

Serum γ -glutamyl transferase and breast cancer risk: A gene-environment interaction and causal analysis

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Table S1. Associations between γ -glutamyl transferase and the risk of breast cancer after excluding participants diagnosed with breast cancer within the first two years of follow-up

GGT, U/L	Events/Total	Model a		Model b		Model c	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Q1 [5.0,16.0]	1,870/55,960	Ref	-	Ref	-	Ref	-
Q2 (16.0,21.2]	1,913/53,960	1.04(0.97, 1.11)	0.236	1.04(0.98, 1.11)	0.200	1.02(0.96, 1.09)	0.466
Q3 (21.2,31.3]	2,127/53,912	1.15(1.08, 1.23)	< 0.001	1.16(1.09, 1.23)	< 0.001	1.11(1.04, 1.19)	0.001
Q4 (31.3,200.0]	2,217/53,316	1.22(1.14, 1.30)	< 0.001	1.22(1.15, 1.30)	< 0.001	1.15(1.08, 1.23)	< 0.001

^a Model a was adjusted for age, ethnicity, education level and Townsend deprivation index; ^b Model b was adjusted for age, ethnicity, education level, Townsend deprivation index, family history of breast cancer, breast cancer screening / mammogram, age of menarche, contraceptive use, hormone replacement therapy; menopausal status and number of live births; ^c Model c was adjusted for age, ethnicity, education level, Townsend deprivation index, family history of breast cancer, breast cancer screening / mammogram, age of menarche, contraceptive use, hormone replacement therapy, menopausal status and number of live births, body mass index, smoking status, drinking status, physical activity, hypertension and diabetes; ^d Abbreviations: GGT, γ -glutamyl transferase; HR, hazard ratio; CI, confidence interval.

Table S2. Associations between γ -glutamyl transferase with categorized into five quartiles and the risk of breast cancer

GGT, U/L	Events/Total	Model a		Model b		Model c	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Q1 [5.0,15.0]	1,643/44,272	Ref	-	Ref	-	Ref	-
Q2 (15.0,18.9]	1,776/44,801	1.04(0.97, 1.11)	0.247	1.05(0.98, 1.12)	0.196	1.03(0.96, 1.10)	0.375
Q3 (18.9,24.2]	1,866/43,568	1.11(1.04, 1.19)	0.001	1.12(1.05, 1.20)	< 0.001	1.09(1.02, 1.16)	0.015
Q4 (24.2,35.2]	1,918/43,062	1.16(1.08, 1.24)	< 0.001	1.16(1.09, 1.24)	< 0.001	1.11(1.04, 1.19)	0.003
Q5 (35.2,200.0]	2,100/43,121	1.27(1.19, 1.35)	< 0.001	1.28(1.19, 1.36)	< 0.001	1.20(1.12, 1.29)	< 0.001

^a Model a was adjusted for age, ethnicity, education level and Townsend deprivation index; ^b Model b was adjusted for age, ethnicity, education level, Townsend deprivation index, family history of breast cancer, breast cancer screening / mammogram, age of menarche, contraceptive use, hormone replacement therapy; menopausal status and number of live births; ^c Model c was adjusted for age, ethnicity, education level, Townsend deprivation index, family history of breast cancer, breast cancer screening / mammogram, age of menarche, contraceptive use, hormone replacement therapy, menopausal status and number of live births, body mass index, smoking status, drinking status, physical activity, hypertension and diabetes; ^d Abbreviations: GGT, γ -glutamyl transferase; HR, hazard ratio; CI, confidence interval.

Table S3. Associations between γ -glutamyl transferase within a narrower range (≤ 120 U/L) and the risk of breast cancer

GGT, U/L	Events/Total	Model a		Model b		Model c	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Q1 [5.0,15.9]	2,107/55,130	Ref	-	Ref	-	Ref	-
Q2 (15.9,21.0]	2,143/53,840	1.01(0.95, 1.08)	0.676	1.02(0.96, 1.08)	0.607	1.00(0.94, 1.06)	0.956
Q3 (21.0,30.6]	2,382/53,735	1.12(1.06, 1.19)	< 0.001	1.13(1.06, 1.19)	< 0.001	1.08(1.02, 1.15)	0.009
Q4 (30.6,120.0]	2,531/53,290	1.2(1.13, 1.28)	< 0.001	1.21(1.14, 1.28)	< 0.001	1.14(1.07, 1.21)	< 0.001

^a Model a was adjusted for age, ethnicity, education level and Townsend deprivation index; ^b Model b was adjusted for age, ethnicity, education level, Townsend deprivation index, family history of breast cancer, breast cancer screening / mammogram, age of menarche, contraceptive use, hormone replacement therapy; menopausal status and number of live births; ^c Model c was adjusted for age, ethnicity, education level, Townsend deprivation index, family history of breast cancer, breast cancer screening / mammogram, age of menarche, contraceptive use, hormone replacement therapy, menopausal status and number of live births, body mass index, smoking status, drinking status, physical activity, hypertension and diabetes; ^d Abbreviations: GGT, γ -glutamyl transferase; HR, hazard ratio; CI, confidence interval.

Table S4. Associations between γ -glutamyl transferase and the risk of breast cancer with adjustments for additional serum biomarkers

GGT, U/L	Events/Total	Model d	
		<i>HR</i> (95% <i>CI</i>)	<i>P</i>
Q1 [5.0,16.0]	1,878/49,643	Ref	-
Q2 (16.0,21.2]	1,974/48,609	1.02(0.95, 1.08)	0.605
Q3 (21.2,31.3]	2,180/48,922	1.08(1.01, 1.15)	0.023
Q4 (31.3,200.0]	2,314/48,630	1.13(1.06, 1.21)	< 0.001

^a Model d was adjusted for age, ethnicity, education level, Townsend deprivation index, family history of breast cancer, breast cancer screening / mammogram, age of menarche, contraceptive use, hormone replacement therapy, menopausal status and number of live births, body mass index, smoking status, drinking status, physical activity, hypertension, diabetes, sex hormone-binding globulin, C-reactive protein, triglycerides and glucose levels; ^b Abbreviations: GGT, γ -glutamyl transferase; HR, hazard ratio; CI, confidence interval

Table S5. Multivariable mendelian randomization results of breast cancer risk

Method	Exposure	Outcome	SNP	Beta	Standard error	OR (95%CI)	P
Inverse variance weighted							
	Body mass index	Breast cancer	459	-0.134	0.052	0.87(0.79,0.97)	0.010
	GGT	Breast cancer	459	0.365	0.144	1.44(1.09,1.91)	0.011
	Alcohol drinker status	Breast cancer	459	1.042	0.907	2.83(0.48,16.77)	0.251
MR Egger							
	Body mass index	Breast cancer	459	-0.205	0.084	0.81(0.69,0.96)	0.014
	GGT	Breast cancer	459	0.354	0.144	1.42(1.07,1.89)	0.014
	Alcohol drinker status	Breast cancer	459	1.004	0.908	2.73(0.46,16.17)	0.268
LASSO							
	Body mass index	Breast cancer	459	-0.085	0.044	0.92(0.84,1.00)	0.053
	GGT	Breast cancer	459	0.504	0.115	1.66(1.32,2.07)	< 0.001
	Alcohol drinker status	Breast cancer	459	1.449	0.719	4.26(1.04,17.42)	0.044
Weighted median							
	Body mass index	Breast cancer	459	-0.082	0.064	0.92(0.81,1.04)	0.198
	GGT	Breast cancer	459	0.438	0.172	1.55(1.11,2.17)	0.011
	Alcohol drinker status	Breast cancer	459	2.300	0.906	9.97(1.69,58.81)	0.011

Abbreviations: GGT, γ -glutamyl transferase; OR, odds ratio; CI, confidence interval; MR, mendelian randomization; LASSO, least absolute shrinkage and selection operator.

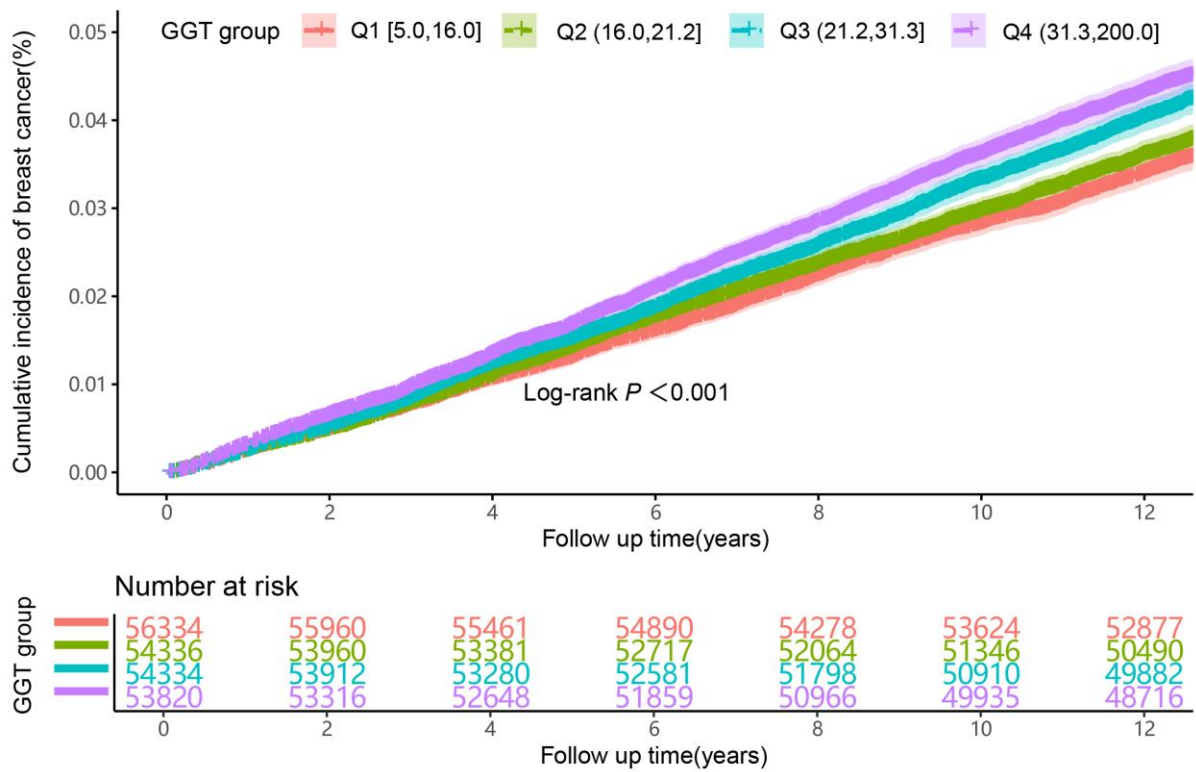


Figure S1. Cumulative incidence curve of breast cancer across γ -glutamyl transferase groups. Abbreviation: GGT, γ -glutamyl transferase;

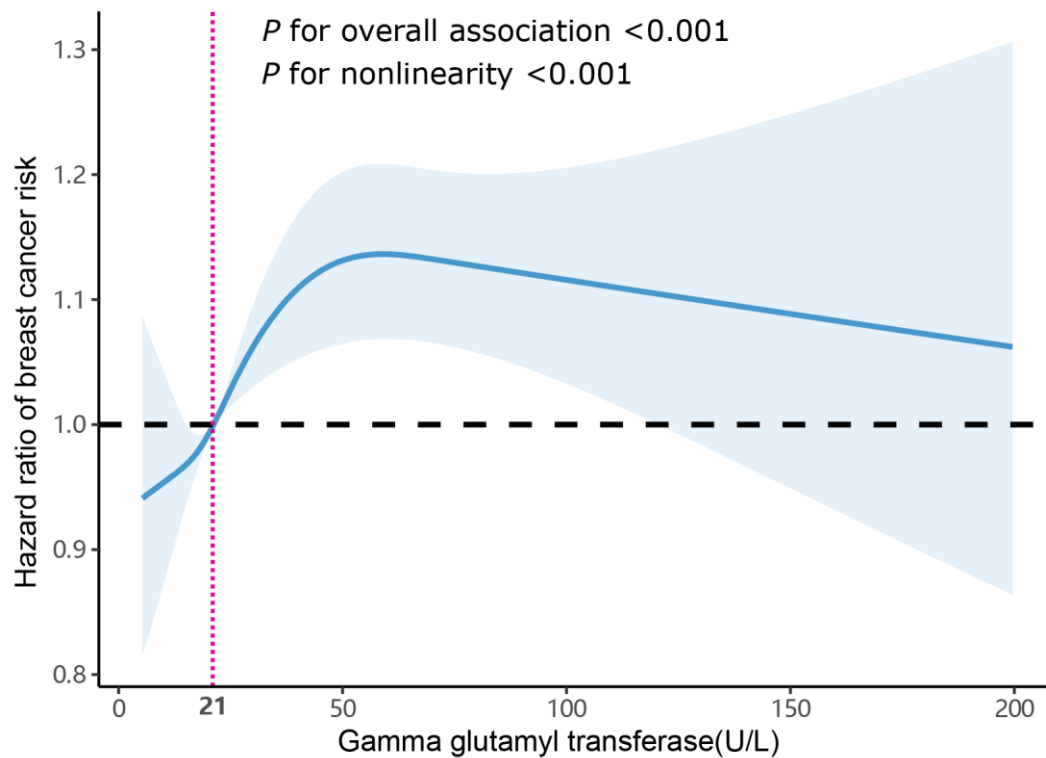


Figure S2. Dose-response relationship between γ -glutamyl transferase levels and breast cancer risk

The model was adjusted for age, ethnicity, education level, Townsend Deprivation Index, family history of breast cancer, breast cancer screening/ mammogram, age at menarche, contraceptive use, hormone replacement therapy, menopausal status and number of live births, body mass index, smoking status, drinking status, physical activity, hypertension, and diabetes.

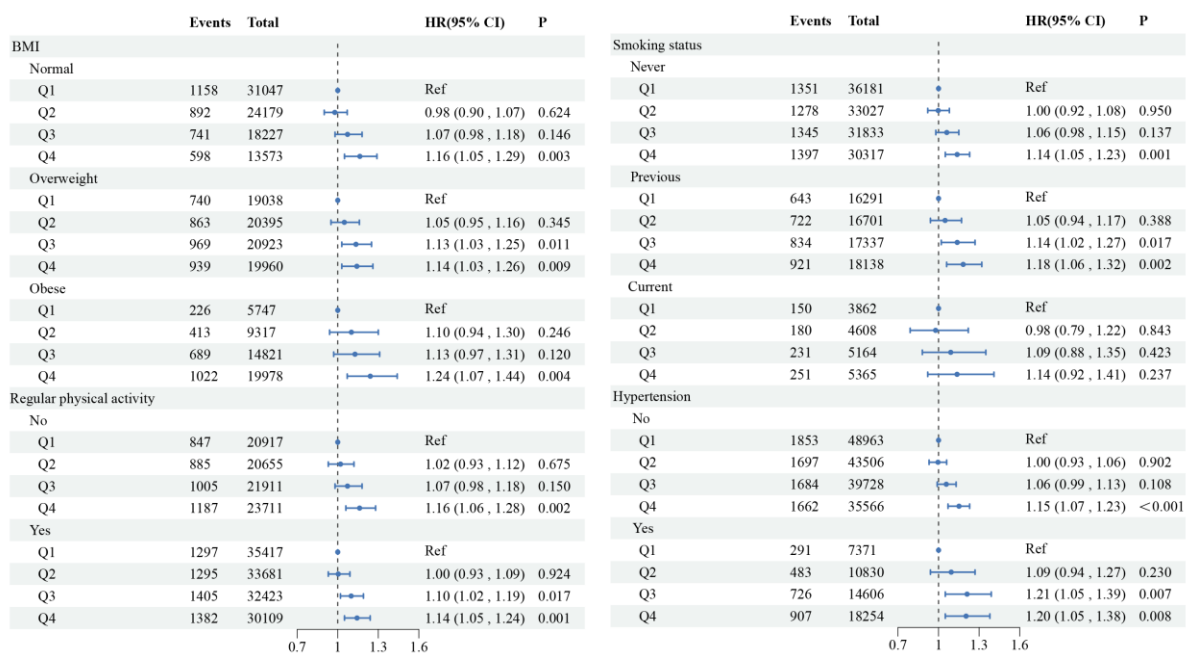


Figure S3. γ -glutamyl transferase levels and breast cancer risk in subgroup analysis of different health-related factors

The unit of GGT is U/L, with the following subgroups: Q1: GGT [5.0, 16.0], Q2: GGT (16.0, 21.2], Q3: GGT (21.2, 31.3], Q4: GGT (31.3, 200.0]. Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index;

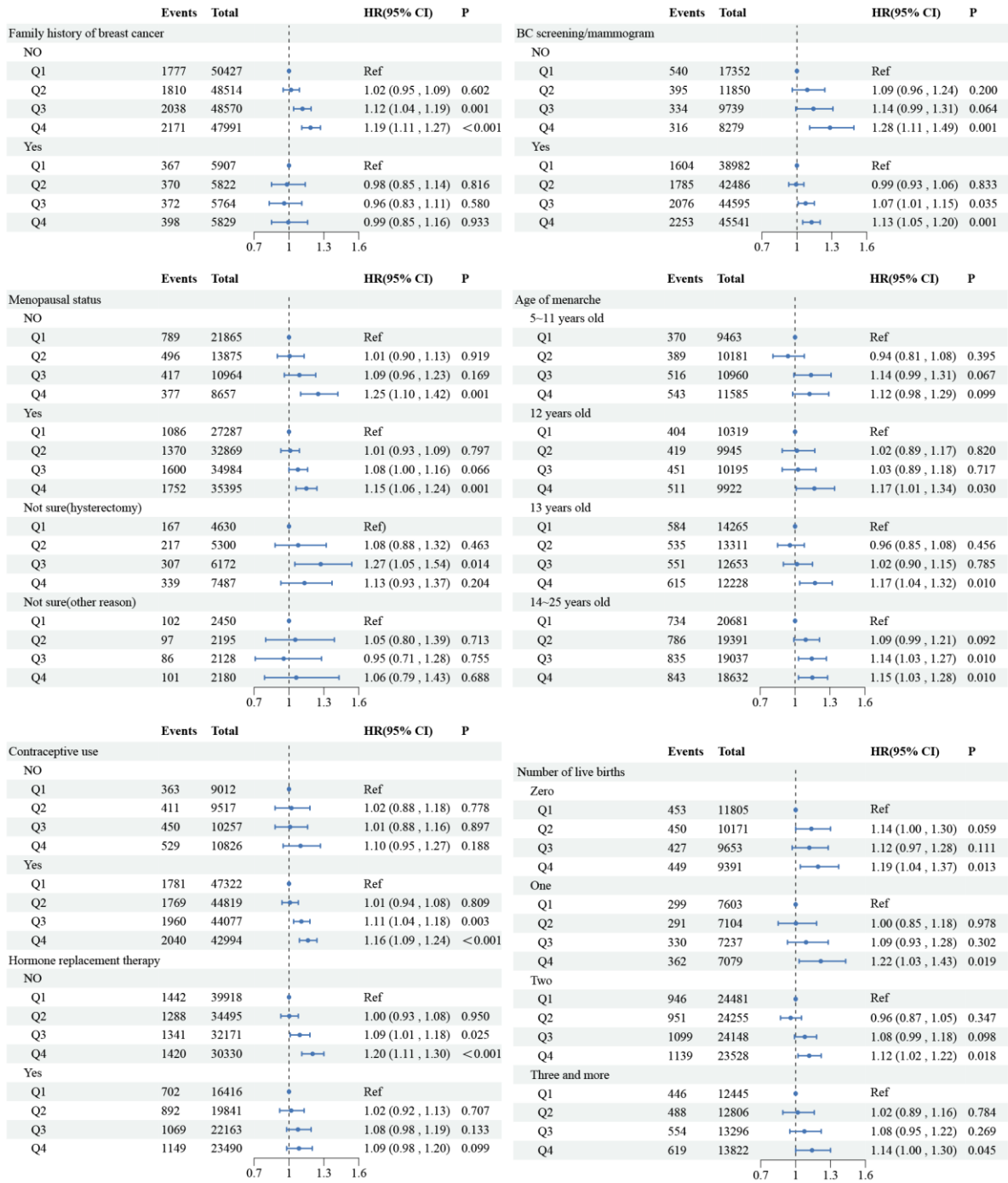


Figure S4. γ -glutamyl transferase levels and breast cancer risk in subgroup analysis of different female-specific factors

The unit of GGT is U/L, with the following subgroups: Q1: GGT [5.0, 16.0], Q2: GGT (16.0, 21.2], Q3: GGT (21.2, 31.3], Q4: GGT (31.3, 200.0]. Abbreviations: HR, hazard ratio; CI, confidence interval;

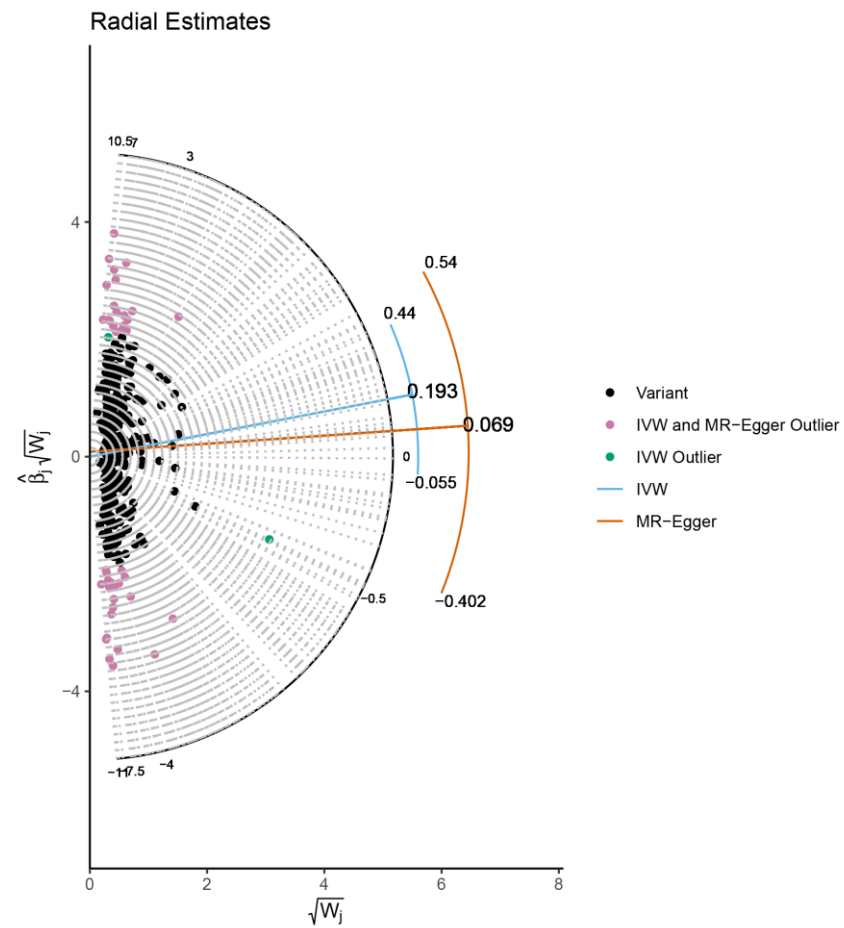


Figure S5. Outliers identified by the MR-Radial method

Abbreviations: IVW, inverse variance-weighted; MR, mendelian randomization.

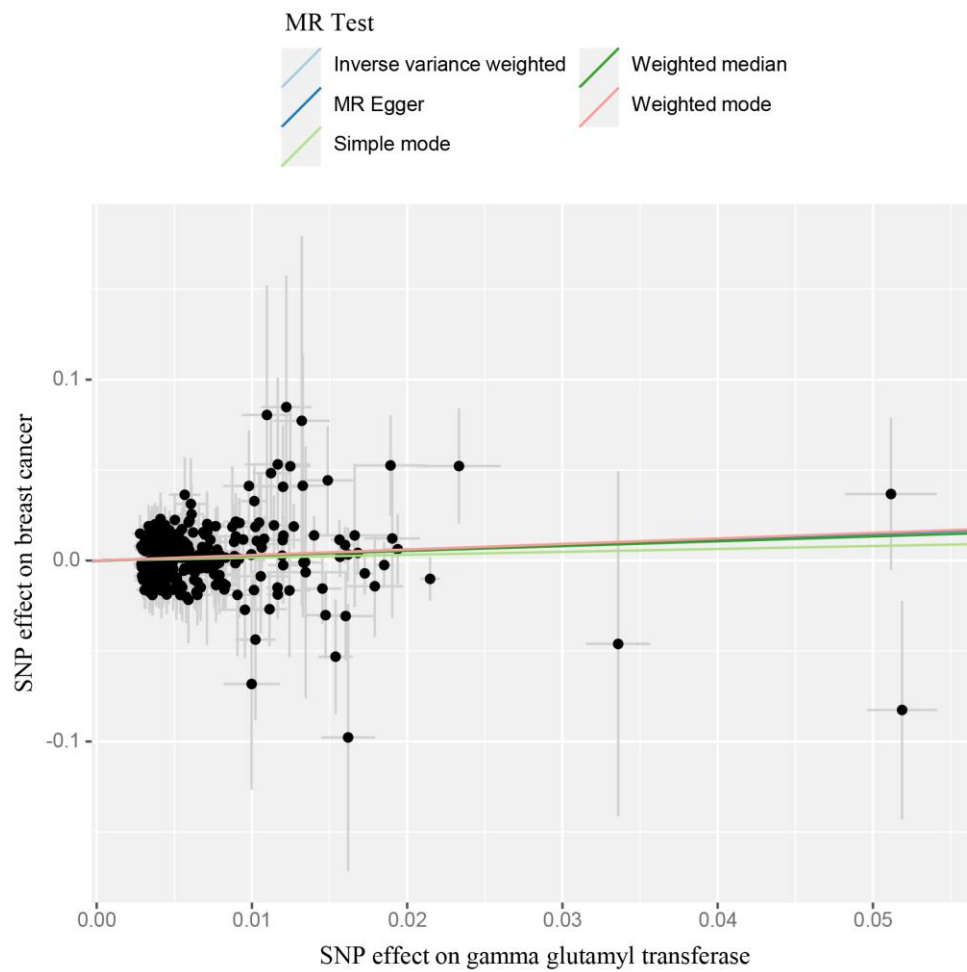


Figure S6. Scatter plot of the Mendelian randomization analysis of γ -glutamyl transferase and breast cancer

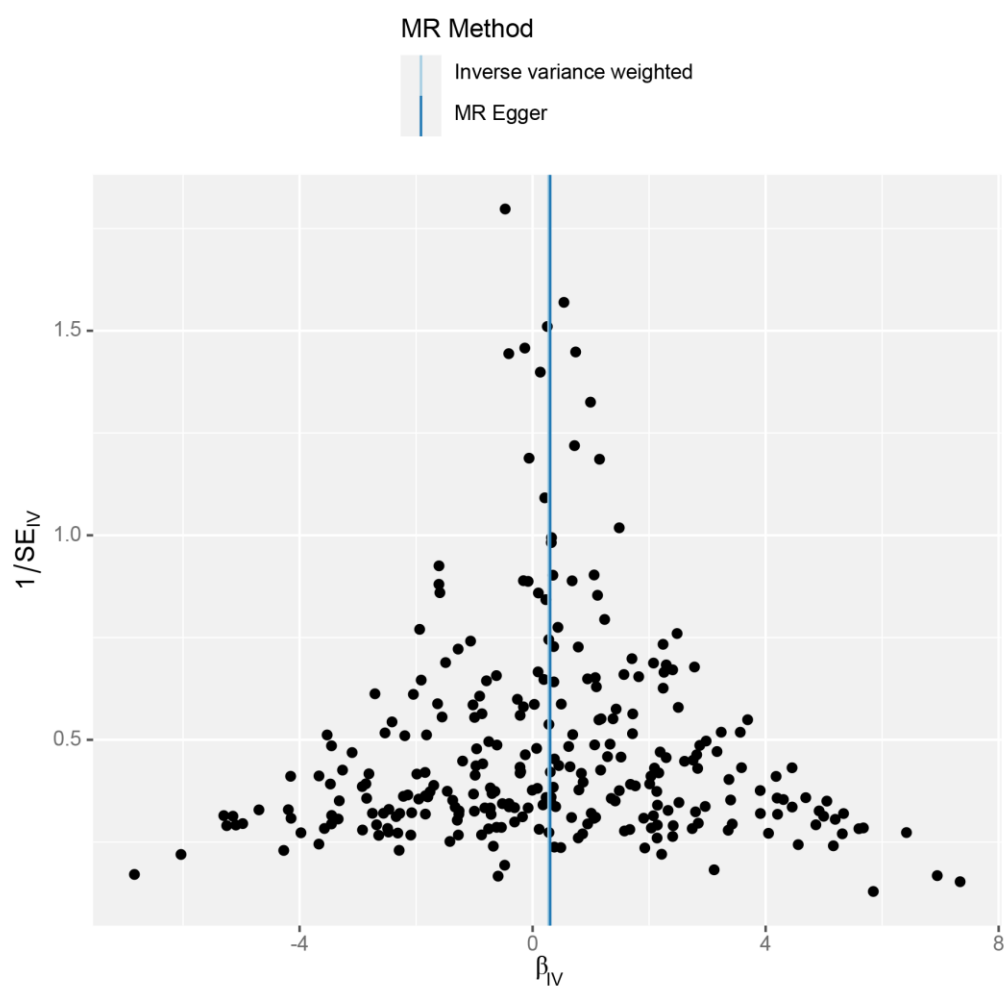


Figure S7. Funnel plot of Mendelian randomization analysis of γ -glutamyl transferase and breast cancer

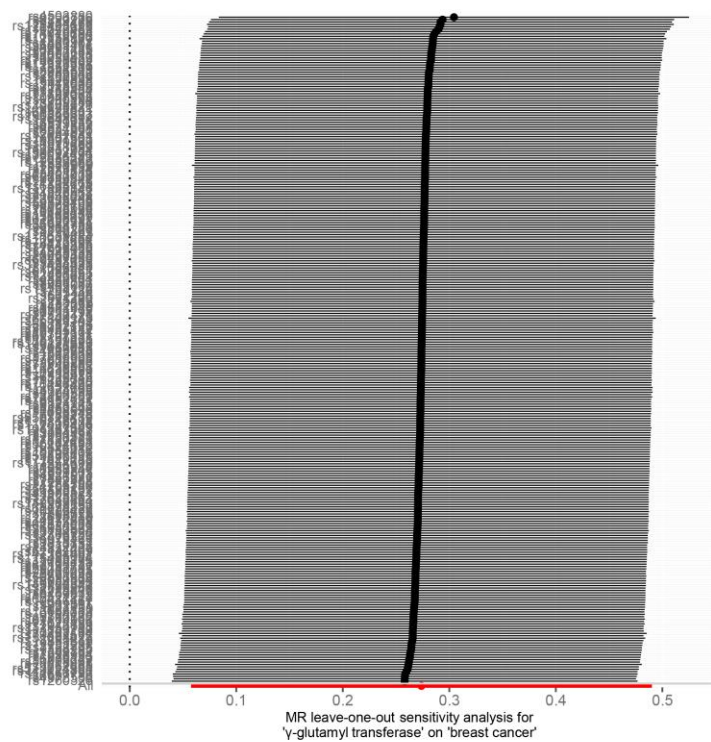


Figure S8. Leave-one-out analysis of mendelian randomization between γ -glutamyl transferase and breast cancer