A Mendelian randomization analysis of circulating lipid traits and breast cancer risk

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A Mendelian randomization analysis of circulating lipid traits and breast cancer risk

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SUMMARY (234/250 words)

Background: Conventional epidemiological studies have evaluated associations between circulating lipid levels and breast cancer risk, but results have been inconsistent. As Mendelian randomization analyses may provide evidence for causal inference, we sought to evaluate potentially unbiased associations between breast cancer risk and four genetically predicted lipid traits.

Methods: Previous genome-wide association studies (GWAS) identified 162 variants associated with high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglycerides, and total cholesterol. We used these variants to construct weighted genetic scores (wGSs) for a total of 101 424 breast cancer cases and 80 253 controls of European ancestry from the Breast Cancer Association Consortium (BCAC). Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations between per standard deviation increase in genetically predicted lipid traits and breast cancer risk. Additional Mendelian randomization analysis approaches and sensitivity analyses were conducted to assess pleiotropy and instrument validity.

Results: Corresponding to approximately 15 mg/dL, one standard deviation increase in genetically predicted HDL-C was associated with a 12% increased breast cancer risk (OR: 1·12, 95% CI: 1·08-1·16). Findings were consistent after adjustment for breast cancer risk factors and were robust in several sensitivity analyses. Associations with genetically predicted triglycerides and total cholesterol were inconsistent, and no association for genetically predicted LDL-C was observed.

Conclusions: This study provides strong evidence that circulating HDL-C may be associated with an increased risk of breast cancer while LDL-C may not be related to breast cancer risk.

Key Words: breast cancer; lipids; cholesterol; genetics; Mendelian randomization; instrumental variable; epidemiology

Key Messages:

- We conducted a large Mendelian randomization analysis to provide unbiased estimates of association for four lipid traits among 181,677 European-ancestry women from the Breast Cancer Association Consortium.
- One standard deviation increase (representing approximately 15 mg/dL increase) in genetically predicted high density lipoprotein-cholesterol (HDL-C) was associated with a 12% increased risk of breast cancer, while no consistent associations were found with low density lipoprotein-cholesterol, triglycerides, or total cholesterol.
- This study strongly suggests that circulating HDL-C levels may influence breast cancer susceptibility.

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INTRODUCTION

Circulating lipids, including high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglycerides, and total cholesterol, have long been hypothesized to influence the risk of breast, colorectal, and other common cancers.[1–4] Early prospective cohort studies reported inverse associations for total cholesterol and cancer risk.[2–4] However, these findings could be due to reverse causation, where disease development or progression leads to lower circulating cholesterol levels years before disease diagnosis.[5–7] It is also possible that confounding factors, such as smoking, alcohol consumption, and socioeconomic status, may have biased associations reported in prior epidemiologic studies.[8,9]

The role of HDL-C in disease risk is controversial. Although it is an established risk factor for coronary heart disease,[10] large Mendelian randomization analyses have suggested that the association between low HDL-C and heart disease may not be causal.[11,12] Furthermore, clinical trials designed to increase circulating HDL-C levels pharmacologically have not demonstrated overall benefits in heart disease prevention.[13,14] With regard to breast cancer, multiple studies have found inverse associations between HDL-C and risk.[15,16] Contrary to these findings, HDL-C was associated with increased breast cancer risk when repeated serum lipid measures were evaluated.[17] Given the current controversy regarding the association between circulating lipid traits and cancer in general, and with breast cancer in particular, this finding has faced skepticism.[18]

Due to methodological limitations such as reverse causation and confounding, it is unlikely that conventional observational studies can resolve the long-standing debate about the role of circulating lipids in breast cancer development. Mendelian randomization analyses can

potentially overcome many of the limitations inherent in conventional epidemiologic studies and may provide evidence for causal inference. Taking advantage of the random assortment of alleles that occurs during gametogenesis, thereby resembling randomized clinical trials, Mendelian randomization analysis uses genetic data to estimate associations that unlikely to be biased due to confounding.[19] To date, genome-wide association studies (GWAS) have linked circulating lipid traits to at least 157 genetic loci.[20,21] We used these lipid-associated variants to create instrumental variables in a Mendelian randomization analysis to evaluate shared genetic components and the association between circulating lipids and breast cancer risk.

METHODS

Study Population

The Breast Cancer Association Consortium (BCAC) is an international collaboration initiated in 2005 to study genetic susceptibility to breast cancer. First, we included individual-level epidemiologic and genetic data from 62 846 breast cancer cases and 43 207 healthy controls of European ancestry from 67 BCAC studies; genetic data included more than 500 000 variants from a custom OncoArray platform that was designed to provide dense coverage across known cancer susceptibility loci as well as common variants.[22] Second, we included independent data from 38 578 cases and 37 046 BCAC controls that were genotyped on the Illumina iSelect genotyping Collaborative Oncological Gene-Environment Study (iCOGS) array (http://ccge.medschl.cam.ac.uk/research/consortia/icogs/).[23] Demographic and selected patient characteristic were harmonized across BCAC studies according to a standardized

protocol. All BCAC studies were approved by relevant institutional review boards, and all participants provided written informed consent.

Variant Genotyping, Imputation, and Selection

Genetic variants associated with lipid traits were selected from the Global Lipids Genetics Consortium. The first lipid-trait GWAS included approximately 100 000 subjects of European ancestry and identified 102 genetic variants in 95 loci.[20] The second GWAS, conducted among 188 577 subjects predominantly of European ancestry, identified 62 additional variants for a total of 157 lipid associated loci.[21] Of the 164 variants in these loci, 87 were genotyped by OncoArray and 75 were imputed with high information quality scores (mean r^2=0·98, range=0.86-0.99). In iCOGS data, 39 selected variants were genotyped, and 123 were successfully imputed (mean r^2=0·82, range=0.35-0.99). Two variants (rs2247056 and rs3177928) were not imputed in either dataset, providing a total of 162 in our analysis (**Supplementary Table 1**). Except for two variants (rs2814982 and rs2814944) in moderate linkage disequilibrium (LD; r^2 =0·51), all included variants were independent ($r^2 < 0{\cdot}1$). Because rs2814982 was associated with total cholesterol and rs2814944 was associated with HDL-C, both were retained in our analysis, as they were not both included together in any one instrumental variable. Thus, based on published GWAS, instrumental variables for HDL-C, LDL-C, triglycerides, and total cholesterol included 74, 57, 43, and 74 variants, respectively.

Mendelian Randomization Analyses

Our primary analysis used individual-level data from BCAC iCOGS and OncoArray to generate weighted-genetic scores (wGSs) for four lipid traits (HDL-C, LDL-C, triglycerides, and total cholesterol). For each lipid trait, we constructed instrumental variables as follows: wGS $=\sum_{i=1}^{n} \beta_{gx} * \alpha_i$, where β_{gx} represents the effect for the genetic variant (g) associated with an increase in lipid levels (x), α_i is effect allele dosage for each genetic variant (ranging from 0 to 2 for each individual), for n genetic variants from the Global Lipids Genetics Consortium GWAS.[20,21]

Associations between wGSs and breast cancer risk factors were assessed using linear or logistic regression for continuous or categorical variables, respectively (**Supplementary Table 2**). Associations between lipid trait wGSs and breast cancer risk were estimated by odds ratios (ORs) and 95% confidence intervals (95% CIs) from unconditional logistic regression using individual level data. Analyses were conducted separately for BCAC participants with iCOGS and OncoArray data (**Supplementary Table 3**), and then combined by random-effects meta-analysis; Cochran's Q statistic was used to evaluate heterogeneity. Models were adjusted for age, principal components (PCs) for European ancestry (iCOGS: 6 PCs; OncoArray: 10 PCs), and either study site (iCOGS) or country (OncoArray), as previously described.[22,24] Additional adjustment included breast cancer risk factors that were associated with lipid trait wGSs. To reduce correlation between instrumental variables, we also constructed amended wGSs that included only genetic variants that were exclusively associated with HDL-C (54 variants), LDL-C (42 variants), or triglycerides (20 variants) at a genome-wide significance level (**Supplementary Table 4**); because total cholesterol includes other lipid traits, no such exclusive variant wGS was created.

We assessed effect measure modification by menopausal status, age (dichotomized at 50 years), and body mass index (dichotomized at 30 kg/m^2) using likelihood ratio tests (LRT) for multiplicative interaction terms in nested models. Polytomous regression was employed to evaluate associations with estrogen receptor (ER) positive (+) and ER negative (-) breast cancer subtypes; tests of equivalence of beta coefficients across subtypes were used to evaluate heterogeneity.

Sensitivity Analyses

In addition to individual-level analyses, we also conducted Mendelian randomization analysis using inverse-variance weighted summary statistics (**Supplementary Table 5**).[25] Three additional sensitivity analyses were used to assess the influence of genetic pleiotropy and validity of our genetic instruments. First, Egger regression was employed to evaluate the presence of directional pleiotropy by testing whether the intercept was statistically different from zero, and to estimate a bias-reduced Mendelian randomization estimate from the regression slope.[26] Second, a weighted multivariable regression-based approach was used to assess the influence of potential pleiotropic effects of genetic variants included in each instrument on other lipid traits; specifically, we regressed beta-coefficients for associations between genetic variants and breast cancer risk (β_{BC}) on beta-coefficients between genetic variants and lipid traits (HDL-C: $\beta_{HDL\text{-}C}$, LDL-C: $\beta_{LDL\text{-}C}$, triglycerides: β_{TG}, and total cholesterol: β_{TC}).[27,28] Third, we estimated associations using a weighted-median Mendelian randomization approach where we assumed that 50% of the variants included in each genetic instrument were invalid (i.e., did not meet at least one of the three assumptions necessary for a valid

instrumental variable); standard errors were estimated by bootstrapping and were subsequently used to calculate 95% CIs.[29] Analyses were completed using SAS (version 9·4), R (version 3·1·2), and Stata (version 12·1).

RESULTS

One genetically predicted standard deviation increase in HDL-C, LDL-C, triglycerides, and total cholesterol was calculated to correspond to approximately 15, 37, 43, and 42 mg/dL increases, respectively. Associations between breast cancer risk factors and lipid trait wGSs were evaluated among all BCAC participants (**Supplementary Table 2**) and also among only controls (data not shown). Several associations were identified; however, the only consistent association across the two populations and genotyping platforms was between increasing age and lower total cholesterol (iCOGS P=4·0x10^{-4} and OncoArray P=0·01). Similarly, the only consistent association among controls was between increasing age and lower triglycerides (iCOGs P=0·04 and OncoArray P=0·03).

Associations for each standard deviation increase in genetically predicted lipid trait from iCOGS and OncoArray genotyped BCAC participants (**Supplementary Table 3**) were combined by random-effects meta-analysis (**Table 1**). HDL-C and total cholesterol were associated with increased breast cancer risk after meta-analysis of unadjusted regression models; however, only increased HDL-C levels were associated with increased breast cancer risk (OR: 1·12, 95% CI: 1·08-1·16) after adjustment for age, study site or country, and principal components for European ancestry. We also created instrumental variables with reduced correlation by using only 54, 42, and 20 exclusive genetic variants for HDL-C, LDL-C, and triglycerides, respectively

(**Supplementary Table 4**). When repeating our primary analysis with these amended instruments, HDL-C wGS was associated with increased breast cancer risk only after multivariable adjustment (OR: 1·14, 95% CI: 1·07-1·22) (**Table 1**). On the contrary, the exclusive variant triglyceride wGS was not associated with breast cancer after multivariable adjustment (OR: 1·00, 95% CI: 0·86-1·16). Regardless of adjustment or whether initial or exclusive variants were included, the wGS for LDL-C was not associated with breast cancer risk.

(Table 1 here)

To examine differences in breast cancer associations by menopausal status, age, and BMI, we conducted stratified analyses; to examine differences in risk by ER status we employed polytomous regression (**Table 2**). No interaction by menopausal status, age or BMI were were observed among iCOGS and Oncoarray genotyped participants for any lipid trait. For the HDL-C wGS, increased breast cancer risk was observed per one standard deviation increase among postmenopausal women (1·11, 95% CI: 1·05-1·17), women less than 50 years of age (1·17, 95% CI: 1·01-1·34), women age 50 or greater (1·11, 95% CI: 1·06-1·16), and non-obese (BMI<30 kg/m^2) women (1·14, 95% CI: 1·08-1·20). Associations were also observed for both ER- (1·10, 95% CI: 1·03-1·18) and ER+ (1·11, 95% CI: 1·07-1·16) breast cancer risk. On the contrary, each standard deviation increase in triglycerides was associated with reduced breast cancer risk among postmenopausal women (OR: 0·93, 95% CI: 0·88-0·99), women age 50 or greater (OR: 0·93, 95% CI: 0·89-0·98), and non-obese women (OR: 0·90, 95% CI: 0·83-0·98); the association was also observed for ER+ breast cancer (OR: 0·91, 95% CI: 0·85-0·91). In these stratified analyses, total cholesterol was associated with breast cancer risk only among premenopausal women (OR: 1·08, 95% CI: 1·00-1·17).

(Table 2 here)

We conducted several sensitivity analyses to assess the validity of our instrumental variables (**Supplementary Table 5**). The inverse-variance weighted Mendelian randomization estimate using summary statistics [25] confirmed our initial findings: increased HDL-C was associated with increased breast cancer risk regardless of data source. On the contrary, triglycerides were associated with reduced breast cancer risk only in OncoArray data (OR: 0·88, 95% CI: 0·83-0·92) and total cholesterol was associated with increased risk only in iCOGS data (OR: 1·06, 95% CI: 1·01-1·12). In Egger regression models, only total cholesterol was associated with breast cancer risk (OR: 0·92, 95% CI: 0·85-1·00), although based on the Egger intercept, this instrumental variable suffered from directional pleiotropy. We also conducted weighted multivariable regression with mutual adjustment for other lipid traits.[27,28] Increasing HDL-C was associated with increased breast cancer risk in iCOGS data (OR: 1·16, 95% CI: 1·08-1·25), and higher triglycerides were associated with decreased breast cancer risk in OncoArray data (OR: 0·88, 95% CI: 0·81-0·95). Finally, we employed a weighted-median approach that assumes half of included variants are invalid.[26] Only HDL-C was associated with increased breast cancer risk after meta-analysis across our data sources (OR: 1·08, 95% CI: 1·02-1·14).

DISCUSSION

In this large-scale Mendelian randomization study using 162 lipid-associated GWAS variants, we found that higher levels of genetically predicted HDL-C were associated with an increased risk of breast cancer. This finding was robust and consistent across a variety of analytic approaches. Genetically predicted triglyceride and total cholesterol levels were also associated with breast cancer risk in some analyses, but these findings were not consistent, and varied by data source and statistical adjustment. Genetically predicted LDL-C was not associated with breast cancer risk in any analyses. Traditional epidemiologic studies that have measured circulating lipids and evaluated breast cancer risk have had conflicting results, likely due to reverse causation, confounding, and selection bias. By using a Mendelian randomization approach, we aimed to overcome limitations inherent in traditional studies, and provide strong evidence supporting a possibly causal association between high HDL-C levels and increased breast cancer risk.

A recent study of serum lipids found that higher HDL-C was associated with increased breast cancer risk when serial measurements were assessed, but not when only one baseline measure was evaluated.[17] This contrasts with a meta-analysis of prospective studies that found modest inverse associations with breast cancer risk for both total cholesterol and HDL-C.[15] Given that circulating cholesterol levels are often decreased several years before cancer diagnosis, inverse associations for this trait could be attributable to bias from reverse causation. In addition, residual confounding from factors such as mammographic breast density or alcohol intake could also affect some reported associations.[18] Menopausal status and female steroid hormones also likely influence associations between circulating lipids and breast cancer risk.[18]

Plasma lipoproteins transport triglycerides and cholesterol between the liver and tissues. HDL-C is the smallest and most dense lipoprotein, and accounts for approximately 30% of total cholesterol, with levels ranging between 40-60 mg/dL. Higher HDL-C concentrations are associated with better cardiovascular health and lower coronary heart disease risk.[10] However, recent Mendelian randomization analyses have suggested that high HDL-C may not be causally related to reduced coronary heart disease risk.[11,12] Furthermore, pharmacologic interventions to increase HDL-C levels have not consistently translated to improved health outcomes,[13,14] and a consensus statement from the National Lipid Association concluded that HDL-C is not currently a therapeutic target.[10] Instead, measures of HDL functionality may be more important than absolute levels, as not all HDL-C functions the same way.[10] For example, oxidized HDL-C and HDL-C from patients with type 2 diabetes had greater capacity to promote proliferation, migration, and metastasis of breast cancer cells.[30] In addition to a major role in reverse cholesterol transport and anti-atherogenic effects, HDL-C also seems to have other functions including the potential to enhance proliferation of breast cancer cells.[30,31] These data provide possible biological mechanisms supporting the increased breast cancer risk seen with increasing levels of genetically predicted HDL-C in our study.

In the current study, associations for triglycerides and total cholesterol in relation to breast cancer risk were inconsistent. The total cholesterol wGS was associated with breast cancer risk only among iCOGS genotyped participants, and multivariate adjustment attenuated this association. Similarly, genetically predicted triglycerides were associated with reduced breast cancer risk only among OncoArray genotyped participants, and the exclusive variant instrument did not influence breast cancer risk. This suggests that some previously reported

associations may be due to residual confounding, and that additional evaluation to understand these discrepant findings may be warranted.

Strengths of this study include a very large sample size, strong instrumental variables for all four lipid traits (F-statistics >10),[32] and multiple analytic approaches to assess instrument validity. We included 162 variants reported by the Global Lipids Genetics Consortium, which account for approximately 13·7%, 14·6%, 11·7%, and 15·0% of the variance in HDL-C, LDL-C, triglycerides, and total cholesterol, respectively.[20,21] Only one variant was associated with breast cancer risk at a genome-wide significance level (rs1121980), and exclusion did not materially alter our results (data not shown). Furthermore, given the large number of variants used to construct our instruments, our wGSs are likely to be most strongly associated with lipids, and not as strongly associated with other traits. Given that pleiotropy remains a concern for Mendelian randomization analyses, we carefully evaluated this possibility using several analytic approaches[26,27] Associations from exclusive variant wGS, inverse variance weighted Mendelian randomization, and weighted-median regression analysis were consistent, showing associations between HDL-C and breast cancer risk. In addition, our results were also unaltered whether fixed-effect or random-effect meta-analysis was conducted (data not shown).

Limitations of our study may include that we did not have direct measurements of circulating lipid levels from our study population to further confirm the validity of our instrumental variables. However, in Mendelian randomization analyses, it is preferable to use externally-derived weights for constructing genetic scores rather than internally-derived weights from the same study population as the Mendelian randomization analysis.[33] We included external weights from a single large GWAS that was conducted predominantly among

Europeans,[20,21] and included only women of European descent in the current analysis. Recently, additional lipid trait genetic variants have been reported;[34] however, weights from this multi-ethnic GWAS would not be applicable to our study population. Additional limitations include incomplete information on all confounding factors, and we could not evaluate or adjust for all such possible covariates. However, when we adjusted for known breast cancer risk factors that were associated with our lipid trait wGSs, our results for HDL-C were unaltered. Finally, many variants included in our analysis were not directly genotyped. However, we used only imputed variants of high quality (iCOGS: mean r^2 =0·82, range=0.35-0.99; OncoArray; mean r^2 =0·98, range=0.86-0.99). Any misclassification of genetic variants would be expected to be non-differential with regard to our outcome, which would be more likely to attenuate rather than amplify an association.

In conclusion, our Mendelian randomization analysis of circulating lipids demonstrated that genetically predicted levels of increasing HDL-C are associated with increased breast cancer risk. Given the strong methodology used in this study, our results may help to clarify the inconsistencies observed across prior conventional observational studies, and support the hypothesis that circulating lipids may influence breast cancer risk.

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Table 1. Associations between one standard deviation (SD) increase in genetically predicted lipid traits and breast cancer risk using individual-level data in the Breast Cancer Association Consortium (BCAC) for original and amended lipid-specific instruments and for different covariate adjustment

Variants used in instrument	Cases	Controls	High density lipoprotein (HDL-C) wGS			Low density lipoprotein (LDL-C) wGS			Triglycerides (TG) wGS			Total cholesterol (TC) wGS		
			OR [a]	95% CI	*P*	OR [a]	95% CI	*P*	OR [a]	95% CI	*P*	OR [a]	95% CI	*P*
All Variants [b]														
No adjustment	101 424	80 253	1·10	1·04-1·17	$2{\cdot}1x10^{-3}$	1·00	0·97-1·03	0·86	1·01	0·97-1·05	0·57	1·08	1·04-1·11	$5{\cdot}7x10^{-5}$
Adjusted [d]	101 424	80 253	1·12	1·08-1·16	$1{\cdot}7x10^{-9}$	1·00	0·96-1·04	0·88	0·93	0·85-1·01	$7{\cdot}5x10^{-2}$	1·05	0·99-1·11	0·11
Exclusive Variants [c]														
No adjustment	101 424	80 253	1·12	0·98-1·28	$9{\cdot}2x10^{-2}$	1·01	0·96-1·05	0·78	1·16	1·08-1·25	$1{\cdot}3x10^{-4}$	NE	NE	NE
Adjusted [d]	101 424	80 253	1·14	1·07-1·22	$9{\cdot}9x10^{-5}$	1·00	0·95-1·05	0·95	1·00	0·86-1·16	0.98	NE	NE	NE

[a] Random-effects meta-analysis estimate and 95% CI summarizing the associations reported in iCOGS and OncoArray BCAC datasets for the association between lipid-specific wGSs and breast cancer risk.

[b] Number of variants included in weighted-genetic score (wGS) per lipid trait: HDL-C = 74, LDL-C = 57, TG = 43, and TC = 74.

[c] Number of variants included in amended wGS per lipid trait: HDL-C = 54, LDL-C = 42, TG = 20; NE not evaluated.

[d] Models adjusted for age, study (iCOGS) or country (OncoArray), and top 6 (iCOGS) or top 10 (OncoArray) principal components for European ancestry.

Table 2. Stratified analyses for the association between one standard deviation (SD) increase in genetically predicted lipid traits and breast cancer risk using individual-level iCOGS and OncoArray data summarized using random-effects meta-analysis in the Breast Cancer Association Consortium (BCAC)

Subgroup	Cases	Controls	High density lipoprotein (HDL-C) wGS [a]			Low density lipoprotein (LDL-C) wGS [a]			Triglycerides (TG) wGS [a]			Total cholesterol (TC) wGS [a]		
			OR [b]	95% CI [b]	*P*	OR [b]	95% CI [b]	*P*	OR [b]	95% CI [b]	*P*	OR [b]	95% CI [b]	*P*
Menopausal status														
Premenopausal	20 782	17 902	1·14	0·96-1·35	0·13	1·00	0·92-1·08	0·89	0·90	0·75-1·08	0·24	1·08	1·00-1·17	0·04
Postmenopausal	43 787	38 847	1·11	1·05-1·17	$3{\cdot}2x10^{-4}$	0·99	0·94-1·05	0·80	0·93	0·88-0·99	0·03	1·00	0·95-1·05	0·96
Test for Interaction [c]			P_{iCOGS} =0·04, P_{Onco} =0·23			P_{iCOGS} =0·31, P_{Onco} =0·41			P_{iCOGS}=0·41, P_{Onco} =0·05			P_{iCOGS} =0·13, P_{Onco} =0·37		
Age														
< 50 years	24 572	22 944	1·17	1·01-1·34	$3{\cdot}4x10^{-2}$	0·96	0·90-1·03	0·30	0·90	0·78-1·05	0·17	1·05	0·98-1·12	0·20
≥ 50 years	71 098	51 700	1·11	1·06-1·16	$2{\cdot}3x10^{-6}$	1·01	0·97-1·05	0·65	0·93	0·89-0·98	$6{\cdot}7x10^{-3}$	1·04	0·99-1·08	0·12
Test for Interaction [c]			P_{iCOGS} =0·07, P_{Onco} =0·74			P_{iCOGS} =0·14, P_{Onco} =0·68			P_{iCOGS} =0·78, P_{Onco} =0·13			P_{iCOGS} =0·71, P_{Onco} =0·99		
Body mass index (BMI)														
BMI < 30 kg/m^2	51 114	41 713	1·14	1·08-1·20	$1{\cdot}0x10^{-6}$	0·99	0·94-1·04	0·70	0·90	0·83-0·98	$1{\cdot}7x10^{-2}$	1·04	0·97-1·12	0·29
BMI ≥ 30 kg/m^2	12 200	9 507	1·06	0·95-1·18	0·31	0·95	0·85-1·05	0·31	1·07	0·95-1·21	0·29	0·96	0·87-1·06	0·41
Test for Interaction [c]			P_{iCOGS} =0·67, P_{Onco} =0·24			P_{iCOGS} =0·16, P_{Onco} =0·99			P_{iCOGS} =0·22, P_{Onco} =$1{\cdot}9x10^{-2}$			P_{iCOGS} =0·10, P_{Onco} =0·68		
Estrogen receptor (ER) status														
ER- breast cancer	43 039	80 253	1·10	1·03-1·18	$7{\cdot}0x10^{-3}$	0·99	0·93-1·05	0·73	0·94	0·87-1·01	$8{\cdot}3x10^{-2}$	1·06	0·93-1·21	0·36
ER+ breast cancer	61 140	80 253	1·11	1·07-1·16	$8{\cdot}6x10^{-8}$	0·99	0·95-1·03	0·63	0·91	0·85-0·98	$1{\cdot}4x10^{-2}$	1·03	0·99-1·07	0·17
Test for Heterogeneity [c]			P_{iCOGS} =0·95, P_{Onco} =0·52			P_{iCOGS} =0·50, P_{Onco} =0·61			P_{iCOGS} =0·97, P_{Onco} =0·26			P_{iCOGS} =0·16, P_{Onco} =0·69		

[a] Number of variants included in lipid-specific weighted-genetic score (wGS): HDL-C = 74, LDL-C = 57, TG = 43, and TC = 74.

[b] Odds Ratios (OR) and 95% Confidence Intervals (CI) represent results from random-effects meta-analysis summarizing the associations from iCOGS and OncoArray datasets for 1 SD increase in wGS in relation to breast cancer risk among stratified groups. Polytomous regression was employed to estimate risk for ER+ and ER- breast cancer in the iCOGS and OncoArray datasets. All models were adjusted for age, BCAC study site (iCOGS) or study country (OncoArray), and either top 6 (iCOGS) or top 10 principal components for European ancestry (OncoArray).

[c] Interactions were assessed on a multiplicative scale using the likelihood ratio test (LRT) for nested models. Differences in stratum-specific ORs and 95% CIs for tumor subtype were assessed using a test for heterogeneity.

Supplementary Table 1. Summary statistics for associations between 162 lipid trait variants from the Global Lipids Genetics Consortium and breast cancer risk in the Breast Cancer Association Consortium (BCAC)

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium							
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray			
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
	rs1077		23439		0·0			0·0			0·0			**0·0**		T/						
1		1		T/		8·3E-04	T/		1·0E-04	T/		1·3E-03	**T/**		**6·4E-09**		0·010	5·1E-01	1·000	-0·011	4·2E-01	1·000
	rs1202		25449		0·0			**0·0**			0·0			**0·0**		T/						
2		1		T/		4·6E-01	**T/**		**1·2E-10**	T/		2·8E-02	**T/**		**4·1E-11**		-0·023	4·1E-02	0·951	-0·007	4·5E-01	0·998
	rs1274		26811		**0·0**			**0·0**			**0·0**			0·0		T/						
3		1		**C/**		**9·7E-16**	**T/**		**3·2E-12**	**T/**		**1·1E-09**	T/		2·9E-06		0·018	4·3E-01	0·732	0·032	5·4E-02	0·989
	rs4660		39562		**0·0**			0·0			0·0			0·0		G/						
4		1		**A/**		**4·0E-10**	G/		4·3E-03	G/		2·3E-06	G/		3·9E-02		0·006	7·3E-01	0·578	0·006	5·8E-01	0·993
	rs2479		55038		0·0		**G**	**0·0**			0·0		**G**	**0·0**		A/						
5		1		A/		3·3E-01			**1·9E-28**	G/		9·2E-03			**3·8E-24**		-0·008	5·7E-01	0·699	-0·010	3·0E-01	1·000
	rs2131		62560		0·0			**0·0**			**0·0**			**0·0**		T/						
6		1		T/		2·8E-03	**T/**		**1·6E-17**	**T/**		**8·8E-43**	**T/**		**2·7E-40**		-0·008	5·0E-01	1·000	0·007	4·9E-01	1·000
	rs7515		92543		0·0			0·0			0·0			**0·0**		A/						
7		1		C/		9·8E-01	A/		1·5E-07	A/		1·8E-01	**A/**		**2·8E-08**		0·005	6·8E-01	0·996	0·010	3·9E-01	0·994
	rs6293		10927		0·0			**0·1**			0·0			**0·1**		T/						
8		1		G/		6·2E-08	**T/**		**9·7E-171**	T/		6·2E-02	**T/**		**5·8E-131**		-0·015	2·4E-01	1·000	0·017	1·1E-01	1·000
	rs2677		15098		0·0			**0·0**			0·0			0·0		G/						
9		1		G/		3·6E-03	**A/**		**5·3E-09**	A/		6·2E-01	A/		3·8E-05		0·020	1·7E-01	1·000	0·013	3·0E-01	1·000
	rs1214		15673													G/						
1		1		**G**	**0·0**	**1·8E-08**	T/	0·0	3·4E-01	T/	0·0	5·6E-04	G/	0·0	6·6E-01		0·005	6·4E-01	0·975	0·000	1·0E+00	0·989
	rs4650		17854													A/						
1		1		**G**	**0·0**	**6·7E-09**	A/	0·0	3·4E-01	A/	0·0	4·0E-01	G/	0·0	3·5E-01		-0·006	5·8E-01	0·875	0·012	1·7E-01	1·000
	rs1689		18219													G/						
1		1		**A/**	**0·0**	**3·2E-10**	G/	0·0	1·4E-01	G/	0·0	1·0E-01	A/	0·0	2·5E-01		0·016	2·5E-01	0·669	0·009	3·3E-01	0·990

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium							
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray			
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
	rs2642		22080		0·0			**0·0**			0·0			**0·0**		T/						
1		1	23015	T/		2·0E-05	**T/**		**1·1E-10**	C/		4·3E-02	**T/**		**5·7E-13**	A/	-0·015	2·4E-01	0·829	-0·015	1·4E-01	0·955
1	rs4846	1	23472	**A/**	**0·0**	**3·7E-21**	G/	0·0	7·6E-01	**G**	**0·0**	**8·1E-14**	A/	0·0	1·7E-01	T/	0·004	8·2E-01	0·455	0·003	7·3E-01	1·000
1	rs5142	1	21002	T/	0·0	8·4E-02	**T/**	**0·0**	**9·4E-12**	T/	0·0	3·3E-01	**T/**	**0·0**	**5·4E-14**	T/	-0·009	4·8E-01	0·676	0·006	4·8E-01	1·000
1	rs1042	2	21041	**C/**	**0·0**	**1·2E-30**	T/	0·0	8·3E-25	**T/**	**0·0**	**1·4E-45**	T/	0·0	3·7E-18	A/	0·012	3·8E-01	1·000	-0·003	8·0E-01	1·000
1	rs1367	2	27508	G/	0·0	2·3E-05	**A/**	**0·1**	**4·5E-114**	A/	0·0	4·1E-10	**A/**	**0·1**	**4·1E-96**	C/	0·015	1·8E-01	1·000	0·001	9·0E-01	1·000
1	rs4299	2	43845	C/	0·0	7·7E-02	T/	0·0	2·3E-04	**T/**	**0·1**	**5·7E-133**	**T/**	**0·0**	**7·3E-27**	T/	-0·002	8·7E-01	1·000	0·023	1·4E-02	0·969
1	rs2710	2	62922	T/	0·0	2·1E-01	**G**	**0·0**	**1·7E-47**	G/	0·0	2·5E-03	**G**	**0·0**	**4·0E-45**	A/	0·023	1·1E-01	0·693	0·005	6·1E-01	1·000
2	rs1049	2	11807	G/	0·0	7·7E-03	**A/**	**0·0**	**6·1E-09**	A/	0·0	4·7E-02	A/	0·0	7·4E-05	A/	-0·008	5·0E-01	1·000	0·002	8·6E-01	1·000
2	rs2030	2	12055	A/	0·0	5·3E-02	**G**	**0·0**	**1·7E-12**	A/	0·0	4·1E-01	**G**	**0·0**	**5·9E-09**	T/	0·024	2·4E-01	1·000	0·008	6·3E-01	1·000
2	rs7570	2	13508	C/	0·0	3·1E-01	**T/**	**0·0**	**8·6E-09**	T/	0·0	4·9E-01	**T/**	**0·0**	**3·6E-08**	A/	0·015	2·2E-01	0·801	-0·001	8·9E-01	1·000
2	rs1019	2	16465	A/	0·0	3·3E-03	A/	0·0	1·7E-06	A/	0·0	7·8E-01	**A/**	0·0	**1·9E-08**	C/	0·004	7·7E-01	0·840	-0·009	4·1E-01	0·870
2	rs1232	2	16468	C/	0·0	9·3E-08	T/	0·0	1·9E-06	**T/**	**0·0**	**1·6E-10**	T/	0·0	1·7E-05	C/	-0·025	2·3E-02	1·000	-0·002	8·1E-01	1·000
2		2		**C/**	**0·0**	**2·7E-10**	T/	0·0	5·7E-02	T/	0·0	2·8E-08	T/	0·0	9·1E-02		0·012	4·7E-01	0·997	0·004	7·4E-01	0·992

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium						
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray		
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
	rs2287		16897		0·0			0·0			0·0		**G**	**0·0**		A/						
2		2		G/		2·0E-03	G/		5·4E-08	A/		9·2E-01			**4·1E-12**		0·023	9·9E-02	0·606	-0·008	3·7E-01	0·996
	rs1169		20266		0·0			0·0			0·0		**G**	**0·0**		G/						
2		2		A/		7·7E-01	G/		8·5E-06	G/		2·5E-05			**2·0E-09**		0·009	4·7E-01	1·000	-0·006	5·5E-01	1·000
	rs1047		21067		**0·0**			0·0			0·0			0·0		A/						
2		2		**C/**		**8·7E-10**	A/		1·4E-01	C/		8·6E-01	C/		1·8E-01		0·032	1·9E-02	0·743	0·004	6·6E-01	1·000
	rs1250		21543		0·0			**0·0**			0·0			0·0		C/						
2		2		T/		4·0E-01	**C/**		**3·1E-08**	C/		1·4E-02	C/		2·4E-07		-0·008	5·4E-01	0·987	0·003	7·9E-01	0·979
	rs2972		22623	**G**	**0·0**			0·0		**0·0**				0·0		T/						
3		2				**2·8E-09**	T/		7·2E-02	**T/**		**2·5E-08**	T/		5·0E-01		0·005	6·7E-01	0·967	-0·002	8·7E-01	0·996
	rs1156		23377		0·0			**0·0**			0·0			**0·0**		T/						
3		2		T/		3·6E-01	**T/**		**4·5E-08**	T/		8·3E-02	**T/**		**1·3E-09**		0·014	4·2E-01	1·000	0·022	1·3E-01	1·000
	rs2606		11358		**0·0**			0·0			0·0			0·0		T/						
3		3		**C/**		**4·8E-08**	T/		9·1E-01	T/		3·2E-05	C/		1·2E-01		-0·015	1·8E-01	0·997	0·019	4·3E-02	0·997
	rs2290		12587		0·0			0·0			0·0		**G**	**0·0**		C/						
3		3		G/		4·4E-01	G/		1·2E-06	G/		2·3E-03			**4·2E-09**		0·000	9·9E-01	0·993	-0·005	6·7E-01	1·000
	rs7640		32491		0·0			**0·0**			0·0			**0·0**		T/						
3		3		T/		7·2E-01	**C/**		**9·8E-09**	C/		5·5E-03	**C/**		**1·7E-08**		0·014	6·0E-01	0·626	0·008	6·2E-01	0·964
	rs2290		47019	**G**	**0·0**			0·0			0·0			0·0		A/						
3		3				**3·7E-09**	A/		7·9E-01	A/		2·2E-02	G/		1·1E-01		0·002	8·8E-01	1·000	-0·009	4·7E-01	0·959
	rs2013		50091		**0·0**			0·0			0·0			0·0		T/						
3		3		**T/**		**8·9E-12**	T/		9·7E-01	C/		4·8E-01	T/		2·1E-02		-0·001	9·0E-01	1·000	-0·023	9·9E-03	1·000
	rs1332		52498		**0·0**			0·0			0·0			0·0		G/						
3		3		**A/**		**9·0E-11**	G/		2·7E-01	G/		3·0E-06	G/		6·3E-01		-0·021	1·6E-01	0·864	0·001	9·6E-01	1·000
	rs1331		58395		0·0			0·0			0·0		**G**	**0·0**		A/						
3		3		G/		1·8E-02	G/		4·7E-07	A/		2·5E-01			**3·5E-08**		-0·017	3·7E-01	0·997	-0·003	8·6E-01	0·999
	rs6805		11984		**0·0**			0·0			0·0			0·0		C/						
3		3		**T/**		**1·3E-08**	T/		1·9E-03	C/		9·9E-01	T/		1·2E-06		-0·004	7·0E-01	0·999	-0·004	6·6E-01	1·000

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]										Breast Cancer Association Consortium					
				HDL-C			LDL-C			TG			TC			iCOGS [b]			OncoArray		
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*	Info Score [c]	β	*P*	Info Score [c]
	rs1740		13244													T/						
				G	**0·0**		**G**	**0·0**			0·0			0·0								
4										G/			G/									
		3				**5·0E-09**			**1·8E-09**			2·2E-02			1·4E-07		-0·033	6·0E-02	0·829	-0·006	6·4E-01	0·983
			13620													T/						
	rs6450				0·0			0·0			**0·0**			0·0								
4				G/			T/			**T/**			T/									
		3				3·3E-06			2·2E-01			**2·5E-08**			3·5E-01		-0·004	7·4E-01	0·991	-0·008	4·8E-01	0·998
	rs6831															G/						
			34714		0·0		**G**	**0·0**		**G**	**0·0**		**G**	**0·0**								
4				A/																		
		4				3·0E-03			**2·0E-08**			**1·6E-12**			**1·0E-10**		-0·023	5·5E-02	0·823	-0·004	6·4E-01	0·976
	rs1001															G/						
			26061		**0·0**			0·0			0·0			0·0								
4				**A/**			G/			G/			G/									
		4				**4·9E-08**			3·2E-04			2·3E-06			1·2E-02		0·026	1·2E-01	0·752	-0·010	4·1E-01	0·990
			87109													T/						
	rs4421				0·0			0·0			**0·0**			0·0								
4				G/			T/			**T/**			T/									
		4				2·7E-07			9·8E-04			**8·7E-12**			4·0E-04		0·017	1·3E-01	1·000	0·025	7·3E-03	0·994
	rs3822		88820													A/						
				G	**0·0**			0·0			0·0			0·0								
4							A/			A/			A/									
		4				**4·1E-12**			3·7E-02			5·7E-07			5·2E-01		0·001	9·6E-01	0·945	-0·004	6·3E-01	0·987
	rs2602		99093													G/						
				0·0				0·0			0·0			0·0								
4				**A/**			G/			G/			A/									
		4				**5·0E-08**			8·3E-01			2·1E-02			6·6E-01		0·002	8·5E-01	0·812	0·014	1·1E-01	1·000
	rs1310		10226													T/						
					0·0			0·0			0·0			0·0								
4				**C/**			C/			T/			C/									
		4				**7·2E-11**			1·2E-01			1·5E-02			2·8E-03		0·010	6·9E-01	0·744	-0·001	9·7E-01	1·000
	rs6450		54002													A/						
				G	**0·0**			0·0			0·0			0·0								
4							A/			A/			A/									
		5				**5·0E-08**			9·1E-02			1·7E-05			5·6E-02		0·028	2·5E-02	0·992	0·007	5·2E-01	1·000
	rs9686		56565													T/						
				0·0			0·0			**0·0**			0·0									
4				C/			T/			**T/**			T/									
		5				7·5E-07			7·2E-03			**1·3E-10**			6·2E-03		-0·019	2·4E-01	0·786	-0·019	9·9E-02	0·993
			75360													C/						
				0·0			**0·0**			0·0			**0·0**									
5	rs1291			C/			**C/**			C/			**C/**									
		5				1·4E-01			**5·1E-45**			3·0E-01			**8·8E-47**		0·008	4·9E-01	0·994	0·011	2·1E-01	1·000
			12351													A/						
	rs4530				0·0			**0·0**			0·0			**0·0**								
5				A/			**A/**			A/			**A/**									
		5				9·3E-01			**3·6E-12**			7·4E-01			**1·7E-09**		0·004	7·0E-01	1·000	0·002	8·1E-01	1·000
			15696													C/						
	rs6882				0·0			**0·0**			**0·0**			**0·0**								
5				T/			**C/**			**C/**			**C/**									
		5				8·9E-01			**1·9E-22**			**1·0E-10**			**7·5E-28**		0·017	2·2E-01	0·648	-0·014	1·4E-01	1·000
	rs3757		16127													T/						
				0·0			**0·0**			0·0			**0·0**									
5				T/			**C/**			C/			**C/**									
		6				3·9E-01			**1·2E-11**			2·1E-01			**2·8E-09**		-0·019	2·0E-01	0·709	-0·003	7·7E-01	0·987

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium							
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray			
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
5	rs1800	6	26092	G/	0·0	1·8E-01	**G**	**0·0**	**6·1E-10**	A/	0·0	7·5E-01	**G**	**0·0**	**2·5E-08**	A/	-0·024	3·2E-01	0·864	0·011	5·8E-01	1·000
5	rs2814	6	34578	C/	0·0	1·3E-06	C/	0·0	4·7E-07	T/	0·0	7·3E-01	**C/**	**0·0**	**4·7E-11**	T/	-0·007	6·9E-01	0·835	-0·012	4·0E-01	1·000
5	rs2814	6	34585	**G**	**0·0**	**3·8E-09**	G/	0·0	6·8E-05	A/	0·0	3·5E-01	G/	0·0	8·9E-08	A/	0·004	7·8E-01	1·000	-0·017	1·7E-01	0·999
5	rs2758	6	39283	G/	0·0	7·3E-01	A/	0·0	1·8E-07	A/	0·0	4·9E-02	**A/**	**0·0**	**3·0E-08**	A/	0·011	3·4E-01	0·992	0·005	5·9E-01	0·997
5	rs9985	6	43790	**C/**	**0·0**	**2·3E-11**	A/	0·0	9·4E-01	**A/**	**0·0**	**3·4E-15**	A/	0·0	5·3E-01	T/	-0·024	3·7E-02	0·868	-0·025	6·5E-03	1·000
5	rs9488	6	11599	A/	0·0	2·5E-01	**A/**	**0·0**	**3·5E-08**	A/	0·0	1·9E-04	**A/**	**0·0**	**1·7E-10**	T/	0·004	7·7E-01	0·831	-0·009	3·5E-01	0·971
6	rs1936	6	12711	**C/**	**0·0**	**3·1E-10**	T/	0·0	2·0E-01	**T/**	**0·0**	**3·8E-07**	T/	0·0	9·8E-01	C/	-0·016	1·9E-01	0·830	-0·017	5·3E-02	1·000
6	rs9376	6	13509	T/	0·0	2·9E-04	T/	0·0	1·9E-06	T/	0·0	3·4E-01	**T/**	**0·0**	**2·6E-09**	T/	0·011	5·0E-01	0·596	0·005	6·6E-01	0·980
6	rs6050	6	13950	**T/**	**0·0**	**2·6E-08**	C/	0·0	2·1E-02	C/	0·0	3·2E-06	C/	0·0	1·7E-01	C/	-0·012	2·5E-01	0·999	0·006	5·0E-01	0·993
6	rs1564	6	16015	T/	0·0	6·9E-02	**C/**	**0·0**	**1·7E-17**	C/	0·0	2·4E-02	**C/**	**0·0**	**9·7E-17**	A/	-0·001	9·4E-01	1·000	-0·016	2·0E-01	1·000
6	rs1084	6	16066	**A/**	**0·0**	**3·0E-08**	G/	0·0	5·5E-01	A/	0·0	1·2E-02	G/	0·0	5·9E-02	G/	-0·044	2·3E-03	1·000	-0·023	5·9E-02	1·000
6	rs1997	7	10441	G/	0·0	2·3E-07	G/	0·0	4·8E-05	G/	0·0	2·7E-01	**G**	**0·0**	**2·7E-10**	G/	0·023	1·3E-01	1·000	-0·014	2·5E-01	0·998
6	rs7024	7	64096	**G**	**0·0**	**6·5E-12**	G/	0·0	7·9E-01	A/	0·0	4·8E-01	G/	0·0	2·9E-04	T/	-0·006	6·8E-01	0·600	0·011	2·2E-01	0·991
6	rs4142	7	17879	**G**	**0·0**	**9·4E-12**	G/	0·0	9·0E-02	T/	0·0	8·8E-03	G/	0·0	1·2E-05	C/	-0·032	1·1E-02	0·765	0·000	9·7E-01	0·994
6	rs1267	7	21567	T/	0·0	9·1E-01	**C/**	**0·0**	**6·9E-10**	C/	0·0	3·0E-02	**C/**	**0·0**	**9·2E-10**		-0·006	6·7E-01	0·760	0·015	1·6E-01	0·995

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium					
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray		
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
6	rs4722	7	25952	C/	0·0	2·5E-02	**C/**	**0·0**	**3·9E-14**	**T/**	**0·0**	**1·6E-09**	**C/**	**0·0**	**7·0E-09**	C/	0·021	2·1E-01	0·795	0·028	2·9E-02	0·894
7	rs2072	7	44539	G/	0·0	7·2E-01	**C/**	**0·0**	**6·7E-11**	C/	0·0	3·4E-03	**C/**	**0·0**	**3·2E-11**	C/	0·033	5·1E-02	0·558	0·005	6·5E-01	1·000
7	rs4917	7	50266	**G**	**0·0**	**1·0E-08**	G/	0·0	2·5E-01	T/	0·0	8·9E-01	G/	0·0	3·6E-05	G/	-0·008	6·4E-01	0·408	0·018	6·8E-02	1·000
7	rs1323	7	72664	T/	0·0	1·7E-02	C/	0·0	2·6E-01	**C/**	**0·0**	**1·1E-09**	C/	0·0	5·8E-02	T/	0·056	1·6E-01	0·630	0·000	1·0E+00	0·859
7	rs1714	7	73568	**T/**	**0·0**	**1·2E-09**	T/	0·0	2·3E-01	**C/**	**0·1**	**6·0E-58**	C/	0·0	7·1E-02	G/	0·077	4·3E-03	0·517	0·019	1·7E-01	1·000
7	rs3885	7	11671	G/	0·0	9·0E-05	A/	0·0	9·7E-01	**A/**	**0·0**	**2·1E-08**	A/	0·0	3·7E-01	T/	0·006	6·1E-01	0·937	-0·002	8·7E-01	1·000
7	rs4731	7	13074	**T/**	**0·0**	**1·2E-15**	C/	0·0	1·7E-02	C/	0·0	1·1E-06	C/	0·0	2·1E-01	C/	0·004	7·6E-01	0·570	0·026	3·6E-03	0·995
7	rs1717	7	15083	**T/**	**0·0**	**1·9E-08**	C/	0·0	3·8E-01	C/	0·0	1·0E-03	T/	0·0	9·9E-01	G/	-0·029	1·1E-01	1·000	-0·046	2·7E-03	0·998
7	rs9987	8	93258	**G**	**0·0**	**6·4E-25**	**G**	**0·0**	**2·0E-14**	A/	0·0	2·1E-02	**G**	**0·0**	**7·1E-23**	C/	0·028	1·4E-01	0·988	0·038	2·5E-02	0·994
7	rs1177	8	10826	G/	0·0	2·8E-03	G/	0·0	2·0E-01	**C/**	**0·0**	**1·3E-08**	G/	0·0	7·5E-01	A/	0·009	4·2E-01	0·976	-0·007	4·8E-01	0·998
7	rs1495	8	18415	A/	0·0	9·3E-01	G/	0·0	1·6E-03	**G**	**0·0**	**4·6E-14**	**G**	**0·0**	**2·7E-08**	G/	-0·024	6·0E-02	1·000	-0·010	3·6E-01	1·000
8	rs1267	8	19986	**G**	**0·1**	**9·7E-98**	A/	0·0	5·7E-01	**A/**	**0·1**	**1·5E-115**	A/	0·0	9·1E-01	A/	0·015	3·9E-01	0·987	0·004	7·9E-01	1·000
8	rs1010	8	54509	G/	0·0	8·0E-01	**A/**	**0·0**	**3·7E-11**	A/	0·0	6·9E-03	**A/**	**0·0**	**4·6E-11**		0·018	1·8E-01	0·973	0·000	9·8E-01	0·999

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]										Breast Cancer Association Consortium					
				HDL-C			LDL-C			TG			TC			iCOGS [b]			OncoArray		
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*	Info Score [c]	β	*P*	Info Score [c]
	rs2081		58476		0·0			**0·0**			0·0			**0·0**		C/						
8		8		T/		4·3E-01	**T/**		**1·7E-08**	T/		8·5E-05	**T/**		**2·0E-12**		-0·034	2·7E-03	0·988	-0·013	1·7E-01	0·993
	rs2293		11558													G/						
				G	**0·0**			0·0			0·0			0·0								
8		8				**5·8E-11**	T/		1·1E-02	T/		6·1E-01	G/		5·9E-01		0·008	4·6E-01	1·000	-0·009	3·2E-01	0·983
	rs2737		11563													C/						
					0·0			0·0			0·0			**0·0**								
8		8		A/		2·9E-01	A/		8·0E-07	A/		1·2E-02	**A/**		**2·5E-08**		-0·036	3·0E-03	0·955	-0·012	2·4E-01	0·970
	rs2954		12547													T/						
					0·0			**0·0**			**0·0**			**0·0**								
8		8		**T/**		**4·9E-18**	**A/**		**5·4E-29**	**A/**		**3·3E-55**	**A/**		**1·2E-35**		0·012	2·9E-01	0·922	0·018	5·0E-02	1·000
	rs1113		14396													G/						
					0·0		**G**	**0·0**			0·0		**G**	**0·0**								
8		8		A/		8·4E-01			**4·4E-13**	A/		9·8E-01			**9·0E-10**		0·027	2·8E-02	0·834	0·008	3·9E-01	1·000
	rs3780		26407		0·0			**0·0**			0·0			**0·0**		G/						
8		9		A/		5·4E-01	**A/**		**1·8E-09**	G/		4·9E-01	**A/**		**6·7E-10**		-0·020	4·6E-01	0·632	-0·027	1·3E-01	1·000
	rs5810		15305		**0·0**			0·0			0·0			**0·0**		C/						
8		9		**C/**		**2·9E-12**	C/		1·8E-02	C/		3·0E-04	**C/**		**3·1E-09**		-0·006	6·6E-01	0·914	0·004	7·3E-01	1·000
	rs1883		10490													T/						
					0·0			0·0			0·0			**0·0**								
8		9		**C/**		**1·8E-33**	C/		1·1E-07	C/		1·0E-03	**C/**		**3·4E-27**		-0·030	1·6E-02	1·000	-0·012	2·4E-01	1·000
	rs9411		13327													T/						
					0·0			**0·0**			0·0			**0·0**								
9		9		T/		5·7E-01	**T/**		**7·3E-03**	C/		8·9E-01	**T/**		**5·3E-03**		0·074	3·0E-07	0·879	0·032	4·3E-03	1·000
	rs1832		52128		0·0			0·0			**0·0**			0·0		G/						
9		10		A/		1·1E-01	A/		1·1E-01	**A/**		**1·7E-12**	A/		4·9E-06		0·027	6·7E-02	1·000	0·021	9·4E-02	0·999
	rs1090		17218													G/						
					0·0			0·0			0·0		**G**	**0·0**								
9		10		G/		2·6E-04	G/		3·1E-07	G/		7·3E-03			**2·6E-11**		0·019	1·0E-01	0·861	0·003	7·7E-01	0·995
	rs9705		45517		**0·0**			0·0			0·0			**0·0**		C/						
9		10		**C/**		**1·7E-10**	C/		6·6E-04	C/		4·6E-01	**C/**		**8·4E-09**		0·004	7·6E-01	1·000	0·028	8·4E-03	0·999
	rs1076		63267													T/						
					0·0			0·0			**0·0**			0·0								
9		10		T/		2·5E-07	T/		3·7E-04	**A/**		**3·5E-12**	T/		1·3E-03		-0·023	3·4E-02	0·996	-0·008	3·5E-01	0·998
	rs2068		93079		0·0			0·0		**G**	**0·0**			0·0		A/						
9		10		A/		1·7E-02	G/		3·8E-03			**2·4E-08**	G/		4·9E-04		-0·021	5·7E-02	1·000	0·001	8·8E-01	1·000

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium							
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray			
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
	rs2255		11217		0·0			**0·0**			0·0			**0·0**		G/						
9		10		A/		3·0E-07	**A/**		**2·2E-09**	G/		2·8E-03	**A/**		**2·0E-10**		0·006	6·3E-01	0·962	0·014	1·6E-01	0·987
	rs2923		10367		**0·0**			0·0			0·0			0·0		G/						
9		11		**A/**		**4·6E-08**	G/		4·2E-02	G/		2·5E-02	A/		9·9E-01		-0·033	3·1E-02	0·792	0·010	4·1E-01	1·000
	rs1012		18611		0·0			0·0			0·0			**0·0**		C/						
9		11		C/		2·1E-01	C/		2·9E-07	C/		4·1E-02	**C/**		**2·6E-08**		0·023	1·1E-01	0·651	0·036	4·4E-04	0·962
	rs3136		46721		**0·0**			0·0			0·0			0·0		C/						
9		11		**C/**		**3·5E-18**	T/		6·4E-01	T/		6·2E-04	C/		9·6E-02		-0·005	7·5E-01	0·978	0·013	3·4E-01	1·000
	rs1124		54607		**0·0**			0·0			0·0			0·0		C/						
1		11		**C/**		**1·7E-10**	C/		5·3E-01	T/		1·9E-01	C/		1·9E-02		0·007	6·5E-01	1·000	0·021	1·3E-01	0·996
	rs1745		61802		**0·0**			**0·0**			**0·0**			**0·0**		T/						
1		11		**C/**		**2·6E-22**	**C/**		**1·8E-21**	**T/**		**5·4E-24**	**C/**		**2·9E-22**		-0·005	6·8E-01	0·989	-0·009	3·6E-01	1·000
	rs1280		65623		**0·0**			0·0			0·0			0·0		A/						
1		11		**A/**		**3·1E-08**	A/		1·4E-01	G/		1·3E-05	A/		2·6E-02		-0·002	8·6E-01	0·991	-0·017	1·2E-01	1·000
	rs4999		75743		**0·0**			0·0			0·0			0·0		A/						
1		11		**C/**		**1·1E-08**	A/		8·3E-01	C/		5·4E-02	C/		8·0E-04		-0·028	4·5E-02	0·993	-0·012	3·2E-01	1·000
	rs9641		11677		**0·1**		**G**	**0·0**		**G**	**0·2**		**G**	**0·1**		C/						
1		11		**C/**		**5·2E-47**			**1·5E-26**			**6·7E-240**			**6·2E-57**		-0·010	5·5E-01	0·972	0·030	2·2E-02	1·000
	rs1160		11861		0·0			0·0			0·0			**0·0**		C/						
1		11		T/		2·3E-03	T/		1·5E-05	T/		5·7E-01	**T/**		**1·2E-08**		-0·017	1·8E-01	0·717	0·010	2·6E-01	1·000
	rs7941		12265		**0·0**			0·0			0·0			**0·0**		C/						
1		11		**C/**		**2·7E-08**	C/		3·5E-06	T/		9·8E-01	**C/**		**1·5E-10**		0·001	9·7E-01	0·671	0·018	5·8E-02	0·988
	rs1122		12637		0·0			**0·0**			0·0			**0·0**		A/						
1		11		G/		3·1E-02	**A/**		**1·2E-15**	A/		1·7E-02	**A/**		**5·6E-11**		-0·005	7·7E-01	0·841	-0·015	2·5E-01	0·990
	rs4883		89299		0·0			0·0			0·0			**0·0**		G/						
1		12		A/		1·0E-03	A/		6·8E-06	A/		3·7E-01	**A/**		**1·7E-09**		-0·011	6·0E-01	0·831	-0·005	7·3E-01	0·980
	rs7134		20320		**0·0**			0·0			0·0			0·0		A/						
1		12		**A/**		**3·8E-08**	C/		6·7E-01	C/		8·3E-04	A/		9·5E-01		0·003	7·7E-01	0·931	0·009	3·1E-01	0·963

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium							
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray			
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
	rs1161															T/						
			57398																			
1					**0·0**			0·0			**0·0**			0·0								
				T/			C/			**C/**			C/									
		12				**4·4E-08**			5·0E-04			**4·4E-10**			3·5E-03		0·032	5·1E-02	0·654	0·010	3·5E-01	1·000
			10956													T/						
	rs7134																					
1					**0·0**			0·0			0·0			0·0								
				T/			T/			T/			T/									
		12				**6·9E-15**			5·6E-01			6·1E-01			1·3E-04		-0·001	9·4E-01	0·997	-0·018	4·8E-02	1·000
	rs1106		11163													G/						
1					0·0			**0·0**			0·0			**0·0**								
				A/			**A/**			G/			**A/**									
		12				5·8E-04			**1·5E-09**			8·7E-01			**6·8E-12**		-0·026	1·6E-02	1·000	-0·025	5·2E-03	1·000
			12097													C/						
	rs1169																					
1					0·0			**0·0**			0·0			**0·0**								
				C/			**C/**			C/			**C/**									
		12				1·6E-02			**1·1E-15**			4·6E-01			**1·5E-14**		-0·028	1·9E-02	0·956	-0·015	1·3E-01	0·968
			12331													T/						
	rs4759																					
1					**0·0**			0·0			0·0			0·0								
				T/			T/			C/			T/									
		12				**7·5E-09**			1·5E-01			1·2E-01			6·2E-03		0·025	3·0E-01	0·537	-0·009	6·0E-01	0·922
			12397													T/						
	rs4765																					
1					**0·0**			0·0		**G**	**0·0**			0·0								
				T/			G/						G/									
		12				**2·9E-10**			9·4E-04			**1·8E-08**			5·1E-03		0·011	4·1E-01	0·716	0·009	3·5E-01	0·998
			12477													T/						
1	rs8388				**0·0**			0·0			0·0			0·0								
				C/			T/			T/			C/									
		12				**2·6E-14**			4·2E-01			8·0E-01			3·1E-02		0·012	4·5E-01	0·534	-0·014	1·5E-01	0·997
	rs4942		32379													C/						
1					0·0			**0·0**			0·0			0·0								
				C/			**T/**			T/			T/									
		13				1·2E-04			**2·3E-11**			2·4E-02			7·1E-08		-0·026	1·7E-02	1·000	-0·013	1·5E-01	1·000
	rs8017		24414													A/						
1					0·0			**0·0**			0·0			0·0								
				G/			**A/**			A/			A/									
		14				7·7E-01			**4·9E-11**			6·9E-01			1·1E-07		-0·042	4·0E-03	0·570	0·004	6·9E-01	1·000
			10481													A/						
	rs4983																					
1				**G**	**0·0**			0·0			0·0			0·0								
							G/			A/			G/									
		14				**9·6E-09**			5·8E-01			9·7E-01			6·3E-03		-0·018	1·0E-01	1·000	-0·015	9·5E-02	1·000
	rs2412		42391													A/						
1					0·0			0·0			**0·1**			0·0								
				G/			G/			**A/**			A/									
		15				6·2E-05			3·1E-01			**1·9E-08**			9·6E-01		-0·033	3·3E-01	0·681	0·002	9·6E-01	1·000
	rs2929		43953													T/						
1					0·0			0·0			**0·0**			0·0								
				A/			A/			**T/**			T/									
		15				2·9E-06			7·7E-01			**1·6E-11**			6·4E-01		-0·061	1·9E-02	0·965	-0·021	3·1E-01	0·999
	rs1532		58391													G/						
1					**0·1**			0·0			**0·0**			**0·0**								
				A/			A/			**A/**			**A/**									
		15				**2·9E-96**			8·5E-01			**1·8E-11**			**8·8E-20**		-0·008	5·0E-01	0·831	-0·001	9·2E-01	1·000
	rs2652		63104													G/						
1				**G**	**0·0**			0·0			0·0			0·0								
							G/			A/			G/									
		15				**8·7E-09**			3·7E-01			3·2E-04			4·3E-02		-0·004	7·9E-01	0·990	0·008	4·6E-01	0·994

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]										Breast Cancer Association Consortium					
				HDL-C			LDL-C			TG			TC			iCOGS [b]			OncoArray		
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*	Info Score [c]	β	*P*	Info Score [c]
1	rs3198	16	15036	T/	0·0	3·3E-05	T/	0·0	6·9E-03	**C/**	**0·0**	**2·2E-08**	T/	0·0	2·7E-01	T/	0·004	8·1E-01	0·465	-0·019	3·6E-02	0·973
1	rs1164	16	30907	G/	0·0	1·9E-03	C/	0·0	1·4E-02	**C/**	**0·0**	**3·3E-08**	C/	0·0	2·0E-02	G/	-0·003	7·8E-01	1·000	0·024	9·9E-03	0·950
1	rs1121	16	53775	**G**	**0·0**	**6·8E-09**	A/	0·0	8·2E-01	**A/**	**0·0**	**1·5E-06**	G/	0·0	1·2E-01	A/	-0·065	2·7E-09	0·999	-0·054	2·4E-09	1·000
1	rs3764	16	56959	**A/**	**0·2**	**0·0E+00**	**C/**	**0·0**	**1·6E-12**	**C/**	**0·0**	**6·2E-12**	**A/**	**0·0**	**6·7E-14**	A/	0·020	7·9E-02	1·000	0·010	3·1E-01	0·996
1	rs1694	16	67894	**A/**	**0·0**	**8·4E-33**	A/	0·0	4·3E-01	G/	0·0	1·2E-01	A/	0·0	7·6E-06	A/	0·036	2·6E-02	0·991	0·011	4·2E-01	1·000
1	rs2000	16	72074	G/	0·0	5·3E-01	**A/**	**0·0**	**1·8E-22**	A/	0·0	5·7E-06	**A/**	**0·0**	**3·2E-24**	C/	-0·023	8·3E-02	1·000	0·000	1·0E+00	0·995
1	rs2925	16	81501	**C/**	**0·0**	**2·1E-11**	T/	0·0	9·5E-01	T/	0·0	9·0E-05	C/	0·0	4·9E-01	C/	-0·002	8·9E-01	0·940	0·015	1·4E-01	1·000
1	rs3142	17	71883	C/	0·0	3·5E-01	**T/**	**0·0**	**3·4E-10**	T/	0·0	3·0E-02	**T/**	**0·0**	**2·8E-10**	C/	-0·004	7·5E-01	1·000	0·022	2·2E-02	1·000
1	rs1186	17	39657	**C/**	**0·0**	**1·3E-13**	C/	0·0	1·5E-01	G/	0·0	2·7E-01	C/	0·0	2·6E-04	C/	0·016	1·6E-01	0·970	0·005	6·0E-01	1·000
1	rs8077	17	43800	A/	0·0	1·5E-06	C/	0·0	9·2E-01	**C/**	**0·0**	**9·9E-09**	A/	0·0	7·4E-01	A/	0·012	4·0E-01	0·913	-0·013	2·6E-01	0·984
1	rs7206	17	47347	A/	0·0	1·7E-03	**A/**	**0·0**	**1·5E-08**	G/	0·0	4·8E-02	**A/**	**0·0**	**1·0E-08**	C/	0·019	9·0E-02	0·974	0·003	7·2E-01	1·000
1	rs1801	17	66214	A/	0·0	8·5E-03	**C/**	**0·1**	**9·8E-12**	A/	0·0	1·5E-01	C/	0·0	3·4E-05	G/	0·027	4·3E-01	0·611	0·017	4·9E-01	1·000
1	rs4148	17	68879	**C/**	**0·0**	**1·8E-10**	G/	0·0	4·4E-03	G/	0·0	4·1E-02	G/	0·0	4·9E-01	A/	-0·026	6·2E-02	0·672	-0·010	2·8E-01	0·990
1	rs4129	17	78407	**A/**	**0·0**	**7·6E-09**	A/	0·0	5·0E-01	G/	0·0	1·0E-02	A/	0·0	1·7E-02	T/	0·002	8·3E-01	0·845	-0·004	6·3E-01	0·985
1	rs7241	18	49634	**T/**	**0·0**	**2·7E-49**	T/	0·0	3·2E-04	G/	0·0	6·9E-01	**T/**	**0·0**	**6·3E-19**		0·019	1·9E-01	0·945	0·006	6·3E-01	1·000

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium						
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray		
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
1	rs1296	18	60181	**G**	**0·0**	**6·6E-09**	G/	0·0	8·1E-01	A/	0·0	1·4E-05	G/	0·0	4·1E-01	A/	-0·024	6·0E-02	0·994	-0·012	2·4E-01	0·999
1	rs7248	19	72244	A/	0·0	5·6E-06	G/	0·0	5·0E-01	**G**	**0·0**	**5·0E-10**	G/	0·0	3·0E-01	A/	-0·012	3·6E-01	0·690	-0·007	4·7E-01	0·996
1	rs7255	19	83683	**A/**	**0·0**	**3·2E-08**	A/	0·0	5·3E-01	C/	0·0	6·4E-02	A/	0·0	3·0E-02	T/	-0·013	3·4E-01	0·620	0·006	5·3E-01	0·982
1	rs6511	19	11091	T/	0·0	1·4E-02	**G**	**0·2**	**4·3E-117**	G/	0·0	1·5E-01	**G**	**0·1**	**6·7E-97**	C/	0·008	7·1E-01	0·674	0·019	1·9E-01	1·000
1	rs7373	19	11236	**T/**	**0·0**	**3·1E-09**	T/	0·0	3·5E-01	C/	0·0	5·1E-01	T/	0·0	8·3E-04	C/	-0·034	2·1E-01	0·369	-0·004	8·0E-01	1·000
1	rs1040	19	19296	C/	0·0	5·8E-01	**T/**	**0·1**	**6·7E-22**	**T/**	**0·1**	**1·6E-29**	**T/**	**0·1**	**2·9E-38**	A/	0·029	1·5E-01	0·971	0·022	1·8E-01	1·000
1	rs7318	19	33408	**A/**	**0·0**	**3·4E-09**	A/	0·0	5·2E-01	**G**	**0·0**	**2·7E-09**	A/	0·0	9·6E-02	C/	-0·025	4·3E-02	0·843	-0·013	1·8E-01	1·000
1	rs4394	19	44911	T/	0·0	6·7E-06	C/	0·0	5·3E-07	**C/**	**0·0**	**1·1E-30**	C/	0·0	3·8E-12	G/	-0·003	7·8E-01	1·000	-0·031	1·0E-03	1·000
1	rs4420	19	44919	**A/**	**0·0**	**4·4E-21**	**G**	**0·2**	**8·7E-147**	G/	0·0	5·4E-22	**G**	**0·1**	**5·2E-111**	G/	-0·024	1·5E-01	0·715	-0·029	1·6E-02	1·000
1	rs4926	19	48703	A/	0·0	7·3E-01	G/	0·0	7·6E-08	G/	0·0	3·1E-04	**G**	**0·0**	**2·0E-10**	A/	0·017	1·3E-01	0·951	0·008	3·5E-01	0·998
1	rs1769	19	51820	**G**	**0·0**	**2·4E-13**	G/	0·0	1·2E-02	A/	0·0	1·1E-02	G/	0·0	2·6E-04	C/	-0·023	9·4E-02	0·830	0·002	8·7E-01	1·000
1	rs3860	19	54288	**C/**	**0·0**	**4·3E-16**	C/	0·0	6·0E-01	G/	0·0	9·4E-01	C/	0·0	1·1E-04	G/	0·012	3·7E-01	0·989	-0·031	9·3E-03	0·878
1	rs3645	20	12982	G/	0·0	8·2E-01	**G**	**0·0**	**4·3E-10**	A/	0·0	4·4E-01	G/	0·0	7·7E-05	C/	0·017	2·0E-01	0·670	-0·005	5·8E-01	0·997
1	rs2328	20	17865	A/	0·0	8·6E-01	**C/**	**0·0**	**5·6E-09**	A/	0·0	1·2E-01	C/	0·0	3·9E-07	T/	0·004	8·6E-01	0·353	-0·017	1·4E-01	1·000
1	rs2277	20	35564	C/	0·0	2·8E-02	C/	0·0	6·5E-06	C/	0·0	2·4E-03	**C/**	**0·0**	**3·8E-10**		-0·001	9·7E-01	1·000	0·009	5·0E-01	1·000

N	Varia	C	Hg38 Locati	Global Lipids Genetics Consortium [a]												Breast Cancer Association Consortium							
				HDL-C			LDL-C			TG			TC			E/	iCOGS [b]			OncoArray			
				E/	β	*P*	E/	β	*P*	E/	β	*P*	E/	β	*P*		β	*P*	Info Score [c]	β	*P*	Info Score [c]
	rs2902		40462													G/						
1					0·0			**0·0**			0·0			**0·0**								
				A/			**A/**			A/			**A/**									
		20				5·2E-01			**1·6E-08**			2·5E-03			**6·1E-11**		0·008	5·3E-01	0·923	-0·002	8·6E-01	1·000
	rs6029		41043													A/						
1					0·0			**0·0**			0·0			**0·0**								
				T/			**A/**			A/			**A/**									
		20				8·7E-01			**3·7E-19**			1·2E-02			**8·5E-17**		0·003	7·7E-01	0·947	0·007	4·4E-01	0·994
	rs1800		44413													T/						
1					**0·1**			0·0			0·0			**0·1**								
				C/			C/			C/			**C/**									
		20				**1·1E-15**			2·4E-05			5·9E-01			**5·7E-13**		-0·025	4·0E-01	1·000	-0·038	1·4E-01	1·000
	rs6065		45925													C/						
1					**0·0**			0·0			**0·0**			0·0								
				T/			C/			**C/**			T/									
		20				**1·9E-22**			3·0E-01			**2·6E-17**			9·7E-01		-0·013	3·6E-01	0·947	-0·021	7·7E-02	1·000
			21577													T/						
1	rs1813				**0·0**			0·0			0·0			0·0								
				C/			C/			C/			C/									
		22				**1·1E-08**			8·3E-02			2·3E-02			2·8E-05		-0·011	4·1E-01	0·977	0·015	1·9E-01	0·999
	rs5763		29982													T/						
1					0·0			**0·0**			0·0			0·0								
				T/			**T/**			C/			T/									
		22				6·4E-03			**1·2E-08**			8·9E-01			7·7E-08		-0·030	4·3E-01	0·956	-0·048	1·2E-01	0·998
			35315													G/						
1	rs1387				0·0			0·0			0·0			**0·0**								
				A/			A/			A/			**A/**									
		22				8·9E-02			4·9E-06			3·8E-01			**4·7E-08**		-0·016	3·3E-01	0·439	0·010	3·1E-01	0·981
	rs5756		38150													C/						
1					0·0			0·0			**0·0**			0·0								
				C/			T/			**T/**			T/									
		22				4·3E-03			1·8E-02			**3·8E-08**			8·3E-03		-0·037	9·6E-04	1·000	-0·049	1·4E-07	0·989
	rs4253		46231													T/						
1					0·0			**0·0**			0·0			**0·0**								
				C/			**T/**			T/			**T/**									
		22				9·1E-01			**4·3E-08**			5·8E-04			**9·9E-09**		-0·030	8·8E-02	0·998	-0·018	2·2E-01	0·989

[a] Summary statistics for each GWAS-identified variant with high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC) from the Global Lipids Genetics Consortium, representing a standard deviation (SD) increase in each lipid trait. Effect alleles correspond to an increase in each lipid trait (i.e., E/R = effect allele/reference allele), and were ascertained from Table 1 of Teslovich et al., 2010, and Tables 1-4 of Willer et al., 2013. Variants included in specific lipid genetics scores are in **bold** (HDL-C: 74 variants; LDL-C: 57 variants; TG: 43 variants; TC: 74 variants).

[b] Summary statistics for BCAC iCOGS exclude 19,018 individuals that overlap with BCAC OncoArray.

[c] Information score for 123 imputed variants and 39 genotyped variants in BCAC iCOGS (average information score = 0.82). Information score for 87 imputed variants and 75 genotyped variants in BCAC OncoArray (average information score = 0.98).

Supplementary Table 2. Associations between genetically predicted lipid trait levels and breast cancer risk factors using individual-level data from the Breast Cancer Association Consortium

Breast cancer risk factor	N	Mean (SD) or %	High density lipoprotein (HDL-C) wGS [a]			Low density lipoprotein (LDL-C) wGS [a]			Triglycerides (TG) wGS [a]			Total cholesterol (TC) wGS [a]		
			B [b]	SE [b]	*P*	B [b]	SE [b]	*P*	B [b]	SE [b]	*P*	B [b]	SE [b]	*P*
BCAC iCOGS														
Age [c]	75 624	56·6 (11·1)	0·25	0·15	0·11	-0·51	0·16	$1{\cdot}1x10^{-3}$	-0·64	0·18	$4{\cdot}0x10^{-4}$	-0·65	0·15	$1{\cdot}1x10^{-5}$
Age at menarche	46 338	13·1 (1·6)	0·04	0·03	0·19	-0·04	0·03	0·21	-0·03	0·03	0·29	-0·04	0·03	0·13
Age at menopause	22 486	48·7 (5·8)	-0·04	0·15	0·80	-0·07	0·15	0·65	-0·29	0·18	0·10	-0·22	0·14	0·13
Age at first live birth [d]	38 483	25·2 (4·9)	0·11	0·10	0·25	-0·02	0·10	0·82	-0·35	0·11	$1{\cdot}6x10^{-3}$	-0·14	0·09	0·12
Number of births [d]	45 149	2·3 (1·0)	-0·01	0·02	0·74	0·01	0·02	0·78	0·01	0·02	0·85	-0·01	0·02	0·79
BMI (Premenopausal Women)	11 249	25·2 (4·9)	-0·21	0·18	0·23	-0·14	0·18	0·44	0·05	0·21	0·80	-0·17	0·17	0·32
BMI (Postmenopausal Women)	27 206	26·3 (4·8)	0·02	0·11	0·85	-0·10	0·11	0·39	-0·05	0·13	0·72	-0·03	0·11	0·76
Ever breastfed [d]	24 028	82·4%	0·15	0·06	$1{\cdot}2x10^{-2}$	0·03	0·06	0·57	-0·30	0·07	$1{\cdot}6x10^{-5}$	-0·13	0·06	0·02
Ever smoked regularly	15 993	45·9%	0·01	0·04	0·94	-0·05	0·04	0·21	-0·01	0·05	0·93	-0·06	0·04	0·13
Family history of breast cancer	8 953	28·1%	0·06	0·05	0·17	-0·01	0·05	0·82	-0·05	0·05	0·40	0·01	0·04	0·82
BCAC OncoArray														
Age [c]	106 053	55·8 (11·7)	0·10	0·13	0·47	-0·23	0·13	0·08	-0·21	0·16	0·18	-0·32	0·12	0·01
Age at menarche	74 572	13·0 (1·6)	0·05	0·02	$9{\cdot}6x10^{-3}$	0·01	0·02	0·85	-0·06	0·02	0·02	-0·01	0·02	0·64
Age at menopause	39 451	48·6 (5·8)	0·04	0·11	0·71	-0·13	0·10	0·21	0·07	0·13	0·58	-0·09	0·10	0·39
Age at first live birth [d]	59 688	25·2 (4·8)	-0·01	0·07	0·95	0·04	0·07	0·62	-0·12	0·08	0·14	-0·04	0·07	0·59
Number of births [d]	66 678	2·3 (1·1)	0·03	0·02	0·10	-0·03	0·01	0·04	-0·01	0·02	0·53	-0·01	0·01	0·42
BMI (Premenopausal Women)	22 797	25·4 (5·1)	0·02	0·12	0·85	-0·08	0·12	0·52	0·21	0·14	0·14	-0·01	0·12	0·96
BMI (Postmenopausal Women)	47 121	26·6 (5·1)	0·04	0·09	0·65	-0·05	0·08	0·58	0·26	0·10	0·01	0·07	0·08	0·40
Ever breastfed [d]	36 224	78·5%	0·05	0·04	0·25	0·02	0·04	0·55	-0·07	0·05	0·13	-0·01	0·04	0·97
Ever smoked regularly	30 183	46·2%	-0·01	0·03	0·99	-0·02	0·03	0·45	-0·04	0·03	0·20	-0·05	0·03	0·09
Family history of breast cancer	18 071	26·6%	-0·01	0·03	0·96	-0·01	0·03	0·64	0·02	0·04	0·58	0·01	0·03	0·62

[a] Genetically predicted lipid traits levels from weighted-genetic scores (wGSs).

[b] Beta estimates (β) and corresponding standard deviations (SD) estimated using either linear or logistic regression for continuous or dichotomous risk factors, respectively. Estimates represent associations per 1 SD increase in lipid trait.

[c] Age at diagnosis for cases, or age at interview for controls. Mean values used for subjects with missing information in regression models.

[d] Among parous women.

Supplementary Table 3. Association between one standard deviation (SD) increase in genetically-predicted lipid traits and breast cancer risk using individual-level data in the Breast Cancer Association Consortium (BCAC) for different covariate adjustment sets by genotyping platform

Genotyping Platform	Cases	Controls	High density lipoprotein (HDL-C) wGS [a]			Low density lipoprotein (LDL-C) wGS [a]			Triglycerides (TG) wGS [a]			Total cholesterol (TC) wGS [a]		
			OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
No adjustment														
iCOGS [b]	38 578	37 046	1·14	1·08-1·21	$2{\cdot}3x10^{-6}$	1·01	0·95-1·06	0·85	1·03	0·96-1·09	0·43	1·10	1·04-1·16	$3{\cdot}4x10^{-4}$
OncoArray [c]	62 846	43 207	1·07	1·02-1·12	$5{\cdot}5x10^{-3}$	0·99	0·95-1·03	0·65	1·00	0·95-1·05	0·95	1·06	1·01-1·10	$1{\cdot}1x10^{-2}$
Minimally-adjusted [d]														
iCOGS [b]	38 578	37 046	1·14	1·08-1·21	$6{\cdot}6x10^{-6}$	1·01	0·95-1·07	0·80	0·97	0·90-1·03	0·31	1·08	1·02-1·14	$9{\cdot}6x10^{-3}$
OncoArray [c]	62 846	43 207	1·10	1·05-1·16	$4{\cdot}3x10^{-5}$	0·99	0·95-1·04	0·77	0·89	0·85-0·94	$5{\cdot}8x10^{-5}$	1·02	0·97-1·06	0·43
Multivariable														
iCOGS [b]														
All women [e]	38 578	37 046	1·14	1·07-1·21	$1{\cdot}1x10^{-5}$	1·01	0·95-1·07	0·87	0·98	0·91-1·04	0·48	1·08	1·02-1·14	$7{\cdot}3x10^{-3}$
Among parous women[f]	13 063	12 503	1·16	1·05-1·28	$4{\cdot}6x10^{-3}$	0·97	0·88-1·07	0·56	0·94	0·83-1·06	0·30	1·02	0·93-1·13	0·62
OncoArray [c]														
All women [e]	40 165	29 789	1·11	1·04-1·17	$6{\cdot}2x10^{-4}$	1·00	0·94-1·06	0·94	0·89	0·83-0·95	$6{\cdot}6x10^{-4}$	1·02	0·96-1·07	0·58
Among parous women[f]	33 469	25 732	1·11	1·04-1·18	$1{\cdot}6x10^{-3}$	1·01	0·95-1·07	0·81	0·90	0·83-0·97	$3{\cdot}9x10^{-3}$	1·02	0·96-1·08	0·51

[a] Number of variantss included in lipid-specific weighted-genetic score (wGS): HDL-C = 74, LDL-C = 57, TG = 43, and TC = 74.

[b] Associations between each lipid-specific wGS and breast cancer risk are estimated from an unconditional logistic regression model adjusted for age, study, and top 6 principal components for European ancestry in the iCOGS sample. The iCOGS analysis excludes 19 018 individuals that overlap with OncoArray.

[c] Associations between each lipid-specific wGS and breast cancer risk are estimated from an unconditional logistic regression model adjusted for age, country, and top 10 principal components for European ancestry in the OncoArray sample.

[d] Models adjusted for age, study (iCOGS) or country (OncoArray), and top 6 (iCOGS) or top 10 (OncoArray) principal components for European ancestry.

[e] For iCOGS data, model adjusted for age, BCAC study, top 6 principal components for European ancestry, breastfeeding (ever/never), and age at first live birth (years). For OncoArray data, model adjusted for age, country, and top 10 principal components for European ancestry, age at menarche (years), parity (number of children), and body mass index (kg/m^2; n=29,787 missing). Additional covariates were chosen based on results from Supplementary Table 2.

[f] For iCOGS data, model adjusted for age, BCAC study, top 6 principal components for European ancestry, breastfeeding (ever/never), and age at first live birth (years), among parous women only. For OncoArray data, model adjusted for age, country, and top 10 principal components for European ancestry, age at menarche (years), parity (number of children), and body mass index (kg/m^2), among parous women only. Additional covariates were chosen based on results from Supplementary Table 2.

Supplementary Table 4. Pearson correlation coefficients among original and amended weighted-genetic scores (wGSs)

	High density lipoprotein (HDL-C) wGS		Low density lipoprotein (LDL-C) wGS		Triglycerides (TG) wGS		Total cholesterol (TC) wGS	
	Coefficient	***P***	**Coefficient**	***P***	**Coefficient**	***P***	**Coefficient**	***P***
BCAC iCOGS								
All Reported Variants [a]								
HDL-C	1·00000							
LDL-C	-0·14101	<0·0001	1·00000					
TG	-0·38380	<0·0001	0·22490	<0·0001	1·00000			
TC	0·09205	<0·0001	0·85017	<0·0001	0·31386	<0·0001	1·00000	
Exclusive Variants 1 [b]								
HDL-C	1·00000							
LDL-C	-0·00158	0·6629	1·00000					
TG	-0·00480	0·1866	0·00414	0·2544	1·00000			
BCAC OncoArray								
All Reported Variants [a]								
HDL-C	1·00000							
LDL-C	-0·14516	<0·0001	1·00000					
TG	-0·38707	<0·0001	0·21194	<0·0001	1·00000			
TC	0·06973	<0·0001	0·85615	<0·0001	0·30255	<0·0001	1·0000	
Exclusive Variants 1 [b]								
HDL-C	1·00000							
LDL-C	-0·00121	0·7286	1·00000					
TG	-0·01324	<0·0001	0·01167	0·0008	1·0000			

[a] Genetically predicted lipid traits levels from weighted-genetic scores (wGS), created by summing the number of risk alleles for each individual, weighted by beta coefficient from the Global Lipids Genetics Consortium, based on 74, 57, 43, and 74 variants for HDL-C, LDL-C, TG, and TC, respectively.

[b] Exclusive weighted-genetic scores for each lipid trait include only variants associated with HDL-C, LDL-C, or triglycerides at a genome-wide significance p value ≤ $5x10^{-8}$. Exclusive variant weighted-genetic scores include 54, 42, and 20 variants for HDL-C, LDL-C, and triglycerides, respectively. A weighted-genetic score was not constructed for total cholesterol.

Supplementary Table 5. Associations between one standard deviation (SD) increase in lipid trait levels and breast cancer risk factors using summary statistics from both iCOGS and OncoArray data to estimate the inverse-variance weighted (IVW) Mendelian randomization association, and associations from three different sensitivity analyses in the Breast Cancer Association Consortium (BCAC)

Approach	Cases	Controls	High density lipoprotein (HDL-C)			Low density lipoprotein (LDL-C)			Triglycerides (TG)			Total cholesterol (TC)		
			OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
IVW MR estimate [a]														
iCOGS	38 578	37 046	1·15	1·09-1·22	$1{\cdot}3x10^{-6}$	1·00	0·95-1·06	0·93	0·96	0·89-1·03	0·22	1·06	1·01-1·12	$2{\cdot}7x10^{-2}$
OncoArray	62 846	43 207	1·10	1·05-1·16	$3{\cdot}4x10^{-5}$	0·99	0·94-1·03	0·58	0·88	0·83-0·92	$1{\cdot}9x10^{-6}$	1·01	0·96-1·05	0·79
Meta-analysis [e]	101 424	80 253	1·12	1·08-1·17	$1{\cdot}8x10^{-7}$	0·99	0·96-1·03	0·74	0·92	0·84-1·00	$4{\cdot}1x10^{-1}$	1·03	0·99-1·08	0·18
$p_{heterogeneity}$				0·25			0·78			$5{\cdot}6x10^{-2}$			0·17	
Egger regression [b]														
iCOGS	38 578	37 046	1·07	0·95-1·21	0·26	0·94	0·81-1·09	0·42	0·96	0·80-1·15	0·64	0·91	0·79-1·04	0·17
OncoArray	62 846	43 207	1·05	0·94-1·17	0·40	0·95	0·86-1·05	0·29	0·89	0·77-1·03	0·12	0·93	0·84-1·03	0·16
Meta-analysis [e]	101 424	80 253	1·06	0·98-1·15	0·17	0·95	0·87-1·03	0·20	0·92	0·82-1·03	0·13	0·92	0·85-1·00	$5{\cdot}5x10^{-2}$
$p_{heterogeneity}$				0·82			0·91			0·52			0·80	
Weighted-regression [c]														
iCOGS	38 578	37 046	1·16	1·08-1·25	$2{\cdot}6x10^{-5}$	1·03	0·96-1·10	0·44	0·97	0·88-1·07	0·57	1·62	0·43-6·01	0·47
OncoArray	62 846	43 207	1·05	0·99-1·11	$8{\cdot}9x10^{-2}$	1·03	0·98-1·08	0·24	0·88	0·81-0·95	$1{\cdot}1x10^{-3}$	1·52	0·55-4·21	0·42
Meta-analysis [e]	101 424	80 253	1·10	1·00-1·21	$5{\cdot}4x10^{-2}$	1·03	0·99-1·07	0·14	0·92	0·84-1·01	$8{\cdot}5x10^{-2}$	1·56	0·70-3·48	0·28
$p_{heterogeneity}$				$3{\cdot}5x10^{-2}$			0·99			0·13			0·94	
Weighted-median [d]														
iCOGS	38 578	37 046	1·09	1·02-1·17	$1{\cdot}3x10^{-2}$	0·92	0·80-1·05	0·21	1·00	0·91-1·11	0·96	1·01	0·86-1·17	0·95
OncoArray	62 846	43 207	1·05	0·95-1·15	0·33	0·96	0·83-1·11	0·59	0·87	0·80-0·94	$4{\cdot}9x10^{-4}$	1·01	0·86-1·17	0·94
Meta-analysis [e]	101 424	80 253	1·08	1·02-1·14	$9{\cdot}4x10^{-3}$	0·94	0·85-1·04	0·21	0·93	0·81-1·07	0·30	1·01	0·91-1·13	0·86
$p_{heterogeneity}$				0·52			0·68			$3{\cdot}3x10^{-2}$			0·99	

[a] Mendelian randomization estimate derived using summary statistics for both iCOGS and OncoArray datasets.[25]

[b] Mendelian randomization estimate accounting for potential directional pleiotropy of genetic variants used in the instrument.[26] For iCOGS, intercept and *p* values for each lipid are as follows: (1) HDL-C: $\beta_{intercept}$ = 0·0052, p=0·11; (2) LDL-C: $\beta_{intercept}$ = 0·0049, p=0·30; (3) TG: $\beta_{intercept}$ = -0·0001, p=0·99; and (4) TC: $\beta_{intercept}$ = 0·0105, $p=7{\cdot}3x10^{-2}$. For OncoArray, intercept and *p* values for each lipid are as follows: (1) HDL-C: $\beta_{intercept}$ = 0·0034, p=0·23; (2) LDL-C: $\beta_{intercept}$ = 0·0031, p=0·32; (3) TG: $\beta_{intercept}$ = 0·0011, p=0·80; and (4) TC: $\beta_{intercept}$ = 0·0053, $p=7{\cdot}3x10^{-2}$.

[c] Mendelian randomization estimate accounting for potential genetic pleiotropy for HDL-C, LDL-C, and TG, and estimates are mutually-adjusted for one another. TC estimate is mutually-adjusted for all three lipids.[27, 28]

[d] Mendelian randomization estimate assuming 50% of the genetic variants used in each lipid-specific instrument are invalid.[29] Standard error for weighted-median approach estimated via bootstrapping and used to calculate 95% CIs.

[e] Random-effects meta-analysis.