast cancer risk factors The Shanghai Breast Cancer Study, 1996–1998.

Characteristics	Cases(n=397)[a]	Controls(n=397)[b]	P-value[d]
Age	47.8 ± 7.8	47.6 ± 7.9	0.20
Education (%)			
Elementary or lower	12.6	14.6	
Middle school	44.3	43.1	
High school	30.5	31.5	
Professional, college and above	12.6	10.8	0.32
Breast cancer in first degree relatives (%)	1.5	0.75	0.16
Physically active (%)	20.9	29.7	0.01
Body mass index	23.5 ± 3.3	22.9 ± 3.2	0.0186
Waist to hip ratio	0.81 ± 0.06	0.80 ± 0.06	<0.001
Age at first live birth (years)[b]	26.9 ± 4.1	26.3 ± 3.9	0.01
Menarcheal age (years)	14.7 ± 1.7	14.9 ± 1.7	0.11
Menopausal age (years)[c]	48.5 ± 4.5	47.8 ± 4.5	0.12
Energy intake (kcal/day)	1905.7 ± 470.3	1862.3 ± 481.9	0.16
Total fat intake (g/day)	37.1 ± 19.3	36.8 ± 15.9	0.79
Total meat intake (g/day)	93.1 ± 69.2	84.3 ± 53.0	0.04
IGF-I[e]	150.6 (144.52,156.92)	138.5 (133.48, 143.80)	<0.001
IGF-II[e]	820.5 (797.38, 844.19)	798.6 (779.46,820.64)	0.034
IGFBP-3[e]	3963.9 (3813.56,4119.54)	3718.2 (3586.50,3854.76)	<0.0001
C-peptide[e]	1.43 (1.34,1.52)	1.19 (1.12,1.26)	<0.0001

Subjects with missing values were excluded from the analysis

[a] Unless otherwise specified, mean ± SD are presented

[b] Among women who had live births

[c] Among post-menopausal women

[d] P-values were derived from χ tests for categorical variables and paired t-tests for continuous variables

[e] Geometric means and 95% CIs are presented

Table 2

Pearson correlation coefficients among energy balance measurements, selected insulin-like growth factors and C-Peptide Shanghai Breast Cancer Study, 1996–1999

Variable	IGF-I	IGF-II	IGFBP-3	C-Peptide
Adolescent Exercise/Sports (MET-hrs/d/yr) [a]	−0.04/−0.03	0.06/0.06	0.002/0.004	0.02/0.002
Adult Exercise/Sports (MET-hrs/d/yr) [a]	**−0.13** [b] /−0.14	0.02/0.02	0.003/0.02	−0.06/−0.08
Occupational Activity (hrs/d/yr)	**−0.01/−0.01**	0.02/0.02	0.08 /0.08	−0.07/−0.11
BMI (kg/m^2)	−0.003/−0.03	0.01/0.009	**0.01** /0.09	**0.22/0.29**
Waist: hip ratio	0.03/0.02	0.07/0.07	0.09 /0.09	**0.11/0.17**
Energy Intake (kcal/d)	0.09/0.08	−0.03/−0.03	0.08 /0.07	−0.04/−0.04

[a] Unadjusted/log transformed

[b] Bolded values are significant at $p<0.05$

Table 3

Median levels (25th, 75th percentile) of IGF-I, IGF-II, IGFBP-3 and C-peptide by quartiles of energy balance measurements among female controls, Shanghai Breast Cancer Study, 1996–1998

Variable	IGF-I	IGF-II	IGFBP-3	C-Peptide
Body mass index (kg/m^2)				
≤ 20.70	135.9(106.8,173.8)	778.5(643.3,923.4)	3635.0(3092.0,4186.0)	0.92(0.66,1.4)
20.70–22.79	154.3(112.8,193.0)	819.5(705.4,1004.0)	3698.0(3079.3,4393.0)	1.09(0.73,1.7)
22.79–25.1	136.9(113.4,183.3)	843.8(695.3,998.8)	3752.0(2961.0,4777.0)	1.16(0.96,1.7)
>25.1	138.0(95.7,178.3)	758.2(646.7,955.2)	3871.0(3178.0,4888.0)	1.34(0.97,2.18)
p for trend [a]	0.04	0.99	0.36	0.0004
Waist : Hip ratio				
≤ 0.764	138.4(108.7,175.4)	826.7(650.3,921.0)	3641.5(3092.0,4384.0)	1.00(0.69,1.60)
0.764–0.799	142.5(102.8,185.1)	735.5(655.9,946.4)	3701.0(2900.3,4378.0)	1.01(0.74,1.53)
0.799–0.835	144.8(106.0,181.2)	822.6(661.7,957.0)	3669.0(2938.0,4424.0)	1.24(0.87,1.93)
>0.835	138.3(108.4,181.8)	863.2(688.4,1008.8)	3914.5(3311.5,4694.0)	1.26(0.90,2.33)
p for trend [a]	0.06	0.10	0.34	0.0077
Adolescent Exercise /Sports (MET-hrs/d/yr)				
0	142.1(107.3,178.5)	797.9(666.7,967.2)	3880.5(3120.0,4989.0)	1.15(0.85,1.79)
0–2.2	133.7(102.8,189.4)	749.8(646.0,945.1)	3677.5(2912.3,4161.0)	1.14(0.75,1.72)
2.2–7.6	147.0(117.9,177.5)	849.0(700.4,1014.5)	3655.1(3153.1,4233.0)	0.99(0.77,1.67)
>7.6	129.6(103.3,179.4)	826.4(661.7,946.4)	3573.0(2843.0,4057.0)	1.06(0.75,1.81)
p for trend [a]	0.12	0.48	0.03	0.24
Adult Exercise /Sports (MET-hrs/d/yr)				
0	147.4(108.2,184.3)	816.7(664.6,974.6)	3669.0(2931.9,4355.0)	1.17(0.83,1.93)
0–1.31	131.5(105.9,174.7)	804.8(681.1,968.7)	3713.5(3201.3,4643.0)	0.97(0.71,1.61)
1.31–6.84	135.1(89.44,167.34)	722.4(629.8,867.7)	4088.0(3478.0,5200.0)	1.01(0.86,1.39)
>6.9	127.7(99.5,164.7)	807.7(675.2,975.1)	3724.0(3414.0,4462.0)	1.06(0.72,1.46)
p for trend [a]	0.64	0.61	0.30	0.26
Occupational Activity (hrs/d/yr.)[b]				
0	148.6(110.6,185.1)	809.0(658.5,969.5)	3687.0(2921.8,4378.0)	1.17(0.83,1.90)
0–2	125.3(99.6,182.5)	798.4(685.3,962.2)	3686.1(3180.0,4893.0)	1.12(0.80,1.90)
2–6	119.4(86.3,162.2)	724.5(653.1,906.5)	4292.0(3440.0,5351.5)	0.96(0.71,1.28)
>6	130.2(109.9,164.7)	755.9(675.0,1068.0)	3763.0(3474.0,4156.0)	1.02(0.70,1.30)
p for trend [a]	0.90	0.96	0.40	0.14
Energy Intake (kcal/d)				
0	135.3(104.8,170.0)	850.0(706.1,992.6)	3526.0(2912.3,4304.0)	1.12(0.86,1.67)
0–1532.2	139.0(102.3,177.0)	824.5(666.4,974.8)	3742.5(3049.0,4504.5)	1.33(0.89,2.10)
1532.2–2084.9	141.8(110.6,181.5)	781.4(664.9,950.8)	3756.5(3116.0,4252.0)	1.06(0.75,1.70)
>2084.9	149.3(107.7,189.4)	744.8(645.1,910.8)	3946.5(3264.0,5089.0)	1.10(0.81,1.63)
p for trend [a]	0.06	0.053	0.13	0.74

All models are adjusted for age and menopausal status.

[a] test for trend based on quartile ranks