Supplementary Materials

Study Population

Blood collection: In 1989–1990, 32,826 NHS participants provided blood samples and completed a short questionnaire. Women arranged to have their blood drawn and shipped with an ice pack, via overnight courier, to our laboratory, where it was processed and separated into plasma, red blood cell, and white blood cell components and frozen in gasketed cryovials in the vapor phase of liquid nitrogen freezers. Between 1996 and 1999, 29,611 NHSII participants provided blood samples and completed a short questionnaire. Premenopausal women (n=18,521) who had not taken hormones, been pregnant, or lactated within the past 6 months provided blood samples drawn 7–9 days before the anticipated start of their next menstrual cycle (luteal phase). Other women (n = 11,090) provided a single 30-mL untimed blood sample. Samples were shipped and processed identically to the NHS samples.

Incident cases of epithelial ovarian cancer were identified through the biennial questionnaires or via linkage with the National Death Index. For women reporting a new ovarian cancer diagnosis or cases identified through death certificates, we obtained related medical records and pathology reports; for cases who had died we linked to the relevant cancer registry is medical records were unattainable. A gynecologic pathologist reviewed the records to confirm the diagnosis and abstract date of diagnosis, invasiveness, stage, and histologic subtype (serous, poorly differentiated [PD], endometrioid, clear cell [CC], mucinous, other/unknown). Date of death was extracted from the death certificate. Participants diagnosed with invasive disease and who died within 3 years of diagnosis were defined as rapidly fatal cases.

Cases were diagnosed with ovarian cancer three years after blood draw until June 1, 2012 (NHS), or June 1, 2013 (NHSII). Two hundred fifty-three cases of invasive and borderline epithelial ovarian cancer (213 in NHS and 40 in NHSII) were confirmed by medical record review. Cases were matched to one control who was alive and at least had one ovary at the time of case diagnosis on: cohort (NHS, NHSII); menopausal status and hormone therapy use at blood draw (premenopausal, postmenopausal and hormone therapy use, postmenopausal and no hormone therapy use, missing/ unknown); menopausal status at diagnosis (premenopausal, postmenopausal, or unknown); age (±1 year), date of blood collection (± 1 month); time of day of blood draw (±2 hours); fasting status (>8 hours or ≤8 hours).

Metabolite Profiling

For each method, pooled plasma reference samples were included every 20 samples and results were standardized using the ratio of the value of the sample to the value of the nearest pooled reference multiplied by the median of all reference values for the metabolite. Samples from the two cohorts were run together, with matched case-control pairs distributed randomly within the batch, and the order of the case and controls within each pair was also randomly designated. Therefore, the case and its control were always directly adjacent to each other in the analytic run, thereby limiting variability in platform performance across matched case-control pairs. In addition to the participants' samples, 64 quality control (QC) samples, to which the laboratory was blinded, were randomly inserted in pairs among participant samples and profiled.

Hydrophilic interaction liquid chromatography (HILIC) analyses of water- soluble metabolites in the positive ionization mode (HILIC-positive) were conducted using an LC-MS system comprised of a Shimadzu Nexera X2 U-HPLC (Shimadzu Corp.; Marlborough, MA) coupled to a Q Exactive mass

spectrometer (Thermo Fisher Scientific; Waltham, MA). Metabolites were extracted from plasma (10 µL) using 90 µL of acetonitrile/methanol/formic acid (74.9:24.9:0.2 v/v/v) containing stable isotope-labeled internal standards (valine-d8, Sigma-Aldrich; St. Louis, MO; and phenylalanine-d8, Cambridge Isotope Laboratories; Andover, MA). The samples were centrifuged (10 min, 9,000 x g, 4°C), and the supernatants were injected directly onto a 150 x 2 mm, 3 µm Atlantis HILIC column (Waters; Milford, MA). The column was eluted isocratically at a flow rate of 250 µL/min with 5% mobile phase A (10 mM ammonium formate and 0.1% formic acid in water) for 0.5 minute followed by a linear gradient to 40% mobile phase B (acetonitrile with 0.1% formic acid) over 10 minutes. MS analyses were carried out using electrospray ionization in the positive ion mode using full scan analysis over 70-800 m/z at 70,000 resolution and 3 Hz data acquisition rate. Other MS settings were: sheath gas 40, sweep gas 2, spray voltage 3.5 kV, capillary temperature 350°C, S-lens RF 40, heater temperature 300°C, microscans 1, automatic gain control target 1e6, and maximum ion time 250 ms.

Plasma lipids were profiled using a Shimadzu Nexera X2 U-HPLC (Shimadzu Corp.; Marlborough, MA) (C8-positive). Lipids were extracted from plasma (10 µL) using 190 µL of isopropanol containing 1,2-didodecanoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids; Alabaster, AL). After centrifugation, supernatants were injected directly onto a 100 x 2.1 mm, 1.7 µm ACQUITY BEH C8 column (Waters; Milford, MA). The column was eluted isocratically with 80% mobile phase A (95:5:0.1 vol/vol/vol 10mM ammonium acetate/methanol/formic acid) for 1 minute followed by a linear gradient to 80% mobile-phase B (99.9:0.1 vol/vol methanol/formic acid) over 2 minutes, a linear gradient to 100% mobile phase B over 7 minutes, then 3 minutes at 100% mobile-phase B. MS analyses were carried out using electrospray ionization in the positive ion mode using full scan analysis over 200–1100 m/z at 70,000 resolution and 3 Hz data acquisition rate. Other MS settings were: sheath gas 50, in source CID 5 eV, sweep gas 5, spray voltage 3 kV, capillary temperature 300°C, S-lens RF 60, heater temperature 300°C, microscans 1, automatic gain control target 1e6, and maximum ion time 100 ms. Lipid identities were denoted by total acyl carbon number and total double bond number.

Raw data from orbitrap mass spectrometers were processed using TraceFinder 3.3 software (Thermo Fisher Scientific; Waltham, MA) and Progenesis QI (Nonlinear Dynamics; Newcastle upon Tyne, UK) and targeted data from the QTRAP 5500 system were processed using MultiQuant (version 2.1, SCIEX; Framingham, MA). For each method, metabolite identities were confirmed using authentic reference standards or reference samples.

Thirty-nine individual metabolites belonging to four metabolite classes (11 LPC, 17 PC, 6 SM and 5 CER) were analyzed in this study. 12 were assessed with the HILIC-positive approach: C34:2 PC, C34:4 PC, C36:2 PC-A, C36:2 PC-B, C14:0 LPC, C22:5 LPC, C22:6 LPC, C14:0 SM, C16:0 SM, C18:0 SM, C20:0 SM, and C24:1 Ceramide. The remaining 27 metabolites were assessed with the C8-positive approach.

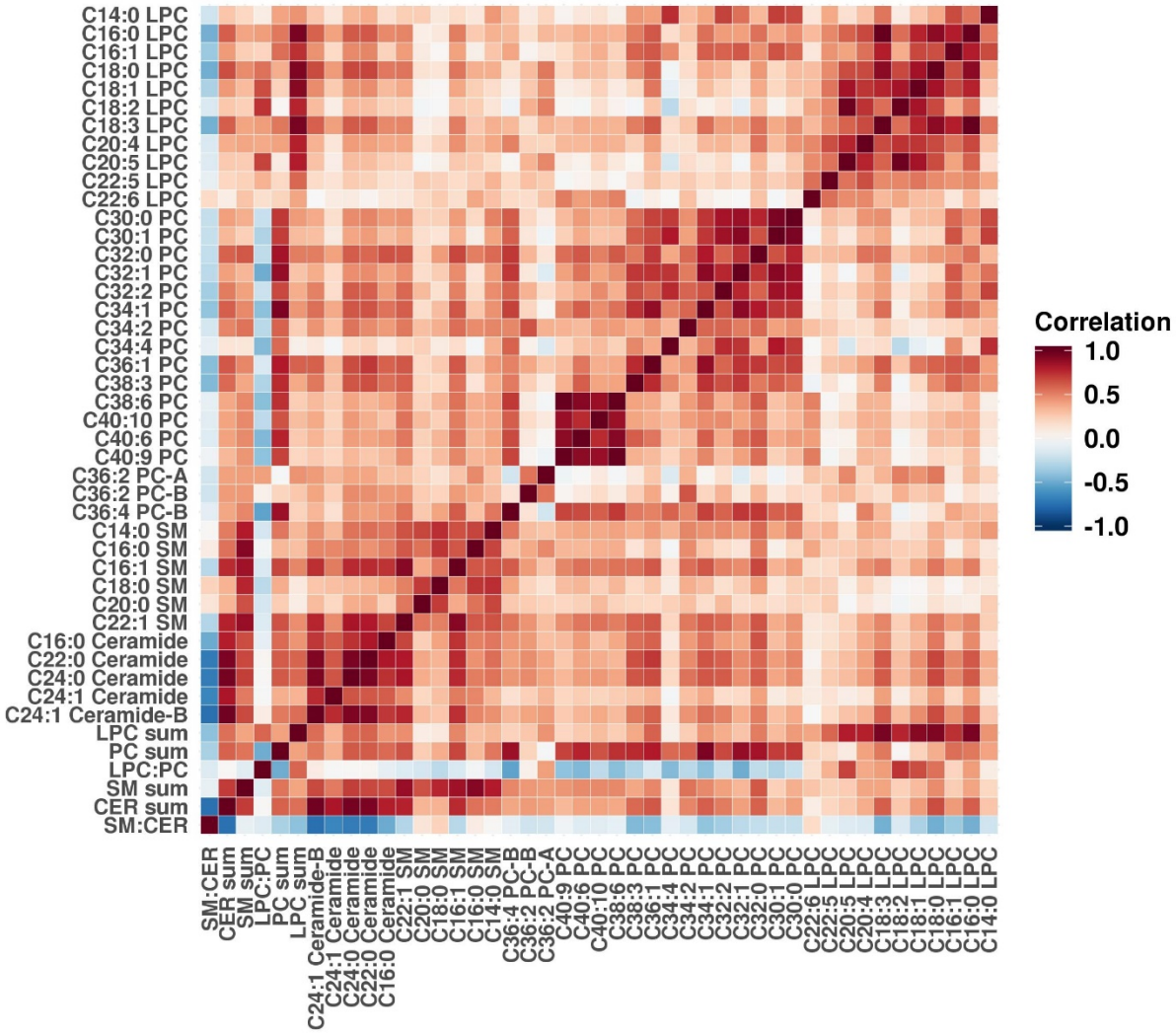
Fifty-four metabolites were assessed in total. Metabolites with a coefficient of variation (CV) among the blinded QC samples higher than 25%, an intra-class correlation coefficient (ICC) <0.75, or with missing values in more than 10% of the participant samples were excluded from this analysis (N=3). Missing values in metabolites with less than 10% missing across participant samples were imputed with 1/2 of the minimum value measured for that metabolite. Metabolites not passing our previously conducted processing delay (N=12) pilot study [39] were also excluded from this analysis. All metabolites included in the analysis exhibited good reproducibility within person over one year [39] (Supplementary Table 1).

Statistical Analysis

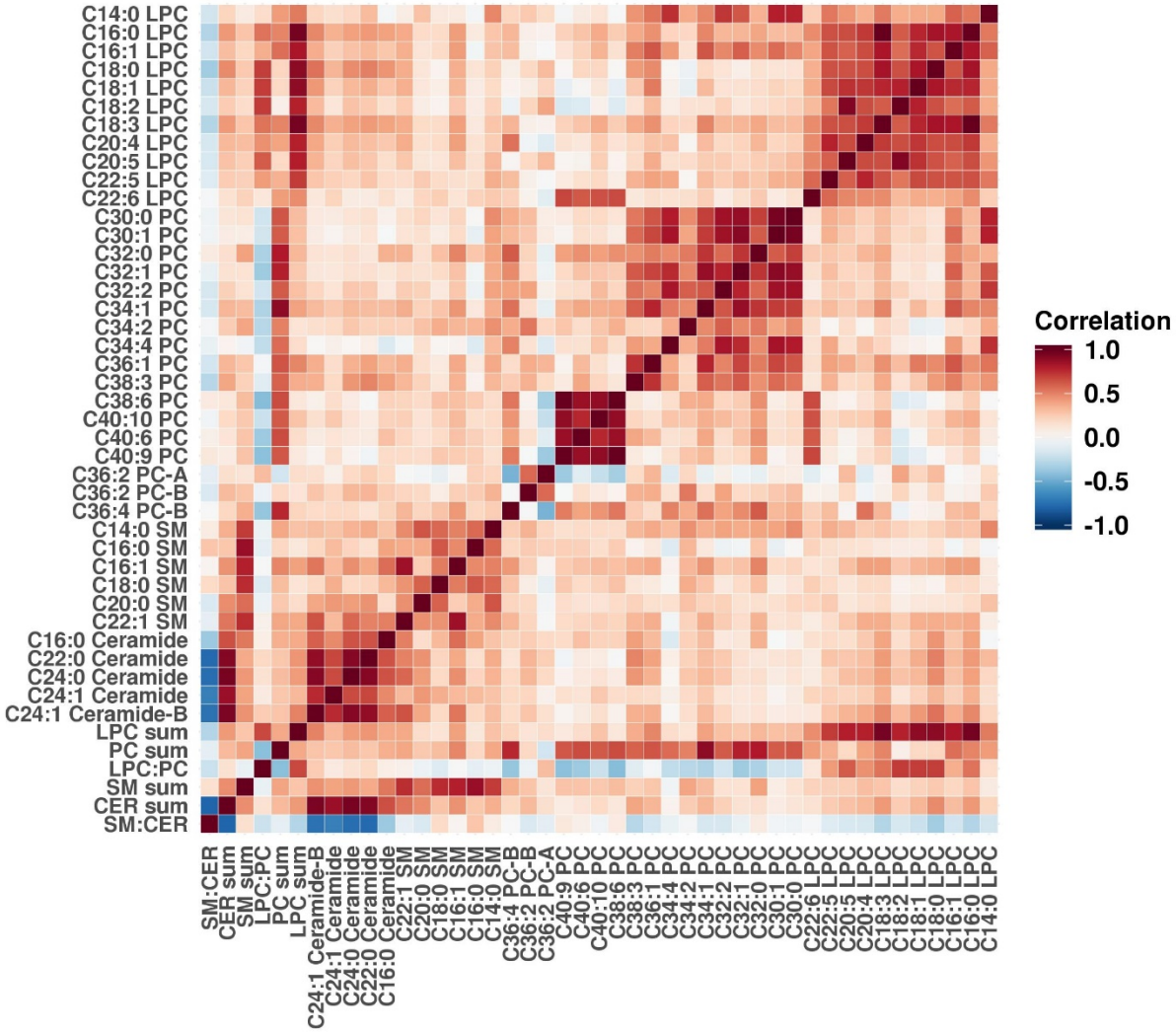
In a sensitivity analysis, we compared conditional logistic regression to unconditional logistic regression adjusting for the matching factors and found similar results (data not shown). Based on this comparison, stratified analyses by histotype (176 serous/poorly differentiated cases; 34 endometrioid/clear cell cases) were conducted using unconditional logistic regression adjusting for the matching factors, allowing the use of all 252 controls. All regression analyses were further adjusted for established ovarian cancer risk factors: duration of oral contraceptive use (none or <3 months, 3 months to 3 years, 3 years to 5 years, more than 5 years), tubal ligation (yes/no) and parity (no children, 1 child, 2 children, 3 children, 4+ children).

Supplementary Figures

Supplementary Figure 1. Correlation among metabolites in premenopausal control samples at blood draw. Pearson correlation was calculated for all pairs of individual metabolites, metabolite sums and metabolite ratios among premenopausal women (N=82 controls) at blood collection. Positive Pearson correlation coefficients are shown in shades of red and negative coefficients are shown in shades of blue.



Supplementary Figure 2. Correlation among metabolites in postmenopausal control samples at blood draw. Pearson correlation was calculated for all pairs of individual metabolites, metabolite sums and metabolite ratios among postmenopausal women (N=137 controls) at blood collection. Positive Pearson correlation coefficients are shown in shades of red and negative coefficients are shown in shades of blue.



Supplementary Tables

Supplementary Table 1. Quality control sample based coefficients of variation (CV) and intra class correlation (ICC); ICCs and correlation coefficient (Rho) from our processing delay, within person stability over 2 years and 10 years pilot studies.

Method	HMDB ID	Metabolite	QC samples		Processing delay pilot study		Within person stability over 2 years pilot study		Within person stability over 10 years pilot study	
			mean CV	ICC	ICC	Rho	ICC	Rho	ICC	Rho
C8-pos	HMDB07869*	C30:0 PC	8.59	0.99	0.91	0.46	0.44	0.81	0.35	0.45
C8-pos	HMDB07870*	C30:1 PC	9.34	1.00	0.93	0.50	0.40	0.93	0.38	0.42
C8-pos	HMDB07871*	C32:0 PC	7.42	0.94	0.75	0.72	0.68	0.59	0.24	0.37
C8-pos	HMDB07873*	C32:1 PC	9.76	0.99	0.89	0.66	0.68	0.93	0.29	0.45
C8-pos	HMDB07874*	C32:2 PC	7.99	0.98	0.82	0.48	0.42	0.68	0.58	0.62
HILIC-pos	HMDB07883*	C34:4 PC	7.68	0.96	0.98	0.44	0.37	0.89	0.46	0.42
C8-pos	HMDB07972*	C34:1 PC	7.69	0.95	0.75	0.66	0.67	0.77	0.05	0.25
HILIC-pos	HMDB07973*	C34:2 PC	13.22	0.91	0.94	0.55	0.70	0.79	0.45	0.43
C8-pos	HMDB07991*	C38:6 PC	7.43	0.98	0.83	0.82	0.82	0.93	0.43	0.69
C8-pos	HMDB08038*	C36:1 PC	8.53	0.96	0.78	0.43	0.58	0.65	0.07	0.27
HILIC-pos	HMDB08039*	C36:2 PC-A	5.70	0.83	0.92	0.65	0.65	0.58	0.18	0.32
HILIC-pos	HMDB08039*	C36:2 PC-B	23.38	0.81	0.92	0.65	0.65	0.58	0.19	0.31
C8-pos	HMDB08047*	C38:3 PC	7.81	0.96	0.83	0.49	0.61	0.87	0.37	0.47
C8-pos	HMDB08057*	C40:6 PC	7.88	0.97	0.80	0.77	0.73	0.81	0.39	0.68
C8-pos	HMDB08138*	C36:4 PC-B	6.87	0.94	0.84	0.77	0.78	0.71	0.44	0.60
C8-pos	HMDB08511*	C40:10 PC	8.29	0.98	0.93	0.79	0.73	0.92	0.40	0.61
C8-pos	HMDB08731*	C40:9 PC	5.71	0.98	0.92	0.82	0.82	0.98	0.47	0.68
C8-pos	HMDB02815*	C18:1 LPC	8.05	0.95	0.87	0.68	0.69	0.85	0.05	0.04
HILIC-pos	HMDB10379	C14:0 LPC	9.01	0.98	0.97	0.47	0.37	0.82	0.25	0.26
C8-pos	HMDB10382	C16:0 LPC	8.43	0.93	0.80	0.54	0.49	0.70	0.01	0.06
C8-pos	HMDB10383*	C16:1 LPC	8.56	0.95	0.85	0.65	0.58	0.88	0.04	0.08
C8-pos	HMDB10384	C18:0 LPC	8.08	0.95	0.85	0.41	0.55	0.68	0.00	~~0.06~~
C8-pos	HMDB10386*	C18:2 LPC	8.35	0.97	0.86	0.71	0.70	0.81	0.26	0.20
C8-pos	HMDB10387*	C18:3 LPC	7.77	0.91	0.87	0.54	0.47	0.85	0.02	0.07
C8-pos	HMDB10395	C20:4 LPC	9.64	0.92	0.87	0.74	0.69	0.82	0.46	0.41
C8-pos	HMDB10397	C20:5 LPC	22.05	0.83	0.96	0.35	0.00	0.87	0.23	0.25
HILIC-pos	HMDB10403*	C22:5 LPC	9.59	0.90	0.94	0.72	0.66	0.98	0.38	0.41
HILIC-pos	HMDB10404	C22:6 LPC	8.91	0.96	0.97	0.76	0.74	0.93	0.52	0.61

HILIC-pos	HMDB01348	C18:0 SM	11.29	0.83	0.94	0.52	0.58	0.76	0.41	0.43
HILIC-pos	HMDB10169	C16:0 SM	8.10	0.85	0.91	0.64	0.51	0.83	0.23	0.21
HILIC-pos	HMDB12097	C14:0 SM	8.35	0.96	0.97	0.75	0.76	0.88	0.57	0.48
HILIC-pos	HMDB12102	C20:0 SM	11.36	0.89	0.93	0.58	0.75	0.79	0.28	0.23
C8-pos	HMDB12104*	C22:1 SM	8.16	0.90	0.56	0.77	0.76	0.83	0.24	0.23
C8-pos	HMDB04949	C16:0 Ceramide (d18:1)	11.49	0.88	0.78	0.56	0.63	0.70	0.27	0.30
C8-pos	HMDB04952	C22:0 Ceramide (d18:1)	8.58	0.95	0.91	0.73	0.80	0.83	0.55	0.56
HILIC-pos	HMDB04953*	C24:1 Ceramide (d18:1)	11.15	0.83	0.96	0.61	0.66	0.85	0.19	0.24
C8-pos	HMDB04953*	C24:1 Ceramide (d18:1)-B	8.75	0.96	0.93	0.57	0.52	0.93	0.38	0.41
C8-pos	HMDB04956	C24:0 Ceramide (d18:1)	8.05	0.95	0.88	0.65	0.79	0.82	0.58	0.52

HMDB ID: unique metabolite identifier from the Human Metabolome Database; * representative HMDB ID.

Supplementary Table 2. Odds ratio (OR) for an increase from the 10th to 90th percentile of metabolite levels and 95% confidence intervals (CI) of ovarian cancer (OC) overall and according to histotype (serous/poorly differentiated [PD] and endometrioid/clear cell [CC]).

Metabolite	HMDB ID	Overall OC (N=252 cases and N=252 controls)			Serous/PD OC (N=176 cases and N=252 controls)			Endometrioid/CC OC (N=34 cases and N=252 controls)		
		OR (95%CI)	P-value†	Adjusted p-value‡	OR (95%CI)	P-value†	Adjusted p-value‡	OR (95%CI)	P-value†	Adjusted p-value‡
C18:0 SM	HMDB01348	2.10 (1.26, 3.49)	0.004	0.08	1.67 (0.99, 2.84)	0.06	0.60	4.06 (1.44, 12.60)	0.01	0.15
C16:0 SM	HMDB10169	2.06 (1.19, 3.56)	0.009	0.17	1.73 (1.00, 3.01)	0.05	0.57	0.93 (0.33, 2.64)	0.90	0.90
SM sum	NA	1.97 (1.16, 3.32)	0.01	0.20	1.77 (1.02, 3.10)	0.05	0.54	1.12 (0.38, 3.28)	0.83	0.83
C16:0 Ceramide	HMDB04949	1.95 (1.16, 3.30)	0.01	0.21	1.61 (0.95, 2.78)	0.08	0.71	1.50 (0.54, 4.19)	0.43	0.65
C34:2 PC	HMDB07973*	1.82 (1.08, 3.06)	0.02	0.36	1.33 (0.77, 2.28)	0.31	1.00	2.16 (0.80, 6.03)	0.13	0.60
C38:3 PC	HMDB08047*	1.67 (1.01, 2.76)	0.05	0.55	1.62 (0.96, 2.76)	0.07	0.69	1.69 (0.63, 4.61)	0.30	0.65
C14:0 SM	HMDB12097	1.65 (1.00, 2.72)	0.05	0.60	1.64 (0.94, 2.88)	0.08	0.71	1.42 (0.52, 3.96)	0.49	0.65
C22:1 SM	HMDB12104*	1.65 (0.98, 2.77)	0.06	0.64	1.58 (0.91, 2.75)	0.11	0.81	0.82 (0.27, 2.44)	0.73	0.73
C20:0 SM	HMDB12102	1.60 (0.97, 2.63)	0.06	0.66	1.80 (1.06, 3.08)	0.03	0.43	1.24 (0.45, 3.36)	0.68	0.68
C16:1 SM	NA	1.44 (0.86, 2.41)	0.17	0.93	1.25 (0.72, 2.17)	0.43	1.00	1.02 (0.34, 2.99)	0.98	0.98
C36:4 PC-B	HMDB08138*	1.43 (0.83, 2.46)	0.20	0.96	0.98 (0.56, 1.70)	0.94	1.00	2.63 (0.93, 7.71)	0.07	0.48
PC sum	NA	1.40 (0.83, 2.37)	0.21	0.96	1.01 (0.58, 1.75)	0.98	1.00	1.99 (0.73, 5.59)	0.18	0.63
CER sum	NA	1.37 (0.84, 2.24)	0.21	0.96	1.44 (0.84, 2.49)	0.19	0.95	1.26 (0.45, 3.54)	0.66	0.66
C24:0 Ceramide	HMDB04956	1.35 (0.82, 2.21)	0.23	0.97	1.48 (0.86, 2.58)	0.16	0.93	0.91 (0.32, 2.53)	0.86	0.86
C22:5 LPC	HMDB10403*	1.30 (0.82, 2.08)	0.27	0.99	1.05 (0.63, 1.76)	0.86	1.00	1.07 (0.40, 2.89)	0.89	0.89
C32:1 PC	HMDB07873*	1.31 (0.80, 2.13)	0.28	0.99	1.05 (0.62, 1.79)	0.85	1.00	1.66 (0.63, 4.55)	0.31	0.65
C34:1 PC	HMDB07972*	1.32 (0.81, 2.13)	0.27	0.99	1.00 (0.59, 1.72)	0.99	1.00	1.42 (0.54, 3.80)	0.47	0.65
LPC:PC	NA	0.76 (0.45, 1.28)	0.30	0.99	0.84 (0.47, 1.50)	0.56	1.00	0.24 (0.08, 0.71)	0.01	0.15
C40:6 PC	HMDB08057*	1.32 (0.77, 2.24)	0.31	0.99	1.09 (0.64, 1.89)	0.74	1.00	1.88 (0.70, 5.26)	0.22	0.64
C24:1 Ceramide	HMDB04953*	1.29 (0.79, 2.11)	0.30	0.99	1.24 (0.74, 2.11)	0.41	1.00	1.70 (0.61, 4.85)	0.31	0.65
C40:10 PC	HMDB08511*	1.31 (0.78, 2.20)	0.31	0.99	1.13 (0.65, 1.96)	0.67	1.00	1.26 (0.49, 3.35)	0.64	0.65
C38:6 PC	HMDB07991*	1.27 (0.73, 2.21)	0.39	1.00	0.93 (0.53, 1.64)	0.81	1.00	2.46 (0.90, 7.11)	0.09	0.51
C36:2 PC-B	HMDB08039*	1.23 (0.77, 1.96)	0.38	1.00	1.24 (0.74, 2.10)	0.41	1.00	0.37 (0.13, 1.01)	0.06	0.43
C14:0 LPC	HMDB10379	0.85 (0.54, 1.36)	0.51	1.00	0.77 (0.46, 1.30)	0.34	1.00	1.02 (0.39, 2.70)	0.96	0.96
C16:0 LPC	HMDB10382	1.08 (0.67, 1.75)	0.76	1.00	0.89 (0.52, 1.50)	0.65	1.00	0.82 (0.30, 2.17)	0.68	0.68
C16:1 LPC	HMDB10383*	1.13 (0.71, 1.79)	0.61	1.00	0.99 (0.60, 1.65)	0.97	1.00	0.68 (0.25, 1.84)	0.45	0.65
C18:0 LPC	HMDB10384	0.95 (0.57, 1.58)	0.85	1.00	0.98 (0.57, 1.71)	0.96	1.00	0.32 (0.10, 0.93)	0.04	0.38
C18:1 LPC	HMDB02815*	0.89 (0.55, 1.45)	0.65	1.00	0.87 (0.51, 1.49)	0.62	1.00	0.24 (0.07, 0.69)	0.01	0.15
C18:2 LPC	HMDB10386*	0.98 (0.61, 1.57)	0.93	1.00	0.93 (0.53, 1.62)	0.81	1.00	0.26 (0.08, 0.75)	0.02	0.18
C18:3 LPC	HMDB10387*	1.08 (0.67, 1.75)	0.75	1.00	0.88 (0.52, 1.49)	0.64	1.00	0.84 (0.31, 2.23)	0.72	0.72

C20:4 LPC	HMDB10395	1.05 (0.65, 1.70)	0.85	1.00	0.81 (0.48, 1.36)	0.43	1.00	0.92 (0.35, 2.41)	0.86	0.86
C20:5 LPC	HMDB10397	1.05 (0.65, 1.67)	0.85	1.00	0.91 (0.53, 1.58)	0.75	1.00	0.53 (0.18, 1.50)	0.23	0.65
C22:6 LPC	HMDB10404	1.23 (0.73, 2.07)	0.43	1.00	0.85 (0.50, 1.44)	0.55	1.00	2.69 (0.96, 7.95)	0.07	0.47
C30:0 PC	HMDB07869*	1.01 (0.63, 1.62)	0.98	1.00	0.87 (0.52, 1.48)	0.62	1.00	1.18 (0.48, 2.98)	0.72	0.72
C30:1 PC	HMDB07870*	0.93 (0.58, 1.50)	0.78	1.00	0.86 (0.51, 1.44)	0.57	1.00	0.91 (0.36, 2.29)	0.84	0.84
C32:0 PC	HMDB07871*	1.11 (0.68, 1.83)	0.67	1.00	0.79 (0.46, 1.36)	0.40	1.00	1.08 (0.40, 2.94)	0.88	0.88
C32:2 PC	HMDB07874*	1.14 (0.71, 1.84)	0.59	1.00	1.12 (0.66, 1.90)	0.67	1.00	0.98 (0.39, 2.48)	0.96	0.96
C34:4 PC	HMDB07883*	0.95 (0.59, 1.54)	0.84	1.00	0.90 (0.53, 1.53)	0.70	1.00	1.30 (0.49, 3.46)	0.60	0.65
C36:1 PC	HMDB08038*	1.05 (0.67, 1.66)	0.83	1.00	0.97 (0.58, 1.62)	0.90	1.00	0.64 (0.24, 1.73)	0.38	0.65
C40:9 PC	HMDB08731*	1.19 (0.69, 2.06)	0.53	1.00	0.90 (0.51, 1.58)	0.70	1.00	2.32 (0.85, 6.67)	0.11	0.56
C36:2 PC-A	HMDB08039*	0.99 (0.61, 1.61)	0.97	1.00	1.21 (0.70, 2.11)	0.50	1.00	0.30 (0.09, 0.89)	0.03	0.33
C22:0 Ceramide	HMDB04952	1.21 (0.74, 1.97)	0.44	1.00	1.20 (0.70, 2.05)	0.50	1.00	1.28 (0.47, 3.52)	0.63	0.65
C24:1 Ceramide-B	HMDB04953*	1.21 (0.74, 1.98)	0.45	1.00	1.28 (0.74, 2.22)	0.38	1.00	0.89 (0.31, 2.52)	0.83	0.83
LPC sum	NA	1.02 (0.63, 1.65)	0.93	1.00	0.89 (0.52, 1.51)	0.66	1.00	0.47 (0.16, 1.28)	0.15	0.62
SM:CER	NA	1.11 (0.68, 1.79)	0.68	1.00	1.00 (0.59, 1.68)	0.99	1.00	0.87 (0.33, 2.28)	0.77	0.77

HMDB ID: unique metabolite identifier from the Human Metabolome Database; NA: HMDB ID not available; * representative HMDB ID;
LPC: lysophosphatidylcholines; PC: phosphatidylcholines; SM: sphingomyelins.

† P-values were calculated with a two-sided Wald test as part of a logistic regression model of ovarian cancer, with the metabolite as a continuous exposure, adjusted for risk factors (duration of oral contraceptive use [none or <3 months, 3 months to 3 years, 3 years to 5 years, more than 5 years], tubal ligation [yes/no] and parity [no children, 1 child, 2 children, 3 children, 4+ children]) and additionally for matching factors (cohort [NHS, NHSII]; menopausal status and hormone therapy use at blood draw [premenopausal, postmenopausal and hormone therapy use, postmenopausal and no hormone therapy use, missing/unknown]; menopausal status at diagnosis [premenopausal, postmenopausal, or unknown]; age [±1 year], date of blood collection [± 1 month]; time of day of blood draw [±2 hours]; fasting status [>8 hours or ≤8 hours]) in subtype analyses.

‡ Adjusted p-values were calculated with the permutation-based Westfall and Young approach [40].

Supplementary Table 3. Odds ratio (OR) for an increase from the 10th to 90th percentile of metabolite levels and 95% confidence intervals (CI) of ovarian cancer (OC) and by menopausal status at blood collection.

Metabolite	HMDB ID	Overall OC (N=252 cases and N=252 controls)		Premenopausal (N=82 cases and N=82 controls)		Postmenopausal (N=137 cases and N=137 controls)	
		P†	OR (95% CI)	P†	OR (95% CI)	P†	OR (95% CI)
C14:0 LPC	HMDB10379	0.51	0.85 (0.54, 1.36)	0.75	0.87 (0.36, 2.08)	0.33	0.72 (0.37, 1.39)
C16:0 LPC	HMDB10382	0.76	1.08 (0.67, 1.75)	0.66	0.80 (0.30, 2.14)	0.90	0.96 (0.50, 1.84)
C16:1 LPC	HMDB10383*	0.61	1.13 (0.71, 1.79)	0.37	0.64 (0.25, 1.68)	0.64	1.16 (0.63, 2.14)
C18:0 LPC	HMDB10384	0.85	0.95 (0.57, 1.58)	0.35	0.61 (0.22, 1.71)	0.72	0.88 (0.44, 1.76)
C18:1 LPC	HMDB02815*	0.65	0.89 (0.55, 1.45)	0.20	0.55 (0.22, 1.38)	1.00	1.00 (0.52, 1.91)
C18:2 LPC	HMDB10386*	0.93	0.98 (0.61, 1.57)	0.57	0.80 (0.37, 1.72)	0.93	1.03 (0.52, 2.04)
C18:3 LPC	HMDB10387*	0.75	1.08 (0.67, 1.75)	0.64	0.79 (0.30, 2.10)	0.91	0.96 (0.50, 1.85)
C20:4 LPC	HMDB10395	0.85	1.05 (0.65, 1.70)	0.13	0.47 (0.17, 1.26)	0.82	1.08 (0.55, 2.14)
C20:5 LPC	HMDB10397	0.85	1.05 (0.65, 1.67)	0.82	0.92 (0.43, 1.98)	0.86	0.94 (0.48, 1.86)
C22:5 LPC	HMDB10403*	0.27	1.30 (0.82, 2.08)	0.28	0.62 (0.26, 1.47)	0.21	1.55 (0.78, 3.08)
C22:6 LPC	HMDB10404	0.43	1.23 (0.73, 2.07)	0.26	1.74 (0.67, 4.55)	0.78	0.90 (0.44, 1.84)
C30:0 PC	HMDB07869*	0.98	1.01 (0.63, 1.62)	0.74	0.85 (0.33, 2.20)	0.75	0.90 (0.47, 1.71)
C30:1 PC	HMDB07870*	0.78	0.93 (0.58, 1.50)	0.57	0.76 (0.30, 1.94)	0.49	0.79 (0.41, 1.54)
C32:0 PC	HMDB07871*	0.67	1.11 (0.68, 1.83)	0.41	0.68 (0.27, 1.70)	0.56	1.23 (0.62, 2.42)
C32:1 PC	HMDB07873*	0.28	1.31 (0.80, 2.13)	0.88	1.07 (0.44, 2.63)	0.78	1.10 (0.56, 2.19)
C32:2 PC	HMDB07874*	0.59	1.14 (0.71, 1.84)	0.68	0.81 (0.31, 2.16)	0.56	1.22 (0.63, 2.35)
C34:1 PC	HMDB07972*	0.27	1.32 (0.81, 2.13)	0.86	0.92 (0.39, 2.21)	0.65	1.17 (0.59, 2.34)
C34:2 PC	HMDB07973*	0.02	1.82 (1.08, 3.06)	0.68	1.22 (0.47, 3.16)	0.03	2.29 (1.08, 4.86)
C34:4 PC	HMDB07883*	0.84	0.95 (0.59, 1.54)	0.30	0.61 (0.24, 1.55)	0.94	0.97 (0.49, 1.95)
C36:1 PC	HMDB08038*	0.83	1.05 (0.67, 1.66)	0.37	0.65 (0.25, 1.66)	0.85	0.94 (0.50, 1.79)
C38:3 PC	HMDB08047*	0.05	1.67 (1.01, 2.76)	0.93	1.05 (0.39, 2.81)	0.36	1.40 (0.67, 2.92)
C38:6 PC	HMDB07991*	0.39	1.27 (0.73, 2.21)	0.59	1.29 (0.50, 3.33)	0.51	1.30 (0.60, 2.78)
C40:10 PC	HMDB08511*	0.31	1.31 (0.78, 2.20)	0.76	1.16 (0.45, 2.97)	0.28	1.46 (0.73, 2.91)
C40:6 PC	HMDB08057*	0.31	1.32 (0.77, 2.24)	0.62	1.26 (0.50, 3.21)	0.59	1.23 (0.58, 2.59)
C40:9 PC	HMDB08731*	0.53	1.19 (0.69, 2.06)	0.66	1.24 (0.48, 3.15)	0.61	1.22 (0.57, 2.60)
C36:2 PC-A	HMDB08039*	0.97	0.99 (0.61, 1.61)	0.64	0.77 (0.26, 2.26)	0.81	1.09 (0.55, 2.12)
C36:2 PC-B	HMDB08039*	0.38	1.23 (0.77, 1.96)	0.77	0.86 (0.30, 2.44)	0.51	1.25 (0.65, 2.40)
C36:4 PC-B	HMDB08138*	0.20	1.43 (0.83, 2.46)	0.28	0.56 (0.20, 1.59)	0.15	1.76 (0.81, 3.79)
C14:0 SM	HMDB12097	0.05	1.65 (1.00, 2.72)	0.38	0.62 (0.22, 1.78)	0.02	2.24 (1.13, 4.41)
C16:0 SM	HMDB10169	0.01	2.06 (1.19, 3.56)	0.61	0.77 (0.27, 2.15)	0.01	2.98 (1.37, 6.51)
C16:1 SM	NA	0.17	1.44 (0.86, 2.41)	0.13	0.44 (0.16, 1.25)	0.02	2.50 (1.18, 5.29)

C18:0 SM	HMDB01348	0.00	2.10 (1.26, 3.49)	0.10	2.49 (0.85, 7.29)	0.04	2.02 (1.03, 3.94)
C20:0 SM	HMDB12102	0.06	1.60 (0.97, 2.63)	0.74	0.85 (0.32, 2.22)	0.06	1.86 (0.97, 3.56)
C22:1 SM	HMDB12104*	0.06	1.65 (0.98, 2.77)	0.07	0.36 (0.12, 1.08)	~~0.00~~	3.11 (1.46, 6.62)
C16:0 Ceramide (d18:1)	HMDB04949	0.01	1.95 (1.16, 3.30)	0.29	1.76 (0.62, 4.99)	0.04	2.16 (1.04, 4.48)
C22:0 Ceramide (d18:1)	HMDB04952	0.44	1.21 (0.74, 1.97)	0.67	0.80 (0.30, 2.17)	0.55	1.22 (0.63, 2.37)
C24:0 Ceramide (d18:1)	HMDB04956	0.24	1.35 (0.82, 2.21)	0.64	0.79 (0.30, 2.11)	0.46	1.28 (0.66, 2.49)
C24:1 Ceramide (d18:1)	HMDB04953*	0.30	1.29 (0.79, 2.11)	0.42	1.48 (0.58, 3.79)	0.82	1.08 (0.55, 2.12)
C24:1 Ceramide (d18:1)-B	HMDB04953*	0.45	1.21 (0.74, 1.98)	0.46	0.68 (0.25, 1.88)	0.48	1.27 (0.66, 2.44)
LPC sum	NA	0.93	1.02 (0.63, 1.65)	0.37	0.65 (0.26, 1.65)	1.00	1.00 (0.52, 1.93)
PC sum	NA	0.21	1.40 (0.83, 2.37)	0.64	0.80 (0.31, 2.02)	0.38	1.40 (0.66, 2.98)
LPC:PC	NA	0.30	0.76 (0.45, 1.28)	0.59	0.78 (0.32, 1.91)	0.50	0.78 (0.37, 1.63)
SM sum	NA	0.01	1.97 (1.16, 3.32)	0.35	0.61 (0.22, 1.72)	~~0.00~~	3.22 (1.51, 6.86)
CER sum	NA	0.21	1.37 (0.84, 2.24)	0.99	1.01 (0.38, 2.70)	0.47	1.28 (0.66, 2.51)
SM:CER	NA	0.68	1.11 (0.68, 1.79)	0.42	0.68 (0.26, 1.75)	0.15	1.64 (0.84, 3.22)

HMDB ID: unique metabolite identifier from the Human Metabolome Database; * representative HMDB ID; NA: HMDB ID not available;
LPC: lysophosphatidylcholines; PC: phosphatidylcholines; SM: sphingomyelins.

† P-values were calculated with a two-sided Wald test as part of a logistic regression model of ovarian cancer, with the metabolite as a continuous exposure, adjusted for risk factors (duration of oral contraceptive use [none or <3 months, 3 months to 3 years, 3 years to 5 years, more than 5 years], tubal ligation [yes/no] and parity [no children, 1 child, 2 children, 3 children, 4+ children]).

Supplementary Table 4. Odds ratio (OR) for an increase from the 10th to 90th percentile of metabolite levels and 95% confidence intervals (CI) of ovarian cancer (OC) and by time between blood collection and diagnosis.

Metabolite	HMDB-ID	Overall OC (N=252 cases and N=252 controls)		3-11 years to DX (N=121 cases and N=252 controls)		12-23 years to DX (N=131 cases and 252 controls)	
		P†	OR (95% CI)	P†	OR (95% CI)	P†	OR (95% CI)
C14:0 LPC	HMDB10379	0.51	0.85 (0.54, 1.36)	0.96	0.98 (0.54, 1.79)	0.11	0.63 (0.35, 1.10)
C16:0 LPC	HMDB10382	0.76	1.08 (0.67, 1.75)	0.12	1.63 (0.88, 3.03)	0.06	0.57 (0.32, 1.02)
C16:1 LPC	HMDB10383*	0.61	1.13 (0.71, 1.79)	0.29	1.38 (0.77, 2.49)	0.29	0.74 (0.42, 1.30)
C18:0 LPC	HMDB10384	0.85	0.95 (0.57, 1.58)	0.69	1.14 (0.60, 2.18)	0.27	0.71 (0.39, 1.29)
C18:1 LPC	HMDB02815*	0.65	0.89 (0.55, 1.45)	0.78	1.09 (0.59, 2.03)	0.08	0.58 (0.32, 1.06)
C18:2 LPC	HMDB10386*	0.93	0.98 (0.61, 1.57)	0.80	1.09 (0.57, 2.08)	0.26	0.70 (0.37, 1.30)
C18:3 LPC	HMDB10387*	0.75	1.08 (0.67, 1.75)	0.12	1.63 (0.89, 3.04)	0.06	0.57 (0.31, 1.01)
C20:4 LPC	HMDB10395	0.85	1.05 (0.65, 1.70)	0.71	1.12 (0.62, 2.03)	0.36	0.77 (0.43, 1.36)
C20:5 LPC	HMDB10397	0.85	1.05 (0.65, 1.67)	0.84	1.07 (0.56, 2.03)	0.43	0.78 (0.42, 1.44)
C22:5 LPC	HMDB10403*	0.27	1.30 (0.82, 2.08)	0.76	1.10 (0.60, 2.02)	0.61	1.16 (0.66, 2.03)
C22:6 LPC	HMDB10404	0.43	1.23 (0.73, 2.07)	0.82	1.07 (0.58, 2.00)	0.92	1.03 (0.58, 1.85)
C30:0 PC	HMDB07869*	0.98	1.01 (0.63, 1.62)	0.38	1.29 (0.73, 2.31)	0.31	0.74 (0.41, 1.32)
C30:1 PC	HMDB07870*	0.78	0.93 (0.58, 1.50)	0.62	1.16 (0.65, 2.06)	0.28	0.73 (0.41, 1.29)
C32:0 PC	HMDB07871*	0.67	1.11 (0.68, 1.83)	0.09	1.70 (0.92, 3.19)	0.13	0.63 (0.34, 1.15)
C32:1 PC	HMDB07873*	0.28	1.31 (0.80, 2.13)	0.07	1.77 (0.97, 3.27)	0.66	0.88 (0.48, 1.58)
C32:2 PC	HMDB07874*	0.59	1.14 (0.71, 1.84)	0.36	1.32 (0.73, 2.38)	0.74	0.91 (0.51, 1.61)
C34:1 PC	HMDB07972*	0.27	1.32 (0.81, 2.13)	0.03	1.94 (1.05, 3.60)	0.33	0.74 (0.40, 1.34)
C34:2 PC	HMDB07973*	0.02	1.82 (1.08, 3.06)	0.01	2.24 (1.20, 4.26)	0.56	1.18 (0.67, 2.10)
C34:4 PC	HMDB07883*	0.84	0.95 (0.59, 1.54)	0.99	1.01 (0.55, 1.83)	0.65	0.87 (0.49, 1.56)
C36:1 PC	HMDB08038*	0.83	1.05 (0.67, 1.66)	0.25	1.42 (0.78, 2.58)	0.23	0.69 (0.38, 1.25)
C38:3 PC	HMDB08047*	0.05	1.67 (1.01, 2.76)	0.07	1.73 (0.96, 3.16)	0.35	1.32 (0.74, 2.38)
C38:6 PC	HMDB07991*	0.39	1.27 (0.73, 2.21)	0.29	1.41 (0.75, 2.69)	0.79	0.92 (0.51, 1.67)
C40:10 PC	HMDB08511*	0.31	1.31 (0.78, 2.20)	0.33	1.36 (0.73, 2.54)	0.87	0.95 (0.53, 1.71)
C40:6 PC	HMDB08057*	0.31	1.32 (0.77, 2.24)	0.36	1.34 (0.72, 2.51)	0.78	1.09 (0.60, 1.98)
C40:9 PC	HMDB08731*	0.53	1.19 (0.69, 2.06)	0.47	1.26 (0.67, 2.40)	0.77	0.91 (0.50, 1.66)
C36:2 PC-A	HMDB08039*	0.97	0.99 (0.61, 1.61)	0.75	1.11 (0.59, 2.10)	0.99	1.00 (0.55, 1.85)
C36:2 PC-B	HMDB08039*	0.38	1.23 (0.77, 1.96)	0.45	1.26 (0.69, 2.30)	0.95	1.02 (0.57, 1.84)
C36:4 PC-B	HMDB08138*	0.20	1.43 (0.83, 2.46)	0.11	1.67 (0.89, 3.14)	0.69	0.88 (0.47, 1.64)
C14:0 SM	HMDB12097	0.05	1.65 (1.00, 2.72)	0.19	1.51 (0.82, 2.81)	0.14	1.58 (0.86, 2.93)
C16:0 SM	HMDB10169	0.01	2.06 (1.19, 3.56)	0.05	1.87 (1.01, 3.50)	0.08	1.75 (0.95, 3.27)
C16:1 SM	NA	0.17	1.44 (0.86, 2.41)	0.10	1.69 (0.90, 3.20)	0.82	1.07 (0.58, 1.98)

C18:0 SM	HMDB01348	0.00	2.10 (1.26, 3.49)	0.02	2.07 (1.13, 3.85)	0.04	1.84 (1.05, 3.28)
C20:0 SM	HMDB12102	0.06	1.60 (0.97, 2.63)	0.77	1.09 (0.60, 2.00)	0.01	2.18 (1.22, 3.94)
C22:1 SM	HMDB12104*	0.06	1.65 (0.98, 2.77)	0.15	1.60 (0.85, 3.02)	0.15	1.57 (0.85, 2.92)
C16:0 Ceramide (d18:1)	HMDB04949	0.01	1.95 (1.16, 3.30)	0.04	1.96 (1.06, 3.67)	0.15	1.54 (0.86, 2.78)
C22:0 Ceramide (d18:1)	HMDB04952	0.44	1.21 (0.74, 1.97)	0.63	1.16 (0.63, 2.16)	0.50	1.22 (0.69, 2.18)
C24:0 Ceramide (d18:1)	HMDB04956	0.24	1.35 (0.82, 2.21)	0.45	1.27 (0.68, 2.38)	0.25	1.42 (0.78, 2.59)
C24:1 Ceramide (d18:1)	HMDB04953*	0.30	1.29 (0.79, 2.11)	0.61	1.17 (0.65, 2.12)	0.28	1.38 (0.78, 2.45)
C24:1 Ceramide (d18:1)-B	HMDB04953*	0.45	1.21 (0.74, 1.98)	0.86	1.06 (0.57, 1.98)	0.40	1.29 (0.71, 2.35)
LPC sum	NA	0.93	1.02 (0.63, 1.65)	0.30	1.39 (0.75, 2.61)	0.08	0.59 (0.32, 1.06)
PC sum	NA	0.21	1.40 (0.83, 2.37)	0.04	1.91 (1.02, 3.60)	0.47	0.80 (0.43, 1.47)
LPC:PC	NA	0.30	0.76 (0.45, 1.28)	0.45	0.77 (0.39, 1.51)	0.27	0.70 (0.37, 1.32)
SM sum	NA	0.01	1.97 (1.16, 3.32)	0.04	1.95 (1.04, 3.71)	0.07	1.77 (0.96, 3.31)
CER sum	NA	0.21	1.37 (0.84, 2.24)	0.46	1.26 (0.68, 2.33)	0.20	1.47 (0.81, 2.67)
SM:CER	NA	0.68	1.11 (0.68, 1.79)	0.52	1.22 (0.67, 2.23)	0.88	0.96 (0.55, 1.69)

HMDB ID: unique metabolite identifier from the Human Metabolome Database; * representative HMDB ID; NA: HMDB ID not available;
LPC: lysophosphatidylcholines; PC: phosphatidylcholines; SM: sphingomyelins.

† P-values were calculated with a two-sided Wald test as part of a logistic regression model of ovarian cancer, with the metabolite as a continuous exposure, adjusted for risk factors (duration of oral contraceptive use [none or <3 months, 3 months to 3 years, 3 years to 5 years, more than 5 years], tubal ligation [yes/no] and parity [no children, 1 child, 2 children, 3 children, 4+ children]) and additionally for matching factors in stratified analyses (cohort [NHS, NHSII]; menopausal status and hormone therapy use at blood draw [premenopausal, postmenopausal and hormone therapy use, postmenopausal and no hormone therapy use, missing/unknown]; menopausal status at diagnosis [premenopausal, postmenopausal, or unknown]; age [±1 year], date of blood collection [± 1 month]; time of day of blood draw [±2 hours]; fasting status [>8 hours or ≤8 hours]).

Supplementary Table 5. Odds ratio (OR) for an increase from the 10th to 90th percentile of metabolite levels and 95% confidence intervals (CI) of ovarian cancer (OC) overall, for rapidly fatal and less aggressive tumors.

Metabolite	HMDB_ID	Overall OC (N=252 cases and N=252 controls)		Rapidly fatal (N=86 cases and 252 controls)		Not-rapidly fatal (N=138 cases and 252 controls)	
		P†	OR (95% CI)	P†	OR (95% CI)	P†	OR (95% CI)
C14:0 LPC	HMDB10379	0.51	0.85 (0.54, 1.36)	0.36	0.80 (0.50, 1.28)	0.14	0.65 (0.37, 1.15)
C16:0 LPC	HMDB10382	0.76	1.08 (0.67, 1.75)	0.92	1.02 (0.64, 1.65)	0.35	0.75 (0.41, 1.36)
C16:1 LPC	HMDB10383*	0.61	1.13 (0.71, 1.79)	0.82	1.06 (0.66, 1.68)	0.38	0.77 (0.43, 1.37)
C18:0 LPC	HMDB10384	0.85	0.95 (0.57, 1.58)	0.83	0.95 (0.57, 1.56)	0.46	0.79 (0.42, 1.47)
C18:1 LPC	HMDB02815*	0.65	0.89 (0.55, 1.45)	0.51	0.85 (0.52, 1.38)	0.32	0.73 (0.40, 1.34)
C18:2 LPC	HMDB10386*	0.93	0.98 (0.61, 1.57)	0.65	0.89 (0.54, 1.47)	0.67	0.87 (0.47, 1.62)
C18:3 LPC	HMDB10387*	0.75	1.08 (0.67, 1.75)	0.92	1.02 (0.64, 1.65)	0.33	0.74 (0.40, 1.35)
C20:4 LPC	HMDB10395	0.85	1.05 (0.65, 1.70)	0.95	0.98 (0.61, 1.58)	0.42	0.79 (0.44, 1.40)
C20:5 LPC	HMDB10397	0.85	1.05 (0.65, 1.67)	0.83	0.95 (0.57, 1.56)	0.70	0.89 (0.48, 1.62)
C22:5 LPC	HMDB10403*	0.27	1.30 (0.82, 2.08)	0.59	1.14 (0.71, 1.83)	0.88	1.05 (0.59, 1.87)
C22:6 LPC	HMDB10404	0.43	1.23 (0.73, 2.07)	0.76	1.08 (0.67, 1.74)	0.98	1.01 (0.56, 1.81)
C30:0 PC	HMDB07869*	0.98	1.01 (0.63, 1.62)	0.85	0.96 (0.60, 1.53)	0.55	0.84 (0.48, 1.48)
C30:1 PC	HMDB07870*	0.78	0.93 (0.58, 1.50)	0.62	0.89 (0.56, 1.42)	0.34	0.76 (0.43, 1.33)
C32:0 PC	HMDB07871*	0.67	1.11 (0.68, 1.83)	0.99	1.00 (0.62, 1.63)	0.61	0.86 (0.47, 1.54)
C32:1 PC	HMDB07873*	0.28	1.31 (0.80, 2.13)	0.44	1.21 (0.75, 1.95)	0.96	0.99 (0.55, 1.76)
C32:2 PC	HMDB07874*	0.59	1.14 (0.71, 1.84)	0.71	1.09 (0.69, 1.75)	0.89	0.96 (0.54, 1.70)
C34:1 PC	HMDB07972*	0.27	1.32 (0.81, 2.13)	0.51	1.18 (0.73, 1.90)	0.92	0.97 (0.54, 1.74)
C34:2 PC	HMDB07973*	0.02	1.82 (1.08, 3.06)	0.07	1.56 (0.97, 2.54)	0.07	1.72 (0.96, 3.12)
C34:4 PC	HMDB07883*	0.84	0.95 (0.59, 1.54)	0.77	0.93 (0.58, 1.50)	0.30	0.74 (0.41, 1.31)
C36:1 PC	HMDB08038*	0.83	1.05 (0.67, 1.66)	0.91	0.97 (0.61, 1.55)	0.70	0.89 (0.50, 1.59)
C38:3 PC	HMDB08047*	0.05	1.67 (1.01, 2.76)	0.08	1.54 (0.96, 2.48)	0.33	1.33 (0.75, 2.38)
C38:6 PC	HMDB07991*	0.39	1.27 (0.73, 2.21)	0.58	1.15 (0.70, 1.90)	0.89	1.04 (0.57, 1.92)
C40:10 PC	HMDB08511*	0.31	1.31 (0.78, 2.20)	0.52	1.17 (0.72, 1.92)	0.99	0.99 (0.55, 1.82)
C40:6 PC	HMDB08057*	0.31	1.32 (0.77, 2.24)	0.45	1.21 (0.74, 1.99)	0.71	1.12 (0.62, 2.06)
C40:9 PC	HMDB08731*	0.53	1.19 (0.69, 2.06)	0.73	1.09 (0.66, 1.80)	0.93	0.97 (0.53, 1.79)
C36:2 PC-A	HMDB08039*	0.97	0.99 (0.61, 1.61)	0.95	1.02 (0.62, 1.65)	0.56	1.19 (0.66, 2.13)
C36:2 PC-B	HMDB08039*	0.38	1.23 (0.77, 1.96)	0.61	1.13 (0.71, 1.81)	0.30	1.36 (0.76, 2.45)
C36:4 PC-B	HMDB08138*	0.20	1.43 (0.83, 2.46)	0.37	1.26 (0.76, 2.10)	0.87	1.05 (0.58, 1.92)
C14:0 SM	HMDB12097	0.05	1.65 (1.00, 2.72)	0.08	1.56 (0.95, 2.58)	0.17	1.52 (0.84, 2.78)
C16:0 SM	HMDB10169	0.01	2.06 (1.19, 3.56)	0.03	1.74 (1.06, 2.90)	0.02	2.06 (1.14, 3.79)
C16:1 SM	NA	0.17	1.44 (0.86, 2.41)	0.24	1.35 (0.82, 2.23)	0.48	1.25 (0.68, 2.29)

C18:0 SM	HMDB01348	0.00	2.10 (1.26, 3.49)	0.01	1.91 (1.19, 3.09)	0.01	2.10 (1.20, 3.75)
C20:0 SM	HMDB12102	0.06	1.60 (0.97, 2.63)	0.06	1.57 (0.98, 2.53)	0.13	1.54 (0.88, 2.73)
C22:1 SM	HMDB12104*	0.06	1.65 (0.98, 2.77)	0.07	1.59 (0.97, 2.63)	0.29	1.39 (0.76, 2.57)
C16:0 Ceramide (d18:1)	HMDB04949	0.01	1.95 (1.16, 3.30)	0.02	1.77 (1.09, 2.91)	0.13	1.58 (0.88, 2.87)
C22:0 Ceramide (d18:1)	HMDB04952	0.44	1.21 (0.74, 1.97)	0.36	1.26 (0.78, 2.04)	0.60	1.17 (0.66, 2.09)
C24:0 Ceramide (d18:1)	HMDB04956	0.24	1.35 (0.82, 2.21)	0.18	1.40 (0.86, 2.31)	0.27	1.40 (0.77, 2.58)
C24:1 Ceramide (d18:1)	HMDB04953*	0.30	1.29 (0.79, 2.11)	0.31	1.28 (0.80, 2.06)	0.52	1.21 (0.68, 2.15)
C24:1 Ceramide (d18:1)-B	HMDB04953*	0.45	1.21 (0.74, 1.98)	0.45	1.21 (0.74, 1.99)	0.43	1.27 (0.70, 2.33)
LPC sum	NA	0.93	1.02 (0.63, 1.65)	0.86	0.96 (0.59, 1.56)	0.33	0.74 (0.40, 1.36)
PC sum	NA	0.21	1.40 (0.83, 2.37)	0.40	1.24 (0.75, 2.05)	0.98	1.01 (0.55, 1.85)
LPC:PC	NA	0.30	0.76 (0.45, 1.28)	0.33	0.77 (0.46, 1.30)	0.27	0.70 (0.37, 1.32)
SM sum	NA	0.01	1.97 (1.16, 3.32)	0.02	1.83 (1.10, 3.05)	0.04	1.88 (1.03, 3.48)
CER sum	NA	0.21	1.37 (0.84, 2.24)	0.17	1.42 (0.87, 2.33)	0.28	1.39 (0.77, 2.53)
SM:CER	NA	0.68	1.11 (0.68, 1.79)	0.91	1.03 (0.64, 1.64)	0.76	1.09 (0.62, 1.93)

HMDB ID: unique metabolite identifier from the Human Metabolome Database; * representative HMDB ID; NA: HMDB ID not available;
LPC: lysophosphatidylcholines; PC: phosphatidylcholines; SM: sphingomyelins.

† P-values were calculated with a two-sided Wald test as part of a logistic regression model of ovarian cancer, with the metabolite as a continuous exposure, adjusted for risk factors (duration of oral contraceptive use [none or <3 months, 3 months to 3 years, 3 years to 5 years, more than 5 years], tubal ligation [yes/no] and parity [no children, 1 child, 2 children, 3 children, 4+ children]) and additionally for matching factors in stratified analyses (cohort [NHS, NHSII]; menopausal status and hormone therapy use at blood draw [premenopausal, postmenopausal and hormone therapy use, postmenopausal and no hormone therapy use, missing/unknown]; menopausal status at diagnosis [premenopausal, postmenopausal, or unknown]; age [±1 year], date of blood collection [± 1 month]; time of day of blood draw [±2 hours]; fasting status [>8 hours or ≤8 hours]).