Original Article

Causal effects of genetically determined metabolites on cancers included lung, breast, ovarian cancer, and glioma: a Mendelian randomization study

Yi Feng[1,2,3#], Runchen Wang[1,2,3#], Caichen Li[1,2#], Xiuyu Cai[4#], Zhenyu Huo[1,2,3#], Ziyu Liu[1,2,3#], Fan Ge[1,2,5], Chuiguo Huang[6], Yi Lu[1,2,3], Ran Zhong[1,2], Jianfu Li[1,2], Bo Cheng[1,2], Hengrui Liang[1,2], Shan Xiong[1,2], Xingyu Mao[7], Yilin Chen[8], Ruying Lan[1,2,3], Yaokai Wen[1,2,3], Haoxin Peng[1,2,3], Yu Jiang[1,2,3], Zixuan Su[1,2,3], Xiangrong Wu[1,2,3], Jianxing He[1,2,9*], Wenhua Liang[1,2,10*]

[1]Department of Thoracic Surgery and Oncology, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [2]Guangzhou Institute of Respiratory Health, Guangzhou, China; [3]Nanshan School, Guangzhou Medical University, Guangzhou, China; [4]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; [5]First Clinical School, Guangzhou Medical University, Guangzhou, China; [6]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China; [7]Department of Economics and Management, Shanghai Institute of Technology, Shanghai, China; [8]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangdong Key Laboratory of Vascular Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [9]Department of Thoracic Surgery, Nanfang Hospital of Southern Medical University, Guangzhou, China; [10]Department of Oncology Medical Center, The First People's Hospital of Zhaoqing, Zhaoqing, China

Contributions: (I) Conception and design: Y Feng, R Wang, C Li, X Cai; (II) Administrative support: W Liang, J He; (III) Provision of study materials or patients: Y Feng, Z Liu, X Mao, Y Chen, R Lan; (IV) Collection and assembly of data: Y Feng, Y Lu, Y Wen, H Peng, Y Jiang, Z Su, X Wu; (V) Data analysis and interpretation: Y Feng, R Wang, Z Huo, F Ge, C Huang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors are joint first authors.

[*]These authors are joint corresponding authors.

Correspondence to: Jianxing He. Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China; State Key Laboratory of Respiratory Disease, Guangzhou 510120, China; National Clinical Research Center for Respiratory Disease, Guangzhou 510120, China; Guangzhou Institute of Respiratory Health, Guangzhou 510120, China. Southern Medical University, Guangzhou, China. Email: drjianxing.he@gmail.com; Wenhua Liang. Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China; State Key Laboratory of Respiratory Disease, Guangzhou 510120, China; National Clinical Research Center for Respiratory Disease, Guangzhou 510120, China; Guangzhou Institute of Respiratory Health, Guangzhou 510120, China; The First People's Hospital of Zhaoqing, Zhaoqing 526000, China. Email: liangwh1987@163.com.

Background: Previous studies have shown that metabolites play important roles in phenotypic regulation, but the causal link between metabolites and tumors has not been examined adequately. Herein, we investigate the causality between metabolites and various cancers through a Mendelian randomization (MR) study.

Methods: We carried out a two-sample MR analysis based on genetic instrumental variables as proxies for 486 selected human serum metabolites to evaluate the causal effects of genetically determined metabotypes (GDMs) on cancers. Summary data from various cancer types obtained from large consortia. Inverse variance weighted (IVW), MR-Egger and weighted-median methods were implemented to infer the causal effects, moreover, we particularly explored the presentence of horizontal pleiotropy through MR-Egger regression and MR-PRESSO Global test. Metabolic pathways analysis and subgroup analyses were further explored using available data. Statistical analyses were all performed in R.

Results: In MR analysis, 202 significant causative relationship features were identified. 7-alpha-hydroxy-3-oxo-4-cholestenoate (OR_{IVW} =1.45; 95% CI: 1.06–1.97; P_{IVW} =0.018), gamma-glutamylisoleucine (OR_{IVW} =1.40; 95% CI: 1.16–1.69; P_{IVW} =0.0004), 1-oleoylglycerophosphocholine (OR_{IVW} =1.22; 95% CI: 1.1–1.35; P_{IVW} =0.0001), gamma-glutamylleucine (OR_{IVW} =4.74; 95% CI: 1.18–18.93; P_{IVW} =0.027) were the most dangerous metabolites

for lung cancer, ovarian cancer, breast cancer, and glioma, respectively; while pseudouridine (OR_{IVW} =0.50; 95% CI: 0.30–0.83; P_{IVW} =0.007), 2-methylbutyroylcarnitine (OR_{IVW} =0.77; 95% CI: 0.68–0.86; P_{IVW} =2.9×10^{-6}), 2-methylbutyroylcarnitine (OR_{IVW} =0.77; 95% CI: 0.70–0.85; P_{IVW} =3.4×10^{-7}), glycylvaline (OR_{IVW} =0.13; 95% CI: 0.02–0.75; P_{IVW} =0.021) were associated with lower risk of lung cancer, ovarian cancer, breast cancer, and glioma, respectively. Interestingly, 2-methylbutyroylcarnitine was also associated with decreased risk of lung cancer (OR_{IVW} =0.59; 0.50–0.70; P_{IVW} =1.98×10^{-9}) expect ovarian cancer and breast cancer. In subgroup analysis, 2-methylbutyroylcarnitine was associated with decreased risk of estrogen receptor (ER) positive breast cancer (OR_{IVW} =0.72; 0.64–0.80; P_{IVW} =3.55×10^{-9}), lung adenocarcinoma (LAC) (OR_{IVW} =0.60; 0.48–0.70; P_{IVW} =1.14×10^{-5}). Metabolic pathways analysis identified 4 significant pathways.

Conclusions: Our study integrated metabolomics and genomics to explore the risk factors involved in the development of cancers. It is worth exploring whether metabolites with causality can be used as biomarkers to distinguish patients at high risk of cancer in clinical practice. More detailed studies are needed to clarify the mechanistic pathways.

Keywords: Serum metabolite; cancer; Mendelian randomization (MR); 2-methylbutyroylcarnitine

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Introduction

Previous researches have shown that metabolites are crucial factor affecting tumorigenesis. For example, liver kinase B1 (LKB1) mutant lung cancers have deficits in nucleotide metabolism that confer hypersensitivity to deoxythymidylate kinase inhibition (1). N-acetylaspartic acid plays a significant role in promoting tumor growth (2). 2-hydroxyglutarate is abnormally elevated in glioma (3). However, a definitive comprehensive summary of the causal effect between metabolites and tumors is scarce, which is the purpose of this research.

Metabolites are the substrates and products of biological metabolism that belong to host organisms and are also produced directly by microorganisms and xenobiotics (4). Metabolomics is the profiling of metabolites biofluids, cells, and tissues, which are regularly applied as a biomarker discovery tool (5). Biomarkers obtained from human studies can help find links between diseases and metabolic pathways (6). Owing to the sensitivity of metabolomics, subtle alterations in biological behavior can be detected to provide insight into the mechanisms that underlie various physiological status and aberrant processes, as well as incorporated disease (4). Though there is a long history of metabolite identification and validation, one of the biggest challenges in biomarker validation is to overcome inter-individual metabolite variation due to the divergence in genetic factors and environmental exposures (7,8). The identification of the metabolites and their biological roles is the essential step. Under these conditions, many studies have shown the tremendous potential of metabolomics in cancer research (9,10).

Cancer is a major public health problem worldwide, especially lung cancer and breast cancer. In 2021, the estimated death rate of lung cancer is still at the top of the list, though the morbidity of breast cancer exceeded lung cancer for the first time. High-mortality has become the label for ovarian cancer and glioma (included in the brain and other nervous systems) (11). Though numerous researches have been carried out to explore these tumors, involving the molecular mechanism, cytological behavior, and biological process, etc., our understandings of the above issues are still limited (12,13). Fortunately, genetics, especially genome-wide association studies (GWAS), emerged as a fundamental pillar in many research areas (14,15), providing more dimensions to explore the causes of cancer.

Mendelian randomization (MR) is a general method based on GWAS summary data to evaluate the causal effects between exposure and outcome using genetic variants as instrumental variables (IVs) (16). In other words, genetic variants from GWAS can be used to mimic a randomized controlled comparison to verify causality between various factors (9,10). Moreover, GWAS has been extended to metabolic profiles. Therefore, this study aimed to use

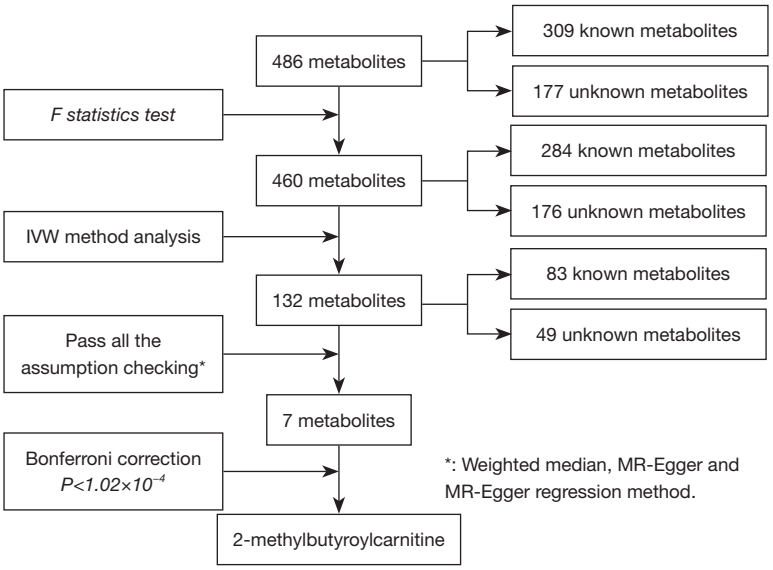

Figure 1 The flow diagram of the filtrating serum metabolites. IVW, inverse variance weighted; MR, Mendelian randomization.

two-sample MR approach to detect the causal effects of genetically determined metabotypes (GDMs) on lung cancer (LC), breast cancer (BC), ovarian cancer (OC), and glioma, due to the limitations of online data access, only four cancers were included in this research. We present the following article in accordance with the STREGA reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-34/rc).

Methods

Genetic variants from GWAS of metabolites

The entire methology implementation process is presented in *Figure 1*. GWAS summary datasets for 486 metabolites were detached from the study by Shin *et al.* (8), which has been the most comprehensive investigation of the genetic effects on human serum metabolism so far. Amount to 7,824 samples of two cohorts comprising of 1,768 participants from Germany KORA F4 and 6,056 participants from British Twins UK cohort. The KORA dataset and Twins UK dataset have been described in previous studies (8,16). The metabolites profiles of 486 fasting serum samples were analyzed by liquid-phase chromatography and gas chromatography (17). Sample preparation, mass spectrometry analysis, compound identification, quantification, and data curation were carried out for metabolic analysis by Metabolon, Inc. (https://www.metabolon.com/). After stringent quality control, 486 metabolites were used for genetic analysis, including 309 known and 177 unknown metabolites. The 309 known metabolites were further divided into 8 broad metabolic classes (amino acids, carbohydrates, cofactors and vitamins, energy, lipids, nucleotides, peptides, and xenobiotic metabolism) as described in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (18). The direct genotyping and imputation steps of the two cohorts were completed by HapMap 2-panel couple with passing stringent quality control metrics, and genome-wide discovery analysis was done based on approximately 2.1 million single nucleotide polymorphism (SNP) (19). Full GWAS summary datasets statistics were publicly available through the Metabolomics GWAS Server at http://metabolomics. helmholtz-muenchen.de/gwas/.

Selection criteria of instrumental variables for 486 metabolites

At the beginning, the unitary criteria were carried out for selecting SNPs from the 486 serum metabolites. we selected SNPs listed in the summary statistic, which have passed quality control with the $P<1\times10^{-5}$, this relaxation statistical threshold was commonly implemented in MR study to account for greater variation when few genome-wide significant SNPs were available for exposures (20). the clumping procedure was done by linkage disequilibrium (LD) analysis with lower P value as independent instruments

while setting the LD threshold of r^2<0.001 in a 10,000-kb window in the European 1000 Genomes reference panel (21). Furthermore, next steps to assess whether these instrumental variables were strong enough to predict the causal effect by two parameters: the explained genetic variation (R^2) and F statistic. the former associated with the corresponding metabolite exposures by formula and the *F* statistic was calculated to avoid weak instrument bias based on the formula $F=R^2(n-k-1)/(1-R^2)k$, which n is the sample size and k represents the number if SNPs (Table S1) (22). Widely speaking, an *F* statistic of more than 10 was taken for a typical threshold for selecting strong instrumental variables. The *F* statistic of each metabolite less than 10 will be screened out (23).

Genetic variants from GWAS of cancer

To evaluate the potential causal relationship between metabolites with four types of cancers, four GWAS summary statistics for cancers form different consortias were included. The integration of different population according to cancer type originated from the consortia: International Lung Cancer Association Consortia (ILCCO) (24) for lung cancer [including 11,348 cases and 15,861 controls, histologically, it can be divided into lung adenocarcinoma (LAC) and squamous cell cancer], Breast Cancer Association Consortium (BCAC) (25) for breast cancer (including 122,977 cases and 105,974 controls, divided into ER-positive breast cancer and ER-negative breast cancer), Ovarian Cancer Association Consortium (OCAC) (26) for ovarian cancer (including 25,509 cases and 40,941 controls). The GWAS about glioma comprised 14 cohorts, 3 case-control studies, and 1 population-based case-only study (including 6,811 cases) (27) (see Table S2).

MR statistical analysis

The rationale of MR was shown in Figure S1. Inverse variance weighted (IVW) method was used to estimate the causal effects between metabolites and four primary cancers (28). And then we utilized a multiple-testing adjusted threshold of $P<1.02\times10^{-4}$ (0.05/486) using the Bonferroni correction to clarify the statistical significance (29). Moreover, results can be biased if instrument SNPs show horizontal pleiotropy and influence the outcome through causal pathways other than the exposure (30). Therefore, the IVs should follow three assumptions: (I) the IVs are strongly associated with the serum metabolites; (II) the IVs affect cancers only through their effect on the serum metabolites; and (III) the IVs are independent of any confounding factors (21). Accordingly, the weighted median, MR-Egger and leave-one-out methods were implemented for sensitivity analysis and to test the second assumption (20). The weighted median and MR-Egger method provided estimates when a subset <50% or up to 50% of the variants came from invalid instrumental variants separately (30,31), leave-one-out method is the most commonly used test for sensitivity. Circos plots were conducted to summarize and visually compare the IVW MR results, MR-Egger estimates and weighted median estimates. Moreover, we particularly detected the presentence of horizontal pleiotropy through MR-Egger regression and MR-PRESSO Global test (32). Finally, subgroup analyses were further explored using the available data.

MR analysis was conducted in R (version 3.6.2) using the package "TwoSampleMR" (version 0.5.5) (21), "MR-PRESSO" (33) and Circos plots were generated using EpiViz (version 0.1.0), a R package built under R (version 4.0.5), Epiviz was built under ComplexHeatmap (34) and Circlize (35) R packages to generate Circos plots to compare association analysis data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (36).

Metabolic pathway analysis

After MR analysis, we next conducted a metabolic pathway analysis for the identified metabolites using web-based MetaboAnalyst 5.0 software (https://www.metaboanalyst.ca/MetaboAnalyst/faces/home.xhtml) (37), which All the metabolites was identified by IVW at P_{IVW} <0.05. When used pathway analysis module to probe potential pathways that might be involved in the biological processes of the four main cancers, a total of 49 human serum metabolic pathways from two metabolite set libraries, including 44 metabolite sets from both The Small Molecule Pathway Database (SMPDB) and KEGG database, 4 metabolites sets from KEGG database solely.

Results

Study overview

We performed a two-sample MR analysis to assess the causal effects of human serum metabolites on four primary

Table 1 The most detrimental and protective factors for four cancers

Trait	Exposure	IVW		MR-Egger		Weighted median	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Lung cancer	7-alpha-hydroxy-3-oxo-4-cholestenoate	1.45 (1.06–1.97)	0.0184	1.30 (0.74–2.26)	0.3625	1.15 (1.01–1.36)	0.0184
Lung cancer	Pseudouridine	0.50 (0.30–0.83)	0.0070	0.72 (0.17–3.06)	0.6536	0.65 (0.31–1.34)	0.2394
Ovarian cancer	Gamma-glutamylisoleucine	1.40 (1.16–1.69)	0.0004	1.18 (0.80–1.74)	0.4098	1.33 (0.99–1.79)	0.0570
Ovarian cancer	2-methylbutyroylcarnitine	0.77 (0.68–0.86)	2.995E-06	1.17 (0.90–1.53)	0.245	0.63 (0.52–0.0.75)	0.000
Breast cancer	1-oleoylglycerophosphocholine	1.22 (1.1–1.35)	0.0001	1.19 (0.97–1.45)	0.0917	1.17 (1.02–1.34)	0.0273
Breast cancer	2-methylbutyroylcarnitine	0.77 (0.70–0.85)	3.418E-07	1.59 (1.27–1.99)	6.233E-05	1.004 (0.91–1.11)	0.935
Glioma	Gamma-glutamylleucine	4.74 (1.18–18.93)	0.0278	3.18 (0.03–296.7)	0.6193	7.93 (1.03–61.02)	0.0466
Glioma	Glycylvaline	0.13 (0.02–0.75)	0.0217	0.12 (0.0002–87.65)	0.5347	0.09 (0.0071–1.20)	0.0683

IVW, inverse variance weighted; MR, Mendelian randomization.

cancers using GWAS summary statistics. For assess the causality between each metabolites with the outcome, we extracted the genetic variants as instrumental variables. The entire filtrate flow was shown in *Figure 1*. The instrumental variants explained from 0.01% to 9.37% in their respective phenotypes. The minimum *F* statistic for validity tests of genetic predictors was 17.21, which illustrate all instrumental variables for the 486 metabotypes were sufficiently credible (*F* statistic >10) (detail see Tables S3-S10).

Causal effects of the 486 metabolites on cancer

By using the genetic variants as proxies, the IVW method was carried out, and 202 significant causative relationship features (corresponding to 132 unique metabolites) in total were identified at P<0.05, including 83 (62.8%) features for known metabolites and 49 features for unknown metabolites (Tables S10,S11). Specifically, 7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca) (OR_{IVW} =1.45; 95% CI: 1.06–1.97; P_{IVW} =0.018), gamma-glutamylisoleucine (OR_{IVW} =1.40; 95% CI: 1.16–1.69; P_{IVW} =0.0004), 1-oleoylglycerophosphocholine (OR_{IVW} =1.22; 95% CI: 1.1–1.35; P_{IVW} =0.0001), gamma-glutamylleucine (OR_{IVW} =4.74; 95% CI: 1.18-18.93; P_{IVW} =0.027) were the most significantly dangerous metabolites for lung cancer, ovarian cancer, breast cancer, and glioma, respectively. On the contrary, pseudouridine (OR_{IVW} =0.50; 95% CI: 0.30–0.83; P_{IVW} =0.007), 2-methylbutyroylcarnitine (OR_{IVW} =0.77; 95% CI: 0.68–0.86; P_{IVW} =3.0×10^{-6}), 2-methylbutyroylcarnitine (OR_{IVW} =0.77; 95% CI: 0.70–0.85; P_{IVW} =3.4×10^{-7}), glycylvaline (OR_{IVW} =0.13; 95% CI: 0.02–0.75; P_{IVW} =0.021) were factors with highest protective value for lung cancer, ovarian cancer, breast cancer, and glioma, respectively (see *Table 1*). *Figure 2* showed all significant causative relationship features between known and unknown metabolites of the different types of cancer. Furthermore, causal relationship features following a multiple-testing-adjusted threshold under the Bonferroni correction (P<1.02×10^{-4}) were used to obtain metabolites. Interestingly, we observed that 2-methylbutyroylcarnitine had a protective value on several types of cancers. Specifically, it lower the incidence of lung cancer (OR_{IVW} =0.59; 95% CI: 0.50–0.70; P_{IVW} =1.98×10^{-9}), breast cancer (OR_{IVW} =0.77; 95% CI: 0.70–0.85; P_{IVW} =3.4×10^{-7}), and ovarian cancer (OR_{IVW} =0.77; 95% CI: 0.68–0.86; P_{IVW} =3.0×10^{-6}). In addition, it is notable that 2-methylbutyroylcarnitine was associated with higher mortality on glioma (OR_{IVW} =2.19; 95% CI: 1.17–4.09; P=0.015), which potentially indicated the 2-methylbutyroylcarnitine shares similar biological

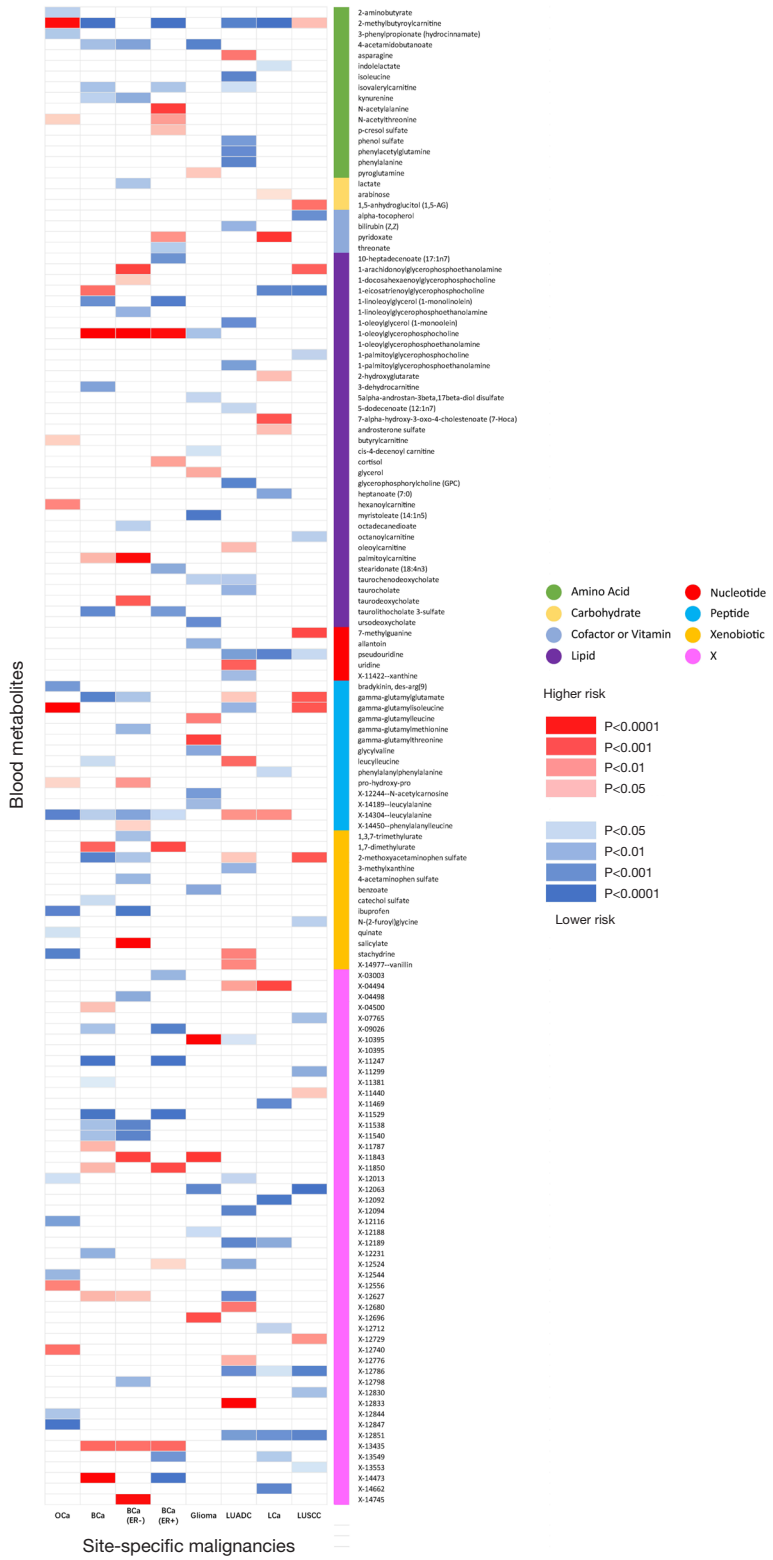

Figure 2 Mendelian randomization estimation of serum metabolites on the risk of 4 primary cancers by inverse-variance weighted analysis, grouped according to known and unknown metabolites. OCa, ovarian cancer; BCa, breast cancer; BCa(ER–), ER-negative breast cancer; BCa(ER+), ER-positive breast cancer; LUADC, lung adenocarcinoma; LCa, lung cancer; LUSCC, lung squamous cell carcinoma.

Table 2 Causal effects, sensitivity and pleiotropy test between 2-methylbutyroylcarnitine with cancers

Cancer type	IVW		MR-Egger		Weighted median		MR-PRESSO	MR-Egger regression	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		Egger intercept	Pleiotropy test
Breast cancer	0.77 (0.70–0.85)	3.42E-07	1.59 (1.27–1.99)	6.23E-05	1.01 (0.91–1.11)	9.35E-01	0.682	–0.0045	0.0458
ER+ breast cancer	0.72 (0.64–0.80)	3.55E-09	1.58 (1.23–2.02)	3.06E-04	1.00 (0.90–1.12)	9.45E-01	0.792	–0.0038	0.1506
Glioma	2.19 (1.17–4.09)	0.015	0.89 (0.16–4.96)	8.95E-01	1.99 (0.75–5.31)	1.67E-01	0.216	–0.0054	0.8026
Lung cancer	0.59 (0.50–0.70)	1.98E-09	1.60 (1.08–2.36)	1.91E-01	0.85 (0.66–1.09)	2.03E-01	<0.001	–0.0025	0.6381
Lung adenocarcinoma	0.60 (0.48–0.75)	1.14E-05	1.72 (1.005–2.96)	4.82E-02	0.59 (0.41–0.87)	7.20E-03	0.123	–0.0002	0.9826
Squamous cell lung cancer	0.78 (0.63–0.98)	3.3E-02	1.97 (1.17–3.32)	1.12E-02	1.28 (0.89–1.84)	1.79E-01	0.452	–0.0079	0.3344
Ovarian cancer	0.77 (0.68–0.86)	3.00E-06	1.17 (0.90–1.53)	2.45E-01	0.63 (0.52–0.75)	4.77E-07	0.319	–0.0040	0.3235

ER, estrogen receptor; IVW, inverse variance weighted; MR, Mendelian randomization.

mechanism among the three cancers except glioma (*Table 2* and Figures S2-S5). These genetic variants explaining the association between 2-methylbutyroylcarnitine with four types of cancers were listed in Tables S12-S15 individually.

Sensitivity and pleiotropy analysis

To avoid horizontal pleiotropy for MR research, sensitivity and pleiotropy analysis was implemented to evaluate the robustness of the estimates, all results were demonstrated in Tables S3-S10. Especially, *Table 3* demonstrated the results of the sensitivity and pleiotropy analysis for 2-methylbutyroylcarnitine on the four primary cancers (see Figure S4). Besides, we found pleiotropy in 2-methylbutyroylcarnitine on breast cancer ($P_{pleiotropy}$ =0.045) and lung cancer ($P_{MR\text{-}PRESSO\ Global}$ <0.0001). The result of IVW, MR-Egger and weighted-median of all known metabolites were integrated shown in *Figure 3*.

We further reported four suggestive association features that passed all sensitive analyses (P<0.05) (see *Table 3* and Figures S6-S9), which respectively were leucylalanine on lung cancer (OR_{IVW} =1.16; 95% CI: 1.01–1.32; P_{IVW} =0.031), 3-dehydrocarnitine on breast cancer (OR_{IVW} =0.88; 95% CI: 0.78–0.98; P_{IVW} =0.019), ibuprofen on ovarian cancer (OR_{IVW} =0.96; 95% CI: 0.93–0.99; P_{IVW} =0.007), leucylalanine on ovarian cancer (OR_{IVW} =0.96; 95% CI: 0.93–0.99; P_{IVW} =0.007). These genetic variants explaining the association between the four metabolites with three types of cancers were listed in Tables S16-S19.

Subgroup analysis of lung cancer and breast cancer

In the exposure obtained from ILCCO and BCAC, lung cancer was divided into adenocarcinoma and squamous cell carcinoma; breast cancer was divided into ER-positive and ER-negative cancer. 2-methylbutyroylcarnitine was associated with protective effects on LAC (OR_{IVW} =0.60; 95% CI: 0.48–0.70; P_{IVW} =1.14×10^{-5}) and ER-positive breast cancer (OR_{IVW} =0.72; 95% CI: 0.64–0.80; P_{IVW} =3.55×10^{-9}) statistically under Bonferroni correction (P<1.02×10^{-4}), but not in ER-negative breast cancer (OR_{IVW} =1.06; 95% CI: 0.88–1.26; P_{IVW} =0.55) and squamous cell lung cancer (SCLC) (OR_{IVW} =0.78; 95% CI: 0.63–0.98; P_{IVW} =0.03), these result might provide potential evidence for the biogenetic mechanisms of different tumors. It is worth noting that the causal association between 2-methylbutyroylcarnitine and LAC was robust when two additional MR tests were conducted ($P_{weighted\text{-}median}$ =0.007, $P_{MR\text{-}Egger}$ =0.019). These genetic variants explaining the association between 2-methylbutyroylcarnitine with two types of cancers were

Table 3 Statistically significant association between seven potential metabolites and cancers

Cancer type	Metabolite	Included SNP	IVW		MR-Egger		Weighted median	
			OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Breast cancer	3-dehydrocarnitine	22	0.88 (0.78–0.98)	0.0194	0.77 (0.60–0.995)	0.047623	0.81 (0.70–0.95)	0.00790012
ER– breast cancer	1-oleoylglycerophosphocholine	16	1.38 (1.17–1.62)	0.0001	1.44 (1.05–1.99)	0.026764	1.36 (1.07–1.73)	0.01233648
	Salicylate	19	1.04 (1.01–1.06)	0.0009	1.05 (1.02–1.08)	0.002736	1.05 (1.02–1.09)	0.00102991
Lung cancer	Leucylalanine	19	1.16 (1.01–1.32)	0.031	1.70 (1.11–2.61)	0.017587	1.37 (1.12–1.66)	0.0019708
Squamous cell lung cancer	Octanoylcarnitine	17	0.74 (0.55–0.98)	0.038	0.53 (0.29–0.95)	0.036358	0.58 (0.36–0.92)	0.0204581
Ovarian cancer	Ibuprofen	101	0.96 (0.93–0.99)	0.007	0.92 (0.85–0.99)	0.033462	0.95 (0.91–0.995)	0.03205872
	Leucylalanine	19	0.96 (0.93–0.99)	0.007	0.92 (0.85–0.99)	0.033462	0.95 (0.91–0.995)	0.03205872

IVW, inverse variance weighted; MR, Mendelian randomization; ER, estrogen receptor; SNP, single nucleotide polymorphism.

listed in Tables S20,S21. Results were consistent in sensitivity analyses, which were listed in Tables S22-S24.

Metabolic pathway analysis

The metabolic pathway analysis identified four metabolic pathways among the four cancers at P<0.05. the results show that "Vitamin B6 metabolism (P=0.028) and Butanoate metabolism (P=0.047)" pathway might be involved in the genesis of lung cancer. "Aminoacyl-tRNA biosynthesis (P=0.006) and Phenylalanine, tyrosine and tryptophan biosynthesis (P=0.033)" pathway might be associated with LAC (Table S25).

Discussion

This MR study provided potential causal effects of human serum metabolites on four primary cancers using standard IVW and alternative weighted median, MR-Egger method. Using genetic variants as proxies, we observed 137 metabolites associated with the risk of cancers. Specifically, 2-methylbutyroylcarnitine, leucylalanine, 3-dehydrocarnitine, ibuprofen, salicylate, 1-oleoylglycerophosphocholine and octanoylcarnitine, were closely related to different cancers, which may play roles in oncogenesis.

In this study, 2-methylbutyroylcarnitine showed a low to moderate protective effect associated with different cancers. In previous research, serum 2-methylbutyroylcarnitine was lower in obese children than normal-weighted children (1.38 folds), but the exact mechanism was unclear (38). We speculate that this metabolite could be involved in tumor genesis through this protective aspect. It is interesting to note the causal relationship presented by different results in the subgroup analysis of lung cancer and breast cancer, which validated the different driving mechanisms (39-41). However, some unknown factors are still involved, leading to bias or the single instrumental variable significantly affects the outcome variable. Therefore, considering that few study has been published on this metabolite, more researches related to this metabolite are warranted to be conducted in the future to elaborate its influence on tumor pathophysiology.

As for the potential metabolites, we found more researches about them. One study about leucylalanine suggested this metabolite is more focused on anti-inflammatory and cardiovascular activities and toxicity (42). On the basis of speculation combined with the mendelian causal effect, leucylalanine may be a protective metabolite in ovarian cancer. But the possible mechanism related to lung cancer is unclear. 3-dehydrocarnitine, a member of the carnitine family, is an intermediate in carnitine

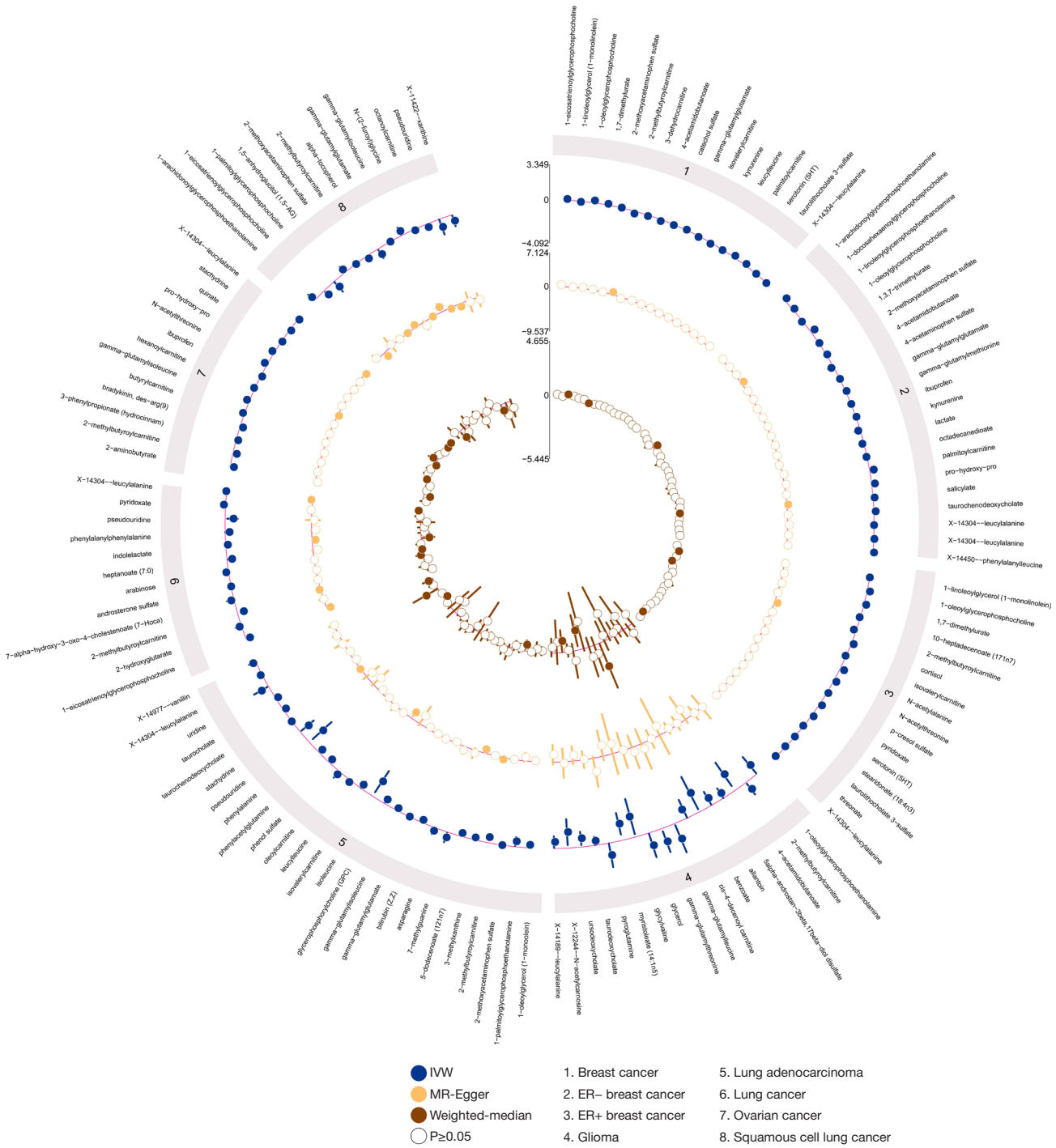

Figure 3 IVW Mendelian randomization estimates, MR-Egger estimates, and weighted-median estimates for the associations between pan metabolites and Four primary cancers. IVW, inverse variance weighted; MR, Mendelian randomization.

degradation, which has long been associated with fatty acid metabolism, glucose tolerance, insulin function (43). Fatty acid metabolism has long been associated to cancer cell metabolism. Limited fatty acid available may control cancer cell proliferation. A research found that fatty acid metabolism contains unexplored plasticity in the cancer cell and tried to explain the metabolic plasticity in fatty acid desaturation (44,45). "Warburg effect" seems to be cancer's favorite, i.e., the enhanced glycolysis or aerobic glycolysis, even when the ambient oxygen supply is sufficient (46-48). Moreover, 3-dehydrocarnitine is an early biomarker for predicting type 2 diabetes, with applications even prior to the development of insulin resistance (49). During the tumor promotional microenvironment in the mammary gland, Ibuprofen administration reduces overall tumor growth and enhances anti-tumor immune characteristics while avoiding adverse autoimmune reactions (50). But its real-world representation remains vague (51,52). One of the enabling characteristics of cancer development is tumor related inflammation and chronic inflammatory disease did promote the possibility of tumor occurrence (53). More notably, non-steroidal anti-inflammatory drugs (NSAIDs) combined with aromatase inhibitors reduce circulating E2, proinflammatory cytokines, and macrophage recruitment in the lung microenvironment after tobacco exposure, which were proved at preclinical studies as preventive agents of tobacco-induced lung cancer (54). The only one study could be retrieved referred to concentration of 1-oleoylglycerophosphocholine was higher when compared to the normal wild type rat using high mass accuracy electrospray ionization multistage tandem mass spectrometry (55). In a cohort study of metabolites involved in chronic disease by the effects of vegetarian dietary patterns, vegans showed lower abundance in acylcarnitine, and many subclasses of this metabolite may play a role in insulin dysregulation, inflammation, and so on (56) together with the effect on myocardium (57) and arterial stiffness (58)

There are some advantages to our study. Firstly, this research is the first MR study associating metabolomics with genomics to detect the causal relation of serum metabolites on cancers. Secondly, the SNPs from consortia we selected have been verified by peer review and have sufficient sample sizes. Thirdly, the methods chosen to evaluate the causal relationship between metabolites and cancers are valid, including IVW, weighted median and MR-Egger. Furthermore, rigorous Bonferroni correction was implemented, and we manually removed the non-significant genetic variants ($P<1\times10^{-5}$) in double verification.

A few drawbacks, however, exist in our study. Firstly, as the MR principle evolving these years, compared with adopting existed ones, refining the methodology and choosing better models is more meaningful. Secondly, some of the result of weighted median and MR-Egger between 2-methylbutyroylcarnitine with some types of cancers except LAC are not up to standard ($P<0.05$), which the weighted median and MR-Egger method needed and be marginalized by statistical calculation. Thirdly, due to the data availability, we could only access the four major cancers data included in the research , but those four tumors were typically representative.

Conclusions

To summarize, our MR study identified 132 metabolites that probably have causal effects on the progress of cancers. Interestingly, 38 metabolites have causal effects on more than one cancer, implying some overlapped metabolic pathways among four different cancers. Our study could also be used as the basis for other cancer research and combine with translational and clinical research to explain how the metabolites induce the development of cancers, Finally, although our study identified many metabolites associated to the incidence rate of cancers, further investigations are needed to reveal their functions in the pathogenesis of relevant diseases in the future.

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Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-34/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-34/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. And the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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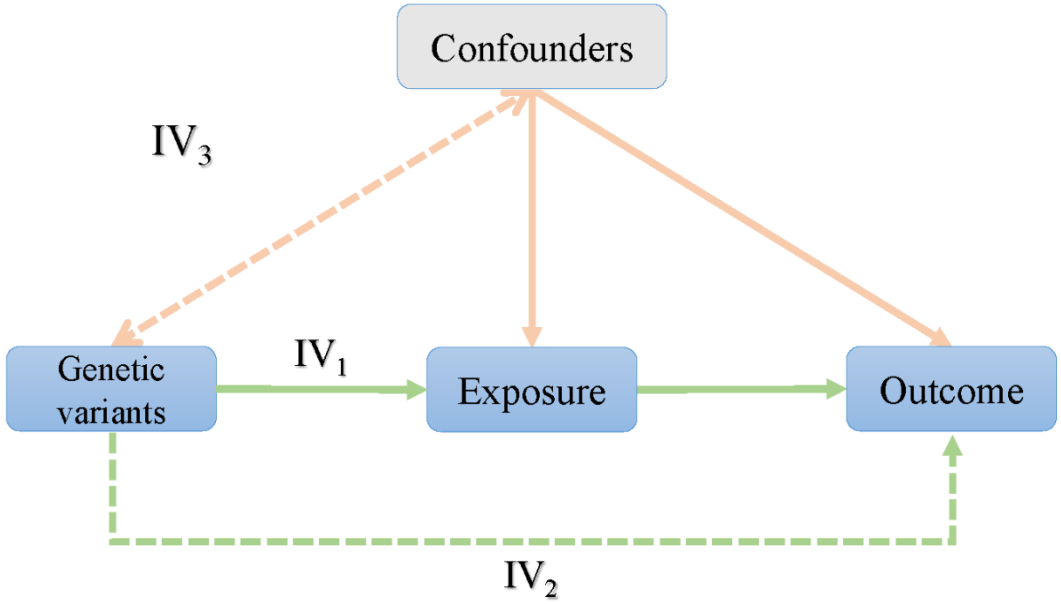
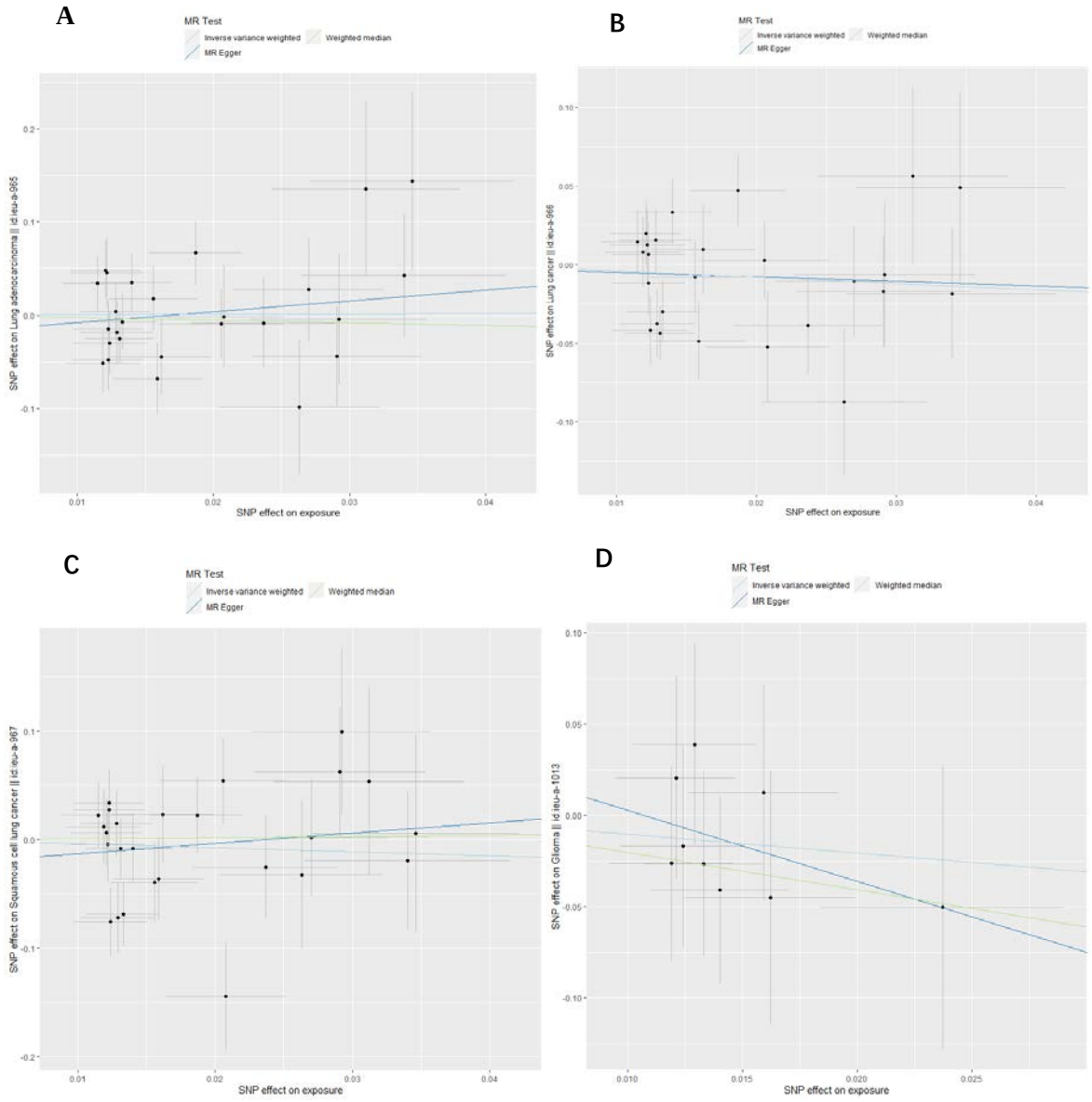


IV assumption 1 represents the instrumental variables (IVs) are strongly associated with the exposure; IV assumption 2 indicates the IVs must influence the outcome only through the exposure; IV assumption 3 shows the IVs must not associate with confounders.

Figure S1 The rationale of Mendelian randomization.



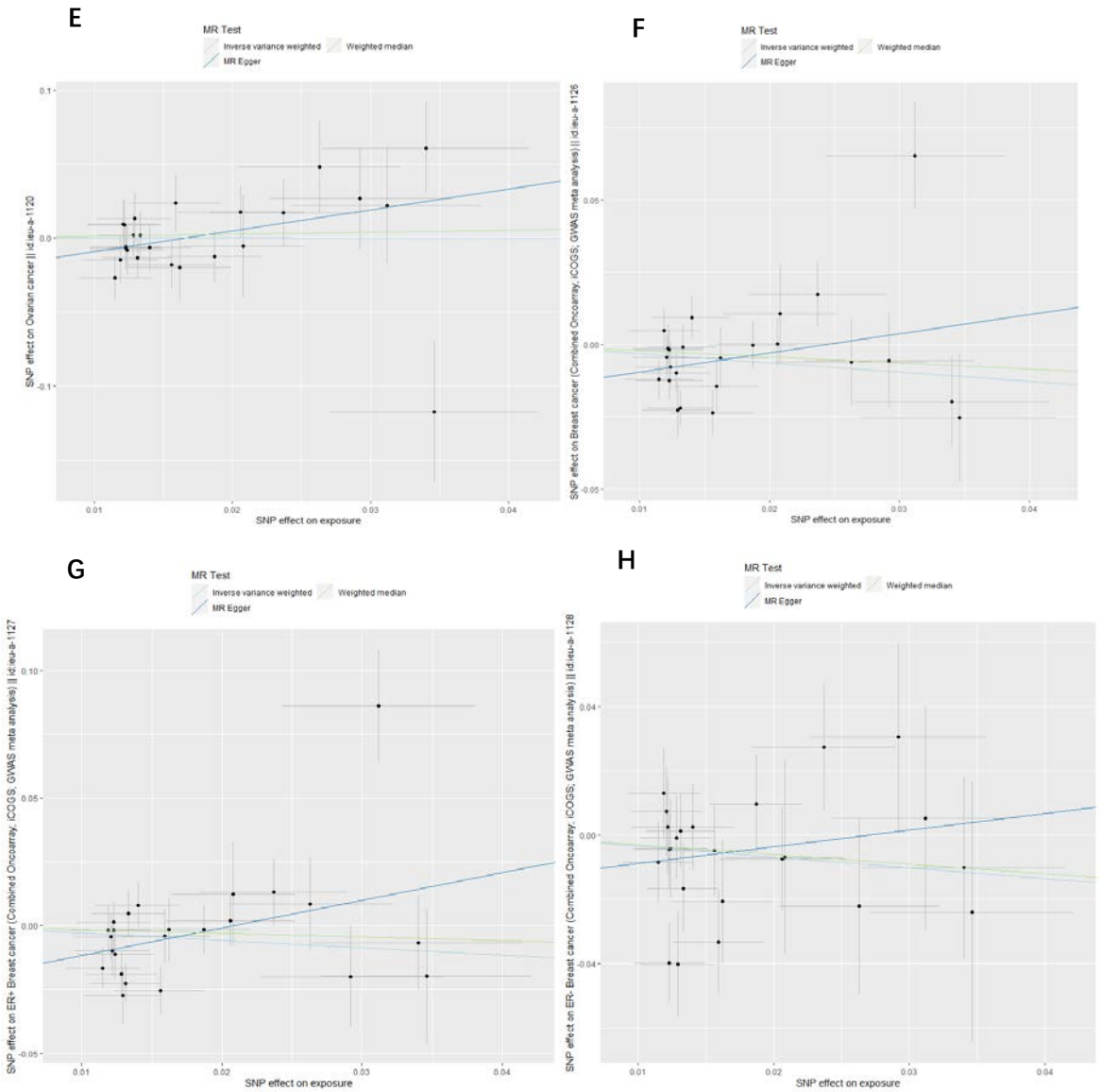
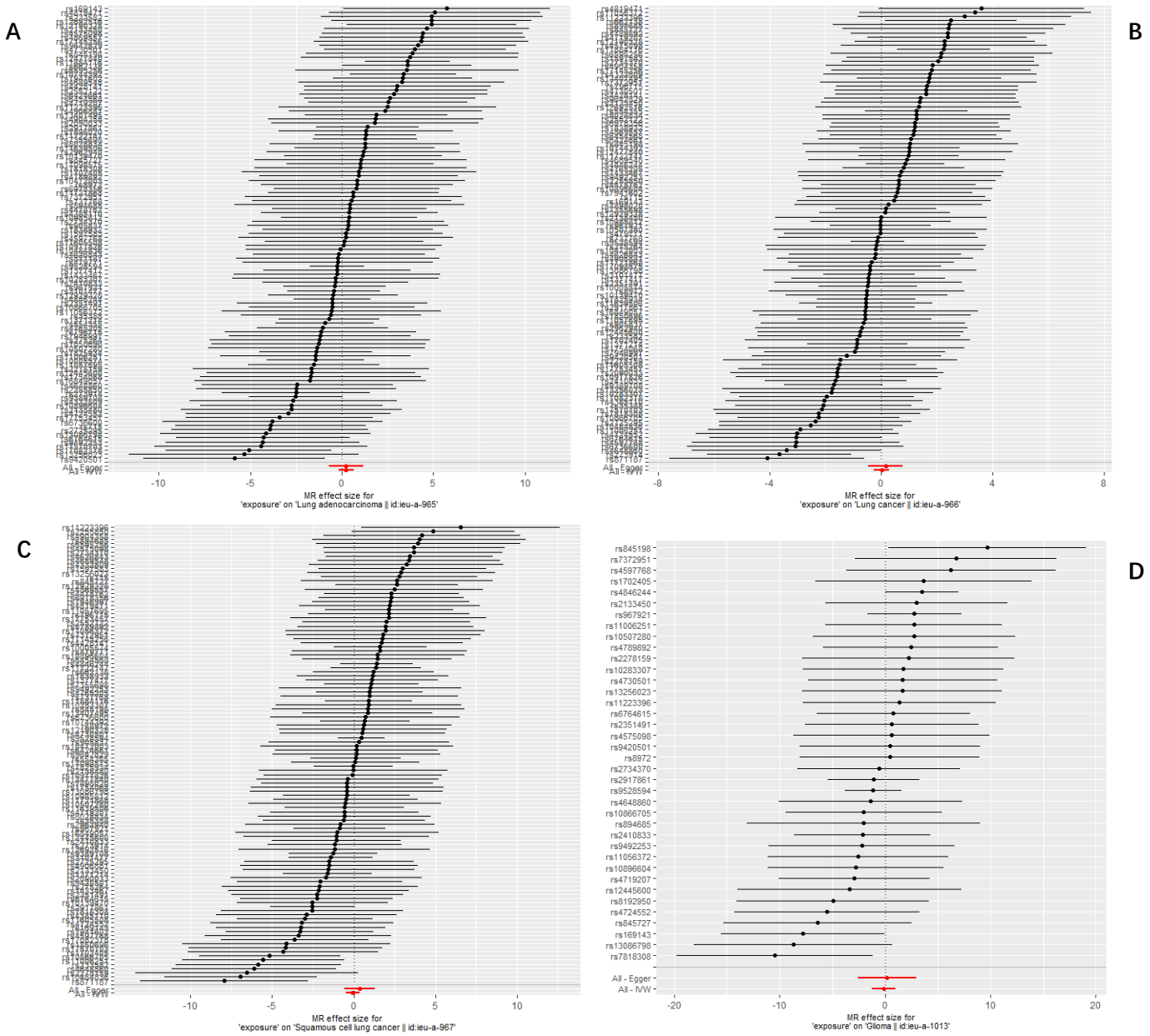


Figure S2 Scatter plots showing the causal association of 2-methylbutyroylcarnitine on the risk of cancers. Lung adenocarcinoma (A), lung cancer (B), squamous cell lung cancer (C), glioma (D), ovarian cancer (E), breast cancer (F), ER+ breast cancer (G), ER- breast cancer (H).



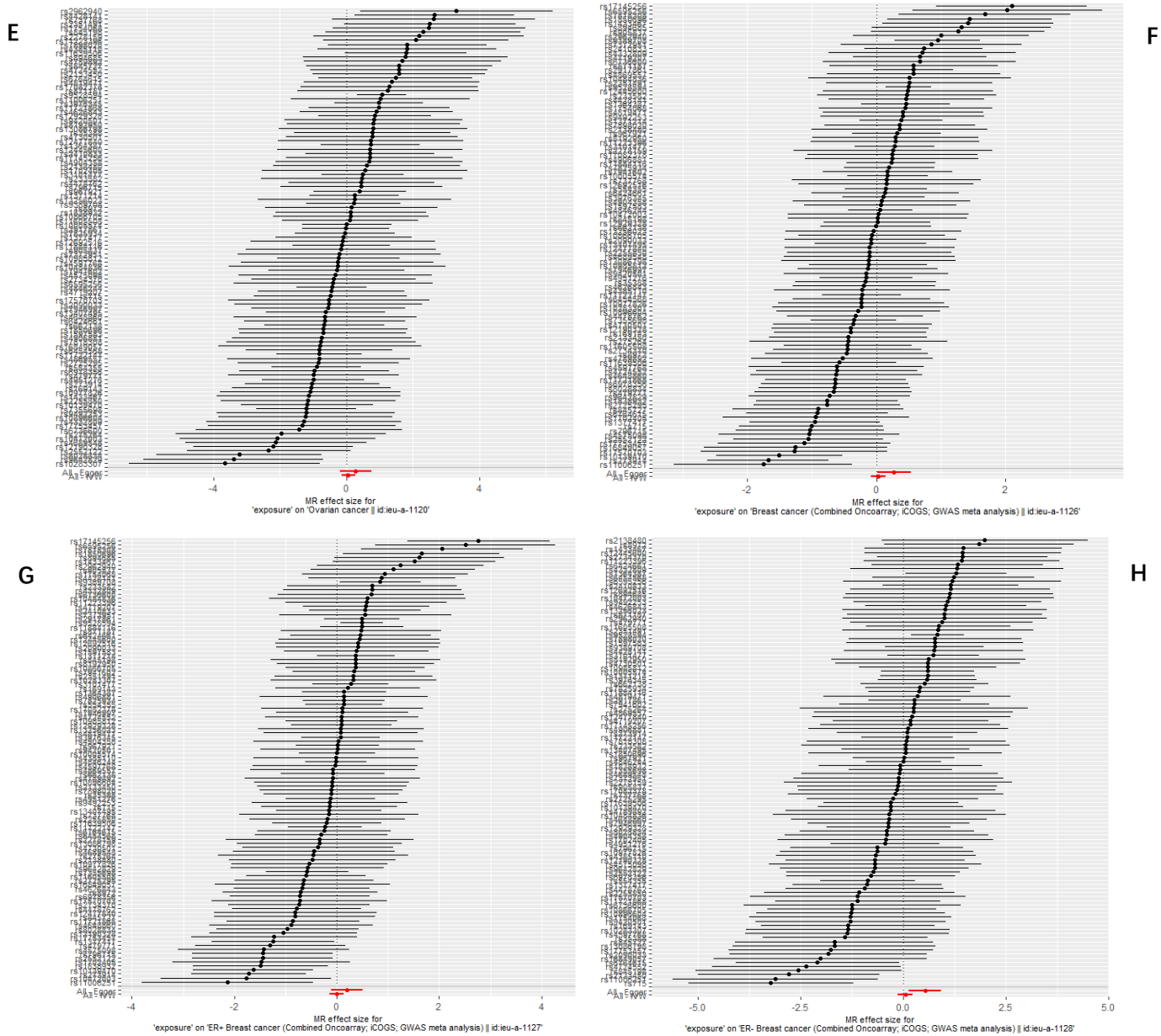
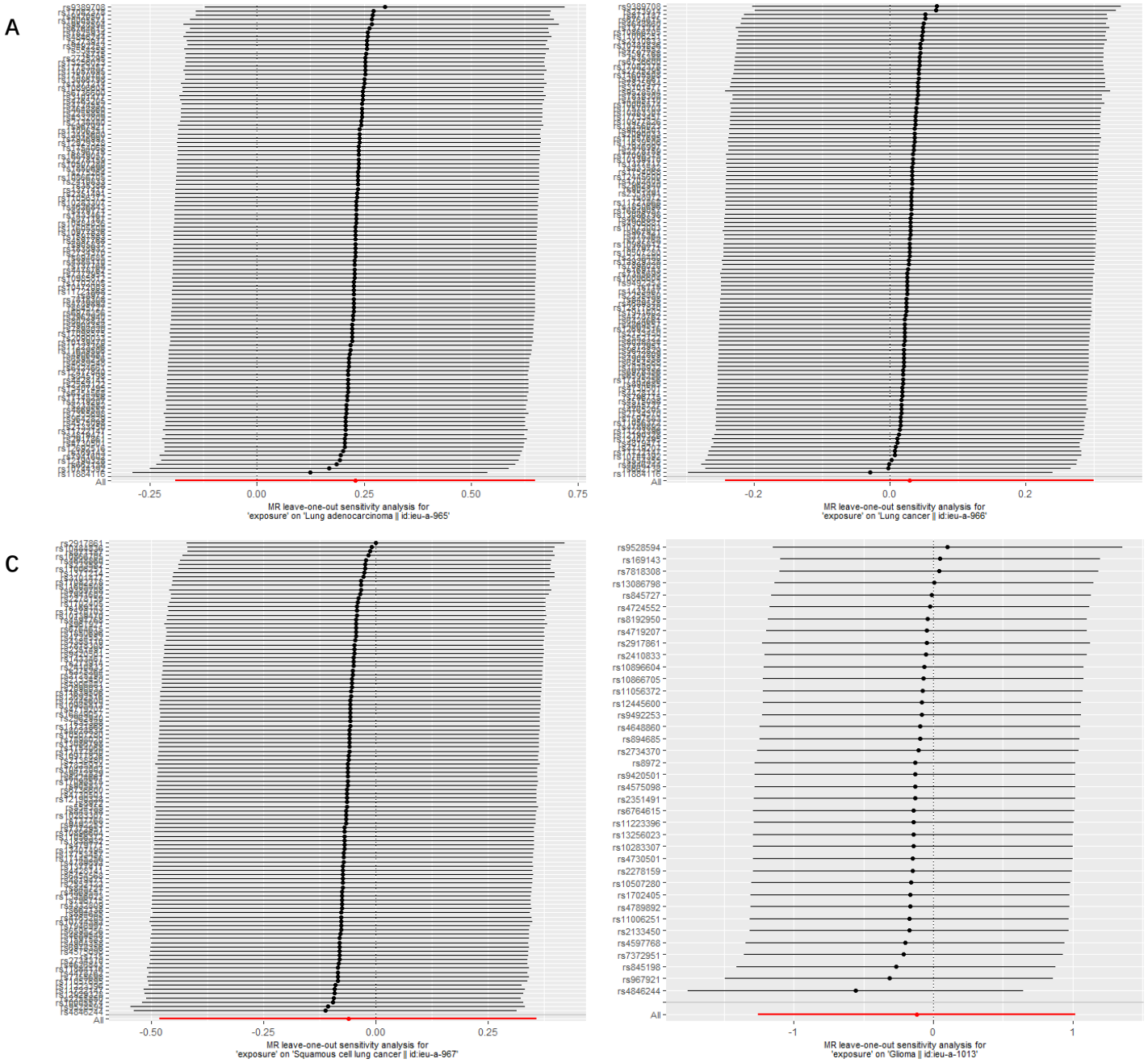


Figure S3 Forest plots for 2-methylbutyroylcarnitine on different cancers. Lung adenocarcinoma (A), lung cancer (B), squamous cell lung cancer (C), glioma (D), ovarian cancer (E), breast cancer (F), ER+ breast cancer (G), ER- breast cancer (H).



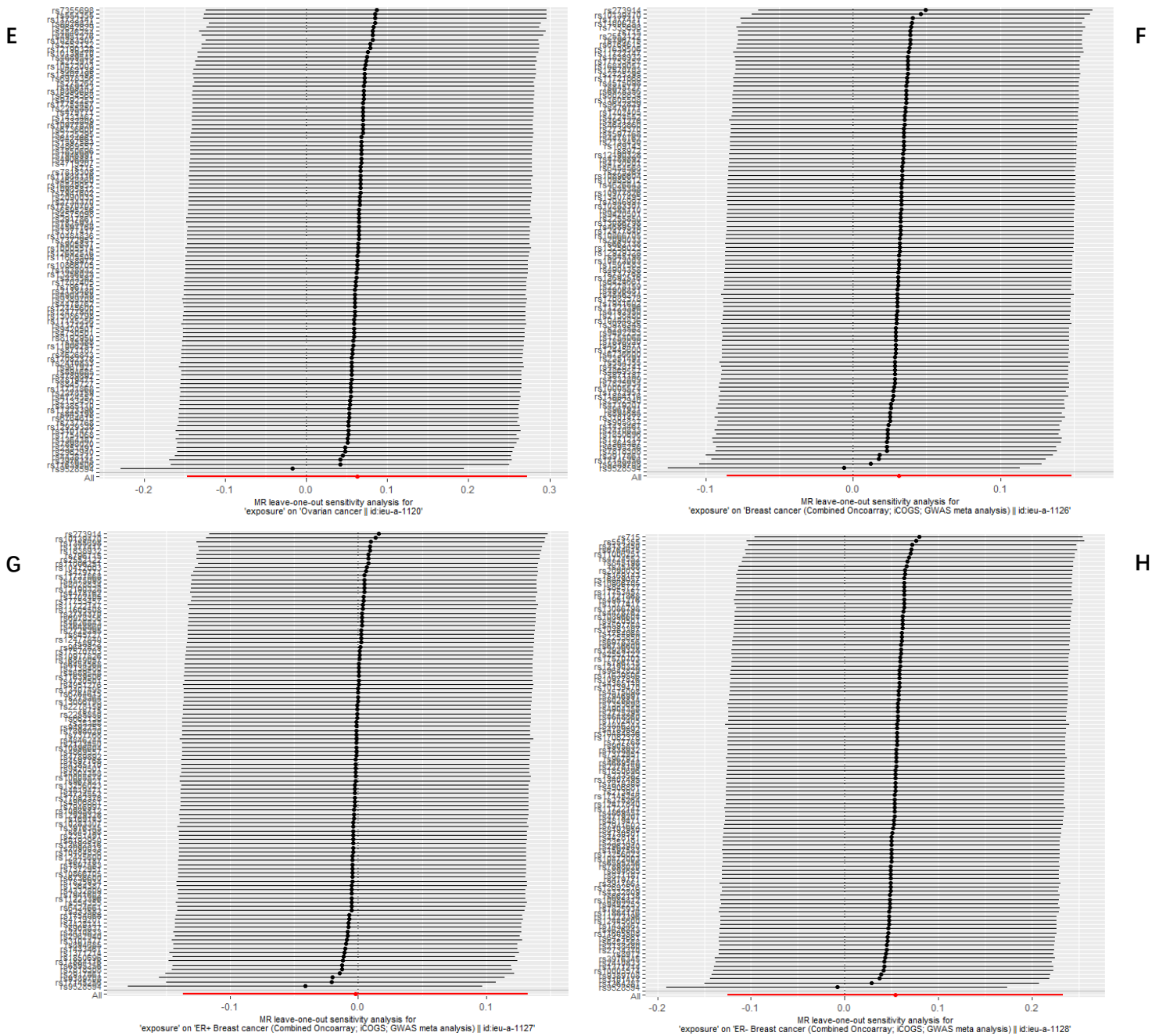
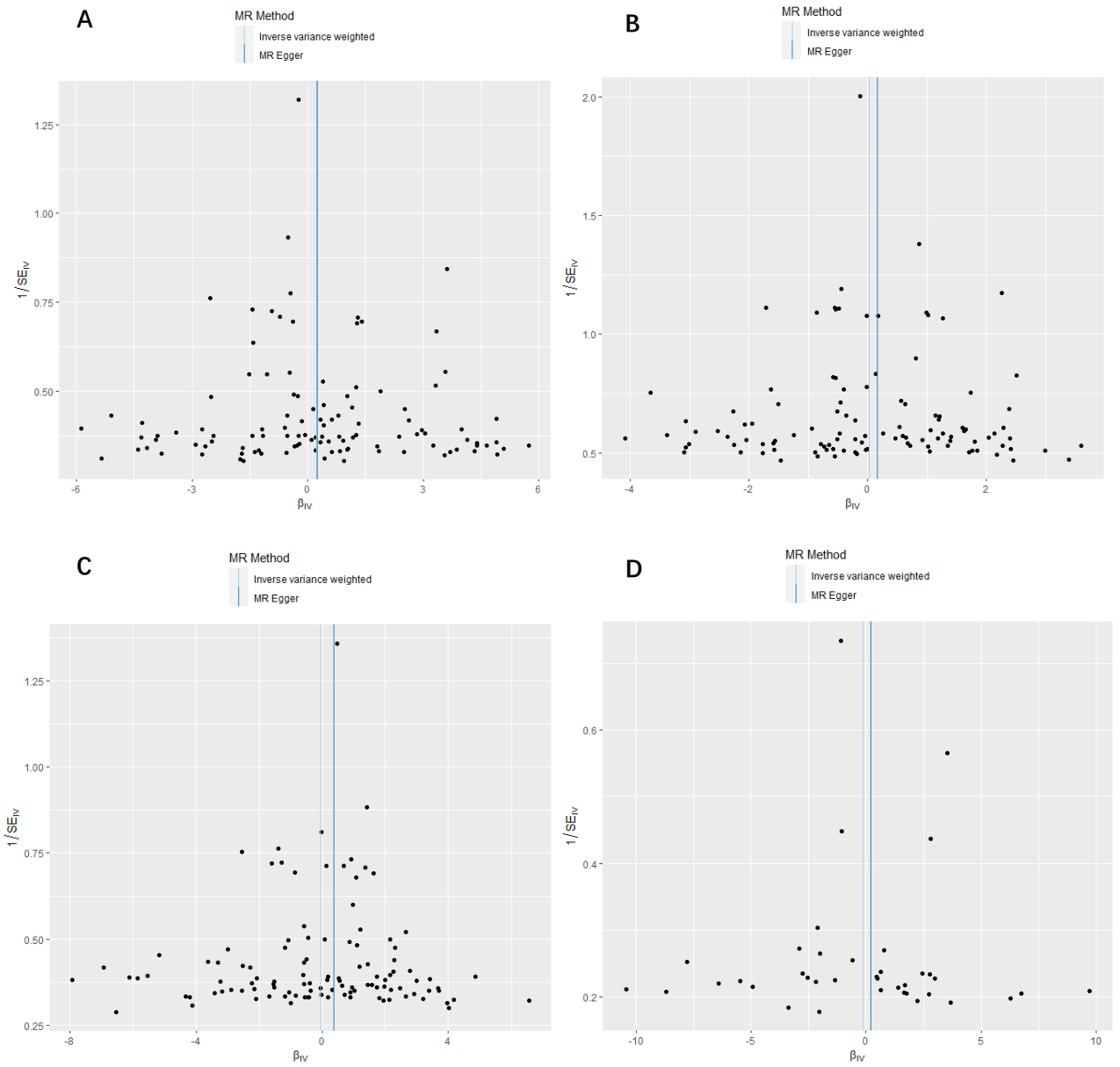


Figure S4 Leave-one-out plots for 2-methylbutyroylcarnitine on different cancers. Lung adenocarcinoma (A), lung cancer (B), squamous cell lung cancer (C), glioma (D), ovarian cancer (E), breast cancer (F), ER+ breast cancer (G), ER- breast cancer (H).



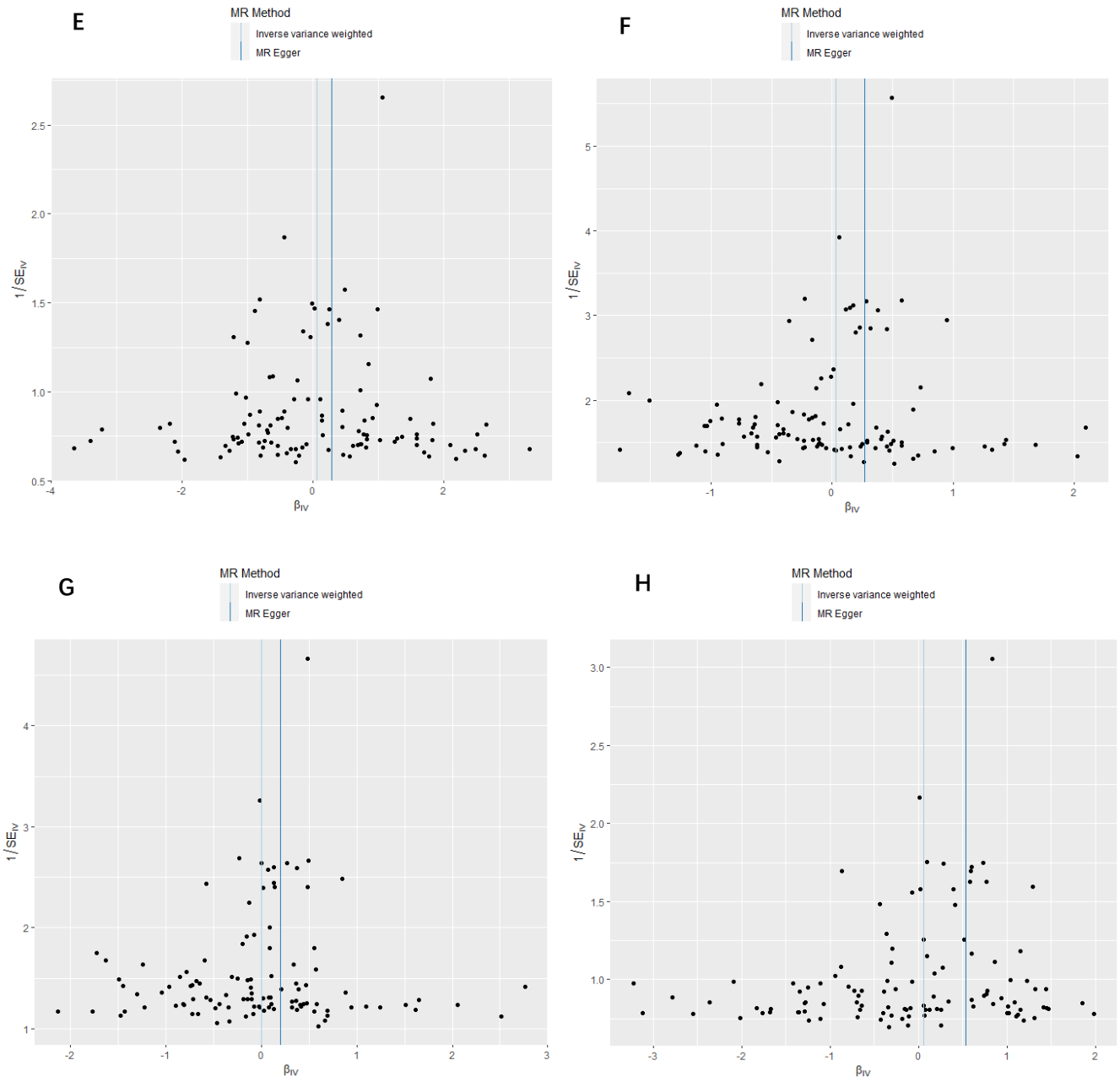
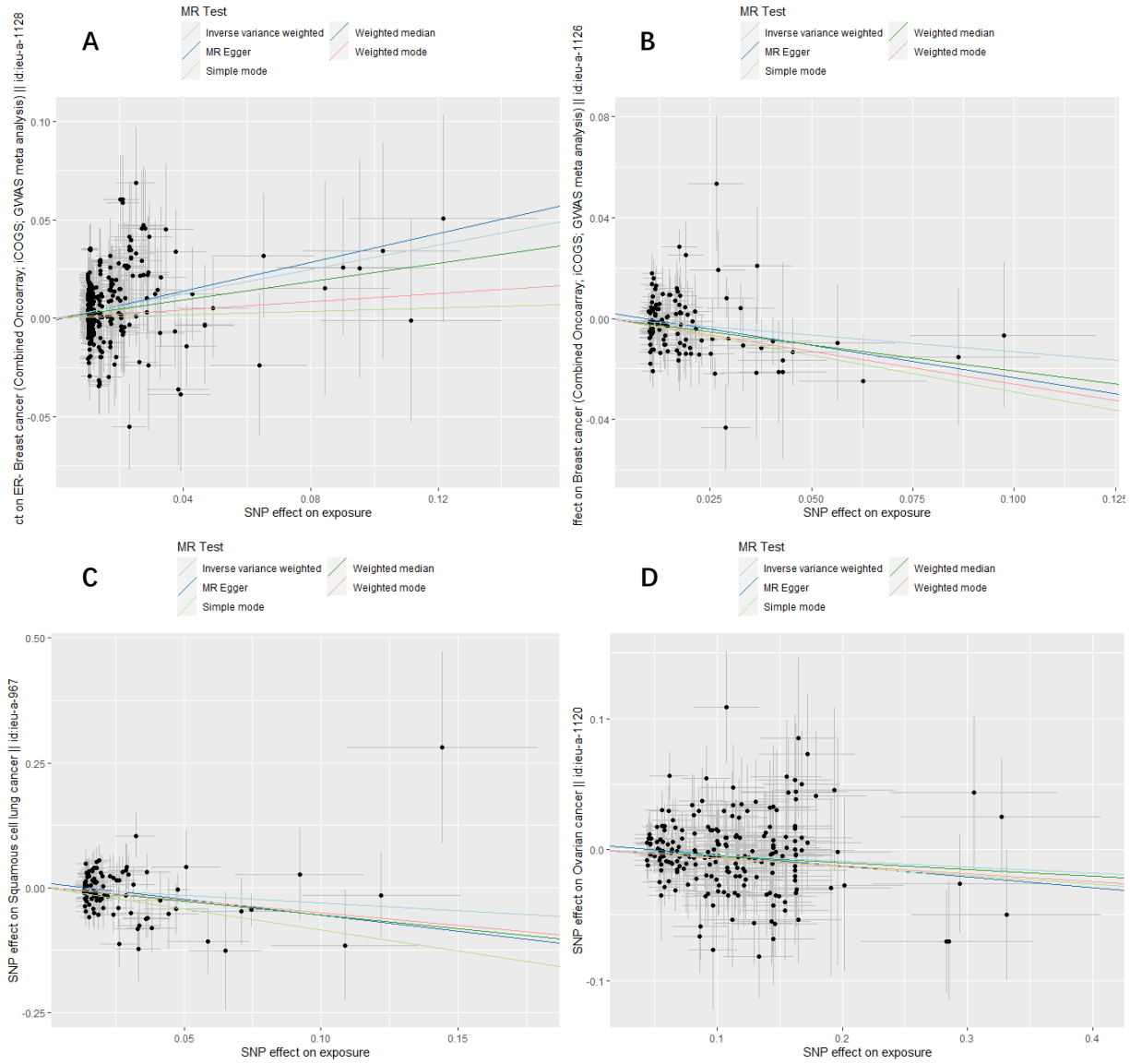


Figure S5 Funnel plots for 2-methylbutyroylcarnitine on different cancers. Lung adenocarcinoma (A), lung cancer (B), squamous cell lung cancer (C), glioma (D), ovarian cancer (E), breast cancer (F), ER+ breast cancer (G), ER- breast cancer (H).



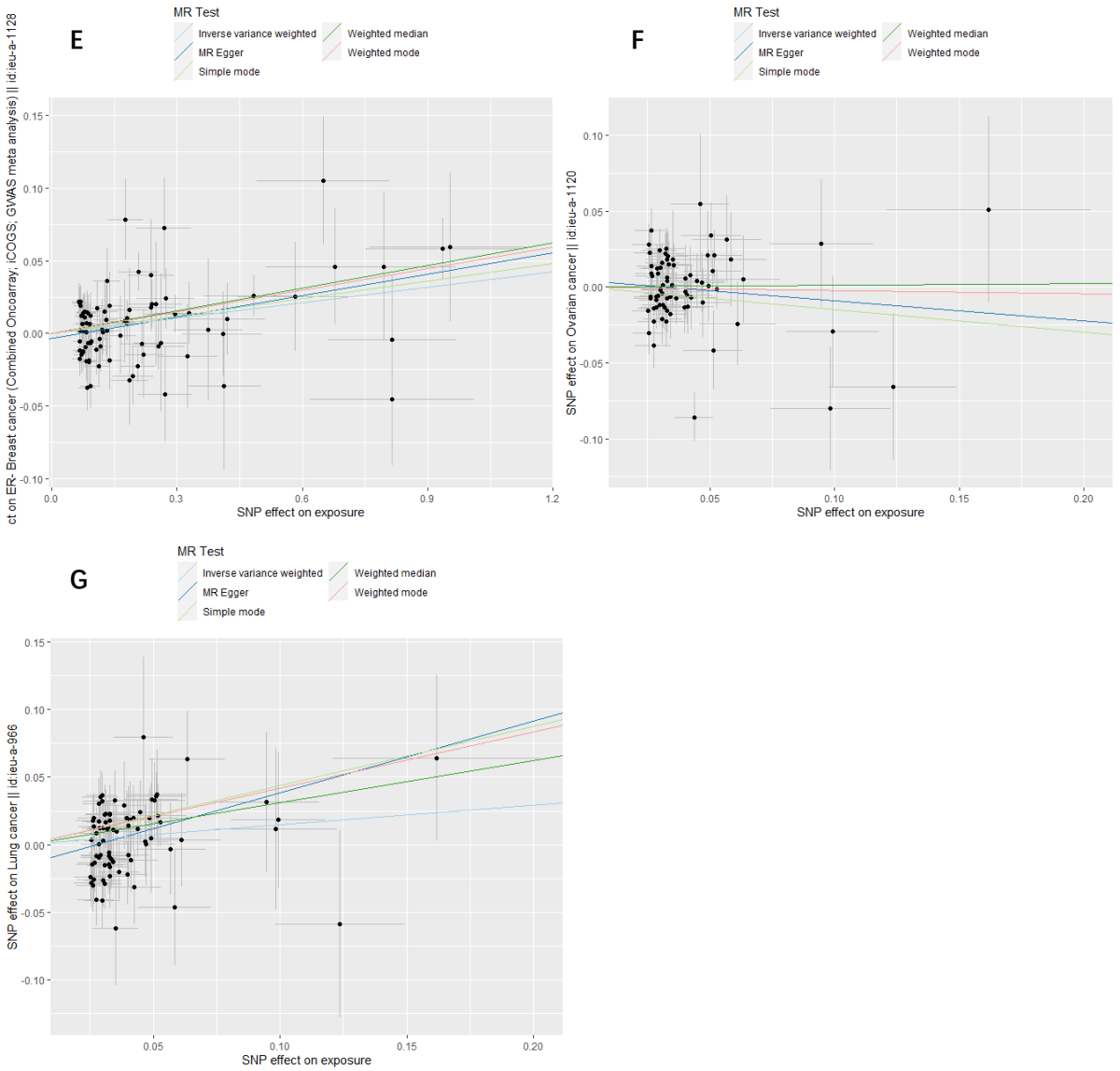
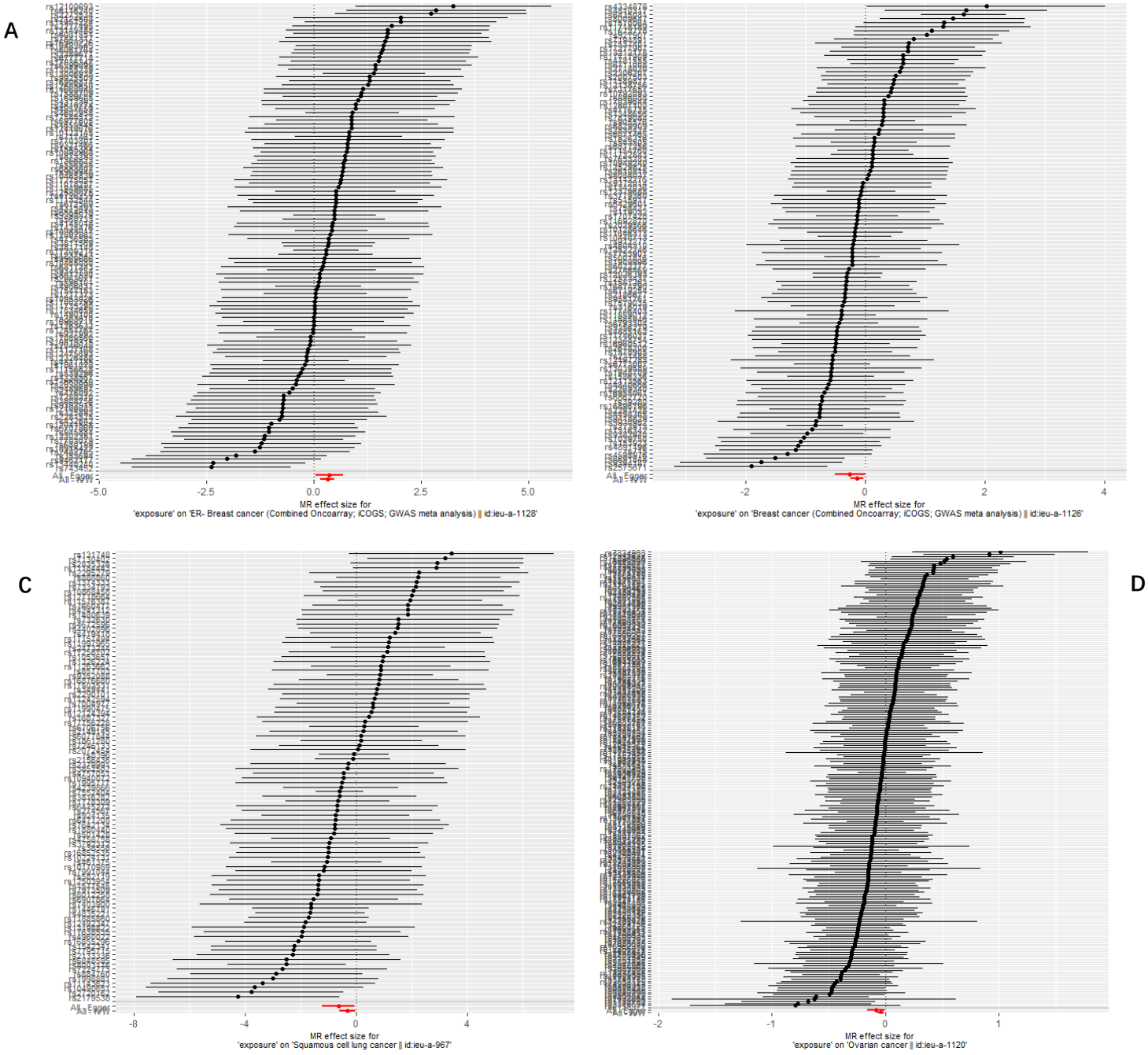


Figure S6 Scatter plots showing the genetic association of seven metabolites on the risk of cancers. 1-oleoylglycerophosphocholine on ER- breast cancer (A), 3-dehydrocarnitine on breast cancer (B), octanoylcarnitine on Squamous cell lung cancer (C), ibuprofen on ovarian cancer (D), salicylate on ER- breast cancer (E), X-14304—leucylalanine on ovarian cancer (F), X-14304—leucylalanine on lung cancer (G).



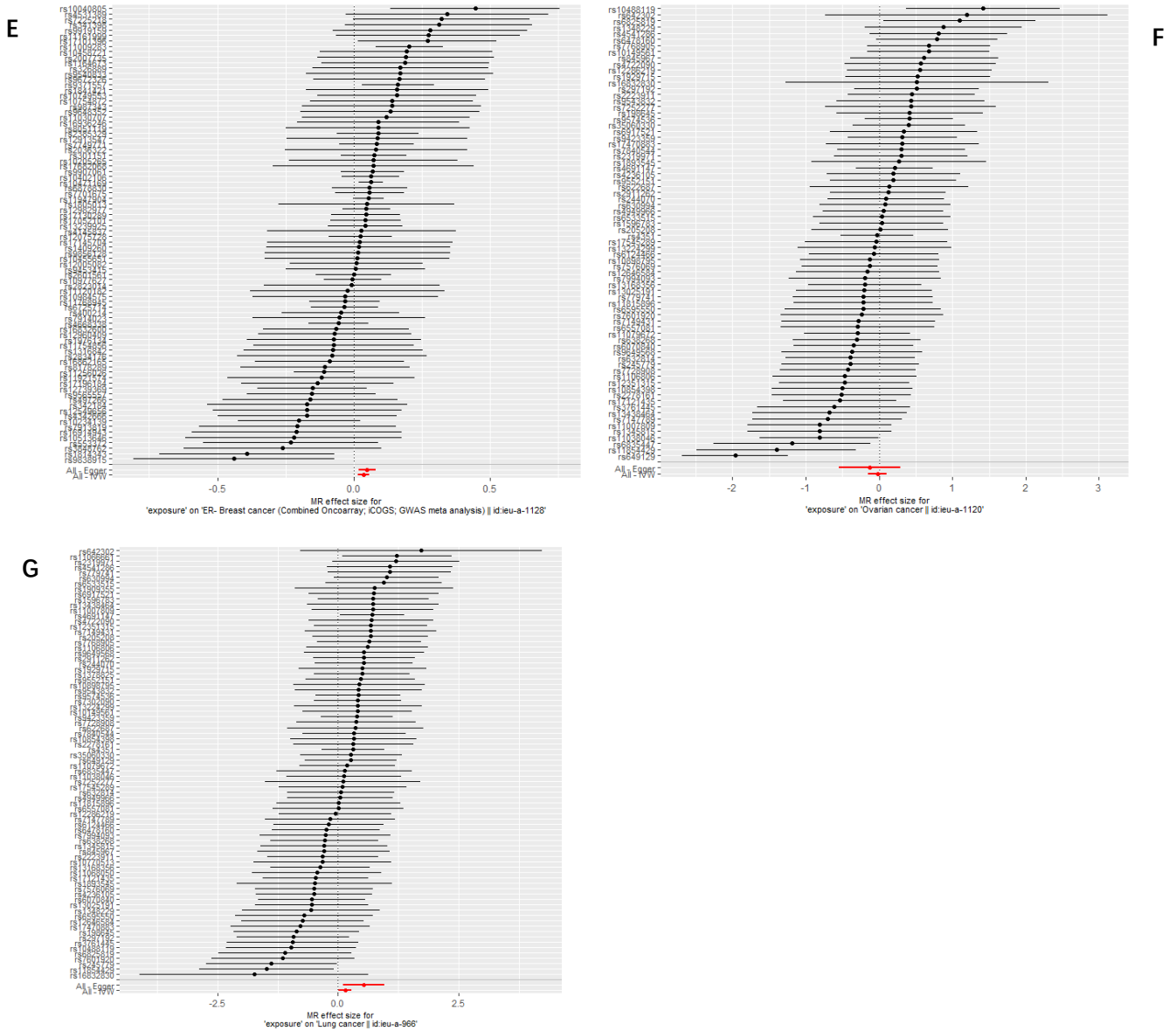
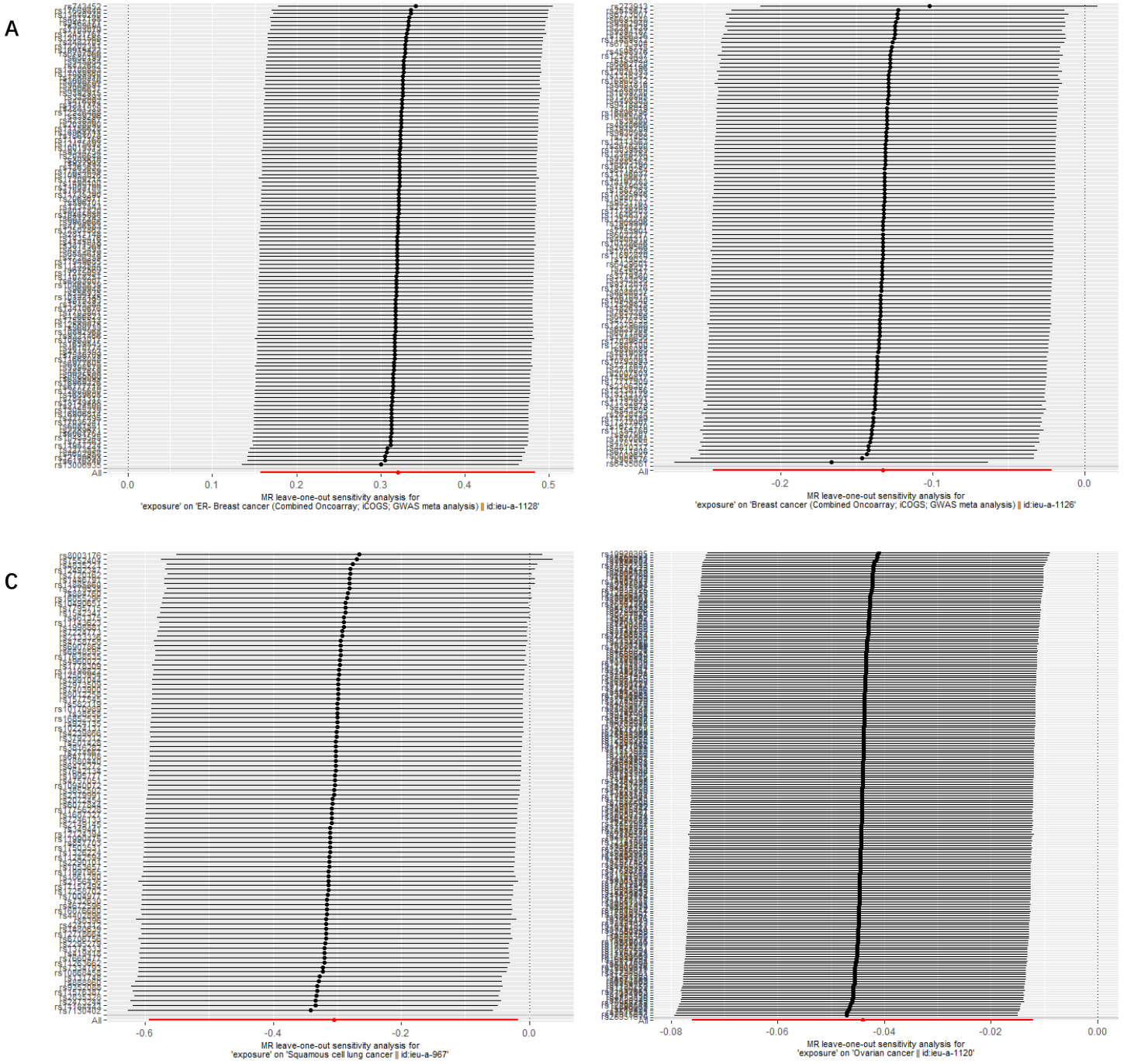


Figure S7 Forest plots for seven potential metabolites on cancers. 1-oleoylglycerophosphocholine on ER- breast cancer (A), 3-dehydrocarnitine on breast cancer (B), octanoylcarnitine on squamous cell lung cancer (C), ibuprofen on ovarian cancer (D), salicylate on ER- breast cancer (E), X-14304—leucylalanine on ovarian cancer (F), X-14304—leucylalanine on lung cancer (G).



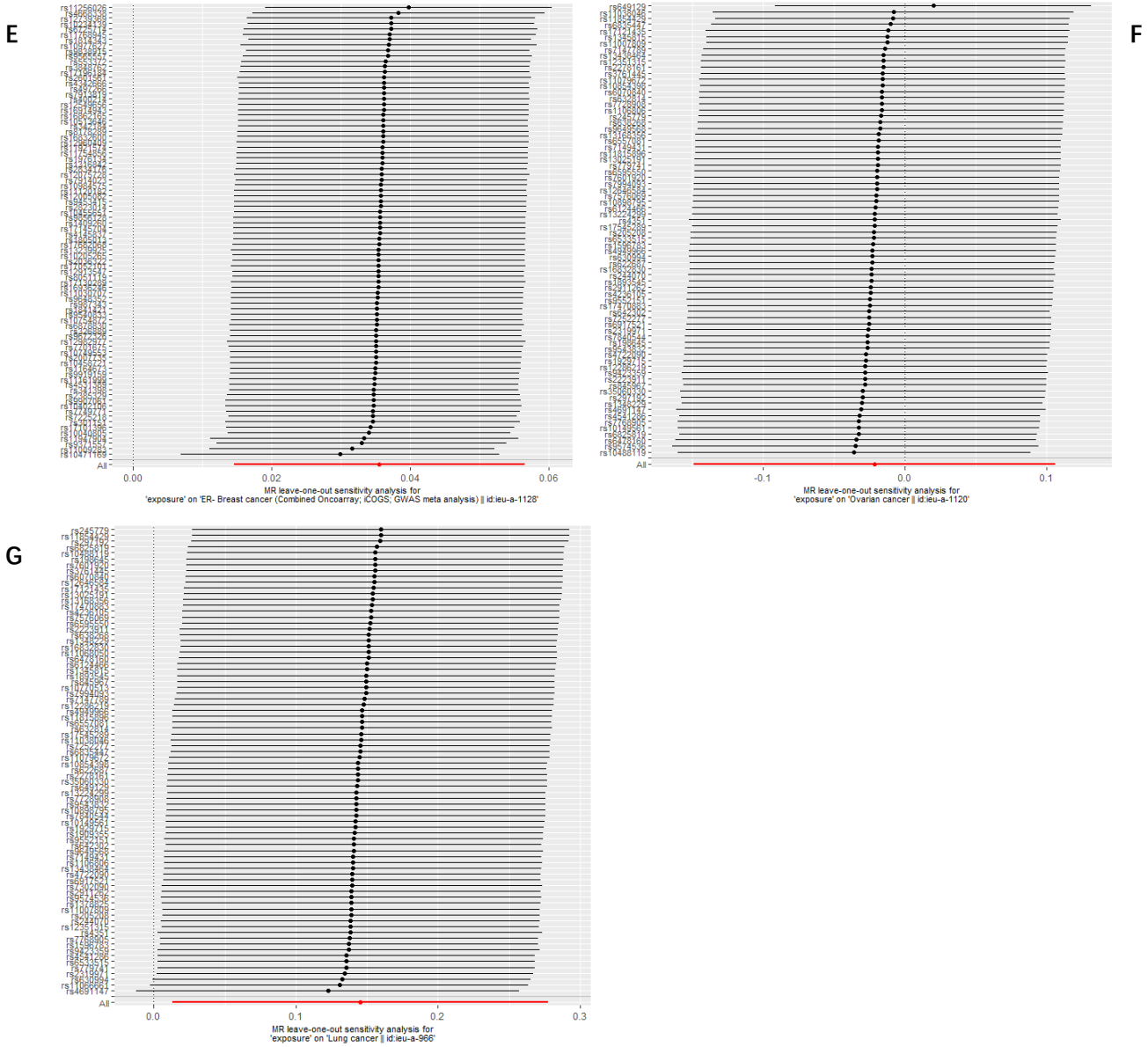
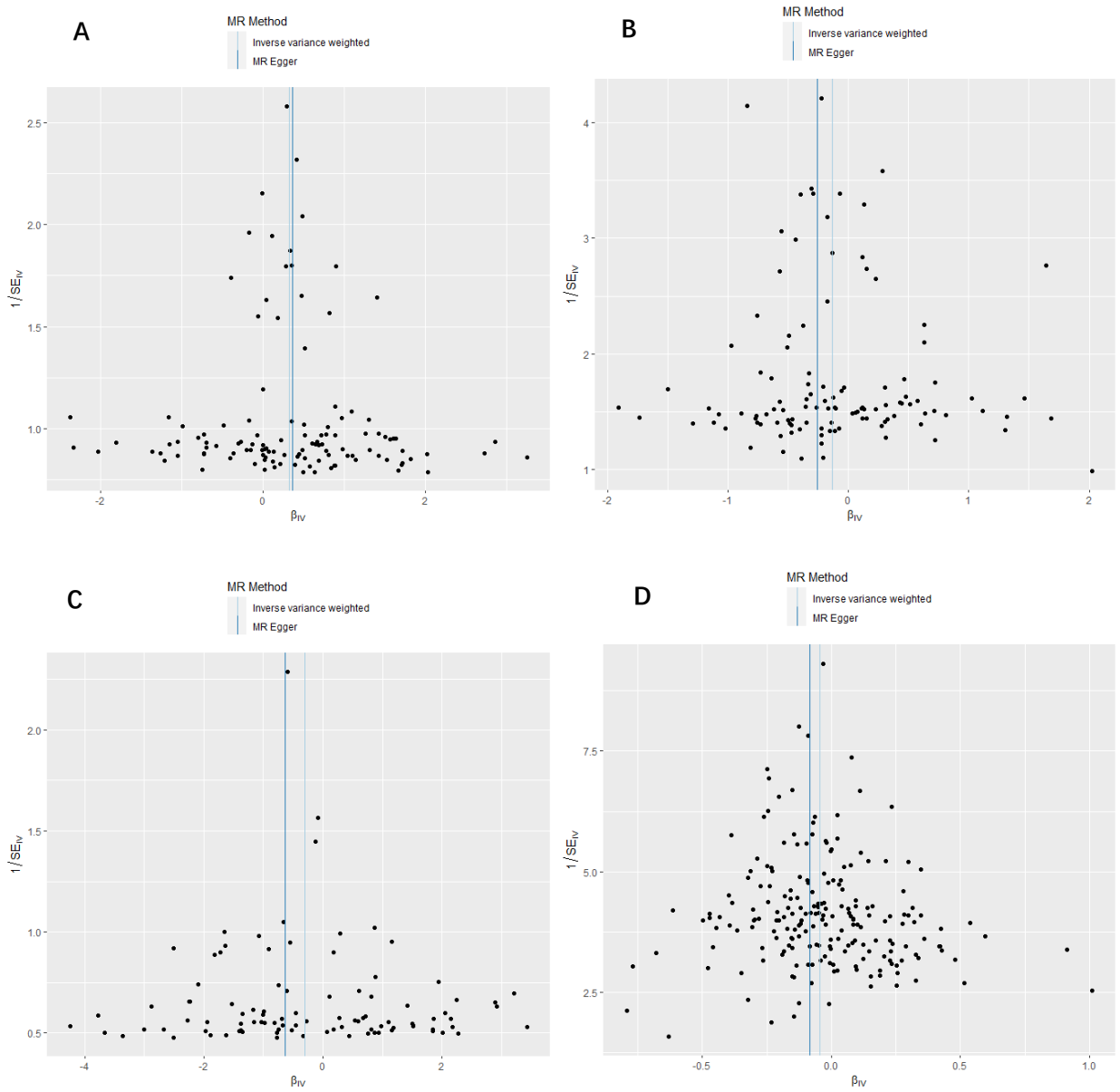


Figure S8 Leave-one-out plots for the seven potential metabolites on cancers. 1-oleoylglycerophosphocholine on ER- breast cancer (A), 3-dehydrocarnitine on breast cancer (B), octanoylcarnitine on squamous cell lung cancer (C), ibuprofen on ovarian cancer (D), salicylate on ER- breast cancer (E), X-14304—leucylalanine on ovarian cancer (F), X-14304—leucylalanine on lung cancer (G)



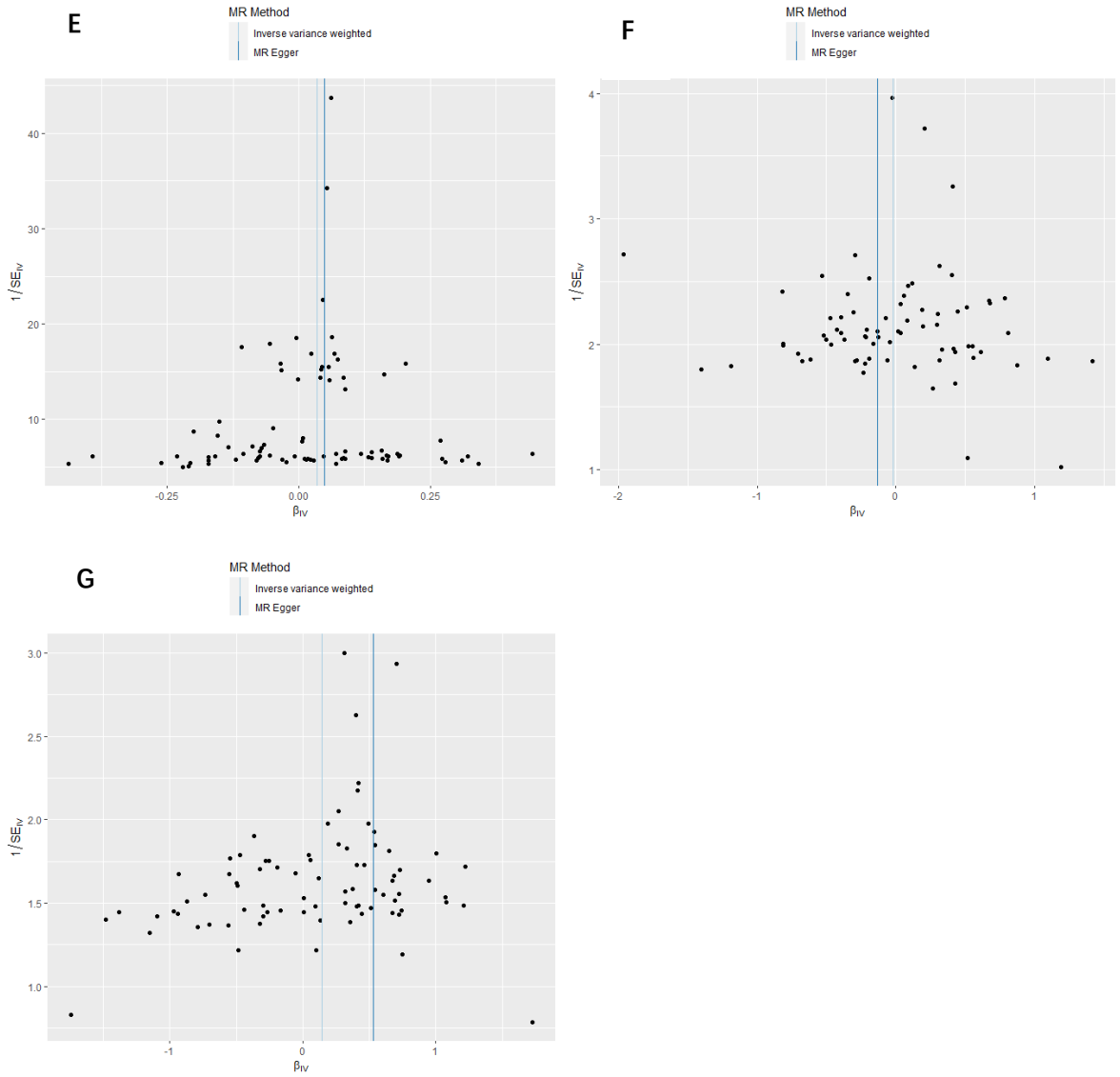


Figure S9 Funnel plots for seven potential metabolites on cancers. 1-oleoylglycerophosphocholine on Er- breast cancer (A), 3-dehydrocarnitine on breast cancer (B), octanoylcarnitine on squamous cell lung cancer (C), ibuprofen on ovarian cancer (D), salicylate on ER- breast cancer (E), X-14304—leucylalanine on ovarian cancer (F), X-14304—leucylalanine on lung cancer (G).

Table S1 The formula used to calculate R^2 and F statistic between exposure and outcome

description	Formula
F statistic	$F=\frac{N-k-1}{2k}\times\frac{R^2}{1-R^2}$
R^2 calculate	$\frac{2\times\beta2\times EAF\times (1-EAF)}{[2\times\beta2\times EAF\times(1-EAF)+2*se(\beta)2*N*EAF*(1-EAF)]}$

* N: the sample size of the GWASs. k: the number of the SNPs (instrumental variants). R^2: the instrumental variable explains the degree of exposure (determinant coefficient of regression equation). EAF: effect allele frequency for the genetic variant of interest. β:the effect size for the genetic variant of interest. Se(β): standard error of effect size for the genetic variant of interest.

Table S2. Summary statistics of the cancers.

Consortium	Phenotype	Note	First author	Year	Sample size	Number of cases	Number of controls	Number of variants	Ancestry
International Lung Cancer Consortium	Lung cancer	ilcco.iarc.fr	Wang Y	2017	27,209	11,348	15,861	8,945,893	European
Ovarian Cancer Association Consortium	Epithelial ovarian cancer	http://ocac.ccge.medschl.cam.ac.uk/schl.cam.ac.uk/	Phelan	2017	66,450	25,509	40,941	0	International
Breast Cancer Association Consortium	Breast cancer	http://apps.ccge.medschl.cam.ac.uk/	Michailidou K	2017	228,951	122,977	105,974	10680,257	International
GliomaScan	Glioma	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3761216/	Rajaraman P	2012	6,811	1,856	4,955	309,636	International

Table S3 Mendelian Randomization estimation for Amino acid on the risk of cancers.

Trait	Exposure	SNPs	R^2	*F* statistics	IVW		MR-Egger		Weighted median		MR-PRESSO	MR-Egger regression	
					OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		Intercept	P value
Breast cancer	2-methylbutyroylcarnitine	100	0.012673	11.26	0.77 (0.70-0.85)	3.418E-07	1.59 (1.27-1.99)	6.233E-05	1.004 (0.91-1.11)	9.351E-01	0.682	-0.0045	0.0458
Breast cancer	4-acetamidobutanoate	33	0.0042	14.51	0.93 (0.70-0.98)	3.116E-02	1.01 (0.69-1.48)	9.650E-01	0.87 (0.71-1.06)	1.638E-01	0.709	-0.0022	0.2749
Breast cancer	Isovalerylcarnitine	18	0.03825	20.24	0.87 (0.76-0.99)	3.231E-02	0.81 (0.61-1.1)	1.527E-01	1.008 (0.87-1.16)	9.086E-01	0.97	0.0016	0.5909
Breast cancer	Kynurenine	32	0.006453	12.93	0.85 (0.73-0.99)	3.888E-02	0.95 (0.70-1.29)	7.333E-01	0.91 (0.74-1.10)	3.247E-01	0.888	-0.0013	0.4277
Breast cancer	Serotonin (5HT)	15	0.002162	12.67	1.1 (1.00-1.21)	4.163E-02	1.04 (0.84-1.29)	7.221E-01	1.07 (0.95-1.21)	2.667E-01	0.366	0.0012	0.5650
ER- Breast cancer	4-acetamidobutanoate	33	0.007484	14.56	0.74 (0.57-0.95)	1.946E-02	0.72 (0.40-1.30)	2.791E-01	0.74 (0.51-1.06)	9.982E-02	0.002	0.0002	0.9385
ER- Breast cancer	Kynurenine	32	0.006453	12.93	0.75 (0.58-0.96)	2.381E-02	0.73 (0.44-1.22)	2.317E-01	0.77 (0.55-1.08)	1.287E-01	0.485	0.0003	0.9262
ER+ Breast cancer	2-methylbutyroylcarnitine	100	0.012673	11.26	0.72 (0.64-0.80)	3.552E-09	1.58 (1.23-2.02)	3.061E-04	1.003 (0.90-1.12)	9.451E-01	0.792	-0.0038	0.1506
ER+ Breast cancer	Isovalerylcarnitine	18	0.03825	20.24	0.86 (0.75-0.99)	3.392E-02	0.83 (0.60-1.13)	2.310E-01	0.95 (0.81-1.12)	5.680E-01	0.72	0.0009	0.7771
ER+ Breast cancer	N-acetylalanine	30	0.002493	10.96	1.36 (1.07-1.74)	1.369E-02	1.36 (0.79-2.33)	2.746E-01	1.45 (1.006-2.07)	4.584E-02	0.005	0.0001	0.9805
ER+ Breast cancer	N-acetylthreonine	12	0.00387	10.76	1.18 (1.01-1.38)	3.456E-02	0.75 (0.52-1.06)	1.088E-01	1.03 (0.83-1.27)	7.919E-01	0.92	0.0081	0.0059
ER+ Breast cancer	p-cresol sulfate	14	0.001784	11.20	1.05 (1.00-1.11)	4.213E-02	1.04 (0.95-1.15)	3.957E-01	1.07 (0.99-1.49)	9.770E-02	0.367	0.0006	0.7738
ER+ Breast cancer	Serotonin (5HT)	15	0.001889	11.07	1.12 (1.02-1.24)	1.956E-02	1.08 (0.86-1.36)	4.959E-01	1.10 (0.95-1.27)	2.136E-01	0.209	0.0008	0.7208
Glioma	2-methylbutyroylcarnitine	57	0.007321	11.35	2.19 (1.17-4.09)	1.455E-02	0.89 (0.16-4.96)	8.954E-01	1.99 (0.75-5.31)	1.673E-01	0.216	-0.0054	0.8026
Glioma	4-acetamidobutanoate	14	0.09351	25.03	0.15 (0.04-0.59)	6.306E-03	0.08 (0.003-2.24)	1.441E-01	0.24 (0.03-1.9)	1.773E-01	0.812	0.0068	0.6802
Glioma	Pyroglutamine	7	0.041396	20.93	3.20 (1.03-9.91)	4.393E-02	18.6 (0.72-479.10)	9.120E-02	2.32 (0.53-10.1)	2.638E-01	0.02	-0.0445	0.2695
Lung adenocarcinoma	2-methylbutyroylcarnitine	100	**0.012673**	11.26	0.60 (0.48-0.75)	1.144E-05	1.72 (1.005-2.96)	4.821E-02	0.59 (0.41-0.87)	7.209E-03	0.123	-0.0002	0.9826
Lung adenocarcinoma	Asparagine	13	0.015418	11.03	1.42 (1.04-1.94)	2.622E-02	2.30 (1.004-5.28)	5.282E-02	1.43 (0.89-2.30)	1.340E-01	0.313	-0.0136	0.2245
Lung adenocarcinoma	Isoleucine	4	**0.006027**	13.89	0.19 (0.0059-0.64)	7.193E-03	0.15 (0.013-1.57)	1.196E-01	0.32 (0.047-2.16)	2.427E-01	0.145	-0.0136	0.2245
Lung adenocarcinoma	Isovalerylcarnitine	18	0.03825	20.24	0.67 (0.46-0.99)	4.540E-02	0.25 (0.10-0.62)	3.378E-03	0.73 (0.40-1.33)	3.004E-01	0.33	0.0209	0.0201
Lung adenocarcinoma	Phenol sulfate	13	0.015261	10.92	0.73 (0.57-0.95)	1.622E-02	0.79 (0.40-1.58)	5.080E-01	0.81 (0.55-1.19)	2.796E-01	0.319	-0.0026	0.8191
Lung adenocarcinoma	Phenylacetylglutamine	18	0.022085	11.49	0.73 (0.57-0.93)	1.055E-02	0.62 (0.38-1.01)	6.050E-02	0.74 (0.52-1.06)	9.635E-02	0.071	0.0063	0.4683
Lung adenocarcinoma	Phenylalanine	4	0.006027	13.89	0.19 (0.0059-0.64)	7.193E-03	0.15 (0.013-1.57)	1.196E-01	0.32 (0.048-2.16)	2.427E-01	0.321	0.0028	0.7855
Lung cancer	2-methylbutyroylcarnitine	100	0.012673	11.26	0.59 (0.50-0.70)	1.984E-09	1.60 (1.08-2.36)	1.911E-02	0.85 (0.66-1.09)	2.025E-01	<0.001	-0.0025	0.6381
Lung cancer	Indolelactate	18	0.015325	11.75	0.80 (0.64-0.98)	4.673E-02	0.60 (0.42-0.87)	8.044E-03	0.79 (0.50-1.24)	3.042E-01	0.268	0.0067	0.0629
Ovarian cancer	2-aminobutyrate	41	0.014784	12.15	0.78 (0.61-0.99)	3.827E-02	0.77 (0.47-1.24)	2.838E-01	0.80 (0.54-1.20)	2.821E-01	0.514	0.0002	0.9413
Ovarian cancer	2-methylbutyroylcarnitine	100	0.033459	30.35	0.77 (0.68-0.86)	2.995E-06	1.17 (0.90-1.53)	2.448E-01	0.63 (0.52-0.0.75)	4.771E-07	0.319	-0.0040	0.3235
Ovarian cancer	3-phenylpropionate (hydrocinnamate)	15	0.005061	11.26	0.92 (0.85-0.99)	3.528E-02	0.92 (0.82-1.04)	1.761E-01	0.94 (0.82-1.07)	3.592E-01	0.342	-0.0040	0.3235
Ovarian cancer	N-acetylthreonine	12	0.00387	10.76	1.28 (1.004-1.64)	4.587E-02	1.49 (0.84-2.65)	1.768E-01	1.62 (1.14-2.32)	7.836E-03	0.16	-0.0027	0.5691
Squamous cell lung cancer	2-methylbutyroylcarnitine	100	**0.121301**	121.05	0.78 (0.63-0.98)	3.321E-02	1.97 (1.17-3.32)	1.122E-02	1.28 (0.89-1.84)	1.787E-01	0.452	-0.0079	0.3344

Table S4 Mendelian Randomization estimation for Carbohydrate on the risk of cancers

Trait	Exposure	SNPs	R^2	*F* statistics	IVW		MR-Egger		Weighted median		MR-PRESSO	MR-Egger regression	
					OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		Intercept	P value
ER- breast cancer	Lactate	12	0.002051	10.91	0.78 (0.62-0.98)	3.446E-02	0.64 (0.39-1.04)	7.778E-02	0.81 (0.58-1.15)	2.416E-01	0.141	0.0034	0.3746
Lung cancer	Arabinose	5	0.004076	11.13	1.2 (1-1.45)	4.965E-02	1.20 (0.88-1.63)	2.653E-01	1.21 (0.90-1.63)	1.988E-01	0.613	0.0003	0.9584
Squamous cell lung cancer	1,5-anhydroglucitol (1,5-AG)	27	0.044294	15.69	1.48 (0.50-2.08)	2.487E-02	1.13 (0.59-2.19)	7.062E-01	1.40 (0.83-2.37)	2.004E-01	0.112	-0.0079	0.3344

Table S5 Mendelian Randomization estimation for Cofactor or vitamin on the risk of cancers

Trait	Exposure	SNPs	R^2	*F* statistics	IVW		MR-Egger		Weighted median		MR-PRESSO	MR-Egger regression	
					OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		Intercept	P value
ER+ breast cancer	Pyridoxate	10	0.001192	10.47	1.18 (1.01-1.38)	3.217E-02	1.10 (0.80-1.51)	5.732E-01	1.12 (0.97-1.28)	1.293E-01	0.272	0.0022	0.6014
ER+ breast cancer	Threonate	17	0.002048	10.59	0.88 (0.79-0.99)	3.645E-02	0.91 (0.72-1.14)	3.975E-01	0.85 (0.73-0.98)	2.565E-02	0.018	-0.0007	0.8125
Lung adenocarcinoma	Bilirubin (Z,Z)	10	0.046523	44.71	0.80 (0.66-0.98)	2.671E-02	0.87 (0.61-1.24)	4.428E-01	0.94 (0.70-1.26)	6.646E-01	0.013	-0.0044	0.6048
Lung cancer	Pyridoxate	5	0.008557	10.67	1.30 (1.06-1.60)	1.148E-02	1.46 (0.94-0.28)	9.754E-02	1.16 (0.84-1.59)	3.576E-01	0.479	-0.0033	0.5713
Squamous cell lung cancer	Alpha-tocopherol	11	0.013017	10.97	0.56 (0.36-0.88)	1.152E-02	0.45 (0.17-1.23)	1.255E-01	0.54 (0.28-1.03)	6.165E-02	0.249	0.0048	0.6402

Table S6 Mendelian Randomization estimation for Lipid on the risk of cancers

Trait	Exposure	SNPs	R^2	*F* statistics	IVW		MR-Egger		Weighted median		MR-PRESSO	MR-Egger regression	
					OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		Intercept	*P* value
Breast cancer	1-eicosatrienoylglycerophosphocholine	20	0.011496	31.66	1.1 (1.01-1.20)	2.400E-02	1.18 (1-1.39)	5.184E-02	1.07 (0.95-1.21)	2.693E-01	0.60	-0.0020	0.3412
Breast cancer	1-linoleoylglycerol (1-monolinolein)	13	0.001292	11.39	0.92 (0.87-0.98)	1.164E-02	1.01 (0.88-1.17)	8.427E-01	0.94 (0.86-1.03)	2.110E-01	0.554	-0.0042	0.1630
Breast cancer	1-oleoylglycerophosphocholine	16	0.001504	10.78	1.22 (1.1-1.35)	1.039E-04	1.19 (0.97-1.45)	9.173E-02	1.17 (1.02-1.34)	2.732E-02	0.694	0.0005	0.7595
Breast cancer	3-dehydrocarnitine	22	0.002628	13.71	0.88 (0.78-0.98)	1.937E-02	0.77 (0.60-0.995)	4.762E-02	0.81 (0.70-0.95)	7.900E-03	0.661	0.0023	0.2839
Breast cancer	palmitoylcarnitine	10	0.001003	11.49	1.13 (1.01-1.27)	4.012E-02	0.95 (0.73-1.22)	6.761E-01	1.09 (0.94-1.27)	2.621E-01	0.001	0.0044	0.1296
Breast cancer	taurolithocholate 3-sulfate	9	0.000825	10.50	0.94 (0.90-0.99)	8.901E-03	1 (0.91-1.1)	9.373E-01	0.95 (0.88-1.02)	1.632E-01	0.441	-0.0035	0.1248
ER- Breast cancer	1-arachidonoylglycerophosphoethanolamine	20	0.010254	32.65	1.21 (1.03-1.41)	1.463E-02	1.08 (0.79-1.48)	6.125E-01	1.12 (0.87-1.44)	3.925E-01	0.415	-0.0015	0.6174
ER- Breast cancer	1-docosahexaenoylglycerophosphocholine	8	0.001334	10.64	1.15 (1.003-1.33)	4.514E-02	1.008 (0.78-1.30)	9.505E-01	0.93 (0.75-1.16)	5.385E-01	0.231	0.0047	0.2147
ER- Breast cancer	1-linoleoylglycerophosphoethanolamine	11	0.003081	17.90	0.83 (0.71-0.98)	2.615E-02	1.07 (0.70-1.63)	7.471E-01	0.76 (0.55-1.05)	1.010E-01	0.152	0.0039	0.4379
ER- Breast cancer	1-oleoylglycerophosphocholine	16	0.0027	10.78	1.38 (1.17-1.62)	1.147E-04	1.44 (1.05-1.99)	2.676E-02	1.36 (1.07-1.73)	1.234E-02	0.513	-0.0009	0.7400
ER- Breast cancer	octadecanedioate	8	0.002819	22.51	0.84 (0.73-0.99)	3.836E-02	1.11 (0.76-1.61)	5.881E-01	0.88 (0.70-1.10)	2.722E-01	0.308	-0.0067	0.1295
ER- Breast cancer	palmitoylcarnitine	10	0.001801	11.50	1.33 (1.11-1.60)	2.316E-03	1.19 (0.79-1.79)	4.006E-01	1.20 (0.93-1.57)	1.662E-01	0.092	0.0027	0.5551
ER- Breast cancer	taurochenodeoxycholate	13	0.002168	10.65	1.08 (1.01-1.15)	1.990E-02	0.92 (0.76-1.12)	4.075E-01	0.97 (0.90-1.07)	6.290E-01	0.244	-0.0032	0.3115
ER+ Breast cancer	1-linoleoylglycerol (1-monolinolein)	13	0.001686	11.40	0.91 (0.85-0.97)	4.365E-03	0.98 (0.84-1.15)	8.463E-01	0.92 (0.83-1.02)	1.234E-01	0.049	-0.0035	0.2644
ER+ Breast cancer	1-oleoylglycerophosphocholine	16	0.001962	10.78	1.19 (1.06-1.33)	2.817E-03	1.50 (0.92-1.44)	2.227E-01	1.19 (1.01-1.41)	3.654E-02	0.058	0.0006	0.7331
ER+ Breast cancer	10-heptadecenoate (17:1n7)	6	0.000712	10.41	0.84 (0.73-0.97)	1.350E-02	0.85 (0.56-1.28)	4.320E-01	0.83 (0.70-0.98)	3.115E-02	0.788	-0.0001	0.9740
ER+ Breast cancer	cortisol	13	0.00158	10.68	1.14 (1.01-1.29)	3.537E-02	1.12 (0.82-1.50)	4.751E-01	1.18 (0.98-1.42)	8.095E-02	0.442	0.0005	0.8655
ER+ Breast cancer	stearidonate (18:4n3)	4	0.014094	11.76	0.88 (0.80-0.98)	2.344E-02	0.85 (0.57-1.08)	1.961E-01	0.92 (0.80-1.06)	2.540E-01	0.608	0.0009	0.7331
ER+ Breast cancer	taurolithocholate 3-sulfate	9	0.00107	10.50	0.93 (0.88-0.98)	1.579E-0	1.04 (0.93-1.17)	5.197E-0	0.91 (0.84-0.99)	4.951E-0	0.139	-0.0058	0.0365

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Glioma	1-oleoylglycerophosphoethanolamine	2	0.006716	11.49	0.34 (0.13-0.91)	3.219E-02	0.90 (0.04-21.59)	9.510E-01	0.37 (0.09-1.44)	1.506E-01	0.504	-0.0253	0.5318
Glioma	5alpha-androstan-3beta,17beta-diol disulfate	5	0.031066	21.81	0.57 (0.34-0.98)	4.081E-02	0.65 (0.12-3.3.38)	6.127E-01	0.63 (0.28-1.43)	2.677E-01	0.846	-0.0048	0.8769
Glioma	cis-4-decenoyl carnitine	3	0.050547	60.38	0.39 (0.15-0.98)	4.630E-02	0.85 (0.11-6.46)	8.759E-01	0.60 (0.16-2.30)	4.590E-01	0.887	-0.0205	0.4180
Glioma	glycerol	5	0.015836	10.94	3.43 (1.08-10.90)	3.721E-02	0.90 (0.018-44.52)	9.585E-01	2.45 (0.43-13.83)	3.099E-01	0.934	0.0193	0.4860
Glioma	myristoleate (14:1n5)	3	0.016356	18.86	0.20 (0.07-0.57)	2.624E-03	0.10 (0.003-2.43)	1.673E-01	0.18 (0.05-0.71)	1.412E-02	0.019	0.0162	0.6465
Glioma	taurodeoxycholate	4	0.012862	11.08	0.66 (0.44-0.98)	3.877E-02	0.95 (0.16-5.70)	9.523E-01	0.87 (0.51-1.49)	6.109E-01	0.709	-0.0214	0.6886
Glioma	ursodeoxycholate	2	0.006532	11.17	0.44 (0.24-0.82)	1.033E-02	0.30 (0.04-2.00)	2.280E-01	0.37 (0.15-0.96)	4.000E-02	0.238	0.0152	0.6725
Lung adenocarcinoma	1-oleoylglycerol (1-monoolein)	16	0.019809	11.57	0.76 (0.62-0.94)	1.104E-02	0.85 (0.58-1.24)	3.906E-01	0.86 (0.61-1.20)	3.692E-01	0.208	-0.0047	0.5318
Lung adenocarcinoma	1-palmitoylglycerophosphoethanolamine	27	0.036261	12.76	0.61 (0.40-0.92)	1.795E-02	0.47 (0.18-1.19)	1.122E-01	0.75 (0.41-1.35)	3.341E-01	0.115	0.0045	0.5447
Lung adenocarcinoma	5-dodecenoate (12:1n7)	18	0.022764	11.85	0.75 (0.57-0.99)	4.115E-02	0.46 (0.26-0.81)	8.760E-03	0.78 (0.52-1.18)	2.434E-01	0.562	0.0166	0.0555
Lung adenocarcinoma	glycerophosphorylcholine (GPC)	18	0.020842	10.83	0.67 (0.50-0.89)	6.826E-03	0.66 (0.40-1.10)	1.114E-01	0.98 (0.57-1.71)	9.559E-01	0.531	0.0001	0.9882
Lung adenocarcinoma	oleoylcarnitine	12	0.015137	11.73	1.51 (1.02-2.23)	4.070E-02	1.59 (0.65-3.90)	3.132E-01	1.39 (0.83-2.33)	2.124E-01	0.172	-0.0014	0.8955
Lung adenocarcinoma	taurochenodeoxycholate	11	0.0127	10.71	0.85 (0.73-0.99)	3.664E-02	0.77 (0.59-1.01)	6.587E-02	0.76 (0.60-0.97)	2.799E-02	0.054	0.0063	0.4122
Lung adenocarcinoma	taurocholate	17	0.020287	11.16	0.87 (0.77-0.98)	2.643E-02	0.86 (0.69-1.07)	1.857E-01	0.97 (0.81-1.16)	7.310E-01	0.648	0.0008	0.9082
Lung cancer	1-eicosatrienoylglycerophosphocholine	19	0.017581	12.80	0.74 (0.60-0.93)	8.063E-03	0.56 (0.35-0.89)	1.692E-02	0.79 (0.57-1.10)	1.718E-01	0.506	0.0082	0.1783
Lung cancer	2-hydroxyglutarate	11	0.008454	10.54	1.34 (1.01-1.77)	4.152E-02	1.20 (0.59-2.44)	6.256E-01	1.34 (0.89-2.01)	1.558E-01	0.48	0.0026	0.7358
Lung cancer	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	14	0.011105	10.91	1.45 (1.06-1.97)	1.835E-02	1.30 (0.74-2.26)	3.625E-01	1.45 (1.06-2.00)	1.835E-02	0.489	0.0068	0.1554
Lung cancer	androsterone sulfate	19	0.035658	26.46	1.11 (1.00-1.23)	4.173E-02	1.10 (0.92-1.30)	2.893E-01	1.18 (1.01-1.36)	3.120E-02	0.512	0.0007	0.8875
Lung cancer	heptanoate (7:0)	34	0.028457	11.70	0.68 (0.49-0.94)	2.070E-02	0.46 (0.18-1.17)	1.057E-01	0.55 (0.33-0.91)	1.895E-02	0.494	0.0042	0.3841
Ovarian cancer	butyrylcarnitine	20	0.007554	12.64	1.14 (1.002-1.29)	4.540E-02	1.28 (0.99-1.65)	5.884E-02	1.23 (1.03-1.48)	2.619E-02	0.171	-0.0037	0.2966
Ovarian cancer	hexanoylcarnitine	16	0.01266	26.62	1.20 (1.02-1.41)	2.922E-0	1.12 (0.79-1.58)	5.300E-0	1.27 (0.95-1.70)	1.090E-0	0.713	0.0017	0.6613

Squamous cell lung cancer	1-arachidonoylglycerophosphoethanolamine	21	0.037528	119.37	1.56 (1.07-2.29)	2.128E-02	1.73 (0.74-4.06)	2.105E-01	1.36 (0.72-2.57)	3.398E-01	0.058	-0.0018	0.7963
Squamous cell lung cancer	1-eicosatrienoylglycerophosphocholine	19	0.017581	12.80	0.62 (0.44-0.87)	5.381E-03	0.41 (0.20-0.93)	1.629E-02	0.50 (0.30-0.84	9.062E-03	0.063	0.0121	0.1961
Squamous cell lung cancer	1-palmitoylglycerophosphocholine	32	**0.038974**	11.58	0.53 (0.29-0.97)	3.999E-02	1.61 (0.24-10.8)	6.231E-01	0.60 (0.24-1.53)	2.877E-01	0.196	-0.0110	0.2264
Squamous cell lung cancer	octanoylcarnitine	16	0.04273	25.52	0.74 (0.55-0.98)	3.797E-02	0.53 (0.29-0.95)	3.636E-02	0.58 (0.36-0.92)	2.046E-02	0.327	0.0088	0.2089

Table S7 Mendelian Randomization estimation for Nucleotide on the risk of cancers

Trait	**Exposure**	**SNPs**	R^2	***F* statistics**	**IVW**		**MR-Egger**		**Weighted median**		**MR-PRESSO**	**MR-Egger regression**	
					OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**		**Intercept**	**P value**
Glioma	Allantoin	6	0.027743	16.17	0.46 (0.23-0.91)	2.577E-02	0.61 (0.16-2.25)	4.614E-01	0.74 (0.26-2.09)	5.709E-01	0.111	-0.0099	0.6202
Lung adenocarcinoma	7-methylguanine	11	0.012357	10.42	1.73 (1.11-2.71)	1.589E-02	1.95 (0.65-5.89)	2.392E-01	1.62 (0.83-3.34)	1.544E-01	0.209	-0.0028	0.8157
Lung adenocarcinoma	Pseudouridine	24	0.029751	11.70	0.40 (0.19-0.85)	1.738E-02	0.29 (0.03-2.45)	2.553E-01	0.41 (0.14-1.26)	1.194E-01	0.396	0.0032	0.7402
Lung adenocarcinoma	Uridine	20	0.028013	13.20	2.34 (1.14-4.82)	2.104E-02	1.48 (0.28-7.82)	6.424E-01	3.38 (1.04-10.97)	4.283E-02	0.234	0.0052	0.5515
Lung cancer	Pseudouridine	24	0.029751	17.37	0.50 (0.30-0.83)	7.024E-03	0.72 (0.17-3.06)	6.536E-01	0.65 (0.31-1.34)	2.394E-01	0.269	-0.0033	0.6090
Squamous cell lung cancer	Pseudouridine	24	0.029751	11.68	0.46 (0.22-0.97)	4.233E-02	0.71 (0.08-5.96)	7.513E-01	0.33 (0.11-1.009)	5.195E-02	0.686	-0.0041	0.6730
Squamous cell lung cancer	Xanthine	8	0.009208	10.63	0.56 (0.33-0.94)	2.998E-02	0.56 (0.13-2.38)	4.377E-01	0.54 (0.25-1.17)	1.176E-01	0.71	-0.0003	0.9855

Table S8 Mendelian Randomization estimation for Peptide on the risk of cancers

Trait	Exposure	SNPs	R^2	*F* statistics	IVW		MR-Egger		Weighted median		MR-PRESSO	MR-Egger regression	
					OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		Intercept	*P* value
Breast cancer	Gamma-glutamylglutamate	17	0.001883	12.70	0.99 (0.98-0.997)	6.492E-03	0.99 (0.98-1.01)	2.187E-01	0.99 (0.98-1)	6.162E-02	0.026	-0.0084	0.1516
Breast cancer	Leucylleucine	9	0.000904	11.51	0.91 (0.83-0.997)	4.353E-02	0.96 (0.91-1.14)	6.586E-01	0.97 (0.86-1.10)	6.718E-01	0.759	-0.0007	0.7348
Breast cancer	Leucylalanine	11	0.001062	11.06	0.90 (0.82-0.99)	3.812E-02	1.13 (0.82-1.54)	4.601E-01	0.97 (0.90-1.05)	5.060E-01	0.24	0.0008	0.7273
ER- Breast cancer	Gamma-glutamylglutamate	19	0.003307	11.13	0.99 (0.98-0.999)	3.438E-02	0.995 (0.97-1.02)	7.256E-01	0.99 (0.97-1.01)	4.211E-01	0.049	0.0048	0.2304
ER- Breast cancer	Gamma-glutamylmethionine	17	0.003382	12.72	0.92 (0.85-0.99)	2.787E-02	0.87 (0.74-1.03)	1.021E-01	0.91 (0.82-1.01)	9.168E-02	0.218	-0.0092	0.1102
ER- Breast cancer	Pro-hydroxy-pro	5	0.000889	11.34	1.23 (1.02-1.49)	3.347E-02	0.93 (0.57-1.52)	7.814E-01	1.12 (0.85-1.47)	4.184E-01	0.432	0.0027	0.5959
ER- Breast cancer	Leucylalanine	9	0.001624	11.51	0.89 (0.81-0.98)	2.035E-02	1.14 (0.84-1.55)	4.106E-01	0.91 (0.79-1.04)	1.693E-01	0.55	-0.0004	0.9006
ER- Breast cancer	Phenylalanylleucine	9	0.001559	11.05	1.10 (1.001-1.21)	4.633E-02	1.04 (0.83-1.30)	7.377E-01	1.06 (0.93-1.21)	3.703E-01	0.019	-0.0061	0.2637
ER+ Breast cancer	Leucylalanine	17	0.002457	12.71	0.89 (0.80-0.997)	4.323E-02	1.06 (0.73-1.52)	7.733E-01	0.98 (0.89-1.08)	6.888E-01	0.013	-0.0064	0.3433
Glioma	Gamma-glutamylleucine	12	0.0170	4.88	4.74 (1.18-18.93)	2.783E-02	3.18 (0.03-296.7)	6.193E-01	7.93 (1.03-61.02)	4.661E-02	0.523	0.0037	0.8568
Glioma	Gamma-glutamylthreonine	2	0.006356	10.88	3.71 (1.30-10.56)	1.394E-02	2.70 (0.07-105.85)	6.002E-01	2.21 (0.48-10.04)	3.064E-01	0.403	0.0061	0.8601
Glioma	Glycylvaline	9	0.045717	18.05	0.13 (0.02-0.75)	2.171E-02	0.12 (0.0002-87.65)	5.347E-01	0.09 (0.0071-1.20)	6.830E-02	0.293	-0.0303	0.2130
Glioma	N-acetylcarnosine	3	0.0100	11.44	0.22 (0.07-0.76)	1.624E-02	1.41 (0.06-31.12)	8.308E-01	0.40 (0.06-2.56)	3.313E-01	0.218	0.0387	0.3354
Glioma	Leucylalanine	2	0.022158	38.54	0.55 (0.32-0.94)	2.952E-02	0.20 (0.03-1.57)	1.393E-01	0.62 (0.29-1.30)	2.050E-01	0.18	0.0377	0.6003
Lung adenocarcinoma	Gamma-glutamylglutamate	10	0.011894	11.03	1.03 (0-1.06)	4.409E-02	1.06 (1.001-1.13)	4.551E-02	1.02 (0.97-1.06)	4.717E-01	0.456	0.0003	0.9654
Lung adenocarcinoma	Gamma-glutamylisoleucine	19	0.025777	12.75	0.82 (0.68-0.98)	2.695E-02	1.04 (0.74-1.48)	8.076E-01	0.86 (0.59-1.26)	4.389E-01	0.132	-0.0151	0.2494
Lung adenocarcinoma	Leucylleucine	6	0.012536	19.39	1.31 (1.04-1.66)	2.291E-02	1.30 (0.83-2.03)	2.481E-01	1.35 (0.92-1.97)	1.267E-01	0.015	0.0032	0.7163
Lung adenocarcinoma	Leucylalanine	27	0.031246	10.94	1.27 (1.02-1.57)	3.233E-02	1.87 (0.93-3.76)	8.145E-02	1.31 (0.96-1.79)	8.758E-02	0.404	-0.0019	0.7872
Lung cancer	Phenylalanylphenylalanine	4	0.003264	11.13	0.73 (0.54-0.99)	4.231E-02	0.52 (0.25-1.11)	9.903E-02	0.80 (0.51-1.25)	3.256E-01	0.369	0.0084	0.3476
Lung cancer	Leucylalanine	19	0.01738	12.66	1.16 (1.01-1.32)	3.103E-02	1.70 (1.11-2.61)	1.759E-02	1.37 (1.12-1.66)	1.971E-03	0.447	-0.0147	0.0680
Ovarian cancer	Bradykinin, des-arg (9)	26	0.008317	10.71	0.83 (0.71-0.96)	1.571E-02	0.82 (0.64-1.05)	1.218E-01	0.80 (0.62-1.03)	8.016E-02	0.271	0.0033	0.3176
Ovarian cancer	Gamma-glutamylisoleucine	19	0.006342	11.16	1.40 (1.16-1.69)	4.092E-04	1.18 (0.80-1.74)	4.098E-01	1.33 (0.99-1.79)	5.697E-02	0.73	-0.0008	0.8608
Ovarian cancer	Pro-hydroxy-pro	19	0.010736	18.97	1.23 (1.002-1.50)	4.678E-02	1.28 (0.76-2.15)	3.501E-01	1.20 (0.89-1.61)	2.345E-01	0.823	-0.0035	0.4334
Ovarian cancer	Leucylalanine	17	0.006485	12.75	0.96 (0.93-0.99)	6.982E-03	0.92 (0.85-0.99)	3.346E-02	0.95 (0.91-0.995)	3.206E-02	0.725	0.0042	0.5906
Squamous cell lung cancer	Gamma-glutamylisoleucine	27	0.031285	10.94	1.59 (1.08-2.35)	1.879E-02	3.41 (1.51-7.70)	3.897E-03	1.66 (0.95-2.89)	7.485E-02	0.086	-0.0143	0.0405
Squamous cell lung cancer	Gamma-glutamylglutamate	10	0.012551	11.63	1.04 (1.005-1.07)	1.912E-02	1.13 (1.06-1.20)	1.172E-04	1.04 (0.99-1.08)	1.009E-01	0.02	0.0019	0.8194

Table S9 Mendelian Randomization estimation for Xenobiotic on the risk of cancers

Trait	Exposure	SNPs	R^2	*F* statistics	IVW		MR-Egger		Weighted median		MR-PRESSO	MR-Egger regression	
					OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		Intercept	*P* value
Breast cancer	1,7-dimethylurate	11	0.001022	10.65	1.09 (1.01-1.18)	2.193E-02	1.12 (0.96-1.32)	1.529E-01	1.09 (0.99-1.21)	7.648E-02	<0.001	-0.0009	0.7068
Breast cancer	2-methoxyacetaminophen sulfate	285	0.026495	10.92	0.99 (0.98-0.997)	6.492E-03	0.99 (0.98-1.01)	2.187E-01	0.99 (0.98-1.0004)	6.162E-02	0.47	-0.0001	0.9390
Breast cancer	catechol sulfate	12	0.001101	10.52	0.91 (0.83-0.997)	4.353E-02	0.96 (0.81-1.14)	6.586E-01	0.97 (0.86-1.10)	6.718E-01	0.01	-0.0019	0.4398
ER- Breast cancer	1,3,7-trimethylurate	11	0.001964	11.40	0.95 (0.91-0.995)	3.177E-02	0.97 (0.89-1.05)	4.397E-01	0.96 (0.92-1.001)	6.007E-02	0.223	-0.0026	0.5330
ER- Breast cancer	2-methoxyacetaminophen sulfate	285	0.047595	11.15	0.99 (0.98-0.999)	3.438E-02	0.995 (0.97-1.02)	7.256E-01	0.99 (0.97-1.01)	4.211E-01	0.028	-0.0022	0.4519
ER- Breast cancer	4-acetaminophen sulfate	7	0.001186	10.81	0.92 (0.85-0.99)	2.787E-02	0.87 (0.74-1.03)	1.021E-01	0.91 (0.82-1.01)	9.168E-02	0.095	-0.0009	0.8263
ER- Breast cancer	ibuprofen	102	0.02032	12.95	0.96 (0.93-0.98)	2.570E-03	0.99 (0.92-1.06)	7.003E-01	0.96 (0.92-1.004)	8.377E-02	0.027	-0.0033	0.3312
ER- Breast cancer	salicylate	18	0.00308	10.93	1.04 (1.01-1.06)	8.786E-04	1.05 (1.02-1.08)	2.736E-03	1.05 (1.02-1.09)	1.030E-03	0.73	-0.0034	0.2560
ER+ Breast cancer	1,7-dimethylurate	11	0.002457	19.64	1.12 (1.02-1.23)	1.607E-02	1.18 (0.98-1.44)	8.147E-02	1.06 (0.94-1.08)	3.350E-01	0.951	-0.0020	0.4988
Glioma	benzoate	9	0.030186	11.75	0.13 (0.02-0.75)	2.171E-02	0.12 (0.0001-87.64)	5.347E-01	0.09 (0.007-1.20)	6.830E-02	0.376	0.0008	0.9780
Lung adenocarcinoma	2-methoxyacetaminophen sulfate	256	0.297739	14.97	1.03 (1-1.06)	4.409E-02	1.06 (1.001-1.13)	4.551E-02	1.02 (0.97-1.06)	4.717E-01	0.727	-0.0082	0.2351
Lung adenocarcinoma	3-methylxanthine	13	0.016745	12.00	0.82 (0.68-0.98)	2.695E-02	1.04 (0.74-1.18)	8.076E-01	0.86 (0.59-1.26)	4.389E-01	0.4	-0.0120	0.1059
Lung adenocarcinoma	stachydrine	7	0.007843	10.35	1.12 (1.01-1.24)	2.845E-02	1.30 (1.02-1.64)	3.614E-02	1.08 (0.92-1.26)	3.612E-01	0.583	-0.0130	0.1854
Lung adenocarcinoma	vanillin	9	0.009974	10.26	1.43 (1.04-1.98)	2.971E-02	1.16 (0.43-3.10)	7.706E-01	1.61 (1.02-2.54)	3.889E-02	0.67	0.0064	0.6537
Ovarian cancer	ibuprofen	102	0.038964	13.19	0.96 (0.93-0.99)	6.982E-03	0.92 (0.85-0.99)	3.346E-02	0.95 (0.91-0.995)	3.206E-02	0.682	0.0040	0.2714
Ovarian cancer	quinate	6	0.001946	10.80	0.90 (0.82-0.998)	4.608E-02	0.98 (0.75-1.27)	8.645E-01	0.89 (0.79-1.002)	5.552E-02	0.714	-0.0043	0.5255
Ovarian cancer	stachydrine	6	0.003506	19.48	0.96 (0.93-0.99)	5.721E-03	0.93 (0.81-1.06)	2.742E-01	0.91 (0.84-0.98)	1.340E-02	0.339	0.0003	0.9532
Squamous cell lung cancer	2-methoxyacetaminophen sulfate	256	0.298112	14.98	1.04 (1.005-1.07)	1.912E-02	1.13 (1.06-1.20)	1.172E-04	1.04 (0.99-1.08)	1.009E-01	0.087	-0.0226	0.0018
Squamous cell lung cancer	N- (2-furoyl)glycine	23	0.028154	11.52	0.92 (0.86-0.995)	3.829E-02	0.83 (0.71-0.96)	1.358E-02	0.97 (0.87-1.08)	5.427E-01	0.079	0.0139	0.0965

Table S10 Mendelian Randomization estimation for X (unknow metabolites) on the risk of cancers

Trait	Exposure	SNPs	R^2	F statistics	IVW		MR-Egger		Weighted median	
					OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Breast cancer	X-04500	67	0.0366	304.48	1.03 (1-1.06)	4.251E-02	1.02 (0.96-1.08)	5.988E-01	1.02 (0.97-1.06)	4.661E-01
Breast cancer	X-09026	106	0.0776	387.90	0.88 (0.78-0.99)	3.253E-02	0.74 (0.54-1.02)	6.797E-02	0.88 (0.75-1.03)	1.131E-01
Breast cancer	X-11247	72	0.0573	345.97	0.91 (0.87-0.96)	6.483E-04	0.88 (0.79-0.99)	3.149E-02	0.91 (0.86-0.97)	3.883E-03
Breast cancer	X-11381	85	0.0963	480.84	0.86 (0.74-1)	4.959E-02	0.996 (0.64-1.56)	9.872E-01	0.83 (0.68-1.01)	6.887E-02
Breast cancer	X-11529	67	0.0412	302.20	0.92 (0.88-0.97)	1.532E-03	0.996 (0.90-1.10)	9.438E-01	0.93 (0.87-1.004)	6.502E-02
Breast cancer	X-11538	67	0.0613	426.58	0.95 (0.80-0.995)	3.168E-02	1.02 (0.92-1.13)	7.219E-01	0.98 (0.88-1.08)	6.199E-01
Breast cancer	X-11540	67	0.0613	426.58	0.95 (0.80-0.996)	3.168E-02	1.02 (0.92-1.14)	7.219E-01	0.98 (0.89-1.08)	6.105E-01
Breast cancer	X-11787	103	0.0498	278.90	1.2 (1.01-1.42)	3.986E-02	1.42 (0.997-2.02)	5.505E-02	1.28 (0.97-1.69)	8.534E-02
Breast cancer	X-11850	71	0.0428	297.00	1.03 (1-1.06)	4.005E-02	1.02 (0.96-1.09)	4.734E-01	1.007 (0.97-1.05)	7.152E-01
Breast cancer	X-12231	82	0.0599	342.07	0.92 (0.85-0.99)	2.567E-02	1.01 (0.88-1.15)	9.071E-01	0.91 (0.84+0.99)	2.239E-02
Breast cancer	X-12627	74	0.0455	300.37	1.08 (1-1.17)	3.996E-02	1.01 (0.87-1.18)	8.988E-01	1.06 (0.96-1.17)	2.830E-01
Breast cancer	X-13435	122	0.0902	421.21	1.12 (1.02-1.24)	2.243E-02	1.02 (0.83-1.25)	8.447E-01	1.15 (1.008-1.31)	3.768E-02
Breast cancer	X-14473	77	0.0523	352.08	9.00 (0.84-0.96)	1.272E-03	0.97 (0.80-1.18)	7.644E-01	0.88 (0.80-0.96)	4.427E-03
ER- Breast cancer	X-04498	97	0.0683	238.93	0.81 (0.68-0.97)	2.344E-02	0.85 (0.59-1.21)	3.685E-01	0.87 (0.67-1.12)	2.793E-01
ER- Breast cancer	X-11538	67	0.0778	321.81	0.87 (0.78-0.96)	7.425E-03	0.94 (0.74-1.18)	5.888E-01	0.92 (0.76-1.11)	3.744E-01
ER- Breast cancer	X-11540	67	0.0822	332.31	0.87 (0.78-0.96)	7.425E-03	0.94 (0.74-1.18)	5.888E-01	0.92 (0.77-1.09)	3.315E-01
ER- Breast cancer	X-11843	60	0.0656	278.16	1.05 (1.009-1.09)	1.438E-02	1.09 (1.03-1.16)	2.807E-03	1.09 (1.02-1.17)	1.208E-02
ER- Breast cancer	X-12627	74	0.0609	231.70	1.12 (1.003-1.27)	4.334E-02	1.26 (0.996-1.59)	5.757E-02	1.09 (0.92-1.32)	3.152E-01
ER- Breast cancer	X-12798	55	0.0782	314.35	0.86 (0.76-0.98)	2.789E-02	0.75 (0.62-0.90)	3.302E-03	0.89 (0.74-1.08)	2.302E-01
ER- Breast cancer	X-13435	122	0.1209	340.12	1.20 (1.02-1.41)	2.447E-02	1.14 (0.82-1.58)	4.468E-01	1.23 (0.99-1.53)	5.933E-02
ER- Breast cancer	X-14745	78	0.0810	288.99	1.26 (1.08-1.48)	2.993E-03	1.26 (0.85-1.88)	2.537E-01	1.19 (0.96-1.49)	1.120E-01
ER+ Breast cancer	X-03003	86	0.0781	331.97	0.86 (0.74-0.98)	2.772E-02	1.04 (0.74-1.47)	8.089E-01	0.98 (0.80-1.22)	8.825E-01
ER+ Breast cancer	X-09026	106	0.0886	348.45	0.82 (0.72-0.94)	5.558E-03	0.66 (0.46-0.95)	2.929E-02	0.78 (0.65-0.94)	1.042E-02
ER+ Breast cancer	X-11247	72	0.0668	314.94	0.90 (0.84-0.95)	3.582E-04	0.84 (0.73-0.96)	1.039E-02	0.88 (0.82-0.94)	2.811E-04
ER+ Breast cancer	X-11529	67	0.0499	276.63	0.90 (0.85-0.96)	6.831E-04	0.98 (0.87-1.11)	7.506E-01	0.91 (0.84-0.99)	2.511E-02
ER+ Breast cancer	X-11850	71	0.0489	263.44	1.04 (1.01-1.08)	1.615E-02	1.04 (0.97-1.13)	2.179E-01	1.04 (0.99-1.09)	1.307E-01
ER+ Breast cancer	X-12524	113	0.0841	270.69	1.25 (1-1.57)	4.719E-02	0.99 (0.599-1.70)	9.690E-01	1.26 (0.91-1.73)	1.639E-01
ER+ Breast cancer	X-13435	122	0.1030	380.86	1.14 (1.02-1.27)	2.293E-02	1.02 (0.81-1.28)	8.811E-01	1.15 (0.99-1.73)	6.569E-02
ER+ Breast cancer	X-13549	116	0.0969	348.53	0.79 (0.65-0.95)	1.403E-02	0.84 (0.51-1.38)	4.841E-01	0.85 (0.64-1.13)	2.631E-01
ER+ Breast cancer	X-14473	77	0.0597	313.48	0.87 (0.81-0.95)	1.111E-03	1.03 (0.80-1.32)	8.152E-01	0.90 (0.81-1.01)	7.470E-02
Glioma	X-10395	62	0.3378	251.59	5.72 (2.04-16.01)	8.947E-04	3.50 (0.57-21.46)	1.815E-01	4.34 (0.66-28.71)	1.277E-01
Glioma	X-11843	15	0.1087	88.18	2.34 (1.20-4.55)	1.224E-02	1.71 (0.189-15.56)	6.402E-01	2.12 (0.92-4.91)	7.869E-02

Glioma	X-12063	40	0.2089	111.84	0.57 (0.37-0.86)	8.128E-03	0.47 (0.23-0.95)	4.106E-02	0.43 (0.22-0.85)	1.482E-02
Glioma	X-12188	16	0.0431	40.07	0.67 (0.45-0.99)	4.318E-02	1.12 (0.49-2.58)	7.948E-01	0.63 (0.36-1.10)	1.024E-01
Glioma	X-12696	42	0.1116	61.32	3.57 (1.26-10.16)	1.693E-02	2.83 (0.35-23.07)	3.374E-01	3.60 (0.73-17.65)	1.144E-01
Lung adenocarcinoma	X-04494	101	0.1784	130.18	1.56 (1.03-2.36)	3.537E-02	3.07 (1.42-6.64)	5.315E-03	1.74 (0.98-3.09)	5.985E-02
Lung adenocarcinoma	X-10395	161	0.4893	2761.80	0.68 (0.47-0.995)	4.711E-02	0.79 (0.44-1.44)	4.460E-01	0.68 (0.36-1.26)	2.173E-01
Lung adenocarcinoma	X-12013	75	0.1974	137.63	0.90 (0.82-0.996)	4.127E-02	1.03 (0.89-1.20)	6.785E-01	0.95 (0.80-1.14)	5.949E-01
Lung adenocarcinoma	X-12094	60	0.0767	85.44	0.61 (0.43-0.88)	7.427E-03	0.51 (0.26-0.99)	5.296E-02	0.46 (0.27-0.77)	3.307E-03
Lung adenocarcinoma	X-12189	104	0.2157	110.59	0.90 (0.84-0.97)	7.832E-03	0.90 (0.81-1.01)	7.772E-02	0.96 (0.87-1.07)	4.710E-01
Lung adenocarcinoma	X-12524	120	0.2681	140.21	0.40 (0.18-0.88)	2.351E-02	1.6 (0.23-11.03)	6.337E-01	0.64 (0.20-1.98)	4.348E-01
Lung adenocarcinoma	X-12627	71	0.1523	106.23	0.70 (0.53-0.92)	1.026E-02	0.64 (0.37-1.10)	1.102E-01	0.69 (0.45-1.06)	9.186E-02
Lung adenocarcinoma	X-12680	69	0.1410	115.63	1.42 (1.04-1.94)	2.622E-02	2.3 (1.004-5.28)	5.282E-02	1.43 (0.90-2.27)	1.254E-01
Lung adenocarcinoma	X-12776	32	0.0372	57.69	3.7 (1.07-12.8)	3.869E-02	2.98 (0.29-31.04)	3.676E-01	3.997 (0.59-27.11)	1.561E-01
Lung adenocarcinoma	X-12786	82	0.2664	193.37	0.69 (0.51-0.92)	1.052E-02	0.81 (0.41-1.60)	5.405E-01	0.83 (0.54-1.28)	3.900E-01
Lung adenocarcinoma	X-12833	91	0.1837	114.41	0.92 (0.88-0.97)	1.030E-03	0.91 (0.83-1.009)	7.953E-02	0.91 (0.85-0.99)	2.090E-02
Lung adenocarcinoma	X-12851	66	0.1665	116.98	0.90 (0.93-0.98)	1.732E-02	0.87 (0.78-0.98)	1.978E-02	0.88 (0.76-1.007)	6.355E-02
Lung cancer	X-04494	101	0.1464	140.70	1.37 (1.06-1.78)	1.535E-02	2.28 (1.40-3.68)	1.142E-03	1.51 (1.05-2.17)	2.447E-02
Lung cancer	X-11469	86	0.2586	235.63	0.86 (0.77-0.96)	9.033E-03	0.90 (0.67-1.21)	4.761E-01	0.90 (0.76-1.07)	2.308E-01
Lung cancer	X-12092	83	0.2933	351.09	0.85 (0.77-0.94)	2.277E-03	0.94 (0.82-1.10)	4.584E-01	0.95 (0.83-1.08)	4.156E-01
Lung cancer	X-12189	104	0.1771	121.27	0.95 (0.90-0.993)	2.344E-02	0.95 (0.89-1.03)	2.121E-01	0.98 (0.92-1.05)	5.753E-01
Lung cancer	X-12712	140	0.1766	101.12	0.96 (0.93-0.998)	3.960E-02	0.97 (0.91-1.03)	2.971E-01	0.96 (0.91-1.03)	2.595E-01
Lung cancer	X-12786	82	0.2187	204.14	0.83 (0.68-0.997)	4.617E-02	1.09 (0.70-1.70)	6.926E-01	0.98 (0.73-1.30)	8.657E-01
Lung cancer	X-12851	66	0.1367	132.63	0.93 (0.88-0.99)	1.262E-02	0.90 (0.84-0.97)	7.272E-03	0.91 (0.83-1)	5.082E-02
Lung cancer	X-13549	120	0.2665	225.38	0.63 (0.41-0.97)	3.565E-02	0.45 (0.15-1.36)	1.572E-01	0.56 (0.29-1.09)	8.973E-02
Lung cancer	X-14662	87	0.1981	174.68	0.87 (0.79-0.96)	7.798E-03	0.83 (0.69-0.997)	5.061E-02	0.95 (0.82-1.10)	4.594E-01
Ovarian cancer	X-12013	72	0.1113	217.45	0.94 (0.89-0.998)	4.511E-02	0.97 (0.88-1.06)	4.675E-01	0.97 (0.89-1.05)	4.720E-01
Ovarian cancer	X-12116	86	0.0807	167.15	0.90 (0.83-0.98)	1.829E-02	0.89 (0.75-1.05)	1.750E-01	0.93 (0.81-1.05)	2.423E-01
Ovarian cancer	X-12544	85	0.0823	170.70	0.93 (0.87-0.99)	2.728E-02	0.95 (0.96-1.05)	3.372E-01	0.96 (0.86-1.08)	5.037E-01
Ovarian cancer	X-12556	111	0.1769	258.67	1.25 (1.02-1.52)	2.818E-02	0.99 (0.65-1.51)	9.545E-01	1.25 (0.93-1.67)	1.432E-01
Ovarian cancer	X-12740	70	0.0881	210.17	1.07 (1.008-1.13)	2.466E-02	1.10 (0.99-1.23)	8.778E-02	1.10 (1.005-1.19)	3.829E-02
Ovarian cancer	X-12844	75	0.0817	175.66	0.79 (0.64-0.98)	3.417E-02	1.07 (0.66-1.76)	7.761E-01	0.76 (0.56-1.03)	8.029E-02
Ovarian cancer	X-12847	65	0.1442	254.37	1.13 (1.05-1.21)	1.010E-03	1.15 (1.03-1.30)	2.093E-02	1.12 (0.99-1.26)	6.553E-02
Squamous cell lung cancer	X-07765	89	0.1625	111.57	0.88 (0.78-0.99)	3.102E-02	0.83 (0.67-1.03)	9.640E-02	0.88 (0.74-1.04)	1.369E-01
Squamous cell lung cancer	X-11299	78	0.2447	165.80	0.85 (0.74-0.98)	2.365E-02	0.83 (0.58-1.19)	3.183E-01	0.86 (0.71-1.05)	1.513E-01
Squamous cell lung cancer	X-11440	102	0.3662	308.08	1.21 (1.004-1.46)	4.424E-02	1.04 (0.73-1.48)	8.465E-01	1.06 (0.79-1.42)	6.891E-01
Squamous cell lung cancer	X-12063	92	0.2282	166.27	0.7 (0.58-0.85)	2.484E-04	0.83 (0.58-1.17)	2.932E-01	0.81 (0.61-1.09)	1.644E-01
Squamous cell lung cancer	X-12729	95	0.2067	109.58	1.11 (1.008-1.21)	3.286E-02	1.10 (0.93-1.30)	2.463E-01	1.09 (0.92-1.30)	3.273E-01
Squamous cell lung cancer	X-12786	82	0.2666	193.35	0.66 (0.49-0.89)	6.432E-03	0.89 (0.45-1.77)	7.355E-01	0.77 (0.50-1.19)	2.394E-01

Squamous cell lung cancer	X-12830	82	0.2235	142.06	0.82 (0.69-0.98)	3.155E-02	0.97 (0.68-1.38)	8.507E-01	0.77 (0.59-1.01)	6.222E-02
Squamous cell lung cancer	X-12851	66	0.1666	116.94	0.89 (0.82-0.97)	7.188E-03	0.87 (0.78-0.97)	1.515E-02	0.91 (0.79-1.04)	1.520E-01
Squamous cell lung cancer	X-13553	70	0.1953	140.68	0.59 (0.36-0.99)	4.675E-02	0.76 (0.26-2.21)	6.151E-01	0.57 (0.30-1.10)	9.383E-02

Table S11 Mendelian Randomization estamites for known metabolites on the risk of cancers

Trait	**Exposure**	**SNPs**	**IVW**		**MR-Egger**		**Weighted median**	
			OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Breast cancer	2-methylbutyroylcarnitine	100	0.77 (0.70-0.85)	3.418E-07	1.59 (1.27-1.99)	6.233E-05	1.004 (0.91-1.11)	9.351E-01
Breast cancer	4-acetamidobutanoate	33	0.93 (0.70-0.98)	3.116E-02	1.01 (0.69-1.48)	9.650E-01	0.87 (0.71-1.06)	1.638E-01
Breast cancer	isovalerylcarnitine	18	0.87 (0.76-0.99)	3.231E-02	0.81 (0.61-1.1)	1.527E-01	1.008 (0.87-1.16)	9.086E-01
Breast cancer	kynurenine	32	0.85 (0.73-0.99)	3.888E-02	0.95 (0.70-1.29)	7.333E-01	0.91 (0.74-1.10)	3.247E-01
Breast cancer	serotonin (5HT)	15	1.1 (1.00-1.21)	4.163E-02	1.04 (0.84-1.29)	7.221E-01	1.07 (0.95-1.21)	2.667E-01
Breast cancer	1-eicosatrienoylglycerophosphocholine	20	1.1 (1.01-1.20)	2.400E-02	1.18 (1-1.39)	5.184E-02	1.07 (0.95-1.21)	2.693E-01
Breast cancer	1-linoleoylglycerol (1-monolinolein)	13	0.92 (0.87-0.98)	1.164E-02	1.01 (0.88-1.17)	8.427E-01	0.94 (0.86-1.03)	2.110E-01
Breast cancer	1-oleoylglycerophosphocholine	16	1.22 (1.1-1.35)	1.039E-04	1.19 (0.97-1.45)	9.173E-02	1.17 (1.02-1.34)	2.732E-02
Breast cancer	3-dehydrocarnitine	22	0.88 (0.78-0.98)	1.937E-02	0.77 (0.60-0.995)	4.762E-02	0.81 (0.70-0.95)	7.900E-03
Breast cancer	palmitoylcarnitine	10	1.13 (1.01-1.27)	4.012E-02	0.95 (0.73-1.22)	6.761E-01	1.09 (0.94-1.27)	2.621E-01
Breast cancer	taurolithocholate 3-sulfate	9	0.94 (0.90-0.99)	8.901E-03	1 (0.91-1.1)	9.373E-01	0.95 (0.88-1.02)	1.632E-01
Breast cancer	gamma-glutamylglutamate	17	0.99 (0.98-0.997)	6.492E-03	0.99 (0.98-1.01)	2.187E-01	0.99 (0.98-1)	6.162E-02
Breast cancer	leucylleucine	9	0.91 (0.83-0.997)	4.353E-02	0.96 (0.91-1.14)	6.586E-01	0.97 (0.86-1.10)	6.718E-01
Breast cancer	leucylalanine	11	0.90 (0.82-0.99)	3.812E-02	1.13 (0.82-1.54)	4.601E-01	0.97 (0.90-1.05)	5.060E-01
Breast cancer	1,7-dimethylurate	11	1.09 (1.01-1.18)	2.193E-02	1.12 (0.96-1.32)	1.529E-01	1.09 (0.99-1.21)	7.648E-02
Breast cancer	2-methoxyacetaminophen sulfate	285	0.99 (0.98-0.997)	6.492E-03	0.99 (0.98-1.01)	2.187E-01	0.99 (0.98-1.0004)	6.162E-02
Breast cancer	catechol sulfate	12	0.91 (0.83-0.997)	4.353E-02	0.96 (0.81-1.14)	6.586E-01	0.97 (0.86-1.10)	6.718E-01
ER- Breast cancer	4-acetamidobutanoate	33	0.74 (0.57-0.95)	1.946E-02	0.72 (0.40-1.30)	2.791E-01	0.74 (0.51-1.06)	9.982E-02
ER- Breast cancer	kynurenine	32	0.75 (0.58-0.96)	2.381E-02	0.73 (0.44-1.22)	2.317E-01	0.77 (0.55-1.08)	1.287E-01
ER- Breast cancer	lactate	12	0.78 (0.62-0.98)	3.446E-02	0.64 (0.39-1.04)	7.778E-02	0.81 (0.58-1.15)	2.416E-01
ER- Breast cancer	1-arachidonoylglycerophosphoethanolamine	20	1.21 (1.03-1.41)	1.463E-02	1.08 (0.79-1.48)	6.125E-01	1.12 (0.87-1.44)	3.925E-01
ER- Breast cancer	1-docosahexaenoylglycerophosphocholine	8	1.15 (1.003-1.33)	4.514E-02	1.008 (0.78-1.30)	9.505E-01	0.93 (0.75-1.16)	5.385E-01
ER- Breast cancer	1-linoleoylglycerophosphoethanolamine	11	0.83 (0.71-0.98)	2.615E-02	1.07 (0.70-1.63)	7.471E-01	0.76 (0.55-1.05)	1.010E-01
ER- Breast cancer	1-oleoylglycerophosphocholine	16	1.38 (1.17-1.62)	1.147E-04	1.44 (1.05-1.99)	2.676E-02	1.36 (1.07-1.73)	1.234E-02
ER- Breast cancer	octadecanedioate	8	0.84 (0.73-0.99)	3.836E-02	1.11 (0.76-1.61)	5.881E-01	0.88 (0.70-1.10)	2.722E-01
ER- Breast cancer	palmitoylcarnitine	10	1.33 (1.11-1.60)	2.316E-03	1.19 (0.79-1.79)	4.006E-01	1.20 (0.93-1.57)	1.662E-01
ER- Breast cancer	taurochenodeoxycholate	13	1.08 (1.01-1.15)	1.990E-02	0.92 (0.76-1.12)	4.075E-01	0.97 (0.90-1.07)	6.290E-01
ER- Breast cancer	gamma-glutamylglutamate	19	0.99 (0.98-0.999)	3.438E-02	0.995 (0.97-1.02)	7.256E-01	0.99 (0.97-1.01)	4.211E-01

ER- Breast cancer	gamma-glutamylmethionine	17	0.92 (0.85-0.99)	2.787E-02	0.87 (0.74-1.03)	1.021E-01	0.91 (0.82-1.01)	9.168E-02
ER- Breast cancer	pro-hydroxy-pro	5	1.23 (1.02-1.49)	3.347E-02	0.93 (0.57-1.52)	7.814E-01	1.12 (0.85-1.47)	4.184E-01
ER- Breast cancer	leucylalanine	9	0.89 (0.81-0.98)	2.035E-02	1.14 (0.84-1.55)	4.106E-01	0.91 (0.79-1.04)	1.693E-01
ER- Breast cancer	phenylalanylleucine	9	1.10 (1.001-1.21)	4.633E-02	1.04 (0.83-1.30)	7.377E-01	1.06 (0.93-1.21)	3.703E-01
ER- Breast cancer	1,3,7-trimethylurate	11	0.95 (0.91-0.995)	3.177E-02	0.97 (0.89-1.05)	4.397E-01	0.96 (0.92-1.001)	6.007E-02
ER- Breast cancer	2-methoxyacetaminophen sulfate	285	0.99 (0.98-0.999)	3.438E-02	0.995 (0.97-1.02)	7.256E-01	0.99 (0.97-1.01)	4.211E-01
ER- Breast cancer	4-acetaminophen sulfate	7	0.92 (0.85-0.99)	2.787E-02	0.87 (0.74-1.03)	1.021E-01	0.91 (0.82-1.01)	9.168E-02
ER- Breast cancer	ibuprofen	102	0.96 (0.93-0.98)	2.570E-03	0.99 (0.92-1.06)	7.003E-01	0.96 (0.92-1.004)	8.377E-02
ER- Breast cancer	salicylate	18	1.04 (1.01-1.06)	8.786E-04	1.05 (1.02-1.08)	2.736E-03	1.05 (1.02-1.09)	1.030E-03
ER+ Breast cancer	2-methylbutyroylcarnitine	100	0.72 (0.64-0.80)	3.552E-09	1.58 (1.23-2.02)	3.061E-04	1.003 (0.90-1.12)	9.451E-01
ER+ Breast cancer	isovalerylcarnitine	18	0.86 (0.75-0.99)	3.392E-02	0.83 (0.60-1.13)	2.310E-01	0.95 (0.81-1.12)	5.680E-01
ER+ Breast cancer	N-acetylalanine	30	1.36 (1.07-1.74)	1.369E-02	1.36 (0.79-2.33)	2.746E-01	1.45 (1.006-2.07)	4.584E-02
ER+ Breast cancer	N-acetylthreonine	12	1.18 (1.01-1.38)	3.456E-02	0.75 (0.52-1.06)	1.088E-01	1.03 (0.83-1.27)	7.919E-01
ER+ Breast cancer	p-cresol sulfate	14	1.05 (1.00-1.11)	4.213E-02	1.04 (0.95-1.15)	3.957E-01	1.07 (0.99-1.49)	9.770E-02
ER+ Breast cancer	serotonin (5HT)	15	1.12 (1.02-1.24)	1.956E-02	1.08 (0.86-1.36)	4.959E-01	1.10 (0.95-1.27)	2.136E-01
ER+ Breast cancer	pyridoxate	10	1.18 (1.01-1.38)	3.217E-02	1.10 (0.80-1.51)	5.732E-01	1.12 (0.97-1.28)	1.293E-01
ER+ Breast cancer	threonate	17	0.88 (0.79-0.99)	3.645E-02	0.91 (0.72-1.14)	3.975E-01	0.85 (0.73-0.98)	2.565E-02
ER+ Breast cancer	1-linoleoylglycerol (1-monolinolein)	13	0.91 (0.85-0.97)	4.365E-03	0.98 (0.84-1.15)	8.463E-01	0.92 (0.83-1.02)	1.234E-01
ER+ Breast cancer	1-oleoylglycerophosphocholine	16	1.19 (1.06-1.33)	2.817E-03	1.50 (0.92-1.44)	2.227E-01	1.19 (1.01-1.41)	3.654E-02
ER+ Breast cancer	10-heptadecenoate (17:1n7)	6	0.84 (0.73-0.97)	1.350E-02	0.85 (0.56-1.28)	4.320E-01	0.83 (0.70-0.98)	3.115E-02
ER+ Breast cancer	cortisol	13	1.14 (1.01-1.29)	3.537E-02	1.12 (0.82-1.50)	4.751E-01	1.18 (0.98-1.42)	8.095E-02
ER+ Breast cancer	stearidonate (18:4n3)	4	0.88 (0.80-0.98)	2.344E-02	0.85 (0.57-1.08)	1.961E-01	0.92 (0.80-1.06)	2.540E-01
ER+ Breast cancer	taurolithocholate 3-sulfate	9	0.93 (0.88-0.98)	1.579E-02	1.04 (0.93-1.17)	5.197E-01	0.91 (0.84-0.99)	4.951E-02
ER+ Breast cancer	leucylalanine	17	0.89 (0.80-0.997)	4.323E-02	1.06 (0.73-1.52)	7.733E-01	0.98 (0.89-1.08)	6.888E-01
ER+ Breast cancer	1,7-dimethylurate	11	1.12 (1.02-1.23)	1.607E-02	1.18 (0.98-1.44)	8.147E-02	1.06 (0.94-1.08)	3.350E-01
Glioma	2-methylbutyroylcarnitine	57	2.19 (1.17-4.09)	1.455E-02	0.89 (0.16-4.96)	8.954E-01	1.99 (0.75-5.31)	1.673E-01
Glioma	4-acetamidobutanoate	14	0.15 (0.04-0.59)	6.306E-03	0.08 (0.003-2.24)	1.441E-01	0.24 (0.03-1.9)	1.773E-01
Glioma	pyroglutamine	7	3.20 (1.03-9.91)	4.393E-02	18.6 (0.72-479.10)	9.120E-02	2.32 (0.53-10.1)	2.638E-01
Glioma	1-oleoylglycerophosphoethanolamine	2	0.34 (0.13-0.91)	3.219E-02	0.90 (0.04-21.59)	9.510E-01	0.37 (0.09-1.44)	1.506E-01
Glioma	5alpha-androstan-3beta,17beta-diol disulfate	5	0.57 (0.34-0.98)	4.081E-02	0.65 (0.12-3.3.38)	6.127E-01	0.63 (0.28-1.43)	2.677E-01
Glioma	cis-4-decenoyl carnitine	3	0.39 (0.15-0.98)	4.630E-02	0.85 (0.11-6.46)	8.759E-01	0.60 (0.16-2.30)	4.590E-01
Glioma	glycerol	5	3.43 (1.08-10.90)	3.721E-02	0.90 (0.018-44.52)	9.585E-01	2.45 (0.43-13.83)	3.099E-01
Glioma	myristoleate (14:1n5)	3	0.20 (0.07-0.57)	2.624E-03	0.10 (0.003-2.43)	1.673E-01	0.18 (0.05-0.71)	1.412E-02
Glioma	taurodeoxycholate	4	0.66 (0.44-0.98)	3.877E-02	0.95 (0.16-5.70)	9.523E-01	0.87 (0.51-1.49)	6.109E-01
Glioma	ursodeoxycholate	2	0.44 (0.24-0.82)	1.033E-02	0.30 (0.04-2.00)	2.280E-01	0.37 (0.15-0.96)	4.000E-02
Glioma	gamma-glutamylleucine	12	4.74 (1.18-18.93)	2.783E-02	3.18 (0.03-296.7)	6.193E-01	7.93 (1.03-61.02)	4.661E-02
Glioma	gamma-glutamylthreonine	2	3.71 (1.30-10.56)	1.394E-02	2.70 (0.07-105.85)	6.002E-01	2.21 (0.48-10.04)	3.064E-01
Glioma	glycylvaline	9	0.13 (0.02-0.75)	2.171E-02	0.12 (0.0002-87.65)	5.347E-01	0.09 (0.0071-1.20)	6.830E-02

Glioma	N-acetylcarnosine	3	0.22 (0.07-0.76)	1.624E-02	1.41 (0.06-31.12)	8.308E-01	0.40 (0.06-2.56)	3.313E-01
Glioma	leucylalanine	2	0.55 (0.32-0.94)	2.952E-02	0.20 (0.03-1.57)	1.393E-01	0.62 (0.29-1.30)	2.050E-01
Glioma	benzoate	9	0.13 (0.02-0.75)	2.171E-02	0.12 (0.0001-87.64)	5.347E-01	0.09 (0.007-1.20)	6.830E-02
Lung adenocarcinoma	2-methylbutyroylcarnitine	100	0.60 (0.48-0.75)	1.144E-05	1.72 (1.005-2.96)	4.821E-02	0.59 (0.41-0.87)	7.209E-03
Lung adenocarcinoma	asparagine	13	1.42 (1.04-1.94)	2.622E-02	2.30 (1.004-5.28)	5.282E-02	1.43 (0.89-2.30)	1.340E-01
Lung adenocarcinoma	isoleucine	4	0.19 (0.0059-0.64)	7.193E-03	0.15 (0.013-1.57)	1.196E-01	0.32 (0.047-2.16)	2.427E-01
Lung adenocarcinoma	isovalerylcarnitine	18	0.67 (0.46-0.99)	4.540E-02	0.25 (0.10-0.62)	3.378E-03	0.73 (0.40-1.33)	3.004E-01
Lung adenocarcinoma	phenol sulfate	13	0.73 (0.57-0.95)	1.622E-02	0.79 (0.40-1.58)	5.080E-01	0.81 (0.55-1.19)	2.796E-01
Lung adenocarcinoma	phenylacetylglutamine	18	0.73 (0.57-0.93)	1.055E-02	0.62 (0.38-1.01)	6.050E-02	0.74 (0.52-1.06)	9.635E-02
Lung adenocarcinoma	phenylalanine	4	0.19 (0.0059-0.64)	7.193E-03	0.15 (0.013-1.57)	1.196E-01	0.32 (0.048-2.16)	2.427E-01
Lung adenocarcinoma	bilirubin (Z,Z)	10	0.80 (0.66-0.98)	2.671E-02	0.87 (0.61-1.24)	4.428E-01	0.94 (0.70-1.26)	6.646E-01
Lung adenocarcinoma	1-oleoylglycerol (1-monoolein)	16	0.76 (0.62-0.94)	1.104E-02	0.85 (0.58-1.24)	3.906E-01	0.86 (0.61-1.20)	3.692E-01
Lung adenocarcinoma	1-palmitoylglycerophosphoethanolamine	27	0.61 (0.40-0.92)	1.795E-02	0.47 (0.18-1.19)	1.122E-01	0.75 (0.41-1.35)	3.341E-01
Lung adenocarcinoma	5-dodecenoate (12:1n7)	18	0.75 (0.57-0.99)	4.115E-02	0.46 (0.26-0.81)	8.760E-03	0.78 (0.52-1.18)	2.434E-01
Lung adenocarcinoma	glycerophosphorylcholine (GPC)	18	0.67 (0.50-0.89)	6.826E-03	0.66 (0.40-1.10)	1.114E-01	0.98 (0.57-1.71)	9.559E-01
Lung adenocarcinoma	oleoylcarnitine	12	1.51 (1.02-2.23)	4.070E-02	1.59 (0.65-3.90)	3.132E-01	1.39 (0.83-2.33)	2.124E-01
Lung adenocarcinoma	taurochenodeoxycholate	11	0.85 (0.73-0.99)	3.664E-02	0.77 (0.59-1.01)	6.587E-02	0.76 (0.60-0.97)	2.799E-02
Lung adenocarcinoma	taurocholate	17	0.87 (0.77-0.98)	2.643E-02	0.86 (0.69-1.07)	1.857E-01	0.97 (0.81-1.16)	7.310E-01
Lung adenocarcinoma	7-methylguanine	11	1.73 (1.11-2.71)	1.589E-02	1.95 (0.65-5.89)	2.392E-01	1.62 (0.83-3.34)	1.544E-01
Lung adenocarcinoma	pseudouridine	24	0.40 (0.19-0.85)	1.738E-02	0.29 (0.03-2.45)	2.553E-01	0.41 (0.14-1.26)	1.194E-01
Lung adenocarcinoma	uridine	20	2.34 (1.14-4.82)	2.104E-02	1.48 (0.28-7.82)	6.424E-01	3.38 (1.04-10.97)	4.283E-02
Lung adenocarcinoma	gamma-glutamylglutamate	10	1.03 (0-1.06)	4.409E-02	1.06 (1.001-1.13)	4.551E-02	1.02 (0.97-1.06)	4.717E-01
Lung adenocarcinoma	gamma-glutamylisoleucine	19	0.82 (0.68-0.98)	2.695E-02	1.04 (0.74-1.48)	8.076E-01	0.86 (0.59-1.26)	4.389E-01
Lung adenocarcinoma	leucylleucine	6	1.31 (1.04-1.66)	2.291E-02	1.30 (0.83-2.03)	2.481E-01	1.35 (0.92-1.97)	1.267E-01
Lung adenocarcinoma	leucylalanine	27	1.27 (1.02-1.57)	3.233E-02	1.87 (0.93-3.76)	8.145E-02	1.31 (0.96-1.79)	8.758E-02
Lung adenocarcinoma	2-methoxyacetaminophen sulfate	256	1.03 (1-1.06)	4.409E-02	1.06 (1.001-1.13)	4.551E-02	1.02 (0.97-1.06)	4.717E-01
Lung adenocarcinoma	3-methylxanthine	13	0.82 (0.68-0.98)	2.695E-02	1.04 (0.74-1.18)	8.076E-01	0.86 (0.59-1.26)	4.389E-01
Lung adenocarcinoma	stachydrine	7	1.12 (1.01-1.24)	2.845E-02	1.30 (1.02-1.64)	3.614E-02	1.08 (0.92-1.26)	3.612E-01
Lung adenocarcinoma	vanillin	9	1.43 (1.04-1.98)	2.971E-02	1.16 (0.43-3.10)	7.706E-01	1.61 (1.02-2.54)	3.889E-02
Lung cancer	2-methylbutyroylcarnitine	100	0.59 (0.50-0.70)	1.984E-09	1.60 (1.08-2.36)	1.911E-02	0.85 (0.66-1.09)	2.025E-01
Lung cancer	indolelactate	18	0.80 (0.64-0.98)	4.673E-02	0.60 (0.42-0.87)	8.044E-03	0.79 (0.50-1.24)	3.042E-01
Lung cancer	arabinose	5	1.2 (1-1.45)	4.965E-02	1.20 (0.88-1.63)	2.653E-01	1.21 (0.90-1.63)	1.988E-01
Lung cancer	pyridoxate	5	1.30 (1.06-1.60)	1.148E-02	1.46 (0.94-0.28)	9.754E-02	1.16 (0.84-1.59)	3.576E-01
Lung cancer	1-eicosatrienoylglycerophosphocholine	19	0.74 (0.60-0.93)	8.063E-03	0.56 (0.35-0.89)	1.692E-02	0.79 (0.57-1.10)	1.718E-01
Lung cancer	2-hydroxyglutarate	11	1.34 (1.01-1.77)	4.152E-02	1.20 (0.59-2.44)	6.256E-01	1.34 (0.89-2.01)	1.558E-01
Lung cancer	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	14	1.45 (1.06-1.97)	1.835E-02	1.30 (0.74-2.26)	3.625E-01	1.45 (1.06-2.00)	1.835E-02
Lung cancer	androsterone sulfate	19	1.11 (1.00-1.23)	4.173E-02	1.10 (0.92-1.30)	2.893E-01	1.18 (1.01-1.36)	3.120E-02
Lung cancer	heptanoate (7:0)	34	0.68 (0.49-0.94)	2.070E-02	0.46 (0.18-1.17)	1.057E-01	0.55 (0.33-0.91)	1.895E-02

Lung cancer	pseudouridine	24	0.50 (0.30-0.83)	7.024E-03	0.72 (0.17-3.06)	6.536E-01	0.65 (0.31-1.34)	2.394E-01
Lung cancer	phenylalanylphenylalanine	4	0.73 (0.54-0.99)	4.231E-02	0.52 (0.25-1.11)	9.903E-02	0.80 (0.51-1.25)	3.256E-01
Lung cancer	leucylalanine	19	1.16 (1.01-1.32)	3.103E-02	1.70 (1.11-2.61)	1.759E-02	1.37 (1.12-1.66)	1.971E-03
Ovarian cancer	2-aminobutyrate	41	0.78 (0.61-0.99)	3.827E-02	0.77 (0.47-1.24)	2.838E-01	0.80 (0.54-1.20)	2.821E-01
Ovarian cancer	2-methylbutyroylcarnitine	100	0.77 (0.68-0.86)	2.995E-06	1.17 (0.90-1.53)	2.448E-01	0.63 (0.52-0.0.75)	4.771E-07
Ovarian cancer	3-phenylpropionate (hydrocinnamate)	15	0.92 (0.85-0.99)	3.528E-02	0.92 (0.82-1.04)	1.761E-01	0.94 (0.82-1.07)	3.592E-01
Ovarian cancer	N-acetylthreonine	12	1.28 (1.004-1.64)	4.587E-02	1.49 (0.84-2.65)	1.768E-01	1.62 (1.14-2.32)	7.836E-03
Ovarian cancer	butyrylcarnitine	20	1.14 (1.002-1.29)	4.540E-02	1.28 (0.99-1.65)	5.884E-02	1.23 (1.03-1.48)	2.619E-02
Ovarian cancer	hexanoylcarnitine	16	1.20 (1.02-1.41)	2.922E-02	1.12 (0.79-1.58)	5.300E-01	1.27 (0.95-1.70)	1.090E-01
Ovarian cancer	bradykinin, des-arg (9)	26	0.83 (0.71-0.96)	1.571E-02	0.82 (0.64-1.05)	1.218E-01	0.80 (0.62-1.03)	8.016E-02
Ovarian cancer	gamma-glutamylisoleucine	19	1.40 (1.16-1.69)	4.092E-04	1.18 (0.80-1.74)	4.098E-01	1.33 (0.99-1.79)	5.697E-02
Ovarian cancer	pro-hydroxy-pro	19	1.23 (1.002-1.50)	4.678E-02	1.28 (0.76-2.15)	3.501E-01	1.20 (0.89-1.61)	2.345E-01
Ovarian cancer	leucylalanine	17	0.96 (0.93-0.99)	6.982E-03	0.92 (0.85-0.99)	3.346E-02	0.95 (0.91-0.995)	3.206E-02
Ovarian cancer	ibuprofen	102	0.96 (0.93-0.99)	6.982E-03	0.92 (0.85-0.99)	3.346E-02	0.95 (0.91-0.995)	3.206E-02
Ovarian cancer	quinate	6	0.90 (0.82-0.998)	4.608E-02	0.98 (0.75-1.27)	8.645E-01	0.89 (0.79-1.002)	5.552E-02
Ovarian cancer	stachydrine	6	0.96 (0.93-0.99)	5.721E-03	0.93 (0.81-1.06)	2.742E-01	0.91 (0.84-0.98)	1.340E-02
Squamous cell lung cancer	2-methylbutyroylcarnitine	100	0.78 (0.63-0.98)	3.321E-02	1.97 (1.17-3.32)	1.122E-02	1.28 (0.89-1.84)	1.787E-01
Squamous cell lung cancer	1,5-anhydroglucitol (1,5-AG)	27	1.48 (0.50-2.08)	2.487E-02	1.13 (0.59-2.19)	7.062E-01	1.40 (0.83-2.37)	2.004E-01
Squamous cell lung cancer	alpha-tocopherol	11	0.56 (0.36-0.88)	1.152E-02	0.45 (0.17-1.23)	1.255E-01	0.54 (0.28-1.03)	6.165E-02
Squamous cell lung cancer	1-arachidonoylglycerophosphoethanolamine	21	1.56 (1.07-2.29)	2.128E-02	1.73 (0.74-4.06)	2.105E-01	1.36 (0.72-2.57)	3.398E-01
Squamous cell lung cancer	1-eicosatrienoylglycerophosphocholine	19	0.62 (0.44-0.87)	5.381E-03	0.41 (0.20-0.93)	1.629E-02	0.50 (0.30-0.84	9.062E-03
Squamous cell lung cancer	1-palmitoylglycerophosphocholine	32	0.53 (0.29-0.97)	3.999E-02	1.61 (0.24-10.8)	6.231E-01	0.60 (0.24-1.53)	2.877E-01
Squamous cell lung cancer	octanoylcarnitine	16	0.74 (0.55-0.98)	3.797E-02	0.53 (0.29-0.95)	3.636E-02	0.58 (0.36-0.92)	2.046E-02
Squamous cell lung cancer	pseudouridine	24	0.46 (0.22-0.97)	4.233E-02	0.71 (0.08-5.96)	7.513E-01	0.33 (0.11-1.009)	5.195E-02
Squamous cell lung cancer	xanthine	8	0.56 (0.33-0.94)	2.998E-02	0.56 (0.13-2.38)	4.377E-01	0.54 (0.25-1.17)	1.176E-01
Squamous cell lung cancer	gamma-glutamylisoleucine	27	1.59 (1.08-2.35)	1.879E-02	3.41 (1.51-7.70)	3.897E-03	1.66 (0.95-2.89)	7.485E-02
Squamous cell lung cancer	gamma-glutamylglutamate	10	1.04 (1.005-1.07)	1.912E-02	1.13 (1.06-1.20)	1.172E-04	1.04 (0.99-1.08)	1.009E-01
Squamous cell lung cancer	2-methoxyacetaminophen sulfate	256	1.04 (1.005-1.07)	1.912E-02	1.13 (1.06-1.20)	1.172E-04	1.04 (0.99-1.08)	1.009E-01
Squamous cell lung cancer	N- (2-furoyl)glycine	23	0.92 (0.86-0.995)	3.829E-02	0.83 (0.71-0.96)	1.358E-02	0.97 (0.87-1.08)	5.427E-01

Table S12 Summary statistics for the associations of the 2-methylbutyroylcarnitine-associated SNPs with these exposures and lung cancer in International Lung Cancer Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	*P* value	Beta	SE	*P* value
2-methylbutyroylcarnitine	rs1003533	5	T	C	0.0125	0.0027	2.330E-06	0.0031	0.0218	8.886E-01
2-methylbutyroylcarnitine	rs10139470	14	T	G	-0.0156	0.0032	1.470E-06	0.0080	0.0231	7.319E-01
2-methylbutyroylcarnitine	rs1016988	5	T	C	-0.0125	0.0027	2.510E-06	0.0046	0.0218	8.352E-01
2-methylbutyroylcarnitine	rs10484836	6	T	C	0.0208	0.0044	2.980E-06	-0.0524	0.0351	1.715E-01
2-methylbutyroylcarnitine	rs10740761	10	A	C	-0.0124	0.0026	2.660E-06	0.0119	0.0214	5.919E-01
2-methylbutyroylcarnitine	rs10866705	5	A	C	-0.0133	0.0026	3.470E-07	0.0300	0.0197	1.482E-01
2-methylbutyroylcarnitine	rs10896604	11	A	G	0.0162	0.0037	8.900E-06	0.0096	0.0283	7.383E-01
2-methylbutyroylcarnitine	rs11006251	10	T	C	0.0129	0.0027	1.550E-06	0.0374	0.0219	1.086E-01
2-methylbutyroylcarnitine	rs11006260	10	A	C	0.0120	0.0027	5.670E-06	0.0245	0.0216	2.776E-01
2-methylbutyroylcarnitine	rs11057695	12	T	C	0.0291	0.0062	2.790E-06	-0.0171	0.0355	6.486E-01
2-methylbutyroylcarnitine	rs11639506	16	A	G	-0.0340	0.0075	5.690E-06	-0.0185	0.0416	6.759E-01
2-methylbutyroylcarnitine	rs11753995	6	A	G	-0.0165	0.0034	1.100E-06	-0.0410	0.0233	9.995E-02
2-methylbutyroylcarnitine	rs11758111	6	T	C	-0.0154	0.0035	9.720E-06	0.0213	0.0276	4.427E-01
2-methylbutyroylcarnitine	rs12477840	2	T	C	0.0122	0.0027	5.890E-06	0.0124	0.0231	5.948E-01
2-methylbutyroylcarnitine	rs12777552	10	T	C	-0.0124	0.0026	2.370E-06	0.0115	0.0214	6.029E-01
2-methylbutyroylcarnitine	rs12929328	16	C	G	-0.0206	0.0046	8.890E-06	0.0028	0.0247	9.102E-01
2-methylbutyroylcarnitine	rs1447059	7	A	G	-0.0115	0.0025	7.060E-06	0.0127	0.0187	4.997E-01
2-methylbutyroylcarnitine	rs1447060	7	A	G	-0.0115	0.0025	7.070E-06	0.0136	0.0187	4.684E-01
2-methylbutyroylcarnitine	rs156322	5	T	C	-0.0114	0.0026	9.190E-06	0.0266	0.0187	1.734E-01
2-methylbutyroylcarnitine	rs1564348	6	T	C	0.0158	0.0034	2.870E-06	-0.0419	0.0233	9.185E-02
2-methylbutyroylcarnitine	rs1596972	7	A	G	-0.0117	0.0025	3.820E-06	0.0093	0.0180	6.096E-01
2-methylbutyroylcarnitine	rs17098575	12	A	C	-0.0270	0.0056	1.540E-06	-0.0107	0.0352	7.718E-01
2-methylbutyroylcarnitine	rs17098581	12	C	G	-0.0267	0.0059	5.200E-06	-0.0015	0.0350	9.678E-01
2-methylbutyroylcarnitine	rs17145256	10	A	G	0.0312	0.0069	6.580E-06	0.0563	0.0570	3.226E-01
2-methylbutyroylcarnitine	rs17435220	10	T	C	-0.0310	0.0069	7.940E-06	0.0527	0.0566	3.527E-01
2-methylbutyroylcarnitine	rs1838932	7	T	C	-0.0128	0.0026	5.070E-07	0.0154	0.0200	4.413E-01
2-methylbutyroylcarnitine	rs183898	5	C	G	-0.0123	0.0026	1.840E-06	-0.0265	0.0187	1.744E-01
2-methylbutyroylcarnitine	rs1981524	5	T	C	0.0123	0.0027	3.530E-06	0.0043	0.0219	8.460E-01
2-methylbutyroylcarnitine	rs2367533	7	T	C	0.0263	0.0059	8.010E-06	0.0873	0.0470	5.263E-02
2-methylbutyroylcarnitine	rs2410833	3	T	C	-0.0237	0.0053	8.270E-06	-0.0386	0.0309	2.435E-01
2-methylbutyroylcarnitine	rs2552122	8	A	C	0.0115	0.0026	6.290E-06	0.0146	0.0198	4.768E-01
2-methylbutyroylcarnitine	rs2631362	5	A	G	-0.0119	0.0026	4.120E-06	-0.0265	0.0187	1.751E-01
2-methylbutyroylcarnitine	rs2631370	5	T	C	-0.0121	0.0025	1.790E-06	-0.0481	0.0174	9.558E-03

2-methylbutyroylcarnitine	rs2631372	5	C	G	0.0124	0.0026	2.010E-06	-0.0272	0.0187	1.630E-01
2-methylbutyroylcarnitine	rs2665348	14	A	C	-0.0123	0.0027	7.010E-06	0.0350	0.0218	1.300E-01
2-methylbutyroylcarnitine	rs270601	5	T	C	0.0124	0.0026	1.380E-06	0.0273	0.0187	1.634E-01
2-methylbutyroylcarnitine	rs270602	5	T	C	0.0123	0.0025	1.090E-06	0.0444	0.0175	1.691E-02
2-methylbutyroylcarnitine	rs270605	5	T	C	-0.0124	0.0025	8.400E-07	0.0482	0.0174	9.349E-03
2-methylbutyroylcarnitine	rs270606	5	A	G	0.0123	0.0026	1.680E-06	0.0265	0.0187	1.741E-01
2-methylbutyroylcarnitine	rs270607	5	A	G	0.0123	0.0026	1.680E-06	0.0244	0.0186	2.093E-01
2-methylbutyroylcarnitine	rs270613	5	A	G	0.0124	0.0025	1.070E-06	0.0468	0.0174	1.158E-02
2-methylbutyroylcarnitine	rs272842	5	A	G	0.0128	0.0025	5.130E-07	0.0480	0.0174	9.690E-03
2-methylbutyroylcarnitine	rs272865	5	A	T	-0.0117	0.0025	3.980E-06	0.0441	0.0175	1.771E-02
2-methylbutyroylcarnitine	rs272867	5	A	G	-0.0123	0.0025	1.040E-06	0.0478	0.0174	9.936E-03
2-methylbutyroylcarnitine	rs272868	5	C	G	0.0126	0.0026	9.130E-07	0.0259	0.0187	1.841E-01
2-methylbutyroylcarnitine	rs272869	5	A	G	0.0123	0.0025	1.020E-06	0.0441	0.0175	1.772E-02
2-methylbutyroylcarnitine	rs272872	5	A	G	0.0125	0.0026	1.180E-06	0.0259	0.0187	1.850E-01
2-methylbutyroylcarnitine	rs272874	5	T	C	-0.0116	0.0026	6.900E-06	0.0441	0.0175	1.783E-02
2-methylbutyroylcarnitine	rs272875	5	T	C	0.0124	0.0025	1.020E-06	0.0480	0.0174	9.645E-03
2-methylbutyroylcarnitine	rs272878	5	T	C	0.0126	0.0026	9.950E-07	0.0259	0.0187	1.851E-01
2-methylbutyroylcarnitine	rs272879	5	C	G	0.0124	0.0025	1.010E-06	0.0480	0.0174	9.645E-03
2-methylbutyroylcarnitine	rs272880	5	T	C	-0.0126	0.0026	9.330E-07	0.0255	0.0187	1.908E-01
2-methylbutyroylcarnitine	rs272881	5	A	G	-0.0124	0.0025	1.010E-06	0.0473	0.0174	1.076E-02
2-methylbutyroylcarnitine	rs272882	5	T	G	-0.0126	0.0026	9.520E-07	0.0259	0.0187	1.850E-01
2-methylbutyroylcarnitine	rs272883	5	A	G	0.0126	0.0026	9.620E-07	0.0265	0.0187	1.745E-01
2-methylbutyroylcarnitine	rs272886	5	T	C	0.0123	0.0025	1.230E-06	0.0475	0.0174	1.048E-02
2-methylbutyroylcarnitine	rs272887	5	A	G	0.0124	0.0026	1.360E-06	0.0249	0.0187	2.016E-01
2-methylbutyroylcarnitine	rs272888	5	T	C	0.0124	0.0026	1.360E-06	0.0257	0.0187	1.880E-01
2-methylbutyroylcarnitine	rs272889	5	A	G	0.0123	0.0025	1.080E-06	0.0437	0.0175	1.878E-02
2-methylbutyroylcarnitine	rs272892	5	T	C	-0.0124	0.0026	1.360E-06	0.0257	0.0187	1.880E-01
2-methylbutyroylcarnitine	rs272893	5	T	C	0.0123	0.0025	1.080E-06	0.0434	0.0175	1.945E-02
2-methylbutyroylcarnitine	rs273901	5	T	G	-0.0124	0.0026	1.520E-06	0.0254	0.0187	1.927E-01
2-methylbutyroylcarnitine	rs273911	5	C	G	0.0124	0.0026	1.360E-06	0.0254	0.0187	1.936E-01
2-methylbutyroylcarnitine	rs273912	5	T	G	-0.0124	0.0026	1.630E-06	0.0257	0.0187	1.888E-01
2-methylbutyroylcarnitine	rs273913	5	T	C	0.0116	0.0025	4.700E-06	0.0471	0.0174	1.119E-02
2-methylbutyroylcarnitine	rs273914	5	A	T	0.0131	0.0025	2.070E-07	0.0478	0.0174	9.936E-03
2-methylbutyroylcarnitine	rs273915	5	C	G	-0.0124	0.0026	1.370E-06	0.0260	0.0187	1.836E-01
2-methylbutyroylcarnitine	rs273916	5	A	C	-0.0124	0.0026	1.370E-06	0.0260	0.0187	1.835E-01
2-methylbutyroylcarnitine	rs274546	5	A	G	0.0121	0.0025	1.590E-06	0.0457	0.0175	1.410E-02
2-methylbutyroylcarnitine	rs274557	5	T	C	-0.0118	0.0025	3.420E-06	-0.0477	0.0175	1.083E-02

2-methylbutyroylcarnitine	rs274558	5	A	G	-0.0118	0.0025	3.430E-06	-0.0475	0.0175	1.120E-02
2-methylbutyroylcarnitine	rs274559	5	A	G	-0.0117	0.0026	4.170E-06	-0.0478	0.0175	1.072E-02
2-methylbutyroylcarnitine	rs274560	5	T	C	-0.0119	0.0025	2.430E-06	-0.0451	0.0176	1.607E-02
2-methylbutyroylcarnitine	rs274561	5	A	C	0.0119	0.0025	2.220E-06	-0.0448	0.0176	1.676E-02
2-methylbutyroylcarnitine	rs274567	5	T	C	0.0121	0.0025	1.710E-06	-0.0455	0.0175	1.465E-02
2-methylbutyroylcarnitine	rs274570	5	T	C	0.0127	0.0026	1.170E-06	-0.0265	0.0187	1.747E-01
2-methylbutyroylcarnitine	rs3778129	6	A	G	-0.0182	0.0041	9.910E-06	0.0213	0.0277	4.434E-01
2-methylbutyroylcarnitine	rs4074995	5	A	G	0.0123	0.0026	1.770E-06	-0.0178	0.0196	3.820E-01
2-methylbutyroylcarnitine	rs4075958	5	A	G	0.0124	0.0026	1.920E-06	-0.0193	0.0195	3.397E-01
2-methylbutyroylcarnitine	rs419291	5	T	C	0.0123	0.0025	1.330E-06	0.0443	0.0175	1.759E-02
2-methylbutyroylcarnitine	rs456598	6	A	G	-0.0155	0.0035	7.090E-06	-0.0569	0.0250	3.595E-02
2-methylbutyroylcarnitine	rs4626843	1	A	G	0.0292	0.0065	7.390E-06	-0.0061	0.0460	8.997E-01
2-methylbutyroylcarnitine	rs4648860	1	T	C	0.0124	0.0027	4.720E-06	-0.0419	0.0215	6.738E-02
2-methylbutyroylcarnitine	rs4719207	7	T	C	-0.0140	0.0030	3.060E-06	-0.0334	0.0204	1.215E-01
2-methylbutyroylcarnitine	rs4730501	7	A	G	-0.0121	0.0026	4.180E-06	-0.0197	0.0204	3.538E-01
2-methylbutyroylcarnitine	rs4732399	7	A	G	-0.0311	0.0070	8.690E-06	0.0826	0.0478	7.285E-02
2-methylbutyroylcarnitine	rs4948546	10	A	G	-0.0125	0.0026	2.370E-06	0.0118	0.0214	5.942E-01
2-methylbutyroylcarnitine	rs6575209	14	T	C	0.0120	0.0026	5.100E-06	0.0002	0.0222	9.944E-01
2-methylbutyroylcarnitine	rs662138	6	C	G	0.0187	0.0034	3.650E-08	-0.0470	0.0226	5.262E-02
2-methylbutyroylcarnitine	rs671473	5	A	C	0.0122	0.0026	2.130E-06	-0.0265	0.0187	1.748E-01
2-methylbutyroylcarnitine	rs6764615	3	C	G	0.0159	0.0033	2.170E-06	0.0487	0.0251	4.665E-02
2-methylbutyroylcarnitine	rs7081819	10	A	G	0.0120	0.0027	5.630E-06	0.0267	0.0215	2.366E-01
2-methylbutyroylcarnitine	rs7087186	10	C	G	0.0126	0.0027	2.230E-06	0.0256	0.0219	2.636E-01
2-methylbutyroylcarnitine	rs715	2	T	C	0.0123	0.0026	2.400E-06	-0.0066	0.0201	7.514E-01
2-methylbutyroylcarnitine	rs7903712	10	C	G	0.0127	0.0027	1.650E-06	0.0186	0.0218	4.130E-01
2-methylbutyroylcarnitine	rs7920393	10	A	G	0.0120	0.0027	6.050E-06	0.0251	0.0215	2.664E-01
2-methylbutyroylcarnitine	rs7946997	11	T	C	-0.0123	0.0026	2.970E-06	0.0116	0.0204	5.717E-01
2-methylbutyroylcarnitine	rs9416742	10	A	G	0.0120	0.0027	5.640E-06	-0.0244	0.0216	2.810E-01
2-methylbutyroylcarnitine	rs9492253	6	A	G	-0.0119	0.0027	8.620E-06	0.0081	0.0221	7.190E-01
2-methylbutyroylcarnitine	rs9641894	7	T	G	-0.0117	0.0025	4.130E-06	0.0086	0.0182	6.398E-01
2-methylbutyroylcarnitine	rs9642829	8	A	G	-0.0346	0.0075	3.610E-06	0.0487	0.0609	4.284E-01
2-methylbutyroylcarnitine	rs9839755	3	T	C	0.0152	0.0034	7.620E-06	0.0493	0.0253	4.595E-02
2-methylbutyroylcarnitine	rs999845	10	T	C	0.0121	0.0027	4.870E-06	0.0240	0.0216	2.891E-01
2-methylbutyroylcarnitine	rs999846	10	A	G	0.0120	0.0027	5.710E-06	0.0234	0.0216	3.007E-01

Table S13 Summary statistics for the associations of the 2-methylbutyroylcarnitine-associated SNPs with these exposures and breast cancer in Breast Cancer Association Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
2-methylbutyroylcarnitine	rs1003533	5	T	C	0.0125	0.0027	2.330E-06	-0.0140	0.0077	7.144E-02
2-methylbutyroylcarnitine	rs10139470	14	T	G	-0.0156	0.0032	1.470E-06	0.0235	0.0078	2.784E-03
2-methylbutyroylcarnitine	rs1016988	5	T	C	-0.0125	0.0027	2.510E-06	-0.0131	0.0078	9.208E-02
2-methylbutyroylcarnitine	rs10484836	6	T	C	0.0208	0.0044	2.980E-06	0.0107	0.0167	5.213E-01
2-methylbutyroylcarnitine	rs10866705	5	A	C	-0.0133	0.0026	3.470E-07	0.0009	0.0077	9.067E-01
2-methylbutyroylcarnitine	rs11006251	10	T	C	0.0129	0.0027	1.550E-06	0.0226	0.0091	1.339E-02
2-methylbutyroylcarnitine	rs11006260	10	A	C	0.0120	0.0027	5.670E-06	0.0175	0.0090	5.207E-02
2-methylbutyroylcarnitine	rs11753995	6	A	G	-0.0165	0.0034	1.100E-06	-0.0036	0.0084	6.649E-01
2-methylbutyroylcarnitine	rs11758111	6	T	C	-0.0154	0.0035	9.720E-06	0.0168	0.0095	7.628E-02
2-methylbutyroylcarnitine	rs12477840	2	T	C	0.0122	0.0027	5.890E-06	-0.0013	0.0082	8.728E-01
2-methylbutyroylcarnitine	rs12777552	10	T	C	-0.0124	0.0026	2.370E-06	0.0155	0.0088	7.877E-02
2-methylbutyroylcarnitine	rs12929328	16	C	G	-0.0206	0.0046	8.890E-06	0.0003	0.0087	9.728E-01
2-methylbutyroylcarnitine	rs1447059	7	A	G	-0.0115	0.0025	7.060E-06	-0.0129	0.0069	6.384E-02
2-methylbutyroylcarnitine	rs1447060	7	A	G	-0.0115	0.0025	7.070E-06	-0.0123	0.0069	7.527E-02
2-methylbutyroylcarnitine	rs156322	5	T	C	-0.0114	0.0026	9.190E-06	0.0262	0.0067	9.460E-05
2-methylbutyroylcarnitine	rs1564348	6	T	C	0.0158	0.0034	2.870E-06	-0.0044	0.0084	5.998E-01
2-methylbutyroylcarnitine	rs1596972	7	A	G	-0.0117	0.0025	3.820E-06	-0.0169	0.0068	1.325E-02
2-methylbutyroylcarnitine	rs17145256	10	A	G	0.0312	0.0069	6.580E-06	0.0653	0.0186	4.529E-04
2-methylbutyroylcarnitine	rs17435220	10	T	C	-0.0310	0.0069	7.940E-06	0.0655	0.0187	4.601E-04
2-methylbutyroylcarnitine	rs1838932	7	T	C	-0.0128	0.0026	5.070E-07	-0.0098	0.0072	1.757E-01
2-methylbutyroylcarnitine	rs183898	5	C	G	-0.0123	0.0026	1.840E-06	-0.0257	0.0067	1.229E-04
2-methylbutyroylcarnitine	rs1981524	5	T	C	0.0123	0.0027	3.530E-06	-0.0138	0.0078	7.521E-02
2-methylbutyroylcarnitine	rs2367533	7	T	C	0.0263	0.0059	8.010E-06	0.0061	0.0150	6.826E-01
2-methylbutyroylcarnitine	rs2410833	3	T	C	-0.0237	0.0053	8.270E-06	0.0173	0.0110	1.159E-01
2-methylbutyroylcarnitine	rs2552122	8	A	C	0.0115	0.0026	6.290E-06	-0.0121	0.0068	7.604E-02
2-methylbutyroylcarnitine	rs2631362	5	A	G	-0.0119	0.0026	4.120E-06	-0.0256	0.0067	1.324E-04
2-methylbutyroylcarnitine	rs2631370	5	T	C	-0.0121	0.0025	1.790E-06	-0.0221	0.0063	4.865E-04
2-methylbutyroylcarnitine	rs2631372	5	C	G	0.0124	0.0026	2.010E-06	-0.0264	0.0067	7.910E-05
2-methylbutyroylcarnitine	rs2665348	14	A	C	-0.0123	0.0027	7.010E-06	-0.0212	0.0081	8.982E-03
2-methylbutyroylcarnitine	rs270601	5	T	C	0.0124	0.0026	1.380E-06	0.0259	0.0067	1.108E-04
2-methylbutyroylcarnitine	rs270602	5	T	C	0.0123	0.0025	1.090E-06	0.0213	0.0063	8.047E-04
2-methylbutyroylcarnitine	rs270605	5	T	C	-0.0124	0.0025	8.400E-07	0.0221	0.0063	4.737E-04

2-methylbutyroylcarnitine	rs270606	5	A	G	0.0123	0.0026	1.680E-06	0.0258	0.0067	1.190E-04
2-methylbutyroylcarnitine	rs270607	5	A	G	0.0123	0.0026	1.680E-06	0.0250	0.0067	1.770E-04
2-methylbutyroylcarnitine	rs270613	5	A	G	0.0124	0.0025	1.070E-06	0.0241	0.0064	1.568E-04
2-methylbutyroylcarnitine	rs272842	5	A	G	0.0128	0.0025	5.130E-07	0.0220	0.0063	5.055E-04
2-methylbutyroylcarnitine	rs272865	5	A	T	-0.0117	0.0025	3.980E-06	0.0221	0.0063	4.851E-04
2-methylbutyroylcarnitine	rs272867	5	A	G	-0.0123	0.0025	1.040E-06	0.0221	0.0063	4.804E-04
2-methylbutyroylcarnitine	rs272868	5	C	G	0.0126	0.0026	9.130E-07	0.0260	0.0067	1.024E-04
2-methylbutyroylcarnitine	rs272869	5	A	G	0.0123	0.0025	1.020E-06	0.0215	0.0063	7.085E-04
2-methylbutyroylcarnitine	rs272872	5	A	G	0.0125	0.0026	1.180E-06	0.0259	0.0067	1.137E-04
2-methylbutyroylcarnitine	rs272874	5	T	C	-0.0116	0.0026	6.900E-06	0.0214	0.0064	7.477E-04
2-methylbutyroylcarnitine	rs272875	5	T	C	0.0124	0.0025	1.020E-06	0.0221	0.0063	4.734E-04
2-methylbutyroylcarnitine	rs272878	5	T	C	0.0126	0.0026	9.950E-07	0.0259	0.0067	1.123E-04
2-methylbutyroylcarnitine	rs272879	5	C	G	0.0124	0.0025	1.010E-06	0.0221	0.0063	4.892E-04
2-methylbutyroylcarnitine	rs272880	5	T	C	-0.0126	0.0026	9.330E-07	0.0256	0.0067	1.322E-04
2-methylbutyroylcarnitine	rs272881	5	A	G	-0.0124	0.0025	1.010E-06	0.0220	0.0063	5.144E-04
2-methylbutyroylcarnitine	rs272882	5	T	G	-0.0126	0.0026	9.520E-07	0.0259	0.0067	1.113E-04
2-methylbutyroylcarnitine	rs272883	5	A	G	0.0126	0.0026	9.620E-07	0.0259	0.0067	1.108E-04
2-methylbutyroylcarnitine	rs272886	5	T	C	0.0123	0.0025	1.230E-06	0.0220	0.0063	4.903E-04
2-methylbutyroylcarnitine	rs272887	5	A	G	0.0124	0.0026	1.360E-06	0.0258	0.0067	1.195E-04
2-methylbutyroylcarnitine	rs272888	5	T	C	0.0124	0.0026	1.360E-06	0.0257	0.0067	1.218E-04
2-methylbutyroylcarnitine	rs272889	5	A	G	0.0123	0.0025	1.080E-06	0.0213	0.0063	7.900E-04
2-methylbutyroylcarnitine	rs272892	5	T	C	-0.0124	0.0026	1.360E-06	0.0259	0.0067	1.089E-04
2-methylbutyroylcarnitine	rs272893	5	T	C	0.0123	0.0025	1.080E-06	0.0214	0.0063	7.435E-04
2-methylbutyroylcarnitine	rs273901	5	T	G	-0.0124	0.0026	1.520E-06	0.0261	0.0067	9.840E-05
2-methylbutyroylcarnitine	rs273911	5	C	G	0.0124	0.0026	1.360E-06	0.0256	0.0067	1.326E-04
2-methylbutyroylcarnitine	rs273912	5	T	G	-0.0124	0.0026	1.630E-06	0.0257	0.0067	1.219E-04
2-methylbutyroylcarnitine	rs273913	5	T	C	0.0116	0.0025	4.700E-06	0.0219	0.0063	5.388E-04
2-methylbutyroylcarnitine	rs273914	5	A	T	0.0131	0.0025	2.070E-07	0.0220	0.0063	5.155E-04
2-methylbutyroylcarnitine	rs273915	5	C	G	-0.0124	0.0026	1.370E-06	0.0260	0.0067	1.053E-04
2-methylbutyroylcarnitine	rs273916	5	A	C	-0.0124	0.0026	1.370E-06	0.0259	0.0067	1.105E-04
2-methylbutyroylcarnitine	rs274546	5	A	G	0.0121	0.0025	1.590E-06	0.0215	0.0064	7.054E-04
2-methylbutyroylcarnitine	rs274557	5	T	C	-0.0118	0.0025	3.420E-06	-0.0220	0.0063	5.174E-04
2-methylbutyroylcarnitine	rs274558	5	A	G	-0.0118	0.0025	3.430E-06	-0.0220	0.0063	5.164E-04
2-methylbutyroylcarnitine	rs274559	5	A	G	-0.0117	0.0026	4.170E-06	-0.0220	0.0063	5.020E-04
2-methylbutyroylcarnitine	rs274560	5	T	C	-0.0119	0.0025	2.430E-06	-0.0217	0.0064	6.365E-04
2-methylbutyroylcarnitine	rs274561	5	A	C	0.0119	0.0025	2.220E-06	-0.0215	0.0064	7.341E-04
2-methylbutyroylcarnitine	rs274567	5	T	C	0.0121	0.0025	1.710E-06	-0.0227	0.0064	3.561E-04

2-methylbutyroylcarnitine	rs274570	5	T	C	0.0127	0.0026	1.170E-06	-0.0255	0.0067	1.455E-04
2-methylbutyroylcarnitine	rs3778129	6	A	G	-0.0182	0.0041	9.910E-06	0.0169	0.0094	7.163E-02
2-methylbutyroylcarnitine	rs4074995	5	A	G	0.0123	0.0026	1.770E-06	0.0055	0.0074	4.570E-01
2-methylbutyroylcarnitine	rs4075958	5	A	G	0.0124	0.0026	1.920E-06	0.0055	0.0075	4.625E-01
2-methylbutyroylcarnitine	rs419291	5	T	C	0.0123	0.0025	1.330E-06	0.0237	0.0064	2.182E-04
2-methylbutyroylcarnitine	rs456598	6	A	G	-0.0155	0.0035	7.090E-06	0.0033	0.0091	7.163E-01
2-methylbutyroylcarnitine	rs4626843	1	A	G	0.0292	0.0065	7.390E-06	-0.0056	0.0165	7.336E-01
2-methylbutyroylcarnitine	rs4648860	1	T	C	0.0124	0.0027	4.720E-06	-0.0077	0.0084	3.598E-01
2-methylbutyroylcarnitine	rs4719207	7	T	C	-0.0140	0.0030	3.060E-06	-0.0094	0.0074	2.013E-01
2-methylbutyroylcarnitine	rs4730501	7	A	G	-0.0121	0.0026	4.180E-06	0.0044	0.0076	5.609E-01
2-methylbutyroylcarnitine	rs4732399	7	A	G	-0.0311	0.0070	8.690E-06	-0.0004	0.0159	9.817E-01
2-methylbutyroylcarnitine	rs4948546	10	A	G	-0.0125	0.0026	2.370E-06	0.0155	0.0088	7.829E-02
2-methylbutyroylcarnitine	rs6575209	14	T	C	0.0120	0.0026	5.100E-06	0.0222	0.0078	4.457E-03
2-methylbutyroylcarnitine	rs662138	6	C	G	0.0187	0.0034	3.650E-08	0.0002	0.0082	9.824E-01
2-methylbutyroylcarnitine	rs6764615	3	C	G	0.0159	0.0033	2.170E-06	0.0145	0.0089	1.034E-01
2-methylbutyroylcarnitine	rs7081819	10	A	G	0.0120	0.0027	5.630E-06	0.0176	0.0090	5.032E-02
2-methylbutyroylcarnitine	rs7087186	10	C	G	0.0126	0.0027	2.230E-06	0.0202	0.0090	2.521E-02
2-methylbutyroylcarnitine	rs715	2	T	C	0.0123	0.0026	2.400E-06	0.0124	0.0070	7.437E-02
2-methylbutyroylcarnitine	rs7903712	10	C	G	0.0127	0.0027	1.650E-06	0.0170	0.0089	5.594E-02
2-methylbutyroylcarnitine	rs7920393	10	A	G	0.0120	0.0027	6.050E-06	0.0189	0.0090	3.530E-02
2-methylbutyroylcarnitine	rs7946997	11	T	C	-0.0123	0.0026	2.970E-06	0.0017	0.0068	8.035E-01
2-methylbutyroylcarnitine	rs9416742	10	A	G	0.0120	0.0027	5.640E-06	-0.0163	0.0092	7.562E-02
2-methylbutyroylcarnitine	rs9492253	6	A	G	-0.0119	0.0027	8.620E-06	0.0048	0.0077	5.320E-01
2-methylbutyroylcarnitine	rs9641894	7	T	G	-0.0117	0.0025	4.130E-06	-0.0162	0.0069	1.816E-02
2-methylbutyroylcarnitine	rs9642829	8	A	G	-0.0346	0.0075	3.610E-06	-0.0253	0.0221	2.512E-01
2-methylbutyroylcarnitine	rs9839755	3	T	C	0.0152	0.0034	7.620E-06	0.0158	0.0089	7.509E-02
2-methylbutyroylcarnitine	rs999845	10	T	C	0.0121	0.0027	4.870E-06	0.0187	0.0090	3.730E-02
2-methylbutyroylcarnitine	rs999846	10	A	G	0.0120	0.0027	5.710E-06	0.0187	0.0090	3.705E-02

Table S14 Summary statistics for the associations of the 2-methylbutyroylcarnitine-associated SNPs with these exposures and ovarian cancer in Ovarian Cancer Association Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
2-methylbutyroylcarnitine	rs1003533	5	T	C	0.0125	0.0027	2.330E-06	-0.0275	0.0164	9.451E-02
2-methylbutyroylcarnitine	rs10139470	14	T	G	-0.0156	0.0032	1.470E-06	0.0183	0.0158	2.455E-01
2-methylbutyroylcarnitine	rs1016988	5	T	C	-0.0125	0.0027	2.510E-06	-0.0268	0.0164	1.030E-01
2-methylbutyroylcarnitine	rs10484836	6	T	C	0.0208	0.0044	2.980E-06	-0.0056	0.0346	8.721E-01
2-methylbutyroylcarnitine	rs10740761	10	A	C	-0.0124	0.0026	2.660E-06	-0.0198	0.0171	2.471E-01
2-methylbutyroylcarnitine	rs10866705	5	A	C	-0.0133	0.0026	3.470E-07	-0.0017	0.0159	9.130E-01
2-methylbutyroylcarnitine	rs10896604	11	A	G	0.0162	0.0037	8.900E-06	-0.0199	0.0217	3.588E-01
2-methylbutyroylcarnitine	rs11006251	10	T	C	0.0129	0.0027	1.550E-06	-0.0131	0.0177	4.590E-01
2-methylbutyroylcarnitine	rs11006260	10	A	C	0.0120	0.0027	5.670E-06	-0.0163	0.0175	3.516E-01
2-methylbutyroylcarnitine	rs11639506	16	A	G	-0.0340	0.0075	5.690E-06	0.0609	0.0316	5.416E-02
2-methylbutyroylcarnitine	rs11753995	6	A	G	-0.0165	0.0034	1.100E-06	0.0153	0.0178	3.899E-01
2-methylbutyroylcarnitine	rs11758111	6	T	C	-0.0154	0.0035	9.720E-06	-0.0349	0.0202	8.388E-02
2-methylbutyroylcarnitine	rs12477840	2	T	C	0.0122	0.0027	5.890E-06	0.0089	0.0173	6.049E-01
2-methylbutyroylcarnitine	rs12777552	10	T	C	-0.0124	0.0026	2.370E-06	-0.0175	0.0171	3.080E-01
2-methylbutyroylcarnitine	rs12929328	16	C	G	-0.0206	0.0046	8.890E-06	0.0174	0.0178	3.286E-01
2-methylbutyroylcarnitine	rs1447059	7	A	G	-0.0115	0.0025	7.060E-06	-0.0027	0.0140	8.450E-01
2-methylbutyroylcarnitine	rs1447060	7	A	G	-0.0115	0.0025	7.070E-06	-0.0037	0.0140	7.898E-01
2-methylbutyroylcarnitine	rs156322	5	T	C	-0.0114	0.0026	9.190E-06	0.0131	0.0143	3.587E-01
2-methylbutyroylcarnitine	rs1564348	6	T	C	0.0158	0.0034	2.870E-06	0.0180	0.0179	3.148E-01
2-methylbutyroylcarnitine	rs1596972	7	A	G	-0.0117	0.0025	3.820E-06	-0.0033	0.0138	8.129E-01
2-methylbutyroylcarnitine	rs17145256	10	A	G	0.0312	0.0069	6.580E-06	0.0218	0.0401	5.870E-01
2-methylbutyroylcarnitine	rs17435220	10	T	C	-0.0310	0.0069	7.940E-06	0.0237	0.0401	5.549E-01
2-methylbutyroylcarnitine	rs1838932	7	T	C	-0.0128	0.0026	5.070E-07	0.0017	0.0148	9.074E-01
2-methylbutyroylcarnitine	rs183898	5	C	G	-0.0123	0.0026	1.840E-06	-0.0123	0.0143	3.906E-01
2-methylbutyroylcarnitine	rs1981524	5	T	C	0.0123	0.0027	3.530E-06	-0.0276	0.0164	9.358E-02
2-methylbutyroylcarnitine	rs2367533	7	T	C	0.0263	0.0059	8.010E-06	-0.0480	0.0315	1.273E-01
2-methylbutyroylcarnitine	rs2410833	3	T	C	-0.0237	0.0053	8.270E-06	0.0170	0.0235	4.694E-01
2-methylbutyroylcarnitine	rs2552122	8	A	C	0.0115	0.0026	6.290E-06	-0.0268	0.0144	6.238E-02
2-methylbutyroylcarnitine	rs2631362	5	A	G	-0.0119	0.0026	4.120E-06	-0.0122	0.0143	3.933E-01
2-methylbutyroylcarnitine	rs2631370	5	T	C	-0.0121	0.0025	1.790E-06	-0.0130	0.0135	3.381E-01
2-methylbutyroylcarnitine	rs2631372	5	C	G	0.0124	0.0026	2.010E-06	-0.0124	0.0143	3.878E-01
2-methylbutyroylcarnitine	rs2665348	14	A	C	-0.0123	0.0027	7.010E-06	-0.0113	0.0171	5.091E-01
2-methylbutyroylcarnitine	rs270601	5	T	C	0.0124	0.0026	1.380E-06	0.0124	0.0143	3.849E-01

2-methylbutyroylcarnitine	rs270602	5	T	C	0.0123	0.0025	1.090E-06	0.0097	0.0136	4.726E-01
2-methylbutyroylcarnitine	rs270605	5	T	C	-0.0124	0.0025	8.400E-07	0.0134	0.0135	3.206E-01
2-methylbutyroylcarnitine	rs270606	5	A	G	0.0123	0.0026	1.680E-06	0.0120	0.0143	4.024E-01
2-methylbutyroylcarnitine	rs270607	5	A	G	0.0123	0.0026	1.680E-06	0.0147	0.0142	3.037E-01
2-methylbutyroylcarnitine	rs270613	5	A	G	0.0124	0.0025	1.070E-06	0.0113	0.0137	4.090E-01
2-methylbutyroylcarnitine	rs272842	5	A	G	0.0128	0.0025	5.130E-07	0.0134	0.0135	3.236E-01
2-methylbutyroylcarnitine	rs272865	5	A	T	-0.0117	0.0025	3.980E-06	0.0134	0.0135	3.207E-01
2-methylbutyroylcarnitine	rs272867	5	A	G	-0.0123	0.0025	1.040E-06	0.0135	0.0135	3.186E-01
2-methylbutyroylcarnitine	rs272868	5	C	G	0.0126	0.0026	9.130E-07	0.0125	0.0143	3.818E-01
2-methylbutyroylcarnitine	rs272869	5	A	G	0.0123	0.0025	1.020E-06	0.0098	0.0136	4.716E-01
2-methylbutyroylcarnitine	rs272872	5	A	G	0.0125	0.0026	1.180E-06	0.0125	0.0143	3.829E-01
2-methylbutyroylcarnitine	rs272874	5	T	C	-0.0116	0.0026	6.900E-06	0.0098	0.0136	4.722E-01
2-methylbutyroylcarnitine	rs272875	5	T	C	0.0124	0.0025	1.020E-06	0.0136	0.0135	3.130E-01
2-methylbutyroylcarnitine	rs272878	5	T	C	0.0126	0.0026	9.950E-07	0.0126	0.0143	3.803E-01
2-methylbutyroylcarnitine	rs272879	5	C	G	0.0124	0.0025	1.010E-06	0.0135	0.0135	3.175E-01
2-methylbutyroylcarnitine	rs272880	5	T	C	-0.0126	0.0026	9.330E-07	0.0122	0.0143	3.954E-01
2-methylbutyroylcarnitine	rs272881	5	A	G	-0.0124	0.0025	1.010E-06	0.0134	0.0135	3.214E-01
2-methylbutyroylcarnitine	rs272882	5	T	G	-0.0126	0.0026	9.520E-07	0.0126	0.0143	3.803E-01
2-methylbutyroylcarnitine	rs272883	5	A	G	0.0126	0.0026	9.620E-07	0.0126	0.0143	3.790E-01
2-methylbutyroylcarnitine	rs272886	5	T	C	0.0123	0.0025	1.230E-06	0.0135	0.0135	3.179E-01
2-methylbutyroylcarnitine	rs272887	5	A	G	0.0124	0.0026	1.360E-06	0.0124	0.0143	3.855E-01
2-methylbutyroylcarnitine	rs272888	5	T	C	0.0124	0.0026	1.360E-06	0.0123	0.0143	3.912E-01
2-methylbutyroylcarnitine	rs272889	5	A	G	0.0123	0.0025	1.080E-06	0.0098	0.0136	4.694E-01
2-methylbutyroylcarnitine	rs272892	5	T	C	-0.0124	0.0026	1.360E-06	0.0125	0.0143	3.816E-01
2-methylbutyroylcarnitine	rs272893	5	T	C	0.0123	0.0025	1.080E-06	0.0099	0.0136	4.664E-01
2-methylbutyroylcarnitine	rs273901	5	T	G	-0.0124	0.0026	1.520E-06	0.0122	0.0143	3.927E-01
2-methylbutyroylcarnitine	rs273911	5	C	G	0.0124	0.0026	1.360E-06	0.0122	0.0143	3.950E-01
2-methylbutyroylcarnitine	rs273912	5	T	G	-0.0124	0.0026	1.630E-06	0.0122	0.0143	3.923E-01
2-methylbutyroylcarnitine	rs273913	5	T	C	0.0116	0.0025	4.700E-06	0.0131	0.0135	3.339E-01
2-methylbutyroylcarnitine	rs273914	5	A	T	0.0131	0.0025	2.070E-07	0.0135	0.0135	3.195E-01
2-methylbutyroylcarnitine	rs273915	5	C	G	-0.0124	0.0026	1.370E-06	0.0124	0.0143	3.865E-01
2-methylbutyroylcarnitine	rs273916	5	A	C	-0.0124	0.0026	1.370E-06	0.0125	0.0143	3.824E-01
2-methylbutyroylcarnitine	rs274546	5	A	G	0.0121	0.0025	1.590E-06	0.0095	0.0136	4.860E-01
2-methylbutyroylcarnitine	rs274557	5	T	C	-0.0118	0.0025	3.420E-06	-0.0133	0.0135	3.254E-01
2-methylbutyroylcarnitine	rs274558	5	A	G	-0.0118	0.0025	3.430E-06	-0.0134	0.0135	3.213E-01
2-methylbutyroylcarnitine	rs274559	5	A	G	-0.0117	0.0026	4.170E-06	-0.0134	0.0135	3.225E-01
2-methylbutyroylcarnitine	rs274560	5	T	C	-0.0119	0.0025	2.430E-06	-0.0100	0.0136	4.625E-01

2-methylbutyroylcarnitine	rs274561	5	A	C	0.0119	0.0025	2.220E-06	-0.0096	0.0136	4.786E-01
2-methylbutyroylcarnitine	rs274567	5	T	C	0.0121	0.0025	1.710E-06	-0.0103	0.0136	4.487E-01
2-methylbutyroylcarnitine	rs274570	5	T	C	0.0127	0.0026	1.170E-06	-0.0122	0.0143	3.928E-01
2-methylbutyroylcarnitine	rs3778129	6	A	G	-0.0182	0.0041	9.910E-06	-0.0259	0.0199	1.948E-01
2-methylbutyroylcarnitine	rs4074995	5	A	G	0.0123	0.0026	1.770E-06	0.0007	0.0152	9.656E-01
2-methylbutyroylcarnitine	rs4075958	5	A	G	0.0124	0.0026	1.920E-06	-0.0039	0.0153	7.994E-01
2-methylbutyroylcarnitine	rs419291	5	T	C	0.0123	0.0025	1.330E-06	0.0075	0.0137	5.852E-01
2-methylbutyroylcarnitine	rs456598	6	A	G	-0.0155	0.0035	7.090E-06	-0.0144	0.0194	4.593E-01
2-methylbutyroylcarnitine	rs4626843	1	A	G	0.0292	0.0065	7.390E-06	0.0267	0.0343	4.368E-01
2-methylbutyroylcarnitine	rs4648860	1	T	C	0.0124	0.0027	4.720E-06	-0.0080	0.0174	6.469E-01
2-methylbutyroylcarnitine	rs4719207	7	T	C	-0.0140	0.0030	3.060E-06	0.0062	0.0157	6.921E-01
2-methylbutyroylcarnitine	rs4730501	7	A	G	-0.0121	0.0026	4.180E-06	-0.0094	0.0160	5.575E-01
2-methylbutyroylcarnitine	rs4732399	7	A	G	-0.0311	0.0070	8.690E-06	-0.0647	0.0336	5.368E-02
2-methylbutyroylcarnitine	rs4948546	10	A	G	-0.0125	0.0026	2.370E-06	-0.0197	0.0171	2.479E-01
2-methylbutyroylcarnitine	rs6575209	14	T	C	0.0120	0.0026	5.100E-06	0.0107	0.0155	4.896E-01
2-methylbutyroylcarnitine	rs662138	6	C	G	0.0187	0.0034	3.650E-08	0.0124	0.0173	4.721E-01
2-methylbutyroylcarnitine	rs6764615	3	C	G	0.0159	0.0033	2.170E-06	-0.0235	0.0188	2.115E-01
2-methylbutyroylcarnitine	rs7081819	10	A	G	0.0120	0.0027	5.630E-06	-0.0188	0.0175	2.811E-01
2-methylbutyroylcarnitine	rs7087186	10	C	G	0.0126	0.0027	2.230E-06	-0.0167	0.0176	3.428E-01
2-methylbutyroylcarnitine	rs715	2	T	C	0.0123	0.0026	2.400E-06	0.0059	0.0145	6.818E-01
2-methylbutyroylcarnitine	rs7903712	10	C	G	0.0127	0.0027	1.650E-06	-0.0196	0.0173	2.556E-01
2-methylbutyroylcarnitine	rs7920393	10	A	G	0.0120	0.0027	6.050E-06	-0.0189	0.0174	2.775E-01
2-methylbutyroylcarnitine	rs7946997	11	T	C	-0.0123	0.0026	2.970E-06	0.0067	0.0145	6.430E-01
2-methylbutyroylcarnitine	rs9416742	10	A	G	0.0120	0.0027	5.640E-06	0.0178	0.0178	3.182E-01
2-methylbutyroylcarnitine	rs9492253	6	A	G	-0.0119	0.0027	8.620E-06	-0.0145	0.0163	3.746E-01
2-methylbutyroylcarnitine	rs9641894	7	T	G	-0.0117	0.0025	4.130E-06	-0.0037	0.0139	7.888E-01
2-methylbutyroylcarnitine	rs9642829	8	A	G	-0.0346	0.0075	3.610E-06	-0.1175	0.0477	1.378E-02
2-methylbutyroylcarnitine	rs9839755	3	T	C	0.0152	0.0034	7.620E-06	-0.0242	0.0189	2.016E-01
2-methylbutyroylcarnitine	rs999845	10	T	C	0.0121	0.0027	4.870E-06	-0.0173	0.0175	3.222E-01
2-methylbutyroylcarnitine	rs999846	10	A	G	0.0120	0.0027	5.710E-06	-0.0171	0.0175	3.280E-01

Table S15 Summary statistics for the associations of the 2-methylbutyroylcarnitine-associated SNPs with these exposures and glioma in GliomaScan

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
2-methylbutyroylcarnitine	rs1003533	5	T	C	0.0125	0.0027	2.330E-06	-0.0406	0.0583	4.873E-01
2-methylbutyroylcarnitine	rs1016988	5	T	C	-0.0125	0.0027	2.510E-06	-0.0075	0.0533	8.879E-01
2-methylbutyroylcarnitine	rs10866705	5	A	C	-0.0133	0.0026	3.470E-07	0.0266	0.0503	5.959E-01
2-methylbutyroylcarnitine	rs10896604	11	A	G	0.0162	0.0037	8.900E-06	-0.0449	0.0689	5.148E-01
2-methylbutyroylcarnitine	rs11006260	10	A	C	0.0120	0.0027	5.670E-06	0.0356	0.0552	5.183E-01
2-methylbutyroylcarnitine	rs11753995	6	A	G	-0.0165	0.0034	1.100E-06	0.0498	0.0616	4.184E-01
2-methylbutyroylcarnitine	rs156322	5	T	C	-0.0114	0.0026	9.190E-06	-0.0397	0.0543	4.650E-01
2-methylbutyroylcarnitine	rs1564348	6	T	C	0.0158	0.0034	2.870E-06	0.0498	0.0616	4.184E-01
2-methylbutyroylcarnitine	rs183898	5	C	G	-0.0123	0.0026	1.840E-06	-0.0453	0.0543	4.041E-01
2-methylbutyroylcarnitine	rs2410833	3	T	C	-0.0237	0.0053	8.270E-06	-0.0502	0.0780	5.203E-01
2-methylbutyroylcarnitine	rs2631362	5	A	G	-0.0119	0.0026	4.120E-06	0.0417	0.0543	4.432E-01
2-methylbutyroylcarnitine	rs2631370	5	T	C	-0.0121	0.0025	1.790E-06	0.0481	0.0520	3.540E-01
2-methylbutyroylcarnitine	rs2665348	14	A	C	-0.0123	0.0027	7.010E-06	0.0571	0.0571	3.176E-01
2-methylbutyroylcarnitine	rs270601	5	T	C	0.0124	0.0026	1.380E-06	-0.0501	0.0542	3.557E-01
2-methylbutyroylcarnitine	rs270602	5	T	C	0.0123	0.0025	1.090E-06	-0.0639	0.0521	2.206E-01
2-methylbutyroylcarnitine	rs270605	5	T	C	-0.0124	0.0025	8.400E-07	0.0522	0.0522	3.166E-01
2-methylbutyroylcarnitine	rs270606	5	A	G	0.0123	0.0026	1.680E-06	-0.0425	0.0542	4.326E-01
2-methylbutyroylcarnitine	rs270607	5	A	G	0.0123	0.0026	1.680E-06	-0.0378	0.0538	4.824E-01
2-methylbutyroylcarnitine	rs270613	5	A	G	0.0124	0.0025	1.070E-06	-0.0999	0.0448	2.559E-02
2-methylbutyroylcarnitine	rs272842	5	A	G	0.0128	0.0025	5.130E-07	-0.0533	0.0521	3.065E-01
2-methylbutyroylcarnitine	rs272865	5	A	T	-0.0117	0.0025	3.980E-06	0.0521	0.0521	3.173E-01
2-methylbutyroylcarnitine	rs272867	5	A	G	-0.0123	0.0025	1.040E-06	-0.0584	0.0521	2.632E-01
2-methylbutyroylcarnitine	rs272872	5	A	G	0.0125	0.0026	1.180E-06	-0.0452	0.0543	4.044E-01
2-methylbutyroylcarnitine	rs272875	5	T	C	0.0124	0.0025	1.020E-06	-0.0584	0.0521	2.632E-01
2-methylbutyroylcarnitine	rs272879	5	C	G	0.0124	0.0025	1.010E-06	0.0530	0.0527	3.150E-01
2-methylbutyroylcarnitine	rs272880	5	T	C	-0.0126	0.0026	9.330E-07	0.0417	0.0543	4.432E-01
2-methylbutyroylcarnitine	rs272882	5	T	G	-0.0126	0.0026	9.520E-07	-0.0786	0.0468	9.261E-02
2-methylbutyroylcarnitine	rs272883	5	A	G	0.0126	0.0026	9.620E-07	-0.0397	0.0543	4.650E-01
2-methylbutyroylcarnitine	rs272886	5	T	C	0.0123	0.0025	1.230E-06	-0.0560	0.0521	2.821E-01
2-methylbutyroylcarnitine	rs272887	5	A	G	0.0124	0.0026	1.360E-06	-0.0769	0.0468	9.995E-02
2-methylbutyroylcarnitine	rs272888	5	T	C	0.0124	0.0026	1.360E-06	-0.0452	0.0543	4.044E-01
2-methylbutyroylcarnitine	rs272889	5	A	G	0.0123	0.0025	1.080E-06	-0.0727	0.0524	1.656E-01

2-methylbutyroylcarnitine	rs272892	5	T	C	-0.0124	0.0026	1.360E-06	0.0441	0.0543	4.169E-01
2-methylbutyroylcarnitine	rs272893	5	T	C	0.0123	0.0025	1.080E-06	-0.0897	0.0448	4.485E-02
2-methylbutyroylcarnitine	rs273901	5	T	G	-0.0124	0.0026	1.520E-06	-0.0786	0.0468	9.261E-02
2-methylbutyroylcarnitine	rs273911	5	C	G	0.0124	0.0026	1.360E-06	0.0440	0.0543	4.180E-01
2-methylbutyroylcarnitine	rs273912	5	T	G	-0.0124	0.0026	1.630E-06	-0.0501	0.0542	3.557E-01
2-methylbutyroylcarnitine	rs273914	5	A	T	0.0131	0.0025	2.070E-07	0.0565	0.0521	2.778E-01
2-methylbutyroylcarnitine	rs273915	5	C	G	-0.0124	0.0026	1.370E-06	0.0402	0.0547	4.626E-01
2-methylbutyroylcarnitine	rs273916	5	A	C	-0.0124	0.0026	1.370E-06	-0.0769	0.0468	9.995E-02
2-methylbutyroylcarnitine	rs274546	5	A	G	0.0121	0.0025	1.590E-06	0.0485	0.0520	3.518E-01
2-methylbutyroylcarnitine	rs274557	5	T	C	-0.0118	0.0025	3.420E-06	0.0485	0.0520	3.518E-01
2-methylbutyroylcarnitine	rs274559	5	A	G	-0.0117	0.0026	4.170E-06	0.0481	0.0520	3.540E-01
2-methylbutyroylcarnitine	rs274567	5	T	C	0.0121	0.0025	1.710E-06	0.0521	0.0521	3.173E-01
2-methylbutyroylcarnitine	rs274570	5	T	C	0.0127	0.0026	1.170E-06	0.0440	0.0543	4.180E-01
2-methylbutyroylcarnitine	rs4075958	5	A	G	0.0124	0.0026	1.920E-06	-0.0535	0.0496	2.798E-01
2-methylbutyroylcarnitine	rs419291	5	T	C	0.0123	0.0025	1.330E-06	-0.0560	0.0521	2.821E-01
2-methylbutyroylcarnitine	rs456598	6	A	G	-0.0155	0.0035	7.090E-06	0.0401	0.0664	5.459E-01
2-methylbutyroylcarnitine	rs4648860	1	T	C	0.0124	0.0027	4.720E-06	-0.0170	0.0551	7.585E-01
2-methylbutyroylcarnitine	rs4719207	7	T	C	-0.0140	0.0030	3.060E-06	0.0408	0.0513	4.261E-01
2-methylbutyroylcarnitine	rs4730501	7	A	G	-0.0121	0.0026	4.180E-06	-0.0205	0.0554	7.113E-01
2-methylbutyroylcarnitine	rs6575209	14	T	C	0.0120	0.0026	5.100E-06	-0.0084	0.0488	8.631E-01
2-methylbutyroylcarnitine	rs671473	5	A	C	0.0122	0.0026	2.130E-06	0.0419	0.0543	4.403E-01
2-methylbutyroylcarnitine	rs7903712	10	C	G	0.0127	0.0027	1.650E-06	-0.0256	0.0538	6.335E-01
2-methylbutyroylcarnitine	rs9416742	10	A	G	0.0120	0.0027	5.640E-06	0.0356	0.0552	5.183E-01
2-methylbutyroylcarnitine	rs9492253	6	A	G	-0.0119	0.0027	8.620E-06	-0.0262	0.0535	6.246E-01
2-methylbutyroylcarnitine	rs9839755	3	T	C	0.0152	0.0034	7.620E-06	0.0124	0.0590	8.338E-01
2-methylbutyroylcarnitine	rs999845	10	T	C	0.0121	0.0027	4.870E-06	-0.0389	0.0552	4.809E-01

Table S16 Summary statistics for the associations of the leucylalanine-associated SNPs with these exposures and lung cancer in International Lung Cancer Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
leucylalanine	rs11079672	17	T	C	-0.0819	0.0180	5.270E-06	0.0183	0.0503	7.239E-01
leucylalanine	rs12494751	3	A	C	0.0429	0.0094	4.942E-06	-0.0435	0.0260	1.194E-01
leucylalanine	rs12617093	2	T	C	-0.0348	0.0076	4.812E-06	-0.0043	0.0206	8.406E-01
leucylalanine	rs13105073	4	A	T	0.1236	0.0261	2.158E-06	-0.0457	0.0590	4.874E-01
leucylalanine	rs16992910	22	A	G	0.0646	0.0141	4.792E-06	-0.0160	0.0385	6.948E-01
leucylalanine	rs2357258	2	A	C	-0.0370	0.0079	2.535E-06	-0.0113	0.0193	5.597E-01
leucylalanine	rs4351	17	A	G	-0.0581	0.0060	3.642E-22	-0.0164	0.0176	3.674E-01
leucylalanine	rs463106	5	T	C	0.0367	0.0081	6.290E-06	0.0027	0.0179	8.804E-01
leucylalanine	rs651007	9	T	C	-0.0461	0.0075	9.578E-10	-0.0115	0.0213	6.025E-01
leucylalanine	rs7229244	18	A	C	-0.0328	0.0072	5.672E-06	0.0049	0.0198	8.058E-01
leucylalanine	rs9479657	6	T	C	-0.0530	0.0118	7.752E-06	-0.0005	0.0326	9.881E-01

Table S17 Summary statistics for the associations of the 3-dehydrocarnitine-associated SNPs with these exposures and breast cancer in Breast Cancer Association Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
3-dehydrocarnitine	rs10792093	11	T	G	0.0164	0.0035	3.149E-06	0.0070	0.0104	4.988E-01
3-dehydrocarnitine	rs11589817	1	A	G	0.0124	0.0026	2.464E-06	-0.0059	0.0076	4.395E-01
3-dehydrocarnitine	rs12138756	1	A	G	0.0116	0.0025	3.598E-06	-0.0054	0.0065	4.037E-01
3-dehydrocarnitine	rs12573437	10	A	C	0.0377	0.0084	7.960E-06	-0.0116	0.0110	2.937E-01
3-dehydrocarnitine	rs1578905	14	T	G	0.0420	0.0090	3.061E-06	0.0212	0.0204	2.988E-01
3-dehydrocarnitine	rs1948709	4	T	C	0.0186	0.0038	7.722E-07	0.0106	0.0117	3.648E-01
3-dehydrocarnitine	rs2186677	11	A	G	-0.0124	0.0027	5.859E-06	-0.0043	0.0077	5.798E-01
3-dehydrocarnitine	rs2269340	1	T	C	-0.0222	0.0044	3.584E-07	-0.0142	0.0124	2.514E-01
3-dehydrocarnitine	rs2291428	10	C	G	-0.0168	0.0026	8.707E-11	0.0127	0.0072	7.952E-02
3-dehydrocarnitine	rs2610815	10	T	C	-0.0195	0.0043	5.841E-06	-0.0015	0.0130	9.064E-01
3-dehydrocarnitine	rs273913	5	T	C	0.0261	0.0025	1.084E-25	0.0219	0.0063	5.388E-04
3-dehydrocarnitine	rs316019	6	A	C	-0.0229	0.0041	2.059E-08	-0.0086	0.0102	3.974E-01
3-dehydrocarnitine	rs4781555	16	A	G	0.0170	0.0036	2.031E-06	-0.0107	0.0081	1.906E-01
3-dehydrocarnitine	rs6429601	1	A	C	0.0119	0.0027	7.078E-06	0.0013	0.0089	8.860E-01
3-dehydrocarnitine	rs6691848	1	A	G	0.0288	0.0061	2.121E-06	0.0432	0.0170	1.084E-02
3-dehydrocarnitine	rs6817256	4	T	C	0.0213	0.0045	1.986E-06	-0.0028	0.0140	8.423E-01
3-dehydrocarnitine	rs6862720	5	T	C	0.0191	0.0041	4.280E-06	-0.0139	0.0104	1.823E-01
3-dehydrocarnitine	rs7819084	8	A	G	0.0123	0.0026	2.447E-06	0.0037	0.0072	6.090E-01
3-dehydrocarnitine	rs927907	10	A	G	-0.0115	0.0026	7.725E-06	-0.0118	0.0071	9.553E-02
3-dehydrocarnitine	rs9382940	6	T	C	0.0172	0.0033	2.312E-07	-0.0167	0.0083	4.303E-02
3-dehydrocarnitine	rs9551761	13	A	G	0.0170	0.0035	1.514E-06	0.0059	0.0121	6.275E-01

Table S18 Summary statistics for the associations of the ibuprofen-associated SNPs with these exposures and ovarian cancer in Ovarian Cancer Association Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
ibuprofen	rs10005912		T	G	0.1151	0.0252	5.094E-06	-0.0109	0.0269	6.862E-01
ibuprofen	rs10015080		A	C	0.1094	0.0176	5.051E-10	0.0172	0.0237	4.681E-01
ibuprofen	rs10068843		A	C	-0.1072	0.0239	7.434E-06	-0.0090	0.0268	7.367E-01
ibuprofen	rs10421478		T	C	-0.0639	0.0143	7.684E-06	0.0002	0.0178	9.931E-01
ibuprofen	rs10425230		T	C	-0.1209	0.0239	4.210E-07	0.0144	0.0309	6.414E-01
ibuprofen	rs10875231		T	G	-0.0515	0.0113	5.427E-06	-0.0173	0.0160	2.806E-01
ibuprofen	rs10900676		C	G	-0.3050	0.0670	5.308E-06	0.0438	0.0584	4.534E-01
ibuprofen	rs10988783		T	C	-0.1623	0.0299	5.624E-08	-0.0180	0.0243	4.607E-01
ibuprofen	rs10998867		A	G	0.1623	0.0299	5.624E-08	0.0206	0.0203	3.095E-01
ibuprofen	rs11127379		A	G	-0.1010	0.0196	2.442E-07	-0.0039	0.0268	8.843E-01
ibuprofen	rs11158062		A	G	-0.0638	0.0141	5.938E-06	-0.0107	0.0150	4.768E-01
ibuprofen	rs11161725		A	C	-0.1623	0.0299	5.624E-08	-0.0533	0.0496	2.829E-01
ibuprofen	rs11265416		A	G	0.0995	0.0202	8.302E-07	0.0231	0.0529	6.628E-01
ibuprofen	rs1138253		A	G	0.0579	0.0129	7.878E-06	0.0182	0.0137	1.835E-01
ibuprofen	rs1165210		T	C	-0.1214	0.0270	6.709E-06	-0.0271	0.0323	4.018E-01
ibuprofen	rs11703458		A	G	-0.1963	0.0432	5.458E-06	0.0020	0.0870	9.820E-01
ibuprofen	rs11803192		T	C	0.1002	0.0172	6.104E-09	-0.0066	0.0237	7.812E-01
ibuprofen	rs11819046		T	C	-0.1237	0.0205	1.676E-09	-0.0292	0.0353	4.092E-01
ibuprofen	rs12238450		A	G	0.1431	0.0307	3.093E-06	0.0550	0.0330	9.516E-02
ibuprofen	rs12327976		A	G	0.1079	0.0195	3.276E-08	0.0165	0.0261	5.286E-01
ibuprofen	rs12622555		T	C	-0.1623	0.0299	5.624E-08	0.0002	0.0297	9.959E-01
ibuprofen	rs12684749		A	G	0.1623	0.0299	5.624E-08	-0.0063	0.0379	8.687E-01
ibuprofen	rs12983955		A	G	-0.1301	0.0271	1.602E-06	0.0082	0.0212	6.983E-01
ibuprofen	rs13007817		A	G	-0.1140	0.0218	1.616E-07	0.0330	0.0216	1.275E-01
ibuprofen	rs13035089		T	G	0.0630	0.0143	9.807E-06	0.0104	0.0182	5.666E-01
ibuprofen	rs13041562		T	C	0.0697	0.0151	3.761E-06	0.0056	0.0168	7.390E-01
ibuprofen	rs1353529		T	G	-0.0569	0.0127	7.455E-06	0.0039	0.0133	7.686E-01
ibuprofen	rs1382668		A	G	0.0927	0.0206	7.014E-06	-0.0174	0.0327	5.953E-01
ibuprofen	rs1429342		A	G	0.1439	0.0284	4.145E-07	0.0180	0.0635	7.771E-01
ibuprofen	rs1462176		T	C	-0.1390	0.0285	1.067E-06	0.0131	0.0316	6.790E-01
ibuprofen	rs1498721		T	C	0.1222	0.0241	3.900E-07	-0.0162	0.0274	5.538E-01
ibuprofen	rs1561803		T	G	0.1304	0.0280	3.282E-06	-0.0366	0.0318	2.492E-01

ibuprofen	rs1608368		T	C	-0.1623	0.0299	5.624E-08	0.0236	0.0282	4.012E-01
ibuprofen	rs16828389		T	C	-0.1650	0.0303	5.009E-08	-0.0849	0.0613	1.657E-01
ibuprofen	rs16834234		T	C	-0.1418	0.0321	9.918E-06	-0.0323	0.0348	3.536E-01
ibuprofen	rs16874680		T	C	0.1181	0.0250	2.378E-06	0.0202	0.0310	5.142E-01
ibuprofen	rs16947929		A	G	-0.1419	0.0282	4.870E-07	-0.0173	0.0406	6.704E-01
ibuprofen	rs16962386		A	C	0.1009	0.0226	8.285E-06	-0.0276	0.0215	1.982E-01
ibuprofen	rs16986678		A	G	-0.1548	0.0224	5.221E-12	-0.0099	0.0446	8.246E-01
ibuprofen	rs17025221		A	T	-0.0944	0.0195	1.319E-06	-0.0151	0.0221	4.950E-01
ibuprofen	rs17069415		A	G	-0.1552	0.0286	5.664E-08	-0.0560	0.0431	1.941E-01
ibuprofen	rs17224513		A	G	-0.0911	0.0192	2.078E-06	-0.0542	0.0249	2.931E-02
ibuprofen	rs17303404		C	G	0.1424	0.0265	7.461E-08	0.0039	0.0327	9.055E-01
ibuprofen	rs17488959		T	G	-0.1116	0.0218	3.194E-07	-0.0256	0.0334	4.444E-01
ibuprofen	rs17506661		T	C	-0.1171	0.0235	6.218E-07	-0.0244	0.0295	4.083E-01
ibuprofen	rs17557803		T	C	0.0971	0.0213	5.386E-06	-0.0003	0.0238	9.895E-01
ibuprofen	rs1790642		A	G	-0.0732	0.0165	8.927E-06	-0.0149	0.0184	4.178E-01
ibuprofen	rs1792131		A	G	0.1008	0.0208	1.208E-06	0.0042	0.0218	8.472E-01
ibuprofen	rs187090		T	C	-0.1623	0.0299	5.624E-08	-0.0160	0.0548	7.704E-01
ibuprofen	rs1896703		T	G	-0.1538	0.0226	9.672E-12	0.0403	0.0251	1.080E-01
ibuprofen	rs1954097		T	C	0.0926	0.0202	4.639E-06	-0.0018	0.0165	9.117E-01
ibuprofen	rs2155977		T	C	0.0964	0.0195	8.179E-07	-0.0765	0.0457	9.430E-02
ibuprofen	rs217763		T	C	0.0552	0.0108	3.233E-07	0.0055	0.0134	6.834E-01
ibuprofen	rs2374150		C	G	-0.1422	0.0282	4.548E-07	0.0333	0.0280	2.348E-01
ibuprofen	rs2469235		A	G	0.1221	0.0204	2.093E-09	-0.0050	0.0388	8.965E-01
ibuprofen	rs2473138		A	G	0.1053	0.0218	1.421E-06	-0.0294	0.0229	2.002E-01
ibuprofen	rs2486578		A	G	0.1523	0.0326	2.988E-06	0.0048	0.0164	7.712E-01
ibuprofen	rs2493147		T	C	-0.0912	0.0184	7.179E-07	0.0194	0.0252	4.412E-01
ibuprofen	rs2623167		A	C	0.0940	0.0210	7.567E-06	0.0113	0.0221	6.098E-01
ibuprofen	rs268125		C	G	0.1492	0.0302	7.714E-07	-0.0354	0.0318	2.648E-01
ibuprofen	rs268424		A	C	-0.1129	0.0237	1.826E-06	-0.0337	0.0217	1.205E-01
ibuprofen	rs276642		A	G	0.1626	0.0299	5.623E-08	0.0036	0.0288	8.997E-01
ibuprofen	rs2861997		A	G	0.0897	0.0187	1.541E-06	0.0065	0.0232	7.800E-01
ibuprofen	rs28951670		T	C	-0.1627	0.0299	5.152E-08	-0.0383	0.0256	1.357E-01
ibuprofen	rs3925748		A	C	-0.0826	0.0182	5.549E-06	0.0026	0.0202	8.973E-01
ibuprofen	rs4141286		C	G	0.1065	0.0231	3.951E-06	0.0089	0.0273	7.446E-01
ibuprofen	rs4295303		A	T	-0.0696	0.0145	1.526E-06	-0.0031	0.0133	8.138E-01
ibuprofen	rs4434498		A	G	-0.0554	0.0120	4.232E-06	-0.0117	0.0133	3.801E-01
ibuprofen	rs4454728		A	G	-0.1672	0.0307	5.209E-08	-0.0501	0.0409	2.210E-01

ibuprofen	rs4488147		T	C	-0.1623	0.0299	5.624E-08	0.0205	0.0419	6.243E-01
ibuprofen	rs463183		A	G	-0.1164	0.0232	4.981E-07	0.0055	0.0281	8.434E-01
ibuprofen	rs4733038		A	C	-0.1718	0.0387	9.034E-06	0.0731	0.0450	1.045E-01
ibuprofen	rs4875362		T	G	-0.1646	0.0355	3.428E-06	0.0534	0.0338	1.143E-01
ibuprofen	rs4905451		T	C	-0.1551	0.0279	2.567E-08	0.0016	0.0531	9.753E-01
ibuprofen	rs5809847		T	C	0.1145	0.0250	4.601E-06	-0.0097	0.0285	7.335E-01
ibuprofen	rs600711		A	G	0.1004	0.0179	2.077E-08	0.0141	0.0237	5.507E-01
ibuprofen	rs6070814		T	C	-0.0813	0.0165	7.875E-07	0.0061	0.0265	8.175E-01
ibuprofen	rs6506569		T	C	0.0541	0.0105	2.400E-07	-0.0080	0.0132	5.453E-01
ibuprofen	rs6783548		T	C	-0.0779	0.0162	1.624E-06	-0.0059	0.0135	6.637E-01
ibuprofen	rs7144659		A	G	0.0554	0.0113	9.857E-07	0.0349	0.0353	3.233E-01
ibuprofen	rs7454011		T	G	-0.1313	0.0235	2.342E-08	-0.0207	0.0296	4.844E-01
ibuprofen	rs7616688		A	G	-0.1630	0.0300	5.502E-08	0.0046	0.0328	8.882E-01
ibuprofen	rs7688643		T	C	0.0830	0.0186	8.233E-06	-0.0223	0.0243	3.581E-01
ibuprofen	rs7692251		A	G	0.1330	0.0280	1.966E-06	0.0816	0.0317	1.005E-02
ibuprofen	rs7701924		A	G	-0.0907	0.0191	2.083E-06	0.0358	0.0234	1.257E-01
ibuprofen	rs7708256		T	C	-0.1541	0.0348	9.602E-06	0.0464	0.0386	2.292E-01
ibuprofen	rs771788		A	G	-0.0881	0.0187	2.515E-06	-0.0369	0.0256	1.485E-01
ibuprofen	rs7751252		T	C	0.1050	0.0227	3.895E-06	0.0323	0.0273	2.355E-01
ibuprofen	rs7755387		T	G	-0.1252	0.0259	1.298E-06	0.0064	0.0289	8.258E-01
ibuprofen	rs7785951		T	G	-0.1396	0.0267	1.666E-07	0.0344	0.0319	2.809E-01
ibuprofen	rs8118890		A	G	0.1147	0.0235	1.059E-06	0.0105	0.0240	6.637E-01
ibuprofen	rs831541		T	C	-0.0567	0.0116	9.874E-07	-0.0014	0.0175	9.384E-01
ibuprofen	rs836533		A	T	0.1623	0.0299	5.624E-08	0.0128	0.0604	8.327E-01
ibuprofen	rs928907		T	C	-0.0749	0.0166	6.037E-06	0.0109	0.0376	7.716E-01
ibuprofen	rs9341191		T	C	-0.1636	0.0301	5.675E-08	0.0303	0.0292	2.992E-01
ibuprofen	rs945493		A	G	-0.1625	0.0301	6.451E-08	0.0330	0.0248	1.835E-01
ibuprofen	rs9497904		A	G	-0.0543	0.0120	6.362E-06	-0.0063	0.0136	6.428E-01
ibuprofen	rs9557045		A	T	-0.1164	0.0234	6.281E-07	0.0352	0.0276	2.021E-01
ibuprofen	rs9861255		A	G	0.1156	0.0231	5.739E-07	0.0140	0.0236	5.536E-01
ibuprofen	rs997892		A	C	0.0925	0.0181	3.139E-07	0.0338	0.0245	1.686E-01
ibuprofen	rs9999552		A	G	0.1464	0.0213	5.697E-12	0.0353	0.0211	9.496E-02

Table S19 Summary statistics for the associations of the leucylalanine-associated SNPs with these exposures and ovarian cancer in Ovarian Cancer Association Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
leucylalanine	rs11079672	7	T	C	-0.0993	0.0185	8.169E-08	-0.0374	0.0142	8.216E-03
leucylalanine	rs13025191	17	C	G	-0.0364	0.0081	6.717E-06	-0.0294	0.0367	4.230E-01
leucylalanine	rs205208	2	T	C	-0.0495	0.0107	4.111E-06	0.0076	0.0172	6.591E-01
leucylalanine	rs6124466	5	T	C	-0.0400	0.0085	2.361E-06	-0.0225	0.0138	1.030E-01
leucylalanine	rs9574536	5	T	C	-0.0517	0.0113	5.060E-06	0.0010	0.0134	9.398E-01
leucylalanine	rs779741	6	A	C	-0.0285	0.0064	8.212E-06	0.0007	0.0236	9.762E-01
leucylalanine	rs1106806	1	A	C	-0.0284	0.0063	6.775E-06	0.0087	0.0136	5.226E-01
leucylalanine	rs17121435	20	A	G	0.1236	0.0256	1.364E-06	0.0039	0.0181	8.298E-01
leucylalanine	rs297192	16	T	G	0.0310	0.0068	4.541E-06	-0.0040	0.0133	7.656E-01
leucylalanine	rs4949966	4	T	C	0.0468	0.0092	3.555E-07	-0.0107	0.0137	4.336E-01
leucylalanine	rs4351	1	A	G	-0.0529	0.0063	3.111E-17	0.0054	0.0220	8.061E-01
leucylalanine	rs7840544	1	A	G	0.0947	0.0208	5.392E-06	-0.0052	0.0289	8.582E-01
leucylalanine	rs2278161	5	T	C	-0.0341	0.0073	3.250E-06	0.0072	0.0177	6.836E-01
leucylalanine	rs6070840	19	A	C	0.0397	0.0084	2.478E-06	-0.0211	0.0290	4.680E-01
leucylalanine	rs6533515	2	A	G	-0.0350	0.0078	7.041E-06	-0.0040	0.0147	7.851E-01
leucylalanine	rs35060330	8	T	C	0.0356	0.0080	9.446E-06	-0.0287	0.0423	4.975E-01
leucylalanine	rs649129	10	T	C	-0.0437	0.0077	1.262E-08	-0.0512	0.0616	4.059E-01
leucylalanine	rs9574536	13	T	C	-0.0517	0.0113	5.060E-06	0.0516	0.0351	1.784E-01

Table S20 Summary statistics for the associations of the 2-methylbutyroylcarnitine-associated SNPs with these exposures and lung adenocarcinoma in International Lung Cancer Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
2-methylbutyroylcarnitine	rs1003533	5	T	C	0.0125	0.0027	2.330E-06	0.0035	0.0333	9.176E-01
2-methylbutyroylcarnitine	rs10139470	14	T	G	-0.0156	0.0032	1.470E-06	-0.0179	0.0343	6.202E-01
2-methylbutyroylcarnitine	rs1016988	5	T	C	-0.0125	0.0027	2.510E-06	0.0027	0.0332	9.374E-01
2-methylbutyroylcarnitine	rs10484836	6	T	C	0.0208	0.0044	2.980E-06	-0.0016	0.0551	9.781E-01
2-methylbutyroylcarnitine	rs10740761	10	A	C	-0.0124	0.0026	2.660E-06	-0.0252	0.0340	4.630E-01
2-methylbutyroylcarnitine	rs10866705	5	A	C	-0.0133	0.0026	3.470E-07	0.0072	0.0307	8.225E-01
2-methylbutyroylcarnitine	rs10896604	11	A	G	0.0162	0.0037	8.900E-06	-0.0444	0.0412	3.232E-01
2-methylbutyroylcarnitine	rs11006251	10	T	C	0.0129	0.0027	1.550E-06	0.0185	0.0343	6.086E-01
2-methylbutyroylcarnitine	rs11006260	10	A	C	0.0120	0.0027	5.670E-06	-0.0018	0.0338	9.585E-01
2-methylbutyroylcarnitine	rs11057695	12	T	C	0.0291	0.0062	2.790E-06	-0.0443	0.0532	4.518E-01
2-methylbutyroylcarnitine	rs11639506	16	A	G	-0.0340	0.0075	5.690E-06	0.0425	0.0663	5.310E-01
2-methylbutyroylcarnitine	rs11753995	6	A	G	-0.0165	0.0034	1.100E-06	-0.0568	0.0350	1.395E-01
2-methylbutyroylcarnitine	rs11758111	6	T	C	-0.0154	0.0035	9.720E-06	-0.0283	0.0401	5.105E-01
2-methylbutyroylcarnitine	rs12477840	2	T	C	0.0122	0.0027	5.890E-06	0.0452	0.0369	2.156E-01
2-methylbutyroylcarnitine	rs12777552	10	T	C	-0.0124	0.0026	2.370E-06	-0.0275	0.0341	4.229E-01
2-methylbutyroylcarnitine	rs12929328	16	C	G	-0.0206	0.0046	8.890E-06	-0.0096	0.0373	8.054E-01
2-methylbutyroylcarnitine	rs1447059	7	A	G	-0.0115	0.0025	7.060E-06	-0.0013	0.0283	9.639E-01
2-methylbutyroylcarnitine	rs1447060	7	A	G	-0.0115	0.0025	7.070E-06	-0.0002	0.0284	9.939E-01
2-methylbutyroylcarnitine	rs156322	5	T	C	-0.0114	0.0026	9.190E-06	0.0221	0.0287	4.651E-01
2-methylbutyroylcarnitine	rs1564348	6	T	C	0.0158	0.0034	2.870E-06	-0.0579	0.0349	1.321E-01
2-methylbutyroylcarnitine	rs1596972	7	A	G	-0.0117	0.0025	3.820E-06	-0.0001	0.0273	9.958E-01
2-methylbutyroylcarnitine	rs17098575	12	A	C	-0.0270	0.0056	1.540E-06	0.0277	0.0555	6.277E-01
2-methylbutyroylcarnitine	rs17098581	12	C	G	-0.0267	0.0059	5.200E-06	0.0362	0.0550	5.181E-01
2-methylbutyroylcarnitine	rs17145256	10	A	G	0.0312	0.0069	6.580E-06	0.1352	0.0936	1.290E-01
2-methylbutyroylcarnitine	rs17435220	10	T	C	-0.0310	0.0069	7.940E-06	0.1276	0.0925	1.501E-01
2-methylbutyroylcarnitine	rs1838932	7	T	C	-0.0128	0.0026	5.070E-07	0.0041	0.0303	8.943E-01
2-methylbutyroylcarnitine	rs183898	5	C	G	-0.0123	0.0026	1.840E-06	-0.0215	0.0289	4.792E-01
2-methylbutyroylcarnitine	rs1981524	5	T	C	0.0123	0.0027	3.530E-06	0.0043	0.0333	9.011E-01
2-methylbutyroylcarnitine	rs2367533	7	T	C	0.0263	0.0059	8.010E-06	0.0989	0.0722	1.581E-01
2-methylbutyroylcarnitine	rs2410833	3	T	C	-0.0237	0.0053	8.270E-06	-0.0084	0.0482	8.689E-01
2-methylbutyroylcarnitine	rs2552122	8	A	C	0.0115	0.0026	6.290E-06	0.0340	0.0294	2.782E-01
2-methylbutyroylcarnitine	rs2631362	5	A	G	-0.0119	0.0026	4.120E-06	-0.0210	0.0288	4.885E-01

2-methylbutyroylcarnitine	rs2631370	5	T	C	-0.0121	0.0025	1.790E-06	-0.0334	0.0271	2.475E-01
2-methylbutyroylcarnitine	rs2631372	5	C	G	0.0124	0.0026	2.010E-06	-0.0234	0.0287	4.389E-01
2-methylbutyroylcarnitine	rs2665348	14	A	C	-0.0123	0.0027	7.010E-06	0.0155	0.0338	6.621E-01
2-methylbutyroylcarnitine	rs270601	5	T	C	0.0124	0.0026	1.380E-06	0.0216	0.0289	4.770E-01
2-methylbutyroylcarnitine	rs270602	5	T	C	0.0123	0.0025	1.090E-06	0.0257	0.0273	3.724E-01
2-methylbutyroylcarnitine	rs270605	5	T	C	-0.0124	0.0025	8.400E-07	0.0332	0.0270	2.471E-01
2-methylbutyroylcarnitine	rs270606	5	A	G	0.0123	0.0026	1.680E-06	0.0216	0.0287	4.748E-01
2-methylbutyroylcarnitine	rs270607	5	A	G	0.0123	0.0026	1.680E-06	0.0236	0.0286	4.350E-01
2-methylbutyroylcarnitine	rs270613	5	A	G	0.0124	0.0025	1.070E-06	0.0323	0.0270	2.602E-01
2-methylbutyroylcarnitine	rs272842	5	A	G	0.0128	0.0025	5.130E-07	0.0329	0.0270	2.519E-01
2-methylbutyroylcarnitine	rs272865	5	A	T	-0.0117	0.0025	3.980E-06	0.0248	0.0274	3.918E-01
2-methylbutyroylcarnitine	rs272867	5	A	G	-0.0123	0.0025	1.040E-06	0.0329	0.0271	2.535E-01
2-methylbutyroylcarnitine	rs272868	5	C	G	0.0126	0.0026	9.130E-07	0.0213	0.0287	4.807E-01
2-methylbutyroylcarnitine	rs272869	5	A	G	0.0123	0.0025	1.020E-06	0.0257	0.0273	3.723E-01
2-methylbutyroylcarnitine	rs272872	5	A	G	0.0125	0.0026	1.180E-06	0.0213	0.0287	4.821E-01
2-methylbutyroylcarnitine	rs272874	5	T	C	-0.0116	0.0026	6.900E-06	0.0257	0.0273	3.721E-01
2-methylbutyroylcarnitine	rs272875	5	T	C	0.0124	0.0025	1.020E-06	0.0332	0.0270	2.475E-01
2-methylbutyroylcarnitine	rs272878	5	T	C	0.0126	0.0026	9.950E-07	0.0212	0.0287	4.824E-01
2-methylbutyroylcarnitine	rs272879	5	C	G	0.0124	0.0025	1.010E-06	0.0332	0.0270	2.475E-01
2-methylbutyroylcarnitine	rs272880	5	T	C	-0.0126	0.0026	9.330E-07	0.0205	0.0288	4.975E-01
2-methylbutyroylcarnitine	rs272881	5	A	G	-0.0124	0.0025	1.010E-06	0.0323	0.0270	2.613E-01
2-methylbutyroylcarnitine	rs272882	5	T	G	-0.0126	0.0026	9.520E-07	0.0211	0.0287	4.855E-01
2-methylbutyroylcarnitine	rs272883	5	A	G	0.0126	0.0026	9.620E-07	0.0219	0.0287	4.684E-01
2-methylbutyroylcarnitine	rs272886	5	T	C	0.0123	0.0025	1.230E-06	0.0322	0.0270	2.621E-01
2-methylbutyroylcarnitine	rs272887	5	A	G	0.0124	0.0026	1.360E-06	0.0199	0.0288	5.112E-01
2-methylbutyroylcarnitine	rs272888	5	T	C	0.0124	0.0026	1.360E-06	0.0209	0.0287	4.884E-01
2-methylbutyroylcarnitine	rs272889	5	A	G	0.0123	0.0025	1.080E-06	0.0250	0.0273	3.851E-01
2-methylbutyroylcarnitine	rs272892	5	T	C	-0.0124	0.0026	1.360E-06	0.0209	0.0287	4.885E-01
2-methylbutyroylcarnitine	rs272893	5	T	C	0.0123	0.0025	1.080E-06	0.0249	0.0273	3.871E-01
2-methylbutyroylcarnitine	rs273901	5	T	G	-0.0124	0.0026	1.520E-06	0.0206	0.0288	4.959E-01
2-methylbutyroylcarnitine	rs273911	5	C	G	0.0124	0.0026	1.360E-06	0.0202	0.0288	5.038E-01
2-methylbutyroylcarnitine	rs273912	5	T	G	-0.0124	0.0026	1.630E-06	0.0203	0.0288	5.025E-01
2-methylbutyroylcarnitine	rs273913	5	T	C	0.0116	0.0025	4.700E-06	0.0311	0.0271	2.791E-01
2-methylbutyroylcarnitine	rs273914	5	A	T	0.0131	0.0025	2.070E-07	0.0329	0.0271	2.535E-01
2-methylbutyroylcarnitine	rs273915	5	C	G	-0.0124	0.0026	1.370E-06	0.0213	0.0287	4.817E-01
2-methylbutyroylcarnitine	rs273916	5	A	C	-0.0124	0.0026	1.370E-06	0.0213	0.0287	4.813E-01
2-methylbutyroylcarnitine	rs274546	5	A	G	0.0121	0.0025	1.590E-06	0.0286	0.0273	3.225E-01

2-methylbutyroylcarnitine	rs274557	5	T	C	-0.0118	0.0025	3.420E-06	-0.0325	0.0272	2.608E-01
2-methylbutyroylcarnitine	rs274558	5	A	G	-0.0118	0.0025	3.430E-06	-0.0325	0.0272	2.608E-01
2-methylbutyroylcarnitine	rs274559	5	A	G	-0.0117	0.0026	4.170E-06	-0.0327	0.0272	2.591E-01
2-methylbutyroylcarnitine	rs274560	5	T	C	-0.0119	0.0025	2.430E-06	-0.0283	0.0274	3.289E-01
2-methylbutyroylcarnitine	rs274561	5	A	C	0.0119	0.0025	2.220E-06	-0.0276	0.0274	3.408E-01
2-methylbutyroylcarnitine	rs274567	5	T	C	0.0121	0.0025	1.710E-06	-0.0284	0.0274	3.273E-01
2-methylbutyroylcarnitine	rs274570	5	T	C	0.0127	0.0026	1.170E-06	-0.0213	0.0288	4.824E-01
2-methylbutyroylcarnitine	rs3778129	6	A	G	-0.0182	0.0041	9.910E-06	-0.0327	0.0401	4.497E-01
2-methylbutyroylcarnitine	rs4074995	5	A	G	0.0123	0.0026	1.770E-06	0.0016	0.0305	9.584E-01
2-methylbutyroylcarnitine	rs4075958	5	A	G	0.0124	0.0026	1.920E-06	0.0029	0.0302	9.258E-01
2-methylbutyroylcarnitine	rs419291	5	T	C	0.0123	0.0025	1.330E-06	0.0268	0.0274	3.554E-01
2-methylbutyroylcarnitine	rs456598	6	A	G	-0.0155	0.0035	7.090E-06	-0.0943	0.0366	2.462E-02
2-methylbutyroylcarnitine	rs4626843	1	A	G	0.0292	0.0065	7.390E-06	-0.0046	0.0701	9.517E-01
2-methylbutyroylcarnitine	rs4648860	1	T	C	0.0124	0.0027	4.720E-06	-0.0303	0.0331	3.913E-01
2-methylbutyroylcarnitine	rs4719207	7	T	C	-0.0140	0.0030	3.060E-06	-0.0353	0.0311	2.891E-01
2-methylbutyroylcarnitine	rs4730501	7	A	G	-0.0121	0.0026	4.180E-06	-0.0484	0.0307	1.463E-01
2-methylbutyroylcarnitine	rs4732399	7	A	G	-0.0311	0.0070	8.690E-06	0.0873	0.0733	2.254E-01
2-methylbutyroylcarnitine	rs4948546	10	A	G	-0.0125	0.0026	2.370E-06	-0.0240	0.0340	4.848E-01
2-methylbutyroylcarnitine	rs6575209	14	T	C	0.0120	0.0026	5.100E-06	-0.0265	0.0329	4.484E-01
2-methylbutyroylcarnitine	rs662138	6	C	G	0.0187	0.0034	3.650E-08	-0.0668	0.0337	7.423E-02
2-methylbutyroylcarnitine	rs671473	5	A	C	0.0122	0.0026	2.130E-06	-0.0211	0.0288	4.874E-01
2-methylbutyroylcarnitine	rs6764615	3	C	G	0.0159	0.0033	2.170E-06	0.0683	0.0386	6.754E-02
2-methylbutyroylcarnitine	rs7081819	10	A	G	0.0120	0.0027	5.630E-06	0.0033	0.0336	9.236E-01
2-methylbutyroylcarnitine	rs7087186	10	C	G	0.0126	0.0027	2.230E-06	0.0025	0.0342	9.430E-01
2-methylbutyroylcarnitine	rs715	2	T	C	0.0123	0.0026	2.400E-06	0.0480	0.0327	1.355E-01
2-methylbutyroylcarnitine	rs7903712	10	C	G	0.0127	0.0027	1.650E-06	-0.0150	0.0344	6.674E-01
2-methylbutyroylcarnitine	rs7920393	10	A	G	0.0120	0.0027	6.050E-06	0.0030	0.0336	9.306E-01
2-methylbutyroylcarnitine	rs7946997	11	T	C	-0.0123	0.0026	2.970E-06	0.0147	0.0312	6.434E-01
2-methylbutyroylcarnitine	rs9416742	10	A	G	0.0120	0.0027	5.640E-06	0.0015	0.0338	9.665E-01
2-methylbutyroylcarnitine	rs9492253	6	A	G	-0.0119	0.0027	8.620E-06	-0.0515	0.0320	1.397E-01
2-methylbutyroylcarnitine	rs9641894	7	T	G	-0.0117	0.0025	4.130E-06	-0.0017	0.0276	9.536E-01
2-methylbutyroylcarnitine	rs9642829	8	A	G	-0.0346	0.0075	3.610E-06	0.1436	0.0952	1.105E-01
2-methylbutyroylcarnitine	rs9839755	3	T	C	0.0152	0.0034	7.620E-06	0.0705	0.0390	6.162E-02
2-methylbutyroylcarnitine	rs999845	10	T	C	0.0121	0.0027	4.870E-06	0.0003	0.0338	9.936E-01
2-methylbutyroylcarnitine	rs999846	10	A	G	0.0120	0.0027	5.710E-06	-0.0010	0.0338	9.771E-01

Table S21 Summary statistics for the associations of the 2-methylbutyroylcarnitine-associated SNPs with these exposures and ER-positive breast cancer in Breast Cancer Association Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
2-methylbutyroylcarnitine	rs1003533	5	T	C	0.0125	0.0027	2.330E-06	-0.0146	0.0092	1.138E-01
2-methylbutyroylcarnitine	rs10139470	14	T	G	-0.0156	0.0032	1.470E-06	0.0255	0.0093	6.366E-03
2-methylbutyroylcarnitine	rs1016988	5	T	C	-0.0125	0.0027	2.510E-06	-0.0143	0.0092	1.205E-01
2-methylbutyroylcarnitine	rs10484836	6	T	C	0.0208	0.0044	2.980E-06	0.0124	0.0204	5.425E-01
2-methylbutyroylcarnitine	rs10740761	10	A	C	-0.0124	0.0026	2.660E-06	0.0220	0.0106	3.791E-02
2-methylbutyroylcarnitine	rs10866705	5	A	C	-0.0133	0.0026	3.470E-07	-0.0048	0.0092	6.003E-01
2-methylbutyroylcarnitine	rs10896604	11	A	G	0.0162	0.0037	8.900E-06	-0.0016	0.0125	8.973E-01
2-methylbutyroylcarnitine	rs11006251	10	T	C	0.0129	0.0027	1.550E-06	0.0275	0.0110	1.210E-02
2-methylbutyroylcarnitine	rs11006260	10	A	C	0.0120	0.0027	5.670E-06	0.0216	0.0108	4.566E-02
2-methylbutyroylcarnitine	rs11639506	16	A	G	-0.0340	0.0075	5.690E-06	-0.0067	0.0185	7.168E-01
2-methylbutyroylcarnitine	rs11753995	6	A	G	-0.0165	0.0034	1.100E-06	-0.0014	0.0100	8.868E-01
2-methylbutyroylcarnitine	rs11758111	6	T	C	-0.0154	0.0035	9.720E-06	0.0100	0.0114	3.785E-01
2-methylbutyroylcarnitine	rs12477840	2	T	C	0.0122	0.0027	5.890E-06	-0.0099	0.0099	3.157E-01
2-methylbutyroylcarnitine	rs12777552	10	T	C	-0.0124	0.0026	2.370E-06	0.0209	0.0106	4.927E-02
2-methylbutyroylcarnitine	rs12929328	16	C	G	-0.0206	0.0046	8.890E-06	0.0018	0.0103	8.622E-01
2-methylbutyroylcarnitine	rs1447059	7	A	G	-0.0115	0.0025	7.060E-06	-0.0201	0.0083	1.524E-02
2-methylbutyroylcarnitine	rs1447060	7	A	G	-0.0115	0.0025	7.070E-06	-0.0198	0.0083	1.684E-02
2-methylbutyroylcarnitine	rs156322	5	T	C	-0.0114	0.0026	9.190E-06	0.0286	0.0080	3.425E-04
2-methylbutyroylcarnitine	rs1564348	6	T	C	0.0158	0.0034	2.870E-06	-0.0022	0.0101	8.268E-01
2-methylbutyroylcarnitine	rs1596972	7	A	G	-0.0117	0.0025	3.820E-06	-0.0247	0.0081	2.395E-03
2-methylbutyroylcarnitine	rs17145256	10	A	G	0.0312	0.0069	6.580E-06	0.0862	0.0221	9.460E-05
2-methylbutyroylcarnitine	rs17435220	10	T	C	-0.0310	0.0069	7.940E-06	0.0843	0.0221	1.425E-04
2-methylbutyroylcarnitine	rs1838932	7	T	C	-0.0128	0.0026	5.070E-07	-0.0191	0.0086	2.665E-02
2-methylbutyroylcarnitine	rs183898	5	C	G	-0.0123	0.0026	1.840E-06	-0.0280	0.0080	4.496E-04
2-methylbutyroylcarnitine	rs1981524	5	T	C	0.0123	0.0027	3.530E-06	-0.0146	0.0092	1.146E-01
2-methylbutyroylcarnitine	rs2367533	7	T	C	0.0263	0.0059	8.010E-06	-0.0084	0.0180	6.398E-01
2-methylbutyroylcarnitine	rs2410833	3	T	C	-0.0237	0.0053	8.270E-06	0.0131	0.0132	3.200E-01
2-methylbutyroylcarnitine	rs2552122	8	A	C	0.0115	0.0026	6.290E-06	-0.0167	0.0081	3.891E-02
2-methylbutyroylcarnitine	rs2631362	5	A	G	-0.0119	0.0026	4.120E-06	-0.0281	0.0080	4.326E-04
2-methylbutyroylcarnitine	rs2631370	5	T	C	-0.0121	0.0025	1.790E-06	-0.0229	0.0075	2.404E-03
2-methylbutyroylcarnitine	rs2631372	5	C	G	0.0124	0.0026	2.010E-06	-0.0285	0.0080	3.492E-04
2-methylbutyroylcarnitine	rs2665348	14	A	C	-0.0123	0.0027	7.010E-06	-0.0266	0.0097	5.863E-03

2-methylbutyroylcarnitine	rs270601	5	T	C	0.0124	0.0026	1.380E-06	0.0285	0.0080	3.634E-04
2-methylbutyroylcarnitine	rs270602	5	T	C	0.0123	0.0025	1.090E-06	0.0210	0.0076	5.438E-03
2-methylbutyroylcarnitine	rs270605	5	T	C	-0.0124	0.0025	8.400E-07	0.0228	0.0075	2.458E-03
2-methylbutyroylcarnitine	rs270606	5	A	G	0.0123	0.0026	1.680E-06	0.0283	0.0080	3.876E-04
2-methylbutyroylcarnitine	rs270607	5	A	G	0.0123	0.0026	1.680E-06	0.0284	0.0079	3.536E-04
2-methylbutyroylcarnitine	rs270613	5	A	G	0.0124	0.0025	1.070E-06	0.0249	0.0076	1.085E-03
2-methylbutyroylcarnitine	rs272842	5	A	G	0.0128	0.0025	5.130E-07	0.0226	0.0075	2.692E-03
2-methylbutyroylcarnitine	rs272865	5	A	T	-0.0117	0.0025	3.980E-06	0.0227	0.0075	2.561E-03
2-methylbutyroylcarnitine	rs272867	5	A	G	-0.0123	0.0025	1.040E-06	0.0228	0.0075	2.507E-03
2-methylbutyroylcarnitine	rs272868	5	C	G	0.0126	0.0026	9.130E-07	0.0286	0.0080	3.344E-04
2-methylbutyroylcarnitine	rs272869	5	A	G	0.0123	0.0025	1.020E-06	0.0213	0.0076	4.826E-03
2-methylbutyroylcarnitine	rs272872	5	A	G	0.0125	0.0026	1.180E-06	0.0284	0.0080	3.646E-04
2-methylbutyroylcarnitine	rs272874	5	T	C	-0.0116	0.0026	6.900E-06	0.0212	0.0076	5.009E-03
2-methylbutyroylcarnitine	rs272875	5	T	C	0.0124	0.0025	1.020E-06	0.0229	0.0075	2.425E-03
2-methylbutyroylcarnitine	rs272878	5	T	C	0.0126	0.0026	9.950E-07	0.0285	0.0080	3.500E-04
2-methylbutyroylcarnitine	rs272879	5	C	G	0.0124	0.0025	1.010E-06	0.0226	0.0075	2.668E-03
2-methylbutyroylcarnitine	rs272880	5	T	C	-0.0126	0.0026	9.330E-07	0.0282	0.0080	4.184E-04
2-methylbutyroylcarnitine	rs272881	5	A	G	-0.0124	0.0025	1.010E-06	0.0226	0.0075	2.678E-03
2-methylbutyroylcarnitine	rs272882	5	T	G	-0.0126	0.0026	9.520E-07	0.0285	0.0080	3.499E-04
2-methylbutyroylcarnitine	rs272883	5	A	G	0.0126	0.0026	9.620E-07	0.0285	0.0080	3.487E-04
2-methylbutyroylcarnitine	rs272886	5	T	C	0.0123	0.0025	1.230E-06	0.0227	0.0075	2.596E-03
2-methylbutyroylcarnitine	rs272887	5	A	G	0.0124	0.0026	1.360E-06	0.0283	0.0080	3.848E-04
2-methylbutyroylcarnitine	rs272888	5	T	C	0.0124	0.0026	1.360E-06	0.0285	0.0080	3.549E-04
2-methylbutyroylcarnitine	rs272889	5	A	G	0.0123	0.0025	1.080E-06	0.0211	0.0076	5.163E-03
2-methylbutyroylcarnitine	rs272892	5	T	C	-0.0124	0.0026	1.360E-06	0.0285	0.0080	3.553E-04
2-methylbutyroylcarnitine	rs272893	5	T	C	0.0123	0.0025	1.080E-06	0.0212	0.0076	5.117E-03
2-methylbutyroylcarnitine	rs273901	5	T	G	-0.0124	0.0026	1.520E-06	0.0286	0.0080	3.435E-04
2-methylbutyroylcarnitine	rs273911	5	C	G	0.0124	0.0026	1.360E-06	0.0281	0.0080	4.286E-04
2-methylbutyroylcarnitine	rs273912	5	T	G	-0.0124	0.0026	1.630E-06	0.0283	0.0080	3.887E-04
2-methylbutyroylcarnitine	rs273913	5	T	C	0.0116	0.0025	4.700E-06	0.0229	0.0075	2.432E-03
2-methylbutyroylcarnitine	rs273914	5	A	T	0.0131	0.0025	2.070E-07	0.0226	0.0075	2.674E-03
2-methylbutyroylcarnitine	rs273915	5	C	G	-0.0124	0.0026	1.370E-06	0.0285	0.0080	3.475E-04
2-methylbutyroylcarnitine	rs273916	5	A	C	-0.0124	0.0026	1.370E-06	0.0285	0.0080	3.542E-04
2-methylbutyroylcarnitine	rs274546	5	A	G	0.0121	0.0025	1.590E-06	0.0212	0.0076	5.141E-03
2-methylbutyroylcarnitine	rs274557	5	T	C	-0.0118	0.0025	3.420E-06	-0.0231	0.0075	2.261E-03
2-methylbutyroylcarnitine	rs274558	5	A	G	-0.0118	0.0025	3.430E-06	-0.0231	0.0075	2.263E-03
2-methylbutyroylcarnitine	rs274559	5	A	G	-0.0117	0.0026	4.170E-06	-0.0232	0.0076	2.159E-03

2-methylbutyroylcarnitine	rs274560	5	T	C	-0.0119	0.0025	2.430E-06	-0.0217	0.0076	4.242E-03
2-methylbutyroylcarnitine	rs274561	5	A	C	0.0119	0.0025	2.220E-06	-0.0213	0.0076	4.900E-03
2-methylbutyroylcarnitine	rs274567	5	T	C	0.0121	0.0025	1.710E-06	-0.0226	0.0076	2.859E-03
2-methylbutyroylcarnitine	rs274570	5	T	C	0.0127	0.0026	1.170E-06	-0.0279	0.0080	4.806E-04
2-methylbutyroylcarnitine	rs3778129	6	A	G	-0.0182	0.0041	9.910E-06	0.0117	0.0112	2.971E-01
2-methylbutyroylcarnitine	rs4074995	5	A	G	0.0123	0.0026	1.770E-06	0.0141	0.0088	1.117E-01
2-methylbutyroylcarnitine	rs4075958	5	A	G	0.0124	0.0026	1.920E-06	0.0147	0.0089	1.001E-01
2-methylbutyroylcarnitine	rs419291	5	T	C	0.0123	0.0025	1.330E-06	0.0228	0.0076	2.890E-03
2-methylbutyroylcarnitine	rs456598	6	A	G	-0.0155	0.0035	7.090E-06	0.0043	0.0109	6.892E-01
2-methylbutyroylcarnitine	rs4626843	1	A	G	0.0292	0.0065	7.390E-06	-0.0200	0.0198	3.111E-01
2-methylbutyroylcarnitine	rs4648860	1	T	C	0.0124	0.0027	4.720E-06	-0.0111	0.0101	2.705E-01
2-methylbutyroylcarnitine	rs4719207	7	T	C	-0.0140	0.0030	3.060E-06	-0.0080	0.0088	3.653E-01
2-methylbutyroylcarnitine	rs4730501	7	A	G	-0.0121	0.0026	4.180E-06	0.0045	0.0091	6.209E-01
2-methylbutyroylcarnitine	rs4732399	7	A	G	-0.0311	0.0070	8.690E-06	-0.0124	0.0190	5.131E-01
2-methylbutyroylcarnitine	rs4948546	10	A	G	-0.0125	0.0026	2.370E-06	0.0209	0.0106	4.829E-02
2-methylbutyroylcarnitine	rs6575209	14	T	C	0.0120	0.0026	5.100E-06	0.0241	0.0092	8.870E-03
2-methylbutyroylcarnitine	rs662138	6	C	G	0.0187	0.0034	3.650E-08	0.0015	0.0097	8.787E-01
2-methylbutyroylcarnitine	rs6764615	3	C	G	0.0159	0.0033	2.170E-06	0.0040	0.0106	7.092E-01
2-methylbutyroylcarnitine	rs7081819	10	A	G	0.0120	0.0027	5.630E-06	0.0217	0.0108	4.435E-02
2-methylbutyroylcarnitine	rs7087186	10	C	G	0.0126	0.0027	2.230E-06	0.0240	0.0109	2.673E-02
2-methylbutyroylcarnitine	rs715	2	T	C	0.0123	0.0026	2.400E-06	0.0018	0.0083	8.260E-01
2-methylbutyroylcarnitine	rs7903712	10	C	G	0.0127	0.0027	1.650E-06	0.0233	0.0107	2.994E-02
2-methylbutyroylcarnitine	rs7920393	10	A	G	0.0120	0.0027	6.050E-06	0.0220	0.0108	4.075E-02
2-methylbutyroylcarnitine	rs7946997	11	T	C	-0.0123	0.0026	2.970E-06	-0.0013	0.0081	8.754E-01
2-methylbutyroylcarnitine	rs9416742	10	A	G	0.0120	0.0027	5.640E-06	-0.0207	0.0111	6.243E-02
2-methylbutyroylcarnitine	rs9492253	6	A	G	-0.0119	0.0027	8.620E-06	-0.0017	0.0092	8.547E-01
2-methylbutyroylcarnitine	rs9641894	7	T	G	-0.0117	0.0025	4.130E-06	-0.0240	0.0082	3.369E-03
2-methylbutyroylcarnitine	rs9642829	8	A	G	-0.0346	0.0075	3.610E-06	-0.0199	0.0264	4.520E-01
2-methylbutyroylcarnitine	rs9839755	3	T	C	0.0152	0.0034	7.620E-06	0.0056	0.0107	5.976E-01
2-methylbutyroylcarnitine	rs999845	10	T	C	0.0121	0.0027	4.870E-06	0.0227	0.0108	3.569E-02
2-methylbutyroylcarnitine	rs999846	10	A	G	0.0120	0.0027	5.710E-06	0.0226	0.0108	3.659E-02

Table S22 Summary statistics for the associations of the 1-oleoylglycerophosphocholine-associated SNPs with these exposures and ER-negative Breast cancer in Breast Cancer Association Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
1-oleoylglycerophosphocholine	rs10019315	4	T	C	0.0121	0.0026	2.990E-06	beta.outcome	se.outcome	pval.outcome
1-oleoylglycerophosphocholine	rs10465080	9	A	T	-0.0121	0.0026	4.693E-06	-0.0090	0.0134	5.027E-01
1-oleoylglycerophosphocholine	rs12202351	6	T	C	0.0118	0.0026	7.135E-06	-0.0011	0.0155	9.438E-01
1-oleoylglycerophosphocholine	rs12605650	18	T	C	0.0120	0.0026	5.134E-06	0.0100	0.0139	4.725E-01
1-oleoylglycerophosphocholine	rs1366823	2	A	G	0.0118	0.0026	6.939E-06	0.0323	0.0152	3.362E-02
1-oleoylglycerophosphocholine	rs16968711	15	A	G	0.0205	0.0041	4.645E-07	-0.0452	0.0332	1.738E-01
1-oleoylglycerophosphocholine	rs17089560	4	T	C	0.0468	0.0092	3.393E-07	0.0258	0.0178	1.461E-01
1-oleoylglycerophosphocholine	rs303610	9	A	T	-0.0117	0.0026	8.877E-06	0.0343	0.0548	5.311E-01
1-oleoylglycerophosphocholine	rs4736583	8	A	C	-0.0120	0.0026	4.893E-06	-0.0055	0.0125	6.566E-01
1-oleoylglycerophosphocholine	rs476092	11	A	C	0.0120	0.0026	5.088E-06	-0.0042	0.0116	7.157E-01
1-oleoylglycerophosphocholine	rs4817185	21	C	G	0.0373	0.0084	7.784E-06	-0.0069	0.0131	5.995E-01
1-oleoylglycerophosphocholine	rs6061764	20	A	G	-0.0140	0.0030	3.061E-06	-0.0013	0.0125	9.186E-01
1-oleoylglycerophosphocholine	rs6977605	7	A	C	-0.0242	0.0050	1.674E-06	-0.0069	0.0120	5.626E-01
1-oleoylglycerophosphocholine	rs743452	21	T	C	-0.0231	0.0052	8.059E-06	0.0084	0.0129	5.153E-01
1-oleoylglycerophosphocholine	rs9489697	6	T	C	0.0116	0.0026	8.364E-06	0.0207	0.0115	7.304E-02
1-oleoylglycerophosphocholine	rs969948	4	T	C	-0.0117	0.0026	5.744E-06	-0.0057	0.0114	6.174E-01

Table S23 Summary statistics for the associations of the octanoylcarnitine-associated SNPs with these exposures and squamous cell lung cancer in International Lung Cancer Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
octanoylcarnitine	rs10170989	2	T	G	0.0198	0.0049	4.767E-05	0.0228	0.0358	5.286E-01
octanoylcarnitine	rs10868458	9	A	T	-0.0165	0.0035	1.923E-06	-0.0339	0.0275	2.472E-01
octanoylcarnitine	rs17638535	6	A	G	-0.0652	0.0132	8.745E-07	0.1265	0.1177	2.755E-01
octanoylcarnitine	rs2133336	17	A	G	0.0152	0.0034	9.562E-06	-0.0346	0.0269	2.281E-01
octanoylcarnitine	rs2720162	2	T	G	-0.0154	0.0034	7.305E-06	0.0582	0.0262	4.159E-02
octanoylcarnitine	rs274567	5	T	C	0.0158	0.0034	3.928E-06	-0.0108	0.0277	7.073E-01
octanoylcarnitine	rs4672596	2	T	C	0.0152	0.0034	9.595E-06	-0.0230	0.0283	4.197E-01
octanoylcarnitine	rs6907864	6	T	C	0.0261	0.0058	5.789E-06	-0.0400	0.0405	3.642E-01
octanoylcarnitine	rs7130402	11	A	G	0.0324	0.0073	9.875E-06	-0.1042	0.0465	5.529E-02
octanoylcarnitine	rs7246133	19	T	C	0.0205	0.0046	9.476E-06	-0.0022	0.0301	9.442E-01
octanoylcarnitine	rs7334793	13	T	C	-0.0152	0.0034	8.042E-06	-0.0328	0.0267	2.476E-01
octanoylcarnitine	rs7552404	1	A	G	0.0746	0.0040	1.269E-77	0.0446	0.0326	1.662E-01
octanoylcarnitine	rs7660477	4	T	C	-0.0151	0.0034	8.230E-06	-0.0280	0.0265	3.169E-01
octanoylcarnitine	rs8396	4	T	C	0.0478	0.0041	1.377E-31	0.0041	0.0305	8.953E-01
octanoylcarnitine	rs884760	6	T	C	0.0188	0.0042	7.161E-06	0.0540	0.0298	9.616E-02
octanoylcarnitine	rs888860	19	A	C	-0.0181	0.0037	9.389E-07	0.0405	0.0273	1.660E-01
octanoylcarnitine	rs924135	16	A	T	-0.0209	0.0034	1.085E-09	-0.0155	0.0283	5.893E-01

Table S24 Summary statistics for the associations of the salicylate-associated SNPs with these exposures and ER-negative Breast cancer in Breast Cancer Association Consortium

Phenotype	SNP	CHR	Effect Allele	Reference Allele	Summary statistics for exposure			Summary statistics for cancer		
					Beta	SE	P value	Beta	SE	P value
salicylate	rs10040805	5	T	C	-0.1765	0.0427	3.620E-05	-0.0785	0.0279	4.830E-03
salicylate	rs10205265	2	T	C	-0.0901	0.0202	7.794E-06	-0.0064	0.0142	6.516E-01
salicylate	rs10402106	19	T	C	0.9529	0.1924	7.348E-07	0.0596	0.0513	2.458E-01
salicylate	rs10458721	10	A	G	-0.0786	0.0175	7.228E-06	-0.0151	0.0127	2.338E-01
salicylate	rs10471169	4	T	C	0.9362	0.1854	4.427E-07	0.0583	0.0214	6.313E-03
salicylate	rs10749553	10	A	G	-0.0868	0.0194	7.554E-06	0.0137	0.0129	2.882E-01
salicylate	rs10977627	9	T	C	0.8146	0.1524	9.061E-08	-0.0040	0.0439	9.273E-01
salicylate	rs10984575	9	A	C	0.1144	0.0257	8.271E-06	-0.0036	0.0199	8.572E-01
salicylate	rs11256026	10	A	G	-0.2061	0.0409	4.601E-07	-0.0223	0.0117	5.638E-02
salicylate	rs1164673	11	C	G	0.0754	0.0168	7.267E-06	0.0142	0.0118	2.316E-01
salicylate	rs12005082	9	A	T	0.1232	0.0265	3.354E-06	0.0010	0.0153	9.479E-01
salicylate	rs12075728	1	T	G	-0.4196	0.0922	5.394E-06	0.0097	0.0248	6.976E-01
salicylate	rs16832600	1	T	C	0.2205	0.0469	2.579E-06	-0.0145	0.0300	6.285E-01
salicylate	rs16862165	3	T	C	-0.4130	0.0890	3.477E-06	-0.0364	0.0577	5.277E-01
salicylate	rs17682068	8	A	G	-0.1299	0.0290	7.452E-06	0.0092	0.0244	7.050E-01
salicylate	rs400214	1	T	C	0.3258	0.0723	6.599E-06	0.0158	0.0358	6.586E-01
salicylate	rs7701675	5	A	G	-0.7943	0.1733	4.558E-06	0.0458	0.0512	3.705E-01
salicylate	rs8178289	17	A	C	-0.1064	0.0233	5.095E-06	-0.0112	0.0168	5.071E-01
salicylate	rs9453415	6	A	G	0.3740	0.0830	6.605E-06	0.0025	0.0488	9.599E-01

Table S25 Sigmifcant Metabolic Associated with 4 Primary Cancers

Trait	Metabolic Pathway	Involved Metabolites	P value	Database
Lung cancer	Vitamin B6 metabolism	4-Pyridoxate	0.028734	KEGG,SMP
Lung cancer	Butanoate metabolism	2-Hydroxyglutarate	0.04752	KEGG,SMP
Lung adenocarcinoma	Aminoacyl-tRNA biosynthesis	L-Asparagine,L-Phenylalanine,L-Isoleucine	0.006411	KEGG
Lung adenocarcinoma	Phenylalanine, tyrosine and tryptophan biosynthesis	L-Phenylalanine	0.03316	KEGG,SMP