Association Between Different Metabolic Obesity Phenotypes and Breast Cancer Risk in Women: A Prospective Cohort Study Postprint

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Abstract

Background Early studies have found that overweight/obesity is associated with an increased risk of breast cancer in women. However, some research suggests that simply analyzing the association between overweight/obesity and breast cancer may not be scientifically rigorous, as overweight/obesity can be categorized into different metabolic phenotypes. Current conclusions regarding the association between different metabolic obesity phenotypes and breast cancer are inconsistent.

Objective To investigate the association between different metabolic obesity phenotypes and the risk of breast cancer in women through a cohort study.

Methods This was a prospective cohort study. Female Kailuan employees who underwent their first health examination at Kailuan General Hospital and its 11 affiliated hospitals in 2006 and 2008 were selected as study subjects (n=23,406). Participants underwent questionnaire surveys, physical examinations, and laboratory tests. Based on metabolic syndrome and BMI status, subjects were divided into four groups: metabolically healthy normal weight (MHNW) (n=12,739), metabolically unhealthy normal weight (MUNW) (n=1,060), metabolically healthy overweight/obese (MHO) (n=6,394), and metabolically unhealthy overweight/obese (MUO) (n=3,213). Participants were followed up from their first physical examination until the occurrence of new-onset breast cancer, death, or the end of the follow-up period (December 31, 2020). Multivariate Cox proportional hazards regression models were used to analyze the association between the four groups and breast cancer risk.

Results The mean follow-up duration was (13.26$±$1.85) years, with 353 new cases of breast cancer identified, yielding an overall incidence density of 11.38 cases per 10,000 person-years. The numbers of incident cases in the MHNW,

MUNW, MHO, and MUO groups were 154, 21, 113, and 65, respectively, with incidence densities of 9.08, 15.37, 13.27, and 15.49 cases per 10,000 person-years, and cumulative incidences of 1.22%, 2.01%, 1.67%, and 1.93%, respectively. Multivariate Cox regression analysis showed that after adjusting for confounding factors, compared with the MHNW group, the MHO and MUO groups had 42% (HR=1.42, 95%CI: 1.11~1.82) and 59% (HR=1.59, 95%CI: 1.17~2.17) increased risks of breast cancer, respectively. Stratified analysis by menopausal status revealed that: in premenopausal women, compared with the MHNW group, the MUO group had a 69% increased risk (HR=1.69, 95%CI: 1.01~2.83); in postmenopausal women, compared with the MHNW group, the MUNW, MHO, and MUO groups had 85% (HR=1.85, 95%CI: 1.09~3.14), 50% (HR=1.50, 95%CI: 1.06~2.13), and 55% (HR=1.55, 95%CI: 1.05~2.28) increased risks of breast cancer, respectively.

Conclusion Overweight/obesity is a risk factor for breast cancer in women, and the risk is further increased when combined with metabolic abnormalities; in postmenopausal women, those with normal weight but metabolic abnormalities also have an increased risk of breast cancer.

Full Text

Association of Different Metabolic Obesity Phenotypes with Breast Cancer Risk in Women: A Prospective Cohort Study

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Abstract

Background: Earlier studies have investigated the association between overweight/obesity and elevated breast cancer risk in women. However, some research suggests that analyzing the association between overweight/obesity and breast cancer without considering metabolic status may be scientifically inadequate, as overweight/obesity can be classified into different metabolic phenotypes. Current findings on the association between different metabolic obesity phenotypes and breast cancer remain inconsistent.

Objective: To prospectively analyze the associations between different metabolic obesity phenotypes and breast cancer risk in women.

Methods: This prospective cohort study selected female employees of Kailuan Group (n=23,406) who participated in physical examinations for the first time at Kailuan General Hospital and its 11 affiliated hospitals in 2006 and 2008. Participants underwent questionnaire surveys, physical examinations, and laboratory tests. Based on metabolic syndrome status and BMI, participants were divided into four groups: metabolically healthy normal weight (MHNW) (n=12,739), metabolically unhealthy normal weight (MUNW) (n=1,060), metabolically healthy overweight/obese (MHO) (n=6,394), and metabolically unhealthy overweight/obese (MUO) (n=3,213). Follow-up began at the first physical examination and ended at breast cancer diagnosis, death, or December 31, 2020. Multivariate Cox proportional hazard models were used to analyze associations between the four groups and breast cancer risk.

Results: During an average follow-up of (13.26$±$1.85) years, 353 new breast cancer cases were identified, with an overall incidence density of 11.38 cases per 10,000 person-years. The MHNW, MUNW, MHO, and MUO groups had 154, 21, 113, and 65 incident cases, respectively, with incidence densities of 9.08, 15.37, 13.27, and 15.49 cases per 10,000 person-years, and cumulative incidences of 1.22%, 2.01%, 1.67%, and 1.93%. After adjusting for confounders, multivariate Cox regression showed that compared with the MHNW group, breast cancer risk increased by 42% in the MHO group (HR=1.42, 95%CI: 1.11–1.82) and by 59% in the MUO group (HR=1.59, 95%CI: 1.17–2.17). Stratified analysis by menopausal status revealed that among premenopausal women, the MUO group had a 69% increased risk (HR=1.69, 95%CI: 1.01–2.83) compared with MHNW. Among postmenopausal women, risks increased by 85% in MUNW (HR=1.85, 95%CI: 1.09–3.14), 50% in MHO (HR=1.50, 95%CI: 1.06–2.13), and 55% in MUO (HR=1.55, 95%CI: 1.05–2.28) groups compared with MHNW.

Conclusion: Overweight/obesity is a risk factor for breast cancer in women, and concomitant metabolic abnormalities further increase this risk. Additionally, normal-weight postmenopausal women with metabolic abnormalities also have increased breast cancer risk.

Keywords: Breast Neoplasms; Obesity; Metabolic Syndrome; Cohort Studies; Prospective Studies; Root Cause Analysis

1. Subjects and Methods

With economic development, unhealthy lifestyles have led to rapidly increasing prevalence of overweight and obesity. According to World Health Organization data, the prevalence of overweight among adult women increased from 29.8% to 38.0% between 1980 and 2013. Concurrently, obesity-related diseases such as diabetes, hypertension, and malignant tumors have risen dramatically. The International Agency for Research on Cancer's 2020 global cancer statistics report identified female breast cancer as the most common cancer among women, accounting for approximately 11.7% of new female cancer cases.

Early studies found that overweight/obesity was associated with increased breast cancer risk in women. However, some research suggests that analyzing the association between overweight/obesity and breast cancer without considering metabolic status may be scientifically inadequate, as overweight/obesity can be classified according to the presence or absence of metabolic abnormalities, with metabolically abnormal individuals potentially experiencing greater effects. KABAT et al. found that both metabolically unhealthy overweight/obese (MUO) and metabolically healthy overweight/obese (MHO) groups had increased breast cancer risk, while PARK et al. found no association between the MHO group and breast cancer risk. Current conclusions regarding different obesity phenotypes and breast cancer associations remain inconsistent. Based on data from the Kailuan Study (registration number: Chi-CTR-TRNC-11001489), this study explores the association between different metabolic obesity phenotypes and breast cancer risk in a Chinese population.

1.1 Study Subjects

The Kailuan Study is an ongoing prospective cohort study of Kailuan Group employees that began in 2006, with physical examinations conducted every two years. This study selected female employees who participated in their first health examination at Kailuan General Hospital and its 11 affiliated hospitals in 2006 and 2008. Inclusion criteria were: (1) female employees participating in their first Kailuan health examination in 2006 or 2008, and (2) agreement to participate with signed informed consent. Exclusion criteria were: (1) previous breast cancer history, (2) missing BMI data, and (3) missing data on blood pressure, fasting glucose, triglycerides, waist circumference, and high-density lipoprotein cholesterol (HDL-C). This study followed the Declaration of Helsinki and was approved by the Kailuan General Hospital Ethics Committee (2006 Medical Ethics No. 5).

1.2 Baseline Survey and Definitions

The baseline survey included questionnaire surveys, physical examinations, and laboratory tests. Questionnaires used the "Kailuan Group Employee Health Examination Form" and were administered through one-on-one interviews by trained physicians or nurses, covering sociodemographic characteristics, lifestyle factors, and medical history. Physical examinations included height, weight, and blood pressure measurements. Height and weight were measured using an RGZ-120 scale (Wuxi Weighing Apparatus Co., Ltd.) to calculate BMI as weight (kg) / height^2 (m^2). After at least 5 minutes of rest, blood pressure was measured on the left arm using a calibrated mercury sphygmomanometer, with two measurements taken 1–2 minutes apart and averaged; if the difference exceeded 5 mmHg (1 mmHg = 0.133 kPa), a third measurement was taken and averaged. Laboratory tests for glucose and lipids required fasting blood samples. Glucose was measured using the hexokinase/glucose-6-phosphate dehydrogenase method, triglycerides using the glycerol phosphate oxidase method, and HDL-C

levels were detected in the supernatant after precipitation of apolipoprotein B with phosphotungstic acid/$MgCl_2$.

Breast cancer outcomes were identified through annual reviews of hospital records (secondary and tertiary hospitals) by trained physicians. Follow-up began at the first physical examination and ended at breast cancer diagnosis, death, or December 31, 2020.

Diagnostic Criteria: (1) Metabolic syndrome was diagnosed using the Chinese Diabetes Society (CDS) 2020 criteria, requiring $ $3 of the following: abdominal obesity (waist circumference $ $85 cm in women), hyperglycemia (fasting glucose $ $6.1 mmol/L or 2-hour postprandial glucose $ $7.8 mmol/L and/or diagnosed diabetes), hypertension (blood pressure $ $130/85 mmHg and/or diagnosed hypertension), fasting triglycerides $ $1.70 mmol/L, and fasting HDL-C < 1.04 mmol/L$. (2) Normal weight was defined as BMI < $25 kg/m^{2}$; overweight/obesity as BMI $ $25 kg/m^{2}$. (3) Metabolic obesity phenotypes were classified into four groups: MHNW (BMI < $25 kg/m^{2}$ without metabolic syndrome), MUNW (BMI <25 kg/m^2 with metabolic syndrome), MHO (BMI $ $25 kg/m^{2}$ without metabolic syndrome), and MUO (BMI $ $25 kg/m^{2}$ with metabolic syndrome), using MHNW as the reference group. (4) Smoking was defined as $ $1 cigarette per day on average. (5) Drinking was defined as >100 ml of spirits (alcohol content $ $50%) per day on average for $ $1 year. (6) Physical exercise was defined as $ $3 sessions per week, each lasting $ $30 minutes.

1.3 Statistical Methods

Data entry and logical verification used CanReg 4 software, and statistical analysis used SAS version 9.4. Normally distributed continuous variables are presented as mean ± standard deviation and compared using ANOVA; non-normally distributed variables are presented as median (P25, P75) and compared using nonparametric tests. Categorical variables were analyzed using ^{2} tests. Kaplan-Meier analysis calculated cumulative incidence rates, with differences compared using Log-rank tests. Multivariate Cox proportional hazard models analyzed associations between metabolic obesity phenotypes and breast cancer risk, with P<0.05 considered statistically significant (two-tailed). Interaction between metabolic obesity phenotypes and menopausal status was tested in the model, and Cox analysis was repeated after stratification. Sensitivity analysis excluded breast cancer cases diagnosed within one year of follow-up.

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2. Results

2.1 Baseline Characteristics

Among 25,828 women who participated in the first Kailuan examination in 2006 and 2008, we excluded 2 with previous breast cancer, 535 with missing BMI data, and 1,885 with missing data on blood pressure, fasting glucose, triglycerides,

waist circumference, or HDL-C, leaving 23,406 participants (12,739 in MHNW, 1,060 in MUNW, 6,394 in MHO, and 3,213 in MUO groups). The mean age was (48.4$±$11.7) years. The four groups differed significantly in age, BMI, fasting glucose, systolic and diastolic blood pressure, HDL-C, triglycerides, waist circumference, total cholesterol, education level, and proportions with diabetes, hypertension, lipid-lowering medication use, smoking, alcohol consumption, and physical exercise (all P<0.01) .

2.2 Breast Cancer Incidence Density and Cumulative Incidence

During an average follow-up of $(13.26\$\pm1.85)years, 353newbreastcancercaseswereidentified, withanoverallin$ $years.TheMHNW, MUNW, MHO, andMUOgroupshad154, 21, 113, and65incidentcases, respectively, withi$ $years, andcumulativeincidencesof1.22\hat{}\{2\}\$=18.60$, P<0.001) [Figure 1: see original paper].

2.3 Multivariate Cox Regression Analysis

Using breast cancer occurrence as the dependent variable (1=yes, 0=no) and metabolic obesity phenotype as the independent variable, multivariate Cox regression models were constructed. Model 1 adjusted for age (continuous) showed increased breast cancer risk in MHO and MUO groups compared with MHNW (P<0.05). Model 2 additionally adjusted for smoking (1=yes, 0=no), alcohol consumption (1=yes, 0=no), education (below high school=1, high school and above=0), family cancer history (1=yes, 0=no), total cholesterol (continuous), menopausal status (postmenopausal=1, premenopausal=0), and physical exercise (none=1, any=0), confirming increased risk in MUO and MHO groups (P<0.05). Model 3 further adjusted for lipid-lowering medication use (none=1, any=0), with results showing increased risk in MUO and MHO groups compared with MHNW (P<0.05) .

Stratified analysis by menopausal status (interaction P=0.371) using Model 3 showed: among premenopausal women, only the MUO group had increased risk (P<0.05) compared with MHNW; among postmenopausal women, MUNW, MHO, and MUO groups all showed increased risk (P<0.05) compared with MHNW .

2.4 Sensitivity Analysis

After excluding 22 breast cancer cases diagnosed within one year of baseline, Model 3 sensitivity analysis confirmed that MUO and MHO groups had increased breast cancer risk compared with MHNW (P<0.05), consistent with the main analysis .

3. Discussion

This study found that overweight/obesity is a risk factor for breast cancer in women, with risk further increasing when overweight/obesity is accompanied by metabolic abnormalities. The impact of metabolic abnormalities on breast cancer risk depends on menopausal status.

Our findings demonstrate that overweight/obese women have increased breast cancer risk regardless of metabolic status, but risk is further elevated when overweight/obesity coexists with metabolic abnormalities. Compared with the MHNW group, the MHO and MUO groups showed 1.42-fold and 1.59-fold increased risks, respectively, suggesting a joint effect between metabolic abnormalities and overweight/obesity. However, among normal-weight women, metabolic abnormalities alone did not increase risk. These results align with KABAT et al., who reported 1.31-fold and 1.61-fold increased risks for MHO and MUO groups, respectively, and with PARK et al., who found a 1.28-fold increased risk in the MUO group.

Menopause is a known risk factor for breast cancer. Although we found no significant interaction between overweight/obesity and menopausal status, stratified analyses revealed menopause-dependent associations. Among premenopausal women, only MUO individuals showed increased risk, whereas among postmenopausal women, MUNW, MHO, and MUO individuals all exhibited increased risk. These findings differ from PARK et al., who reported an inverse association between MUO and breast cancer risk in premenopausal women. This discrepancy may reflect differences in metabolic abnormality definitions (their study diagnosed metabolic abnormality with only one abnormal index and did not measure glucose or lipids), as well as racial and geographic variations in study populations. Our results emphasize the importance of maintaining both normal weight and metabolic health in postmenopausal women, as postmenopausal women face increased risks not only for breast cancer but also for atherosclerotic cardiovascular disease.

Lipid-lowering medications are commonly used for ASCVD prevention. To exclude their potential confounding effects, we adjusted for lipid-lowering medication use in our final model. Unexpectedly, after adjustment, breast cancer risk in MUNW and MUO groups increased further in both the overall and postmenopausal populations. Previous case-control studies have reported conflicting results regarding statins and breast cancer risk: COOGAN et al. found a 1.5-fold increased risk (OR=1.50, 95%CI: 1.00–2.30), while other studies found no association. Given our single-population cohort with few statin users, we cannot draw definitive conclusions, necessitating further research.

Potential mechanisms linking obesity and breast cancer include: (1) elevated estrogen levels from androgen aromatization in adipose tissue promoting breast cell proliferation; (2) increased insulin concentrations exerting mitogenic and anti-apoptotic effects, stimulating cell cycle progression, with chronic hyperinsulinemia increasing free/bioactive insulin-like growth factor 1 (IGF-1) levels that

promote tumor-favoring signaling pathways; and (3) inflammatory cytokines including TNF-α, IL-6, and prostaglandin E2 interfering with PI3K-AKT-mTOR pathway signaling that regulates cell cycle progression, apoptosis, and protein synthesis, thereby promoting cell proliferation and carcinogenesis.

This study has several limitations. First, the cohort lacks data on female reproductive factors. Second, the sample size is relatively small with limited breast cancer cases. Finally, the study population is primarily from northern China, requiring multi-regional validation.

In conclusion, overweight/obesity increases breast cancer risk in women, with even higher risk among those with concurrent metabolic abnormalities, demonstrating that metabolic health partially offsets the adverse effects of overweight/obesity on breast cancer. Additionally, normal-weight postmenopausal women with metabolic abnormalities have increased breast cancer risk. Therefore, both overweight/obesity and metabolic abnormalities should be considered when assessing breast cancer risk.

Author Contributions: ZHOU Jing conceptualized the study, collected and curated data, performed statistical analysis, and wrote the manuscript. JIA Jianguo collected and curated data and performed statistical analysis. LIN Yixin collected and curated data. WU Shuang designed the statistical approach and assisted with editing. DAI Shilong and WANG Mingjun curated data. ZHANG Qingsong revised the final version, provided project management, conceptual guidance, resources, and supervised the manuscript.

Conflicts of Interest: None declared.

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Note: Figure translations are in progress. See original paper for figures.