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Original Article

Association of insulin resistance with breast, ovarian, endometrial and cervical cancers in non-diabetic women

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Abstract: Hyperinsulinemia and insulin resistance were reported to play a crucial role in diabetes-cancer relationship. This study aimed to explore the associations between insulin resistance and several female cancers in a non-diabetic population. This cross-sectional study was conducted in 121,230 middle-aged and elderly non-diabetic women. Cancer diagnosis was self-reported and further validated by medical records. Insulin resistance was defined as homeostasis model assessment of insulin resistance (HOMA-IR) ≥ 2.50. The prevalence of both premenopausal and postmenopausal breast cancer, postmenopausal ovarian cancer and premenopausal endometrial cancer were higher in insulin-resistant participants than in insulin-sensitive participants (premenopausal breast cancer, 0.45 vs 0.28%; postmenopausal breast cancer, 0.86 vs 0.63%; postmenopausal ovarian cancer, 0.17 vs 0.09%; premenopausal endometrial cancer, 0.43 vs 0.25%, respectively, all $P < 0.05$). Individuals with insulin resistance had higher odds ratio (OR) of breast cancer, both premenopausal and postmenopausal (OR 1.98, 95% confidence interval (CI) 1.19-3.32; OR 1.29, 95% CI 1.01-1.63), postmenopausal ovarian cancer (OR 2.17, 95% CI 1.10-3.40) as well as total endometrial cancer (OR 1.47, 95% CI 1.02-2.12). Subgroup analysis revealed that the possitive association between insulin resistance and risk of prevalent breast cancer was observed in popualtion with younger

age, overweight or obesity, higher education and impaired glucose tolerance (IGR). No relationships were observed for the risk of prevalent cervical cancers with insulin resistance. Non-diabetic women with insulin resistance had higher risk of prevalent breast, ovarian and endomatrial cancer, which suggests special attentions to these female cancer screening and prevention.

Keywords: Insulin resistance, non-diabetic, breast, ovarian, endometrial and cervical cancers

Introduction

Diabetes has been recognized as a risk factor for certain female cancers [1-6]. Insulin resistance is believed to play a crucial role in diabetes-cancer relationship. Previous research indicated that in diabetes patients, as a consequence of insulin resistance, elevated level of insulin and signaling transduction through the IGF-1 receptor pathway could stimulate cell proliferation and inhibit apoptosis, thus contribute to tumor promotion and metastasis [4, 5, 7, 8]. Another biological mechanism that linking diabetes and female cancer is the elevated level of sex hormones that was caused by insulin-mediated reduction of hepatic sex hormone binding globulin and increase of endogenous sex steroid hormones [9]. However, in spite of the large amount of epidemiological evidence on the association of diabetes and female cancers, especially breast and endometrial cancers [10, 11], fewer studies have directly assessed the association between insulin resistance and female cancers in non-diabetic population.

Cancers of the breast, ovary, endometrium and cervix are common cancers with high incident rates in women. Breast cancer comprised 25.2% of the cancers diagnosed in women, making it the most common female cancer [12]. Worldwide, ovarian cancer contributed to 160,000 deaths in 2010, up from 113,000 cases in 1990 [13]. Endometrial cancer affect approximately 320,000 women and kill 76,000 cases every year, making it the sixth most common cancer in women [12]. In 2012, 528,000 cervical cancer cases and 266,000 deaths was reported worldwide [12], making it the fourth in both cancer incidence and mortality in women [12].

Previous studies directly regarding the relationship between insulin resistance and several female cancers were limited, especially in Chinese population, and didn't provided consistence information [7, 14-18]. Given the pandemic of female cancers in China, it is imperative to detect whether insulin resistance in non-diabetic population posed a higher risk for female cancers. Here, we investigated the association between insulin resistance and female cancers, including breast, ovarian, endometrial and cervical cancers, in a large population of Chinese non-diabetic women aged 40 years and older.

Materials and methods

Study population and data collection

The study population was drawn from the Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study which is a multicenter prospective study designed to evaluate the association between glucose metabolism and cancer risks [19, 20]. The study cohort consisted of 259,657 participants aged 40 years or older, recruited from 25 communities across mainland China during 2011 to 2012 [19-22]. The design and methodology of REACTION study has previously been described in details [19, 20]. Briefly, a personal interview was conducted to collect information on sociodemographic characteristics, lifestyle factors, medical history, and family history of cancer and type 2 diabetes mellitus (T2DM) among the first degree relatives. A 2-hour oral glucose tolerance (OGTT) test was performed and a blood sample was collected for measuring insulin, HbA1c and lipid protein levels.

The current analysis is a cross-sectional study using the baseline data of the REACTION study. There are a total of 169,628 female participants in the REACTION study. For the current study, we excluded 5251 subjects with missing blood glucose value, 14,114 with missing insulin value and 29,033 women with diabetes. This comes to a total of 121,230 non-diabetic women in the current analysis.

Ethics, consent and permissions

The REACTION study is supported by the Chinese Society of Endocrinology and led by Rui Jin Hospital affiliated to Shanghai Jiao-Tong University School of Medicine. The Institutional

Review Board of Shanghai Jiao-Tong University School of Medicine approved the study protocol. Written informed consents were obtained from all study participants.

Assessment of diagnosed cancer

Cancer status were self reported by participants themselves, as well as information on cancer type, diagnosis date and the treatment history. The accuracy of the data was verified by the Adjudication Committee, which was composed of clinical experts of radiologists, pathologists and endocrinologist. The accuracy rate of these data is more than 90%.

Definition of variables analyzed in this study

Overweight was defined as body mass index (BMI, kg/m^2) ≥ 25 but < 30, obesity as BMI ≥ 30, central obesity as waist circumference ≥ 80 cm. Systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg was considered as hypertension. Dyslipidemia was defined as total cholesterol (TC) ≥ 6.22 mmol/L or triglycerol (TG) ≥ 2.26 mmol/L or low density lipid protein cholesterol (LDL-C) ≥ 4.14 mmol/L or high density lipid protein cholesterol (HDL-C) ≤ 1.04 mmol/L. Insulin resistance was defined as homeostasis model assessment of insulin resistance (HOMA-IR) higher than 2.50. In accordance with the 1999 World Health Organization (WHO) diagnostic criteria [23], diabetes was defined as fasting plasma glucose (FPG) ≥ 7.0 mmol/L, and/or OGTT-2 h postload plasma glucose (PPG) ≥ 11.1 mmol/L, and/or previous diagnosis for diabetes. Fasting glucose higher than 6 mmol/L and less then 7 mmol/L, and/or post challenge plasma glucose (PPG) higher than 7.8 mmol/L and less than 11.1 mmol/L in participants, and/or without previous diagnosis for diabetes was considered as impaired glucose regulation (IGR). FPG < 6.1 mmol/L and OGTT-2h PPG < 7.8 mmol/L was defined as normal glucose regulation (NGR). Cases were defined as premenopausal and postmenopausal based on self-report of age at menopause and the date of first diagnosis of any kind of those female cancers obtained from self-report.

Statistical analysis

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA). Continuous variables were presented as Mean ± SD and categorical variables were presented as proportions. Comparisons of means and proportions were performed with the Student's t tests and χ^2 test, respectively.

To investigate the association between insulin resistance and each type of female cancers, the multivariate adjusted logistic regression analysis models were used to assess odds ratios (OR) and corresponding 95% confidence intervals (CI). The OR were adjusted for age, obesity(normal weight/overweight or obesity), dyslipidemia, hypertension, status of menstruation, history of cigarette smoking and alcohol drinking, family history of cancer, education and physical activity, age of menarche, number of child births and usage of contraceptive. In the adjustment, age, age at menarche and number of births were adjusted as continuous variables, overweight or obesity (yes/no), dyslipidemia (yes/no), hypertension (yes/no), status of menstruation (yes/no), history of cigarette smoking and alcohol drinking (yes/no), family history of cancer (yes/no), high education (yes/no), physical activity (low/moderate/high) were fitted as categorical variables. A *p* value of less than 0.05 was considered as statistically significant.

Results

General characteristics of the study population

In this study of 121,230 female, the prevalence of breast, ovarian, endometrial and cervical cancers was 0.55% (n=667), 0.09% (n=109), 0.34% (n=411) and 0.12% (n=146), respectively. The demographic and biochemical characteristics of this study population by strata of cancer types are shown in **Table 1**.

In comparison to individuals without breast cancer, those with breast cancer were older, more educated and had higher frequencies of central obesity, insulin resistance, family history of cancer, using contraceptive, being postmenopausal, they also had an earlier age at menarche, higher level of TG, PPG, fasting insulin, HbA1c, and HOMA-IR. On the other hand, breast cancer patients had lower level of alcohol consumption and physically activity, and fewer numbers of child birth, compared with those without breast cancer (all $P < 0.05$).

In comparison to participants without ovarian cancer, ovarian cancer patients were more edu-

Table 1. Baseline characteristics of the study population by status of breast, ovarian, endometrial and cervical cancer (2011-2012)

	Breast cancer		Ovarian cancer		Endometrial cancer		Cervical cancer	
	Yes	No	Yes	No	Yes	No	Yes	No
N (%)	667 (0.55)	120563 (99.45)	109 (0.09)	121121 (99.91)	411 (0.34)	120819 (99.66)	146 (0.12)	121084 (99.88)
Age (years)[a]	57.67±8.73**	55.96±9.29	55.05±7.40	55.97±9.29	54.82±8.81**	55.97±9.29	53.38±7.10*	55.97±9.29
High school education or above N (%)[b]	294 (44.08)**	39398 (32.68)	52 (47.71)*	39640 (32.73)	164 (39.90)*	39528 (32.72)	53 (36.30)**	39639 (32.74)
Current smoker N (%)[b]	7 (1.05)	1615 (1.34)	2 (1.83)	1620 (1.34)	6 (1.46)	1616 (1.34)	6 (4.11)*	1616 (1.33)
Current drinker N (%)[b]	4 (0.6)*	2123 (1.76)	4 (3.67)	2123 (1.75)	8 (1.95)	2119 (1.75)	5 (3.42)	2122 (1.75)
MET-min/week[c]	1386 (198-2772)*	1386 (0-2772)	1386 (0-2772)	1386 (0-2772)	1386 (0-2772)*	1386 (0-2772)	1386 (0-2772)	1386 (0-2772)
BMI (kg/m^2)[a]	24.28±3.32	24.21±3.51	24.44±3.60	24.21±3.51	24.56±3.40	24.21±3.51	24.28±3.37*	24.21±3.51
Normal weight N (%)[b]	413 (61.92)	77002 (63.91)	64 (58.72)	77351 (63.9)	249 (60.58)	77166 (63.91)	89 (60.96)	77326 (63.90)
Overweight N (%)[b]	218 (32.68)	37238 (30.91)	38 (34.86)	37418 (30.9)	132 (32.12)	37324 (30.91)	51 (34.93)	37405 (30.91)
Obesity N (%)[b]	36 (5.4)	6250 (5.19)	7 (6.42)	6279 (5.19)	30 (7.3)	6256 (5.18)	6 (4.11)	6280 (5.19)
Waist circumference (cm)[a]	83.24±9.11*	82.04±9.56	81.98±8.51	82.05±9.56	83.12±9.09	82.04±9.56	82.32±9.87*	82.05±9.55
Central obesity N (%)[b]	436 (65.37)**	69226 (57.42)	65 (59.63)	69597 (57.46)	263 (63.99)	69399 (57.44)	87 (59.59)	69575 (57.46)
SBP (mmHg)[a]	130.17±19.87	129.92±20.76	124.86±19.90*	129.92±20.76	128.66±20.38	129.92±20.76	126.58±18.03	129.92±20.76
DBP (mmHg)[a]	76.90±10.31	76.73±10.93	75.62±10.61	76.73±10.92	77.20±11.82	76.73±10.92	77.35±11.03	76.73±10.92
Hypertension N (%)[b]	274 (41.08)*	44604 (37.00)	31 (28.44)	44847 (37.03)	155 (37.71)	44723 (37.02)	50 (34.25)	44828 (37.02)
TG (mmol/L)[c]	1.35 (1.00-1.97)**	1.24 (0.90-1.75)	1.30 (0.91-1.84)	1.24 (0.90-1.75)	1.25 (0.88-1.74)	1.24 (0.90-1.75)	1.25 (0.99-1.77)	1.24 (0.90-1.75)
TC (mmol/L)[a]	5.01±1.16	4.95±1.12	4.96±1.14	4.95±1.12	4.84±1.08*	4.95±1.12	5.13±1.09	4.95±1.12
LDL-C (mmol/L)[a]	2.89±0.89	2.85±0.86	2.90±0.82	2.85±0.86	2.79±0.83*	2.85±0.86	3.02±0.88	2.85±0.86
HDL-C (mmol/L)[a]	1.34±0.34*	1.38±0.35	1.34±0.32	1.38±0.35	1.34±0.33	1.38±0.35	1.38±0.34*	1.38±0.35
Dyslipidemia N (%)[b]	294 (44.08)**	41567 (34.48)	40 (36.7)	41821 (34.53)	146 (35.52)	41715 (34.53)	54 (36.99)	41807 (34.53)
FPG (mmol/L)[a]	5.41±0.53	5.40±0.54	5.37±0.53	5.40±0.54	5.41±0.56	5.40±0.54	5.41±0.52	5.40±0.54
PPG (mmol/L)[a]	7.25±1.67**	6.90±1.62	6.80±1.43	6.90±1.62	7.02±1.68	6.90±1.62	6.96±1.66	6.90±1.62
HbA1c (%)[c]	5.8 (5.5-6.0)**	5.7 (5.5-6.0)	5.8 (5.6-6.1)	5.7 (5.5-6.0)	5.4 (5.8-6.0)	5.5 (5.7-6.0)	5.7 (5.4-6.0)	5.7 (5.5-6.0)
Fasting insulin (IU/ml)[c]	7.60 (5.50-10.50)**	6.70 (4.90-9.20)	7.60 (5.40-10.80)	6.70 (4.90-9.20)	7.10 (5.20-9.80)*	6.70 (4.90-9.20)	7.30 (5.60-10.00)*	6.70 (4.90-9.20)
HOMA-IR[c]	1.81 (1.29-2.55)**	1.61 (1.15-2.26)	1.78 (1.25-2.59)	1.61 (1.15-2.26)	1.72 (1.22-2.40)*	1.61 (1.15-2.26)	1.82 (1.27-2.38)*	1.61 (1.15-2.26)
Insulin resistance N (%)[b]	173 (25.94)**	23135 (19.19)	31 (28.44)*	23277 (19.22)	93 (22.63)	23215 (19.21)	30 (20.55)	23278 (19.22)
Family history of cancer N (%)[b]	146 (21.89)**	13662 (11.33)	27 (24.77)**	13781 (11.38)	68 (16.55)*	13740 (11.37)	22 (15.07)**	13786 (11.39)
Family history of diabetes N (%)[b]	85 (12.74)	12884 (10.69)	19 (17.43)*	12950 (10.69)	51 (12.41)	12918 (10.69)	21 (14.38)	12948 (10.69)
Menopause N (%)[b]	413 (80.19)**	60830 (64.66)	68 (85.00)**	61175 (64.73)	85 (47.75)**	61158 (64.78)	95 (89.62)**	61148 (64.72)
Age at menarche (years)[a]	15.18±2.04*	15.45±2.05	15.24±2.45	15.45±2.05	14.95±2.03*	15.45±2.05	15.18±2.08	15.45±2.05
Usage of contraceptive N (%)[b]	33 (4.95)*	4096 (3.40)	7 (6.42)	4122 (3.40)	21 (5.11)	4108 (3.40)	6 (4.11)	4123 (3.41)
Number of births[a]	1.56±0.91*	1.82±1.11	1.54±0.81*	1.82±1.11	1.60±0.91*	1.82±1.11	1.56±0.87*	1.82±1.11

[a]Data are represented as means±standard deviation. [b]Data are represented as number(percentage). [c]Data are represented as medians (interquartile range). Abbreviation: MET, metabolic equivalent; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-c, low density lipoprotein; HDL-c, high density lipoprotein; FPG, fasting plasma glucose; PPG, post-challenge plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance. Comparisons of means and proportions were performed with the Student's tests and χ^2 test. *P < 0.05, **P < 0.0001.

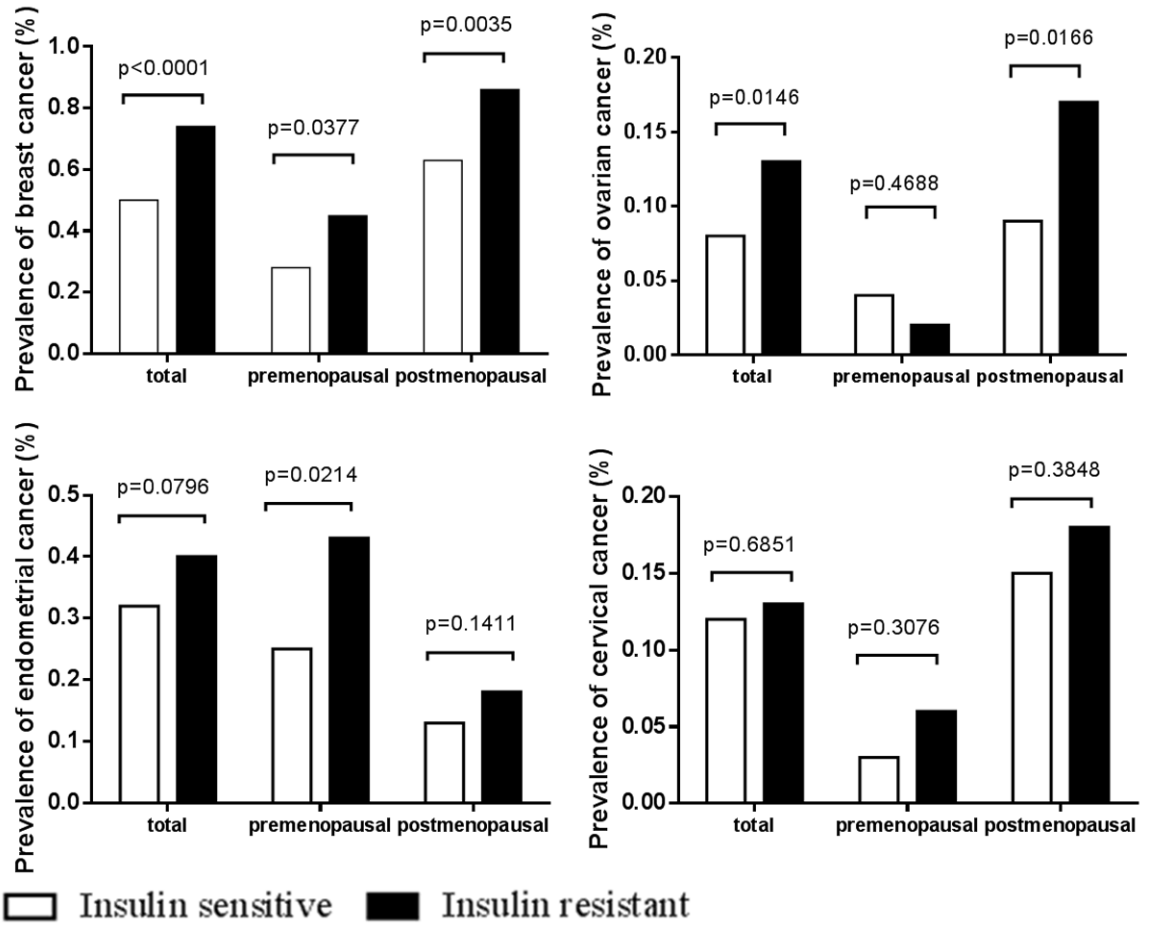

Figure 1. Prevalence of breast, ovarian, endometrial and cervical cancer according to menopause status and insulin sensitivity. Prevalence of both premenopausal and postmenopausal breast cancer, postmenopausal ovarian cancer and premenopausal endometrial cancer were significantly higher in insulin-resistant participants than in insulin-sensitive participants (premenopausal breast 0.45 vs 0.28%; postmenopausal breast cancer, 0.86 vs 0.63%; postmenopausal ovarian cancer, 0.17 vs 0.09%; premenopausal endometrial cancer, 0.43 vs 0.25%, respectively). No significant difference in the prevalence of cervical cancer by status of insulin sensitivity.

cated, having a higher level of SBP and higher frequencies of insulin resistance, family history of cancer and diabetes and being postmenopausal, but fewer child births (all $P < 0.05$).

Patients with endometrial cancer were younger, having an earlier age at menarche, fewer child births, a higher level of education and a lower level of physical activity, as well as a higher frequency of family history of cancer and being postmenopausal than those without endometrial cancer. Participants with endometrial cancer also had a higher level of fasting insulin and HOMA-IR, but lower levels of TC and LDL-c (all $P < 0.05$).

Patients with cervical cancers were younger, less educated, and more likely to be a smoker, having fewer child births, a higher level of BMI, waist circumference, fasting insulin, HOMA-IR, a higher frequency of family history of cancer and being premenopausal, but having a lower level of HDL-C than those without cervical cancer.

Association between insulin resistance and female cancers

The prevalence of breast cancer, both premenopausal and postmenopausal, postmenopausal ovarian cancer and premenopausal endometrial cancer were higher in patients with insulin resistance compared with those who were insulin sensitive (premenopausal breast cancer, 0.45 vs 0.28%; postmenopausal breast cancer, 0.86 vs 0.63%; postmenopausal ovari-

Table 2. Association between insulin resistance and female cancers risk by status of menopause

		Breast cancer		Ovarian cancer		Endometrial cancer		Cervical cancer	
		Insulin sensitive	Insulin resistant	Insulin sensitive	Insulin resistant	Insulin sensitive	Insulin resistant	Insulin sensitive	Insulin resistant
Total population	Number of cancers, n/N	494/97922	173/23308	78/97922	31/23308	318/97792	93/23308	116/97922	30/23308
	Prevalence of cancers, %	0.50	0.74	0.08	0.13	0.32	0.40	0.12	0.13
	OR (95% CI)	ref	1.39 (1.12-1.72)	ref	1.86 (1.07-3.23)	ref	1.47 (1.02-2.12)	ref	1.31 (0.80-2.12)
Premenopausal population	Number of cancers, n/N	78/28012	24/5335	11/28012	1/5335	70/28012	23/5335	8/28012	3/5335
	Prevalence of cancers, %	0.28	0.45	0.04	0.02	0.25	0.43	0.03	0.06
	OR (95% CI)	ref	1.98 (1.19-3.32)	ref	0.45(0.05-3.90)	ref	1.51 (0.86-2.65)	ref	2.30 (0.53-10.08)
Postmenopausal population	Number of cancers, n/N	304/48623	109/12620	46/48623	22/12620	62/48623	23/12620	72/48623	23/12620
	Prevalence of cancers, %	0.63	0.86	0.09	0.17	0.13	0.18	0.15	0.18
	OR (95% CI)	ref	1.29 (1.01-1.63)	ref	2.17 (1.22-3.89)	ref	1.46 (0.87-2.44)	ref	1.23 (0.73-2.05)

Age, age at menarche and number of births were adjusted as continuous variables. Hypertension (yes/no), dyslipidemia (yes/no), status of menopause (yes/no), status of smoking and drinking (yes/no), family history of cancer (yes/no), higher education (low/moderate/high), vigorous activity (yes/no) and usage of contraceptive (yes/no) were adjusted as category variables.

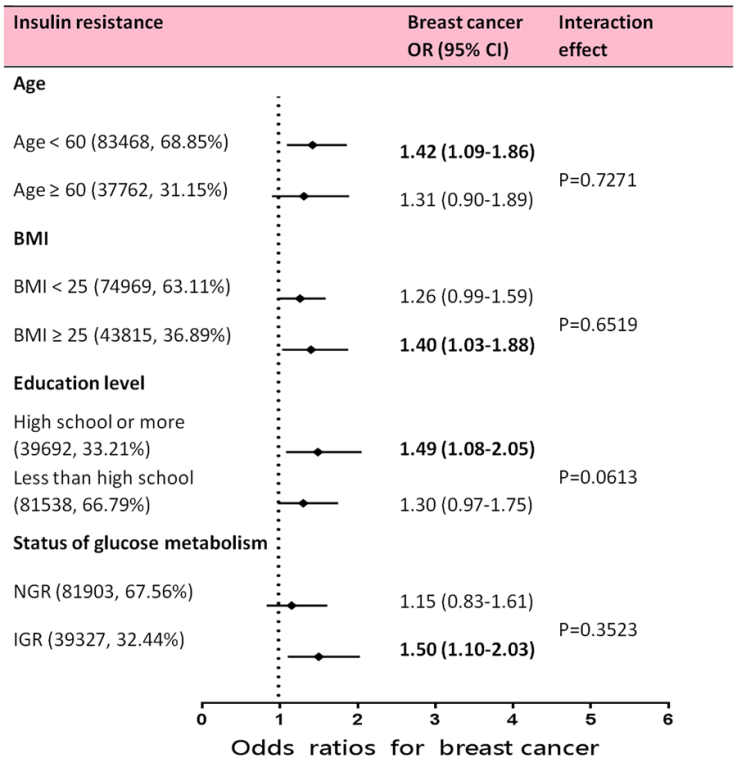

Figure 2. Odds of breast cancer according to status of IR stratified by potential risk modifiers. Age, age at menarche and number of births were adjusted as continuous variables. Hypertension (yes/no), dyslipidemia (yes/no), status of menopause (yes/no), status of smoking and drinking (yes/no), family history of cancer (yes/no), higher education (low/moderate/high), vigorous activity (yes/no) and usage of contraceptive (yes/no) were adjusted as category variables. (Except for each stratified factor).

an cancer, 0.17 vs 0.09%; premenopausal endometrial cancer, 0.43 vs 0.25%, respectively, all $P < 0.05$) (**Figure 1**). No significant difference in the prevalence of cervical cancers by strata of insulin sensitivity was observed (**Figure 1**).

Mulitivariable logistic regression analysis demonstrated that breast cancer was positively and significantly correlated with insulin resistance (**Table 2**). In fully adjusted models, the risk of premenopausal and postmenopausal breast cancer were raised by 98% (95% CI=1.19-3.32) and 29% (95% CI=1.01-1.63), respectively, for insulin-resistant participants in comparison to insulin-sensitive participants (**Table 2**). Individuals with insulin resistance conferred a 117% (95% CI=1.22-3.89, P=0.022) higher risk of postmenopausal ovarian cancer compared with those who were insulin sensitive (**Table 2**).

However, the association between insulin resistance and endometrial cancer was only observed in total popualtion, with 47% increased risk of endomatrial cancer in insulin resistant participants compared to insulin-sensitive participants (95% CI=1.02-2.12). No significant relationships were found between insulin resistance and cervical cancer.

Subgroup analysis of association between breast cancer and insulin resistance

To assess the potential interactions of insulin resistance with known risk factors for breast cancer, we conducted subgroup analysis by the strata of age, BMI, education level and status of glucose metabolism.

The association between insulin resistance and prevalent breast cancer remained significant in women with younger age, overweight or obesity, higher education level and impaired glucose regulation (IGR). The corresponding Ors (95% CI) is 1.42 (1.09-1.86), 1.40 (1.03-1.88), 1.49 (1.08-2.05) and 1.50 (1.10-2.03), respectively (all $P < 0.05$) (**Figure 2**). On the other hand, this relationship was absent or non-statistically significant in older, normal-weight, less educated and NGR women. There were no interaction between the covariates and insulin resistance on breast cancer.

Discussion

This research investigated the association between insulin resistance and female cancers in a large population of non-diabetic women in China. Our study demonstrated that insulin resistance was associated with increased risk of prevalent breast cancer, ovarian cancer and endomentrial cancer, but not with the risk of prevalent cervical cancer.

Hyperinsulinemia has been considered as a possible risk factor for breast cancer with supporting laboratory evidence [7]. However, epidemiological studies on the association of insulin resistance and risk of breast cancers, espe-

cially in different menopausal status, were inconsistent [7, 14-16, 24]. In our study, we observed a stronger association of insulin resistance with prevalent breast cancer in non-diabetic women, both in premenopausal 98% (95% CI=1.19-3.32) and postmenopausal women (OR, 1.29, 95% CI=1.01-1.63). Sieri et al. reported that [25] only in women with breast cancer diagnosed after 55 years, most of whom were postmenopausal, the highest HOMA-IR quartile confered higher breast cancer risk (OR, 1.56, 95% CI, 1.01-2.41), however, in breast cancer diagnosed before 55 years, no significant association was observed. Lawlor et al. demonstrated that risk of breast cancer for one unit increase in HOMA-IR was 1.31 (95% CI, 0.99-1.74), only borderline significant. These inconsistent findings may be due to variations in the different population and insufficient sample size. Our findings regarding the effect of menopausal status were in agreement with results of previous studies. A study conducted by Del Giudice ME et al. suggested that the risk of breast cancer increased with the level of insulin in non-diabetic premenopausal women (OR, 2.83, 95% CI, 1.22-6.58) [26]. Marc J. Gunter [27] et al. revealed a positive association between fasting insulin level and risk of breast cancer (OR, 1.46, 95% CI, 1.00-2.13) in non-diabetic postmenopausal women. However, these research only found association between fasting insulin level and breast cancer, we used HOMA-IR as an indicator of insulin resistance, which reflects euglycemic clamp insulin resistance more accurately than fasting insulin levels alone [28]. Moreover, in stratification analysis, significant association was found between insulin resistance and breast cancer in overweight or obese, high educated or IGR population, while in their counterparts, no significant association was observed. As obesity, sedentary lifestyle and IGR are known risk factors for insulin resistance, these factors might also contribute to development of breast cancer.

The potential pathophysiological mechanism linking insulin resistance and breast cancer risk is not fully established. Insulin is a pleiotropic hormone, promoting cell proliferation and tumorigenesis in animal models [29]. Insulin could also promote breast cancer development by increased angiogenesis, bioactivity of estrogens and testosterone as well as decreased adiponectin [30].

Previous studies focusing on the relationship between insulin resistance and ovarian cancer provide limited information. In a case control study conducted by Otokozawa S et al. [17], an increased risk of ovarian cancer was obeserved in high tertile of serum insulin level compared with the low tertile (P trend < 0.001). While, a study with small sample size demonstrated that HOMA-IR was not a valid predictor for risk of ovarian tumor [18]. Moreover, several studies revealed insulin could stimulate ovarian steroid production, probably via insulin receptors found in ovarian stroma, thecal cells and granulosa cells [31, 32]. It was proposed that insulin cooperating with follicle stimulating hormone (FSH) lead to higher levels of estrogen than did either insulin or FSH alone [33].

Previous prospective research findings revealed increased risk of endometrial cancer (HR, 2.33, 95% CI, 1.13-4.82) with elevated circulating insulin levels, independent of estrogen level [34]. It was reported that the expression of total insulin receptor and insulin receptor α increased in endometrial carcinomas compared to normal endometria, and overexpression of insulin receptor α enhances the growth of endometrial cancer cells in vitro [35]. These results suggested that activation of insulin signaling is directly involved in the development of endometrial cancer in vivo.

Very few studies [36] have investigated the association between insulin resistances with cervical cancer. Human papillomavirus (HPV) infection is the most important risk factor for cervical cancer and other risk factors included starting sex at a young age and having many sexual partners. The failure in demonstrating an association of insulin resistance and cervical cancer may suggest that insulin plays a less important role in cervical cancer [37].

There are several strengths in our study, including a large representative sample of the Chinese women, diagnosis of diabetes based on both fasting and postprandial glucose level. Our study has several potential limitations that merit comment. First, a major limitation of this study is that it is cross-sectional and may confuse cause and effect, as cancer-related weight loss might improve insulin sensitivity and beta-cell dysfunction and insulin resistance may appear in cancer patients after systemic treatment [38]. Therefore, prospective studies are

needed to clarify their precise interrelationship. Secondly, the study may subject to a selection bias due to the self-reported diagnosis of female cancer. We can't exclude the possibility that certain patients with female cancers in serious conditions did not take part in the survey. Thirdly, although our analyses were adjusted for an extensive set of confounding factors, residual confounding due to the measurement error in the assessment of confounding factors, unmeasured factors such as dietary factors and other chronic diseases cannot be excluded. Last but not the least, possitive associations were found between obesity and endometrial, ovarian and postmenopausal breast cancer, even cervical cancer [24, 39-41]. In our study, we only investigated the influence of BMI on the association between IR and breast cancer but not other female cancers, since the average prevalence of the other female cancers were lower than breast cancers, the statistical power is insufficient for subgroup analysis. Recently, study results suggested that metabolic health may be more biologically relevant and more useful for female cancer risk stratification than adiposity per se [42].

In conclusion, our research results added to the existing epidemiological evidence that insulin resistance are associated with increased prevalent breast, ovarian and endometrial cancer even in non-diabetic females. Further prospective study is required to confirm these observations. These findings highlight the need for increased attention and efforts in preventing and screening some female cancers, even in non-diabetic females with insulin resistance, to reduce the burden of these cancers.

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Disclosure of conflict of interest

None.

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