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Association between triglyceride-glucose related indicators, genetic risk, and incident breast cancer among postmenopausal women in UK Biobank

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Abstract

Background The potential links between triglyceride-glucose (TyG) related indicators and breast cancer incidence after menopause have been less well studied, and the joint associations between genetic risk, TyG related indicators, and breast cancer are unknown.

Methods Simple surrogate indicators of insulin resistance including TyG, TyG-waist circumference (TyG-WC), TyG-waist to height ratio (TyG-WHtR), TyG-waist to hip ratio (TyG-WHR), TyG-body mass index (TyG-BMI). Genetic susceptibility in breast cancer was estimated by categorizing polygenic risk scores (PRS). For estimating the associations, we used Cox proportional hazards regression modeling. Correlation shapes were evaluated using restricted cubic splines (RCS). Mediation analyses for assessing the role of sex hormone-binding globulin (SHBG), C-reactive protein (CRP), testosterone, and glycosylated hemoglobin (HbA1c) in mediating the associations were conducted.

Results The study included 83,873 UK biobank participants who were followed for a median of 13.8 years, with 3,561 new cases of postmenopausal breast cancer. Genetic risk and TyG related indicators were monotonically related to breast cancer, with additive but not multiplicative interactions between them. The highest quartiles of TyG, TyG-WC, TyG-WHtR, TyG-WHR, and TyG-BMI were significantly associated with increased breast cancer risk with hazard ratio (95% confidence interval) were 1.12 (1.01–1.25), 1.35 (1.23–1.49), 1.16 (1.05–1.28), 1.22(1.12–1.33), and 1.31 (1.19–1.44), respectively. TyG-WC was nonlinearly linked to breast cancer (*P* for nonlinear = 0.006). Individuals with high genetic risk and high TyG related indicators exhibited a substantially elevated breast cancer risk by 4- to 5-fold compared with reference group. The associations were mainly mediated by SHBG, CRP, and testosterone, with mediation proportions ranging from 10.24% to 68.29%.

Conclusions TyG related factors are linked to incident postmenopausal breast cancer, and the combined effects with genetic risk significantly optimize risk stratification. High levels of TyG related indicators may amplify the influence of genetic factors on postmenopausal breast cancer.

Trial registration Not applicable.

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Keywords Insulin resistance, Breast cancer, Polygenic risk score, TyG index, Obesity

Introduction

Breast cancer stands as the most prevalent form of cancer among women and the primary cause of cancer-related mortality in women, with its burden anticipated to rise consistently [1, 2]. Notably, metabolic risks, such as an elevated body mass index (BMI) and heightened fasting glucose levels, are significant contributors to the risk of breast cancer-related deaths [3]. Hyperglycemia, hyperlipidemia, and obesity create a favorable environment for breast cancer occurrence and development, in which insulin resistance (IR) takes an important role [4, 5]. IR refers to the impaired response of insulin-sensitive tissues to normal insulin levels, indicating a decrease in their sensitivity or responsiveness [6]. Epidemiologic and clinical studies have shown that IR represents a potential hazard element for breast cancer and relates to a poor prognosis [7–9]. While the eugenic hyperinsulinemic clamp technique is considered the gold standard in assessing IR, its complex and time-consuming operation limits its widespread use [10]. Over the years, several simple surrogates have been developed for assessing IR, with the homeostasis model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI) being among the best and most widely validated [11].

In addition, the triglyceride-glucose (TyG) index, an indicator based on fasting blood glucose and triglycerides, correlates strongly with the euglycemic-hyperinsulinemic clamp test, is less costly, making it a convenient and reliable surrogate proxy for IR [12, 13]. Emerging research advancements indicate that combinations of TyG indexes with obesity indicators, including triglyceride glucose-body mass index (TyG-BMI), triglyceride glucose-waist to height ratio (TyG-WHtR), triglyceride glucose-waist to hip ratio (TyG-WHR), and triglyceride glucose-waist circumference (TyG-WC), more accurately predict the severity for IR, which are reliable indicators of assessing IR [14–18]. Most previous studies on TyG and breast cancer have been cross-sectional association studies or prognostic studies [19–21]. The only cohort study has not yet found a statistically significant association, possibly related to the extremely limited number of covariates [22].

Risk factors for breast cancer are diverse and include modifiable factors such as behavioral lifestyle and non-modifiable factors such as family history and genetics [23]. Personalized risk assessment based on polygenic risk scores (PRS) and single nucleotide polymorphisms is of great significance for stratified screening and protection against breast cancer [24, 25]. However, combined effects of genetic risk and TyG related indicators on breast cancer development is largely unknown, although this would help to further stratify risk for precision prevention.

Several studies have linked TyG to breast cancer risk, but none have attempted to assess the mediating role of known markers, although this contributes to our understanding of the mechanistic pathways of how TyG affects breast cancer risk. The sex steroid biomarkers sex hormone-binding globulin (SHBG) and testosterone [26, 27], inflammatory biomarker C-reactive protein (CRP) [28, 29], as well as glycemic marker glycated haemoglobin (HbA1c) [30] are breast cancer risk factors that have also been associated with IR [31–33]. Thus, these biomarkers may be key mediators in linking TyG related indicators to the risk of breast cancer.

Therefore, this study explored the effect of TyG related indicators on breast cancer incidence among postmenopausal women, assessing interaction between TyG related indicators and genetic risk, as well as their combined effect on breast cancer. In addition, we also analyzed whether the sex steroid biomarkers SHBG and testosterone, the inflammatory biomarker CRP, and the glycemic marker HbA1c could act as mediators to mediate the correlations of TyG related indicators with breast cancer incidence.

Materials and methods

Data source and study population

Our research is grounded in data from the UK Biobank prospective cohort of 502,336 UK adults from 37–73-year-olds recruited between 2006–2010, of whom 273,280 were female. Extensive environmental, lifestyle, and genetic data on participants were obtained during the baseline assessment and tracked their health condition by linking to their health-related records.

From the UK Biobank database, there were 273,280 female participants, excluding participants having cancer from baseline, lost to follow-up, missing triglycerides (TG), glucose, WC, BMI, height, hip circumference, HbA1c, CRP, SHBG, testosterone measurements, taking cholesterol lowering or insulin medication, and non-menopausal populations ($n=189,407$); a total of 83,873 eligible participants were used for the association analysis. For association analyses regarding genetic risk, we further excluded Non-White participants, those with missing genetic information, and those whose self-reported race did not match their genetic race ($n=12,010$), resulting in the inclusion of 71,863 participants (Figure S1).

This study was limited to postmenopausal women. Women were classified as postmenopausal if they met any of the following criteria: their baseline age exceeded the age of menopause by at least one year, the time since

their last menstrual period exceeds 365 days at baseline, or they had a history of bilateral oophorectomy (both ovaries removed) at baseline [34]. Additionally, in cases where no other relevant information was available, women were deemed postmenopausal if their baseline age exceeded 55 years.

Ascertainment of outcome

A diagnosis of breast cancer was obtained from the National Cancer Registries utilizing International Classification of Disease 10th revision (ICD-10) code C50 and ICD-9 code 174. The date of death was determined by contact with the National Death Registries. The participants were tracked from their enrollment date until the occurrence of the earliest event among the following: a diagnosis of breast cancer, death, or the culmination of the study period on December 31, 2022.

Estimation of TyG related indicators

Blood samples were randomly collected from participants who recruited into UK Biobank at baseline, and the fasting time prior to blood collection was recorded [35]. At the UK Biobank's central laboratory, a range of non-fasting serum biochemical markers were analyzed using the Beckman Coulter AU5800 Clinical Chemistry Analyzer. These markers encompassed glucose levels, TG, total cholesterol (TC), high-density cholesterol (HDC), low-density cholesterol (LDC), and high sensitivity CRP. The data of body size measures were taken manually at the assessment center includes such as WC, Hip circumference, Standing height, and BMI.

The formulas for TyG, TyG-WC, TyG-WHtR, TyG-WHR and TyG-BMI are as follows: (1) $TyG = \ln(TG\ [mg/dl] \times glucose\ [mg/dl]/2)$; (2) $TyG\text{-}WC = TyG \times WC$ (cm); (3) $TyG\text{-}WHtR = TyG \times WC$ (cm) /Standing height (cm); (4) $TyG\text{-}WHR = TyG \times WC$ (cm) /Hip circumference (cm); (5) $TyG\text{-}BMI = TyG \times BMI\ (kg/m^2)$.

Assessment of covariates and mediators

Covariates included age and Townsend Deprivation Index (TDI) obtained from the local NHS Primary Care Trust registers; race, education, walking, education, smoking, drinking, history of cardiovascular diseases, history of diabetes, family history of breast cancer, breast cancer screening, age at menarche, age at menopause, number of live births, oral contraceptive use, fasting time, and hormone replacement therapy (HRT) collected in a touch screen questionnaire completed at the assessment center; and the biochemical markers TC, LDC, and HDC, which were measured in blood samples.

Mediating variables included the SHGB, testosterone, CRP, and HbA1c. SHGB and testosterone were measured in a central laboratory using immunoassay analysers (Beckman Coulter DXI 800). HbA1c was measured by HPLC analysis on a Bio-Rad VARIANT II Turbo. In conducting the mediational analysis, the log-transformed versions of SHGB, testosterone, CRP, and HbA1c were employed to enhance the normality of the data.

Polygenic risk score

Concise explanations regarding the genotyping process, array design, sample handling, quality control and interpolation procedures for UK Biobank samples has been provided elsewhere [36]. To determine whether the impact of TyG related indicators varies by genetic susceptibility to breast cancer, PRS for breast cancer was created based on 313 GWAS significant SNPs [24]. Details of the selected 313 SNPs and the calculated PRS score for breast cancer are given in Table S1 and Supplementary Methods.

Statistical analyses

Baseline characteristics of 83,873 participants were described by quartile groupings of TyG, TyG-WC, TyG-WHtR, TyG-WHR, and TyG-BMI. Continuous variables were presented as mean (SD) in cases of normal distribution or median [IQR] for skewed distribution; Categorical variables were represented as frequency (percentage). For the comparison of the baseline characteristics in each group, categorical variables underwent the $\chi 2$ test, while One-way ANOVA was utilized for continuous variables exhibiting normal distribution, and the Kruskal–Wallis test was employed for those with skewed distributions.

Multivariable Cox regression analyses was conducted to evaluate the links of TyG related indicators and breast cancer risk through hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption of the Cox model was tested using the Schoenfeld residual test and results were satisfactory. Three models were utilized: Model 1 (adjusted for the covariates of age (years), race (white or others), and TDI (continuous variable)), Model 2 (further adjusted for walking (minutes/day), education (college degree or above or others), smoking (never, previous, or current), drinking (never, previous, or current), family history of breast cancer (no or yes), history of cardiovascular diseases (no or yes), screening (no or yes), contraceptives (no or yes), age at menarche (years), number of live births (0 or 1 or 2 or ≥ 3), HRT (no or yes), and age at menopause (years)), and Model 3 (further adjusted for diabetes (no or yes), fasting time (hours), TC (mmol/L), and HDL (mmol/L) based on Model 2). Due to collinearity with other covariates, LDC was excluded from the final multivariable Cox proportional hazards model.

The HRs and 95% CIs of breast cancer per 1-standard deviation (SD) increase on TyG related indicators

were also estimated. In addition, the median values in the quartiles of TyG related indicators were evaluated as continuous variables to estimate the *P*-values for trend. Moreover, we utilized restricted cubic spline (RCS) cox regression with 3 knots positioned at the 10th, 50th, 90th percentiles, after multivariate adjustment to investigate the dose–response relationships of TyG related indicators with breast cancer risk. We also used Cox regression analysis to explore the potential link of PRS with breast cancer risk in three models. The adjustment for the three models were based on the three models described above, but the race variable was removed and adjustments for first five principal components of ancestry and genotyping batch variables were added.

Stratified analysis between TyG related indicators and breast cancer according to PRS category was conducted. Multiplicative interaction between TyG related indicators and genetic susceptibility to breast cancer was conducted by the likelihood ratio tests in models both with and without cross-product terms. The additive interaction was evaluated by relative excess risk due to interaction (RERI) and the attributable proportion due to the interaction (AP). The analysis of the joint effects of PRS and TyG related indicators with breast cancer risk were presented in forest plots, using the lowest genetic risk group and the lowest quartile of TyG related indicators as the references. To explore whether TyG related indicators affect breast cancer incidence through SHGB, testosterone, CRP, and HbA1c, we conducted mediation analyses. The detailed methodology of mediation analyses is described elsewhere [37, 38]. To validate the robustness of our findings, we performed a series of sensitivity analyses. Detailed methodology for sensitivity analyses can be found in the Supplementary Methods.

Missing covariates were handled, and for continuous variables, the mean was filled in if normally distributed, and the median if skewed; for categorical variables, we used the missing indicator approach. The number and percentage of covariates with missing data are summarized in Table S2. Our study adhered to a two-sided testing approach, and a significance level of $P<0.05$ was used. We performed all statistical analyses using the R language version 4.3.2. We applied the regmedint package in R to evaluate the mediation effects [39].

Results

Baseline characteristics

There were 273,280 female participants in the UK Biobank from 2006 to 2010. The number of participants available after a series of exclusion criteria was 83,873, of whom 3561 were breast cancer patients, and the number of participants available for polygenic risk score analysis was 71,863, of whom 3,076 were breast cancer patients (Figure S1). Table 1 illustrates the baseline characteristics of the 83,873 participants according to TyG index quartiles. Individuals with higher TyG index quartiles were older, had a lower proportion of whites, more history of cardiovascular disease and diabetes, higher BMI, waist circumference, and hip circumference, higher breast cancer screening rates, older age at menopause, a lower proportion of oral contraceptives, higher HbA1c, TC, TG, LDC, glucose, and CRP, and lower HDC and SHBG, in comparison to those in the lowest quartile group. The Supplementary file (Tables S3-S6) presents a comprehensive overview of the baseline characteristics, segmented according to quartiles of various TyG-related indicators, including TyG-WC, TyG-WHtR, TyG-WHR, and TyG-BMI.

TyG related indicators and breast cancer risk among postmenopausal women

The median follow-up duration for the postmenopausal women in our study cohort was 13.8 years (totaling 1,115,306 person-years), with 3,561 breast cancer cases out of 83,873, yielding an incidence density for breast cancer of 319.28 per 100,000 person-year. Table 2 showed the links of TyG related indicators and breast cancer risk for postmenopausal women ($n=83,873$). After adjusting the potential confounders (in Model 3), for TyG index, TyG-WC, TyG-WHtR, TyG-WHR, and TyG-BMI, the HRs (95% CIs) for breast cancer in the higher quartiles were 1.12 (1.01–1.25), 1.35 (1.23–1.49), 1.16 (1.05–1.28), 1.22 (1.12–1.33), 1.31 (1.19–1.44) respectively, compared to the lower quartiles. The HRs (95% CIs) for breast cancer was 1.10 (1.06–1.14), 1.05 (1.01–1.08), 1.07 (1.03–1.10), 1.09 (1.06–1.13) for each SD increase in TyG-WC, TyG-WHtR, TyG-WHR, TyG-BMI, respectively. However, it is noteworthy that the per 1-SD increase in TyG index alone did not significantly correlate with breast cancer risk. In addition, we observed a statistically significant increasing trend in breast cancer risk with rising quartiles of TyG-WC, TyG-WHtR, TyG-WHR, and TyG-BMI (all *P* for trend <0.05). These findings remained robust in our sensitivity analysis (Tables S7-S11).

By RCS regression, a nonlinear correlation was found for TyG-WC with breast cancer incidence (*P* for nonlinear $=0.006$, Fig. 1). In contrast, TyG-WHtR, TyG-WHR and TyG-BMI were linearly and positively correlated with breast cancer incidence, with nonlinear P of 0.075, 0.607 and 0.089, respectively (Fig. 1).

Genetic risk and breast cancer risk among postmenopausal women

Table 3 demonstrated a highly positive correlation of genetic risk with postmenopausal breast cancer incidence. After adjusting for age, TDI, first five principal

Table 1 Baseline characteristics according to quartiles of TyG index among postmenopausal women ($n = 83,873$)

Characteristic[a]	Total	Quartiles of TyG index				*P* value
		Q1 (6.86–8.24)	Q2 (8.24–8.58)	Q3 (8.58–8.94)	Q4 (8.94–10.94)	
Number of participants	83873	20916	20969	20956	21032	
Age, years (median [IQR])	61.00 [57.00, 64.00]	60.00 [57.00, 64.00]	60.00 [57.00, 64.00]	61.00 [57.00, 64.00]	61.00 [57.00, 64.00]	< 0.001
TDI (median [IQR])	−2.38 [−3.74, −0.01]	−2.39 [−3.75, −0.03]	−2.38 [−3.75, 0.00]	−2.37 [−3.76, −0.01]	−2.37 [−3.72, −0.02]	0.902
Race, (%)						0.006
White	80894 (96.4)	20214 (96.6)	20236 (96.5)	20197 (96.4)	20247 (96.3)	
Others	2748 (3.3)	666 (3.2)	662 (3.2)	707 (3.4)	713 (3.4)	
Missing	231 (0.3)	36 (0.2)	71 (0.3)	52 (0.2)	72 (0.3)	
Education status, (%)						0.428
College degree or above	24143 (28.8)	6098 (29.2)	6057 (28.9)	5984 (28.6)	6004 (28.5)	
Others	58863 (70.2)	14619 (69.9)	14695 (70.1)	14734 (70.3)	14815 (70.4)	
Missing	867 (1.0)	199 (1.0)	217 (1.0)	238 (1.1)	213 (1.0)	
Walking, minutes/day (median [IQR])	30.00 [20.00, 60.00]	30.00 [20.00, 60.00]	30.00 [20.00, 60.00]	30.00 [20.00, 60.00]	30.00 [20.00, 60.00]	0.413
Smoking, (%)						0.799
Never	49283 (58.8)	12287 (58.7)	12337 (58.8)	12262 (58.5)	12397 (58.9)	
Previous	27529 (32.8)	6849 (32.7)	6838 (32.6)	6903 (32.9)	6939 (33.0)	
Current	6740 (8.0)	1702 (8.1)	1712 (8.2)	1707 (8.1)	1619 (7.7)	
Missing	321 (0.4)	78 (0.4)	82 (0.4)	84 (0.4)	77 (0.4)	
Drinking, (%)						0.328
Never	4578 (5.5)	1133 (5.4)	1194 (5.7)	1133 (5.4)	1118 (5.3)	
Previous	2758 (3.3)	646 (3.1)	709 (3.4)	693 (3.3)	710 (3.4)	
Current	76457 (91.2)	19113 (91.4)	19050 (90.8)	19106 (91.2)	19188 (91.2)	
Missing	80 (0.1)	24 (0.1)	16 (0.1)	24 (0.1)	16 (0.1)	
History of cardiovascular diseases, (%)						< 0.001
No	63611 (75.8)	16057 (76.8)	15975 (76.2)	15830 (75.5)	15749 (74.9)	
Yes	20118 (24.0)	4819 (23.0)	4961 (23.7)	5088 (24.3)	5250 (25.0)	
Missing	144 (0.2)	40 (0.2)	33 (0.2)	38 (0.2)	33 (0.2)	
History of diabetes, (%)						< 0.001
No	82756 (98.7)	20735 (99.1)	20750 (99.0)	20679 (98.7)	20592 (97.9)	
Yes	978 (1.2)	157 (0.8)	184 (0.9)	234 (1.1)	403 (1.9)	
Missing	139 (0.2)	24 (0.1)	35 (0.2)	43 (0.2)	37 (0.2)	
Family history of breast cancer, (%)						0.461
No	73119 (87.2)	18280 (87.4)	18214 (86.9)	18293 (87.3)	18332 (87.2)	
Yes	9597 (11.4)	2331 (11.1)	2459 (11.7)	2388 (11.4)	2419 (11.5)	
Missing	1157 (1.4)	305 (1.5)	296 (1.4)	275 (1.3)	281 (1.3)	
BMI (mean (SD))	27.01 (4.89)	26.86 (4.84)	26.97 (4.82)	26.99 (4.89)	27.22 (5.02)	< 0.001
Waist circumference, cm (mean (SD))	84.66 (11.97)	84.22 (11.84)	84.57 (11.80)	84.69 (11.98)	85.14 (12.23)	< 0.001
Hip circumference, cm (mean (SD))	103.30 (9.96)	103.08 (9.85)	103.27 (9.82)	103.24 (9.91)	103.62 (10.23)	< 0.001
Standing height, cm (mean (SD))	162.09 (6.15)	162.10 (6.18)	162.08 (6.14)	162.14 (6.17)	162.03 (6.13)	0.332
Breast cancer screening, (%)						0.001
No	3317 (4.0)	874 (4.2)	848 (4.0)	857 (4.1)	738 (3.5)	
Yes	80512 (96.0)	20024 (95.7)	20111 (95.9)	20093 (95.9)	20284 (96.4)	
Missing	44 (0.1)	18 (0.1)	10 (0.0)	6 (0.0)	10 (0.0)	
Age at menarche, years (mean (SD))	12.95 (1.58)	12.96 (1.58)	12.97 (1.58)	12.94 (1.57)	12.94 (1.58)	0.134

Table 1 (continued)

Characteristic[a]	Total	Quartiles of TyG index				*P* value
		Q1 (6.86–8.24)	Q2 (8.24–8.58)	Q3 (8.58–8.94)	Q4 (8.94–10.94)	
Age at menopause, years (mean (SD))	49.84 (4.54)	49.80 (4.51)	49.86 (4.55)	49.78 (4.53)	49.91 (4.57)	0.011
Number of live births, (%)						0.751
0	13198 (15.7)	3306 (15.8)	3260 (15.5)	3324 (15.9)	3308 (15.7)	
1	10241 (12.2)	2543 (12.2)	2565 (12.2)	2571 (12.3)	2562 (12.2)	
2	38958 (46.4)	9720 (46.5)	9804 (46.8)	9761 (46.6)	9673 (46.0)	
> = 3	21414 (25.5)	5329 (25.5)	5324 (25.4)	5282 (25.2)	5479 (26.1)	
Missing	62 (0.1)	18 (0.1)	16 (0.1)	18 (0.1)	10 (0.0)	
Oral contraceptive use, (%)						0.001
No	17805 (21.2)	4247 (20.3)	4470 (21.3)	4450 (21.2)	4638 (22.1)	
Yes	65877 (78.5)	16612 (79.4)	16459 (78.5)	16456 (78.5)	16350 (77.7)	
Missing	191 (0.2)	57 (0.3)	40 (0.2)	50 (0.2)	44 (0.2)	
Fasting time, hours (median [IQR])	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	< 0.001
HbA1c, mmol/L (median [IQR])	35.60 [33.40, 37.80]	35.40 [33.30, 37.50]	35.60 [33.40, 37.80]	35.60 [33.50, 37.90]	35.80 [33.60, 38.10]	< 0.001
Hormone replacement therapy, (%)						0.352
No	41770 (49.8)	10331 (49.4)	10398 (49.6)	10441 (49.8)	10600 (50.4)	
Yes	41898 (50.0)	10534 (50.4)	10515 (50.1)	10460 (49.9)	10389 (49.4)	
Missing	205 (0.2)	51 (0.2)	56 (0.3)	55 (0.3)	43 (0.2)	
TC, mmol/L (mean (SD))	5.87 (1.13)	5.44 (0.98)	5.76 (1.03)	5.98 (1.10)	6.30 (1.21)	< 0.001
TG, mmol/L (median [IQR])	1.33 [0.97, 1.90]	0.79 [0.68, 0.90]	1.15 [1.04, 1.26]	1.58 [1.43, 1.76]	2.44 [2.10, 3.01]	< 0.001
HDC, mmol/L (mean (SD))	1.59 (0.36)	1.77 (0.38)	1.66 (0.35)	1.55 (0.32)	1.40 (0.29)	< 0.001
LDC, mmol/L (mean (SD))	3.63 (0.87)	3.22 (0.72)	3.53 (0.78)	3.75 (0.85)	3.99 (0.93)	< 0.001
Glucose, mmol/L (median [IQR])	4.94 [4.64, 5.29]	4.80 [4.50, 5.10]	4.93 [4.63, 5.25]	4.98 [4.68, 5.33]	5.09 [4.77, 5.50]	< 0.001
CRP, mg/L (median [IQR])	1.48 [0.72, 3.06]	1.43 [0.69, 2.94]	1.47 [0.71, 3.01]	1.49 [0.73, 3.06]	1.54 [0.74, 3.24]	< 0.001
SHBG, nmol/L (median [IQR])	56.44 [40.95, 75.87]	57.31 [41.92, 76.89]	56.63 [41.23, 76.00]	56.36 [40.73, 75.96]	55.44 [39.73, 74.62]	< 0.001
Testosterone, nmol/L (median [IQR])	0.97 [0.69, 1.32]	0.97 [0.69, 1.31]	0.97 [0.69, 1.31]	0.97 [0.70, 1.33]	0.97 [0.69, 1.33]	0.345

TyG Triglyceride-glucose, *TDI* Townsend Deprivation Index, *BMI* Body mass index, *TC* Cholesterol, *TG*, Triglycerides, *HDC* High-density cholesterol, *LDC* Low-density cholesterol, *HbA1c* Glycated hemoglobin, *CRP* C-reactive protein, *SHBG* sex hormone-binding globulin, *IQR* Interquartile range

[a] Continuous variables with normal distribution are expressed as mean (SD); Continuous variables with skewed distribution are expressed as (median [IQR]); Categorical variables are expressed as frequency (percentage)

components of ancestry, and genotyping batch, individuals with a high genetic risk exhibited a 3.94-fold increase in breast cancer incidence, and for per 1-SD increase in PRS, the HR of breast cancer (95% CI) was 1.75 (1.69–1.81). The risk of breast cancer incidence escalated in tandem with an ascending genetic risk classification, displaying a significant trend (*P* for trend < 0.001). The findings also remained stable in the fully adjusted model.

TyG related indicators and breast cancer risk by PRS category among postmenopausal

Figure 2 showed the TyG related indicators and breast cancer risk by PRS category, using Quartile 1 of each index as a reference (detailed information in tableS12). Our analysis revealed a gradual augmentation in breast cancer incidence risk among individuals in the high genetic risk group as the quartiles of TyG-WC, TyG-WHtR, TyG-WHR, or TyG-BMI ascended (all *p* for

Table 2 Associations between TyG index and its combination with obesity indicators and breast cancer risk among postmenopausal women in UK Biobank ($n = 83,873$)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per 1-SD increase	P for trend
TyG						
Median	8.03	8.42	8.75	9.20		
No. of cases/person-years	838/279,674	891/278,915	878/278,589	954/278,128		
Model 1, HR (95% CI)	1.00	1.06 (0.96–1.16)	1.04 (0.95–1.14)	1.13 (1.03–1.24)	1.04 (1.00–1.07)	0.017
Model 2, HR (95% CI)	1.00	1.06 (0.96–1.16)	1.04 (0.95–1.14)	1.13 (1.03–1.24)	1.04 (1.00–1.07)	0.019
Model 3, HR (95% CI)	1.00	1.06 (0.96–1.16)	1.04 (0.94–1.15)	1.12 (1.01–1.25)	1.03 (0.99–1.08)	0.059
TyG-WC						
Median	606.3	681.04	750.74	860.56		
No. of cases/person-years	727/278,955	905/279,921	918/278,975	1011/277,455		
Model 1, HR (95% CI)	1.00	1.22 (1.11–1.35)	1.24 (1.12–1.36)	1.37 (1.24–1.50)	1.10 (1.07–1.14)	< 0.001
Model 2, HR (95% CI)	1.00	1.22 (1.11–1.35)	1.23 (1.12–1.36)	1.36 (1.23–1.49)	1.10 (1.06–1.13)	< 0.001
Model 3, HR (95% CI)	1.00	1.22 (1.11–1.35)	1.23 (1.12–1.36)	1.35 (1.23–1.49)	1.10 (1.06–1.14)	< 0.001
TyG-WHtR						
Median	3.73	4.20	4.64	5.33		
No. of cases/person-years	786/279,386	853/279,531	922/279,085	1000/277,307		
Model 1, HR (95% CI)	1.00	1.05 (0.95–1.15)	1.09 (0.99–1.20)	1.17 (1.06–1.28)	1.05 (1.02–1.08)	< 0.001
Model 2, HR (95% CI)	1.00	1.05 (0.95–1.15)	1.09 (0.99–1.20)	1.16 (1.06–1.28)	1.05 (1.01–1.08)	< 0.001
Model 3, HR (95% CI)	1.00	1.05 (0.95–1.15)	1.09 (0.99–1.20)	1.16 (1.05–1.28)	1.05 (1.01–1.08)	< 0.001
TyG-WHR						
Median	6.22	6.76	7.23	7.88		
No. of cases/person-years	815/280,358	867/279,793	908/278,957	971/276,199		
Model 1, HR (95% CI)	1.00	1.05(0.96–1.14)	1.08(0.99–1.17)	1.21(1.11–1.31)	1.06(1.03–1.10)	0.001
Model 2, HR (95% CI)	1.00	1.04(0.96–1.14)	1.08(0.99–1.18)	1.22(1.12–1.32)	1.07(1.04–1.10)	0.001
Model 3, HR (95% CI)	1.00	1.04(0.96–1.14)	1.08(0.99–1.18)	1.22(1.12–1.33)	1.07(1.03–1.10)	0.003
TyG-BMI						
Median	187.23	213.12	238.40	282.69		
No. of cases/person-years	765/278,469	880/279,486	894/278,896	1022/278,456		
Model 1, HR (95% CI)	1.00	1.14 (1.03–1.25)	1.15 (1.04–1.26)	1.32 (1.20–1.45)	1.10 (1.06–1.13)	< 0.001
Model 2, HR (95% CI)	1.00	1.13 (1.03–1.25)	1.14 (1.04–1.26)	1.31 (1.19–1.44)	1.09 (1.06–1.13)	< 0.001
Model 3, HR (95% CI)	1.00	1.13 (1.03–1.25)	1.14 (1.04–1.26)	1.31 (1.19–1.44)	1.09 (1.06–1.13)	< 0.001

TyG triglyceride-glucose, *HR* hazard ratio, *CI* confidence interval, *SD* standard deviation, *TyG-WC* triglyceride glucose-waist circumference, *TyG-WHtR* triglyceride glucose-waist to height ratio, *TyG-WHR* triglyceride glucose-waist to hip ratio, *TyG-BMI* triglyceride glucose-body mass index

Model 1: adjusted for age, race, and Townsend Deprivation Index

Model 2: further adjusted for walking, education, smoking, drinking, family history of breast cancer, history of cardiovascular diseases, screening, contraceptives, age at menarche, number of live births, hormone replacement therapy, age at menopause

Model 3: further adjusted for diabetes, fasting time, cholesterol, high-density cholesterol

trend < 0.01). In intermediate genetic risk group, the highest quartiles of TyG-WC, TyG-WHtR and TyG-BMI correlated to elevated breast cancer risk with HRs (95% CIs) was 1.40 (1.17–1.69), 1.35 (1.12–1.63), 1.44 (1.19–1.73), respectively. However, no correlations were found to be statistically significant between TyG and breast cancer across the low, intermediate, or high genetic risk groups. No multiplicative interactions were observed in TyG related indicators with PRS.

In addition, TyG related indicators exhibited significant additive interactions among women with high genetic risk (Table 4). Compared with the low genetic risk and low TyG related indicators group, the RERIs (95% CI) of breast cancer in the TyG-WC, TyG-WHtR, TyG-WHR and TyG-BMI high joint exposure groups were 1.00 (0.33, 1.66), 1.04 (0.46, 1.61), 0.78 (0.18, 1.37), and 0.96 (0.28, 1.64), respectively, and the APs (95% CI) of breast cancer were 0.21 (0.07, 0.34), 0.25 (0.11, 0.38), 0.19 (0.04, 0.33), and 0.19 (0.06, 0.32), respectively. Additive interactions were also observed for the high TyG-WHtR or TyG-BMI group with intermediate genetic risk, with RERIs (95% CI) were 0.69 (0.22, 1.15)

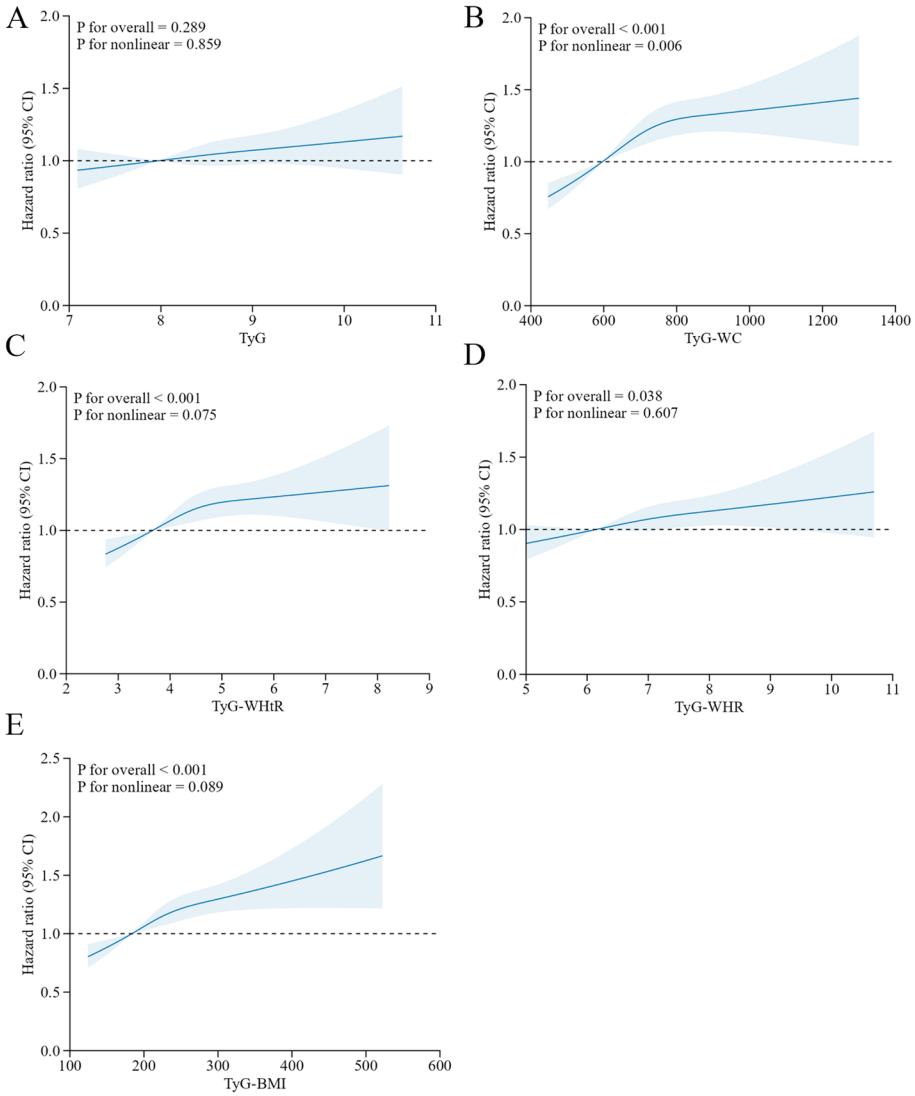

Fig. 1 Restricted cubic spline plots of the associations between TyG (**A**), TyG-WC (**B**), TyG-WHtR (**C**), TyG-WHR (**D**), TyG-BMI (**E**) and risk of breast cancer. The associations were adjusted for age, race, Townsend Deprivation Index, walking, education, smoking, drinking, family history of breast cancer, history of cardiovascular diseases, screening, contraceptives, age at menarche, number of live births, hormone replacement therapy, age at menopause, diabetes, fasting time, cholesterol, high-density cholesterol. TyG, triglyceride-glucose; TyG-WC, triglyceride glucose-waist circumference; TyG-WHtR, triglyceride glucose-waist to height ratio; TyG-WHR, triglyceride glucose-waist to hip ratio; TyG-BMI, triglyceride glucose-body mass index; CI, confidence interval

and 0.65 (0.11, 1.20); and APs were 0.28 (0.09, 0.48) and 0.23 (0.03, 0.42).

We further evaluated the joint effect of TyG related indicators and PRS on breast cancer risk. Positive associations of TyG related indicators with breast cancer were found in individuals with intermediate to high genetic risk groups, utilizing the quartiles with low genetic risk and the lowest TyG related indices as the reference group (Fig. 3 and Figure S2-S5). Notably, those belonging to the high genetic risk and the highest TyG related indices quartiles had the highest breast cancer risk compared to the reference groups, with an HR (95% CI) of 4.05 (3.06–5.34) for TyG index, 4.90 (3.67–6.55) for TyG-WC, 4.25 (3.24–5.57) for TyG-WHtR, 4.22 (3.20–5.55) for TyG-WHR, and 5.05 (3.78–6.75) for TyG-BMI (Fig. 3 and Figure S2-S5).

Mediation analysis of TyG related indicators and breast cancer risk among postmenopausal women

Mediation analysis identified that SHBG, testosterone, and CRP were the significant mediators in the associations between TyG related indicators and breast cancer

Table 3 Association between genetic risk and breast cancer risk among postmenopausal women in UK Biobank ($n = 71,863$)

	No. of cases/person-years	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)
PRS category				
Low genetic risk	244/194,193	1.00	1.00	1.00
Intermediate genetic risk	970/385,199	2.01 (1.74–2.31)	1.99 (1.73–2.29)	1.99 (1.73–2.29)
High genetic risk	1862/377,390	3.94 (3.45–4.50)	3.87 (3.38–4.42)	3.86 (3.38–4.42)
Per 1-SD increase		1.75 (1.69–1.81)	1.73 (1.67–1.80)	1.73 (1.67–1.80)
P for trend		< 0.001	< 0.001	< 0.001

TyG, triglyceride-glucose, *HR* hazard ratio, *CI* confidence interval, *SD* standard deviation

Model 1: adjusted for age, Townsend Deprivation Index, first five principal components of ancestry and genotyping batch

Model 2: further adjusted for walking, education, smoking, drinking, family history of breast cancer, history of cardiovascular diseases, screening, contraceptives, age at menarche, number of live births, hormone replacement therapy, age at menopause

Model 3: further adjusted for diabetes, fasting time, cholesterol, high-density cholesterol

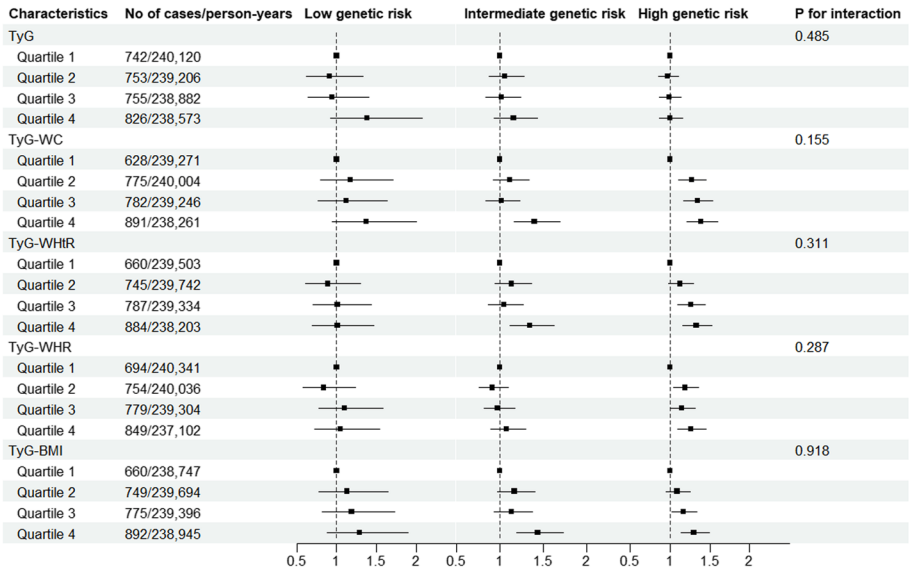

Fig. 2 Forest plot of associations between TyG index and its combination with obesity indicators and breast cancer risk by PRS category among postmenopausal women in UK Biobank. Model was adjusted for age, Townsend Deprivation Index, first five principal components of ancestry, genotyping batch, walking, education, smoking, drinking, family history of breast cancer, history of cardiovascular diseases, screening, contraceptives, age at menarche, number of live births, hormone replacement therapy, age at menopause, diabetes, fasting time, cholesterol, high-density cholesterol. TyG, triglyceride-glucose; PRS, polygenic risk scores; TyG-WC, triglyceride glucose-waist circumference; TyG-WHtR, triglyceride glucose-waist to height ratio; TyG-WHR, triglyceride glucose-waist to hip ratio; TyG-BMI, triglyceride glucose-body mass index

risk after adjusting for confounders, with mediation proportions ranging from 10.24% to 68.29% (Table S13). For the relationship of TyG to breast cancer risk, SHBG explained 16.28% (95% CI: −4.67%, 37.24%) of the total effect, testosterone explained 4.56% (95% CI: −1.88%, 11.01%), and CRP explained 9.91% (95% CI: −2.92%, 22.75%), but none of these results reached statistical significance. The proportion of SHBG mediated the positive associations of TyG-related indicators and breast cancer risk were 28.64% (95% CI: 8.68%, 48.60%) for TyG-WC, 51.52% (95% CI: 16.80%, 86.23%) for TyG-WHtR, 68.29% (95% CI: 9.63%, 126.94%) for TyG-WHR and 29.75% (95% CI: 9.71%, 49.78%) for TyG-BMI. Testosterone significantly mediated the relationships of TyG-related indicators with breast cancer risk, and the proportion of mediation in TyG-WC, TyG-WHtR, TyG-WHR, and TyG-BMI were 10.24% (95% CI: 5.48%, 14.99%), 15.53% (95% CI: 6.79%, 24.27%), 10.84% (95% CI: 1.97%, 19.71%), 12.83% (95% CI: 6.76%, 18.90%) respectively. The ratios of CRP-mediated correlations of TyG-WC, TyG-WHtR, TyG-WHR, and TyG-BMI with breast cancer risk were 29.17% (95% CI: 7.87%, 50.47%), 54.96% (95% CI: 17.48%,

Table 4 Additive interaction between TyG index and its combination with obesity indicators and genetic risk on the risk of breast cancer among postmenopausal women in UK Biobank

	PRS category			
	Intermediate genetic risk		High genetic risk	
	RERI (95% CI)	AP (95% CI)	RERI (95% CI)	AP (95% CI)
TyG				
Quartile 2	0.22 (−0.27, 0.71)	0.10 (−0.13, 0.34)	0.01 (−0.61, 0.63)	0.00 (−0.16, 0.17)
Quartile 3	0.16 (−0.34, 0.67)	0.08 (−0.17, 0.33)	0.08 (−0.56, 0.73)	0.02 (−0.14, 0.18)
Quartile 4	−0.03 (−0.59, 0.52)	−0.02 (−0.26, 0.23)	−0.19 (−0.93, 0.55)	−0.05 (−0.22, 0.13)
TyG-WC				
Quartile 2	0.06 (−0.51, 0.62)	0.02 (−0.22, 0.27)	0.85 (0.22, 1.48)	0.19 (0.05, 0.33)
Quartile 3	−0.08 (−0.66, 0.51)	−0.03 (−0.30, 0.23)	1.12 (0.49, 1.75)	0.24 (0.10, 0.37)
Quartile 4	0.54 (−0.02, 1.10)	0.18 (−0.01, 0.38)	1.00 (0.33, 1.66)	0.21 (0.07, 0.34)
TyG-WHtR				
Quartile 2	0.33 (−0.12, 0.79)	0.17 (−0.07, 0.40)	0.55 (0.01, 1.10)	0.15 (0.00, 0.30)
Quartile 3	0.05 (−0.44, 0.54)	0.03 (−0.24, 0.29)	0.83 (0.28, 1.38)	0.21 (0.07, 0.34)
Quartile 4	0.69 (0.22, 1.15)	0.28 (0.09, 0.48)	1.04 (0.46, 1.61)	0.25 (0.11, 0.38)
TyG-WHR				
Quartile 2	0.00 (−0.50, 0.50)	0.00 (−0.27, 0.27)	0.80 (0.24, 1.36)	0.20 (0.06, 0.34)
Quartile 3	−0.13 (−0.67, 0.40)	−0.07 (−0.33, 0.20)	0.41 (−0.16, 0.99)	0.11 (−0.05, 0.26)
Quartile 4	0.17 (−0.34, 0.68)	0.08 (−0.15, 0.31)	0.78 (0.18, 1.37)	0.19 (0.04, 0.33)
TyG-BMI				
Quartile 2	0.22 (−0.33, 0.77)	0.09 (−0.15, 0.33)	0.31 (−0.35, 0.97)	0.07 (−0.08, 0.22)
Quartile 3	0.04 (−0.53, 0.60)	0.02 (−0.24, 0.27)	0.48 (−0.17, 1.13)	0.11 (−0.04, 0.25)
Quartile 4	0.65 (0.11, 1.20)	0.23 (0.03, 0.42)	0.96 (0.28, 1.64)	0.19 (0.06, 0.32)

Model was adjusted for age, Townsend Deprivation Index, first five principal components of ancestry, genotyping batch, walking, education, smoking, drinking, family history of breast cancer, history of cardiovascular diseases, screening, contraceptives, age at menarche, number of live births, hormone replacement therapy, age at menopause, diabetes, fasting time, cholesterol, high-density cholesterol

To estimate RERI and AP, the lowest TyG index and its combination with obesity indicators category and the lowest genetic risk groups were the reference categories

TyG triglyceride-glucose, *HR* hazard ratio, *CI* confidence interval, *PRS* polygenic risk score, *RERI* relative excess risk due to interaction, *AP* the attributable proportion due to the interaction, *TyG-WC* triglyceride glucose-waist circumference, *TyG-WHtR* triglyceride glucose-waist to height ratio, *TyG-WHR* triglyceride glucose-waist to hip ratio, *TyG-BMI* triglyceride glucose-body mass index

92.43%), 57.10% (95% CI: 8.57%, 105.63%), and 32.50% (95% CI: 8.72%, 56.29%), respectively. In contrast, no mediating effect of HbA1c on these associations has been detected.

Discussion

Based on UK biobank, this study explored the relationships between TyG, its integration with obesity indices, and the incidence of breast cancer among postmenopausal women. A notable elevation in the TyG related indicators is positively correlated with a substantial augmentation in the potential risk of breast cancer, but the association of TyG was unstable. When genetic risk was considered, the groups of high genetic risk with the highest quartile of TyG related indicators had the highest breast cancer risk. There was an additive but not multiplicative interaction between the TyG related indicators and PRS. Analysis of mediation revealed SHBG, testosterone, and CRP mediated the above associations.

A few prior investigations have consistently demonstrated that an elevated TyG index serves as a significant indicator of an augmented risk for breast cancer among women. A National Health and Nutrition Examination Survey (NHANSE) study stated that breast cancer risk augmented a 2.25-time, with an OR and 95% CI of 2.25 (1.50–3.37) for per 1-SD increment in TyG index [40]. An Indonesian case–control investigation revealed a non-linear correlation between the TyG index and the risk of breast cancer [20]. The augmentation of TyG index was associated with a 2.53-fold heightened risk of advanced breast cancer in a Chinese study, pointing to its potential as an emerging serum biomarker for the onset and progression of breast cancer [19]. However, it is noteworthy that, despite aligning with some previous research findings, our results do not fully concur with a prior study based on six European cohorts, which failed to identify a significant association between the TyG index and the risk of postmenopausal breast cancer

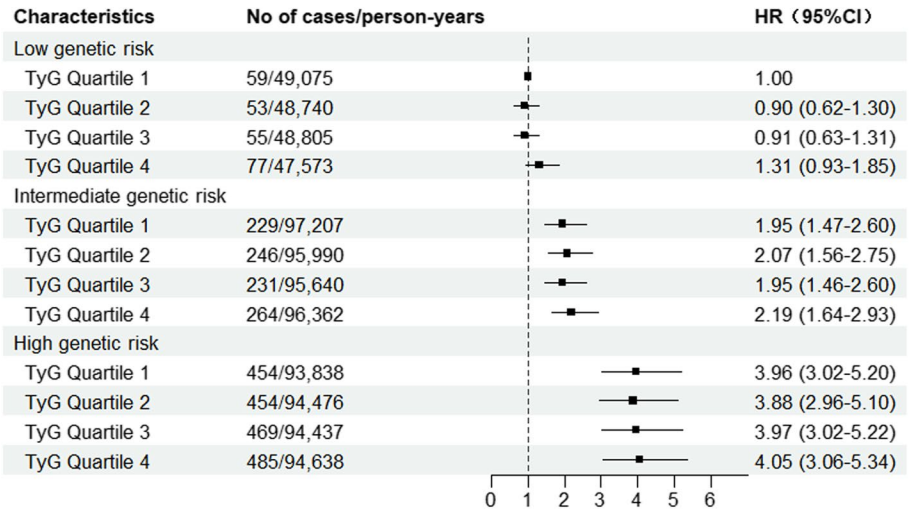

Fig. 3 Joint effect of genetic risk and TyG index on breast cancer incidence. Model was adjusted for age, Townsend Deprivation Index, first five principal components of ancestry, genotyping batch, walking, education, smoking, drinking, family history of breast cancer, history of cardiovascular diseases, screening, contraceptives, age at menarche, number of live births, hormone replacement therapy, age at menopause, diabetes, fasting time, cholesterol, high-density cholesterol. TyG, triglyceride-glucose; HR, hazard ratio; CI, confidence interval

[22]. Possible reasons for this discrepancy include the following: firstly, differing definitions of postmenopausal breast cancer; secondly, our study excluded patients who were taking medications for cholesterol or diabetes; and finally, our research conducted more extensive adjustments for reproductive factors. In our study, after multivariate adjustment, we observed a 12% elevated risk of breast cancer incidence in the highest quartile TyG group compared to the lowest quartile, but no significant correlation between per 1-SD increase of TyG and breast cancer.

Some investigations have found that markers incorporating TyG with obesity metrics, including TyG-WC, TyG-WHtR, TyG-WHR, TyG-BMI, have higher performance than TyG, and are also simple and effective tools for assessing IR [41–43]. Epidemiologic research has demonstrated that postmenopausal breast cancer risk is strongly related to obesity and hyperinsulinemia, and metabolically impaired obesity is being emphasized by researchers [9, 44]. Our study delved deeper into the TyG combined with obesity indicators and postmenopausal breast cancer. It was found that with each 1-SD increase in TyG-related indicators (TyG-WC, TyG-WHtR, TyG-WHR, TyG-BMI), risk for breast cancer increased by 10%, 5%, 7%, and 9%, respectively. The robustness of these findings was further validated through sensitivity analysis. The linkage between TyG related indicators with breast cancer opens a novel perspective for primary prevention strategies, facilitating the determination of high-risk groups and the development of tailored interventions for breast cancer prevention.

Research from a UK Biobank study suggested that an overall healthy lifestyle can diminishes invasive breast cancer risk among postmenopausal women with a higher genetic susceptibility [45]. Our study is the first to combine genetic risk with TyG related indicators to explore their interactions and joint effects with breast cancer. The likelihood of breast cancer escalated progressively with rising TyG-related markers (excluding TyG) in the high genetic risk group. The combined effect showed a significant 4- to fivefold increment of breast cancer risk for individuals with high TyG related indicators in the high genetic risk versus the reference group. We did not observe multiplicative interactions between TyG-related indicators and PRS on the onset of postmenopausal breast cancer, but found additive interactions. The coexistence of genetic susceptibility and TyG-related indicators enhances their overall impact on postmenopausal breast cancer. These revelations hold substantial public health implications, suggesting that among postmenopausal women, lifestyle interventions related to weakening IR may have the utmost impact among those genetically predisposed to breast cancer, thus offering novel preventative measures for this high-risk demographic.

The biological mechanisms underlying the linkage of TyG related indicators to breast cancer are unclear. Upon conducting mediation analyses, it was evident that the linkages between TyG related markers and breast cancer risk among postmenopausal women were predominantly mediated through SHBG, CRP and testosterone. Decreased SHBG levels due to IR lead to increased levels

of free estrogen and androgens, and aromatization of androgens in adipose tissue augments estrogen plasma concentrations, providing postmenopausal breast with additional amounts of plasma estrogen, which has been linked to a heightened risk of breast cancer [44]. CRP, an acute phase marker of inflammatory response and can be used as a proxy for systemic low-grade inflammation [46]. The high-inflammatory state environment in which IR resides creates favorable conditions for breast cancer development, encompassing the generation of free radicals and an augmentation in DNA damage, thereby promoting carcinogenesis [47–49]. In women, hyperinsulinemia stimulates androgen production in the ovaries [50, 51]. Elevated serum testosterone levels in individuals undergoes conversion to estradiol by aromatase within breast tissue, thereby stimulating breast cancer cell proliferation and exerting an indirect pro-cancer effect [52, 53]. Other possible mechanisms include alteration in glucose metabolism, where hyperglycemia provides abundant energy for cancer cell proliferation affecting tumor growth [54].

Strengths and limitations

The study has some strengths. First, it adopts a prospective cohort design with a large sample size that provides a temporal order of causation. Second, study combines genetic risk information for dual exploration of genetic and environmental factors. Our study also has some limitations. First, we used non-fasting blood glucose and TG in TyG calculations, rather than the traditionally required fasting values. Despite adjusting for fasting time, their impact on the results cannot be eliminated. Evidence suggests that blood glucose and lipid indicators in the semi-fasting state (≥4 h) are not significantly different from those in the fasting state (≥8 h) and are closely correlated [55]. In sensitivity analyses, we analyzed participants with a fasting time of >4 h and obtained similar results, implying that the influence of fasting time on the study findings is limited. Second, although we controlled for as many confounders as possible, including demographic characteristics, lifestyle factors, female-specific factors, and blood biochemical markers, etc., we could not completely control for all confounders. Furthermore, the TyG related indicators are calculated based on information measured at a single time point at baseline, and future studies could focus on assessing the consequences of alterations in these indices on breast cancer incidence. Our study participants were all white postmenopausal women, so it may be necessary to verify the universality of our findings across diverse demographic groups. Information on breast cancer stage and hormone receptor subtypes is not currently available from the UK Biobank, and therefore we are unable to determine whether the observed associations vary by these breast cancer characteristics. Finally, despite the acknowledged healthy volunteer bias within the UK Biobank, which may not fully represent the general UK populace, valid assessments of association of exposure with outcome may still be broadly generalizable [56].

Conclusions

In summary, our research underscores significant correlations between heightened TyG related indices and augmented risk of postmenopausal breast cancer. Notably, this risk exhibits a consistent upward trend in conjunction with increments in TyG-WC, TyG-WHtR, TyG-WHR, and TyG-BMI among individuals with high genetic risk populations, and additive interactions have been observed between these indicators and genetic risk. These associations were mainly mediated by SHBG, CRP and testosterone.

Abbreviations

TyG	Triglyceride-glucose
TyG-WC	TyG-waist circumference
TyG-WHtR	TyG-waist to height ratio
TyG-WHR	TyG-waist to hip ratio
TyG-BMI	TyG-body mass index
PRS	Polygenic risk scores
SHBG	Sex hormone-binding globulin
CRP	C-reactive protein
HbA1c	Glycosylated hemoglobin
IR	Insulin resistance
HOMA	Homeostasis model assessment
QUICKI	Quantitative insulin sensitivity check index
ICD-10	International Classification of Disease 10th revision
TG	Triglycerides
TC	Total cholesterol
HDC	High-density cholesterol
LDC	Low-density cholesterol
TDI	Townsend Deprivation Index
HRT	Hormone replacement therapy
CIs	Confidence intervals
HRs	Hazard ratios
RCS	Restricted cubic spline
SD	Standard deviation
NHANSE	National Health and Nutrition Examination Survey
RERI	Relative excess risk due to interaction
AP	The attributable proportion due to the interaction

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13970-y.

Supplementary Material 1.

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Authors' contributions

ZL, ML, and YZ conceived the project. ZLZ, TCZ, and HC performed the data curation and statistical analyses. XRY, XLY and HB interpreted the results and

wrote the original draft. XJL and TMC reviewed and edited manuscripts. ML and YZ contributed to project management and funding acquisition. All authors read and approved the final version.

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Data availability
The data for our study is available in the public UK Biobank Resource (www.ukbiobank.ac.uk/).

Declarations

Ethics approval and consent to participate
The UK Biobank study obtained ethical clearance from the North West Multi-center Research Ethical Committee (11/NW/0382). All participants were thoroughly informed and provided their explicit consent for participation and follow-up. The study adhered to the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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