

1 **Ovarian tumors of different histologic type and clinical stage induce similar changes**
2 **in lipid metabolism**

3 Running title: Various ovarian tumors affect blood lipidome

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20

21 **Abstract**

22

23 **Background:** Previous results obtained from serum samples of late-stage, high-grade serous ovarian
24 carcinoma patients showed large alterations in lipid metabolism. To validate and extend the results,
25 we studied lipidomic changes in early-stage ovarian tumors. In addition to serous ovarian cancer, we
26 investigated whether these changes occur in mucinous and endometrioid histological subtypes as
27 well.

28 **Methods:** Altogether, 354 serum or plasma samples were collected from three centers, one from
29 Germany and two from Finland. We performed lipidomic analysis of samples from patients with
30 malignant (N=138) or borderline (N=25) ovarian tumors, and 191 controls with benign pathology.
31 These results were compared to previously published data.

32 **Results:** We found 39 lipids that showed consistent alteration both in early- and late-stage ovarian
33 cancer patients as well as in pre- and postmenopausal women. Most of these changes were already
34 significant at an early stage and progressed with increasing stage. Furthermore, 23 lipids showed
35 similar alterations in all investigated histological subtypes.

36 **Conclusion:** Changes in lipid metabolism due to ovarian cancer occur in early-stage disease but
37 intensify with increasing stage. These changes occur also in other histological subtypes besides high
38 grade serous carcinoma. Understanding lipid metabolism in ovarian cancer may lead to new
39 therapeutic and diagnostic alternatives.

40

41 **Key words:** ovarian cancer; lipid; lipidomic; diagnostic; early-stage; histology; biomarker

42

43

44 **Background**

45 Prognosis of ovarian cancer improves remarkably if the disease is diagnosed at an early-stage, as
46 early detection affords better opportunities for curative treatment. Current diagnostic methods
47 primarily include vaginal ultrasound combined with the blood test to measure cancer antigen 125 (CA
48 125) levels. These methods lack specificity and sensitivity, especially in non-advanced ovarian
49 cancer.¹ Therefore, there is a demand for new detection methods and biomarkers for distinguishing
50 benign and borderline ovarian tumors, as well as early-stage and advanced ovarian cancer.

51

52 Malignant tumors, including ovarian cancer, adopt many metabolic abnormalities to meet the
53 increased energy demand associated with increased cellular proliferation and tumor growth.² In
54 ovarian cancer, the metabolic alterations in tissues and body fluids have been investigated by
55 metabolic profiling to identify biomarkers for early detection and reliable prognosis.³⁻⁵ Recently,
56 using liquid chromatography-mass spectrometry (LC-MS), Gaul et al. found from serum 16
57 diagnostic metabolites, including many lipids and fatty acids, that distinguish early-stage ovarian
58 cancer samples from healthy control samples.⁶ In a lipidomic study, Buas et al. showed 34
59 significantly altered metabolites between serous ovarian carcinoma and benign serous ovarian tumor
60 patients, and the plasma levels of the lipids were reduced in patients with a malignant disease.⁷
61 Recently, our metabolomic analyses of tumor and blood samples from high-grade serous ovarian
62 carcinoma (HGSOC) patients showed elevated concentrations of hydroxybutyric acids, implicating
63 that these molecules could act as diagnostic and prognostic biomarkers.⁸ Subsequently, lipidomic
64 profiling of the same samples showed an overall reduction in the levels of most of the lipid species
65 but elevations in specific ceramide (Cer) and triacylglycerol (TAG) lipids in metastatic ovarian cancer
66 patients.⁹

67

68 Despite several studies showing lipidomic alterations in ovarian cancer, we are not aware of any
69 studies that confirm which lipid species are the most consistently altered. To this end, as well as to
70 validate our published lipidomic results and extend the analyses to low malignant potential
71 (borderline) ovarian tumors and early-stage ovarian cancers, we applied the same previously used
72 methodology⁹ to analyze blood samples from patients with early-stage ovarian cancers. These results
73 were subsequently compared to the results obtained from patients with benign gynecological disease.
74 Our further aim was to investigate whether the lipidomic alterations found in patients with HGSOC
75 can be applied to other histological subtypes, i.e., to mucinous and endometrioid ovarian carcinoma.

76 **Materials and methods**

77 *Patients and samples*

78 We performed lipidomic profiling on two study cohorts, one from Charité (N=189) and another from
79 Finland (N=165, from Tampere (N=111) and Oulu (N=54) University Hospitals). In addition, we
80 used data from an independent, previously published study⁹, referred herein as the Charité discovery
81 (N=250). The Charité discovery study included 5 additional samples from patients with endometrioid
82 tumors that were excluded from the original publication.⁹ Clinical characteristics of these three study
83 cohorts are shown in **Table 1**. The samples from both Charité studies were serum samples, while the
84 Finnish samples were a mixture of serum and plasma, as shown in **Table 1**. All samples were
85 collected preoperatively. In total, in these three studies, 290 samples were collected from patients
86 with malignant ovarian tumors, 25 samples from subjects with borderline ovarian tumors, and 289
87 from women with benign gynecological tumors, endometriosis, infection, or other conditions. The
88 diagnosis of invasive and borderline ovarian tumors was based on the WHO Classification.¹⁰ The
89 gynaecologists at the respective hospitals (University Hospitals of Oulu and Tampere, Finland,
90 and Charité, Berlin, Germany) did the histological analyses, and immunohistochemistry was used
91 when needed. The Charité samples were collected at the Tumor Bank - Ovarian Cancer Network
92 (www.toc-network.de) at the Charité Medical University (Berlin, Germany) between 07/2013 and
93 09/2016. The Finnish samples, from Tampere University Hospital and Oulu University Hospital,
94 were collected between 2/2011-11/2014 and between 01/2009-12/2015, respectively.

95

96 *Lipidomic analysis of serum samples (LC-MS/MS)*

97 The samples were randomized within each cohort before lipidomic analysis. The lipidomic analysis
98 has been previously described in detail.⁹ Briefly, lipidomic analyses were performed using two
99 platforms, a global screening method and a phosphosphingolipid platform. For the screening method,
100 10 µl of sample was needed for the extraction of the lipids using a modified Folch extraction.¹¹ For

101 the phosphosphingolipid method, 25 µl of sample was needed for the extraction of lipids using protein
102 precipitation in methanol.

103

104 Lipidomic screening and phosphosphingolipid platforms were both analyzed on a hybrid triple
105 quadrupole/linear ion trap mass spectrometer (QTRAP 5500, AB Sciex, Concord, Canada) equipped
106 with ultra-high-performance liquid chromatography (UHPLC) (Nexera-X2, Shimadzu, Kyoto,
107 Japan). Chromatographic separation of the lipidomic screening platform was performed on an
108 Acquity BEH C18, 2.1 × 50 mm id. 1.7 µm column (Waters Corporation, Milford, MA, USA).
109 Chromatographic separation of the phosphosphingolipid platform was performed on an AQUASIL
110 C18, 2.1 × 50 mm, 5 µm (Thermo Fisher Scientific, Waltham, MA, USA) column set at 60 °C. For
111 the MS analysis, a targeted approach in the positive ion mode was used for both platforms. The data
112 were collected using a scheduled multiple reaction monitoring (sMRM™) algorithm for the
113 lipidomics screening platform¹² and multiple reaction monitoring (MRM) for phosphosphingolipids.
114 The lipidomic data were processed using Analyst and MultiQuant 3.0 software (AB Sciex), and the
115 area or height ratios of the analyte and its corresponding IS peak were normalized with the IS amount
116 and the sample volume. The details of the chromatography and mass spectrometry conditions have
117 been previously described.⁹

118

119 The number of lipids and the mean coefficient of variation for each lipid class, determined from the
120 quality control samples (6 in each 96-well plate), are shown in **Supplementary Table S1**. The list of
121 all analyzed lipids has been published previously.⁹

122

123 *Statistical analyses*

124 Group comparisons (patients vs. controls) were performed by calculating the mean relative difference
125 between the groups, and the p-values were determined by parametric t-tests on log-transformed
126 concentrations. R version 3.4.2 was used for all statistical analyses. Tableau 10.1 was used for

127 heatmap visualizations. For diagnostic calculations, logistic regression models were developed using
128 all samples in the Charité cohort and tested in the Finnish cohort. The AUC values were determined
129 using the *pROC* package.¹³ The top models presented in the article were selected by calculating the
130 sum of the AUC values in both cohorts, and selecting the models with the highest values.
131

132 **Results**

133 *Validation of altered lipidomic profile in ovarian cancer patients*

134 To validate the lipidomic alterations detected in ovarian cancer patients, we determined which lipids
135 were similarly altered between the patients and the controls in the two study cohorts (Charité and
136 Finland), in addition to the previously published Charité discovery cohort (**Table 1**), provided that
137 the change between the patients and the controls was significant in at least two cohorts. The results
138 confirmed that ovarian cancer causes wide lipidomic changes as 155 lipids showed the same direction
139 of change in all cohorts, and most of these changes were also statistically significant in all three
140 independent cohorts (**Supplementary Table S2**). All further analyses were limited to these 155
141 lipids.

142

143 *Lipidomic changes emerge in early-stage ovarian cancer patients*

144 To identify which lipids have the best diagnostic potential, or those already altered in early-stage
145 (I/II) cancer, we selected lipids that showed consistent increase or decrease both in stage I/II vs.
146 controls and stage III/IV vs. controls, including all cohorts and histological subtypes. In addition, the
147 lipids had to be significantly altered at least in stage III/IV patients in the Charité and Finnish cohorts.
148 This approach resulted in 39 lipids which are shown in a heatmap in **Figure 1**. Samples from patients
149 with ovarian cancer revealed a consistent decrease in the concentration of most of the analyzed lipid
150 classes and included phospholipids (phosphatidylcholines (PCs), lysophosphatidylcholines (LPCs)
151 and phosphatidylinositols (PIs)), cholesteryl esters (CEs), glucosyl/galactosyl ceramides
152 (Glc/GalCers) and sphingomyelins (SMs). In turn, an increase was observed in many ceramides
153 (Cers) with certain fatty acyl (FA) side chain compositions. Cers with 18:0, 20:0 and 24:1 FAs were
154 increased, while 24:0 FA-containing Cers were decreased. The TAG lipid species also showed a
155 variable trend depending on the FA side chains; TAGs with shorter FA side chains were decreased,
156 whereas those with longer FA side chains were increased. In many lipid species, the alterations were

157 more significant in advanced stage (III/IV) patients but were already present in early-stage patients
158 (I/II) (**Figure 1**). The lipidomic changes were consistent in both pre- and postmenopausal patient
159 populations (**Figure 1**).

160
161 ***Tumors of various histological subtypes induce similar lipid changes***

162 As the previous results were derived from HGSOE patients only⁹, we investigated whether some
163 changes in lipid species are also significant in patients with other histological subtypes (mucinous
164 and endometrioid). Thus, we selected lipids showing the same direction of alteration in all histological
165 subtypes of the Charité and Finnish cohorts. In addition, the selected lipids had to be significant in
166 either mucinous or endometrioid subtypes in either of the cohorts. Twenty-one of 23 lipids were
167 decreased in all histological subtypes (**Figure 2**), and only Cer(d18:1/18:0) and TAG(18:1/18:1/20:4)
168 were increased. The most significant alterations were observed in PCs and LPCs. All lipid changes
169 were significant in the serous subtype, which was expected based on the large number of cases in
170 both cohorts. Interestingly, CA 125 was not significantly altered in mucinous subtype samples, while
171 most lipid changes were significant in the Charité cohort despite a low number of mucinous cases
172 (N=6). For endometrioid histology, none of the lipids were significant in the Charité cohort (N=9),
173 whereas the Finnish cohort, with a slightly greater number of cases (N=14), showed significant
174 alterations.

175
176 ***Fewer lipid changes are seen in borderline tumors than in malignant tumors***

177 We also analyzed whether the observed lipidome alterations are present in borderline ovarian tumors.
178 When only those lipids that were altered in the same direction in both cohorts and significant in at
179 least one of them were selected, there were only a few significant alterations (**Figure 3**). Thus, it
180 appears that borderline tumors do not cause as much of a change to the lipidome as malignant tumors.

181

182 *Lipids improve the diagnostic value of CA125 for the detection of early-stage cancer*

183 Finally, we investigated whether lipids can improve the diagnostic value of CA 125. As lipid ratios
184 have shown diagnostic value in other diseases¹⁴, we investigated combinations of all lipids and lipid
185 ratios together with CA125. The lipids used for this analysis are shown in **Figure 1**. For the ratio
186 calculations, the increased lipids in ovarian cancer patients and CA 125 were used as numerators, and
187 all other lipids were used as denominators. To find more robust biomarkers, those lipids and lipid
188 ratios were excluded that were significantly different (t-test $p < 0.05$ and mean relative change $> 10\%$)
189 between control samples of the Charité and Finland cohorts. The models were generated using all
190 subjects in the Charité cohort, and tested in the stage I/II and III/IV ovarian cancer patients separately,
191 in addition to the validation in the Finnish cohort. As an example, the models with the highest
192 improvement in both the Charité and Finnish cohorts are shown in **Table 2**. In the Charité cohort, CA
193 125 as a continuous variable instead of using the 35 U/mL cut-off improved the AUC values, and
194 further improvement was seen for the detection of early-stage cases with incorporation of lipids, but
195 not for late-stage cases where already CA 125 alone performed well. In the Finnish cohort, which had
196 a higher proportion of other than serous malignant tumors, the AUC values for CA 125 and also the
197 models with lipids were lower than in the Charité, but again the lipids improved the diagnostic value
198 of CA 125 for the detection of stage I/II cancers.

199

200

201 **Discussion**

202 The present global lipidomics study investigating early- and advanced-stage ovarian cancer of various
203 histological subtypes was performed to validate and extend our previous results on lipid changes in
204 HGSOE patients. Altered lipid metabolism seems to be linked to ovarian cancer, but specific findings
205 are still strikingly variable. Our data are in line with those earlier studies showing an overall decrease
206 in the serum/plasma concentration of lipid metabolites⁷ and glycerophospholipids^{15,16} in ovarian
207 cancer patients. The intensification of lipid changes in the advanced stage ovarian cancer patients
208 suggests that the tumors are exploiting circulating lipids and lipoproteins with proportion to their size.
209 The overall decrease of PCs may be associated with reduction of HDL cholesterol and ApoA1 in the
210 ovarian cancer patients^{17,18}, as PCs are known to be abundant especially in the HDL particles.¹⁹
211 However, this phenomenon cannot be used to explain the increase of lipid species in ovarian cancer
212 patients. It has been suggested that changes in lipid metabolism during ovarian cancer pathogenesis
213 reflect higher levels of cell division²⁰, enhanced fatty acid β -oxidation⁵, and increased cellular
214 proliferation or motility due to increased PI3-kinase activity²¹, yet there are likely to be additional
215 mechanisms explaining the alterations of specific lipids.

216

217 These results confirm our previous report describing an increase in the serum concentration of
218 Cer(d18:1/18:0), Cer(d18:0/18:0) and TAG(18:1/18:1/20:4) in ovarian cancer patients.⁹ Moreover,
219 the phenomenon is evident at the early stages of disease development, i.e. stage I/II, but was found
220 to become more pronounced with disease progression. In addition to HGSOE, Cer(d18:1/18:0) and
221 TAG(18:1/18:1/20:4) were also significantly increased in mucinous and endometrioid ovarian cancer
222 samples from the Finnish cohort. However, the number of mucinous and endometrioid carcinoma
223 samples was likely too low in the Charitè cohort to show any significant difference. Interestingly,
224 Cer(d18:1/18:0) and its precursor Cer(d18:0/18:0) have been associated with the development of
225 insulin resistance and type 2 diabetes.²²⁻²⁴ Taken together, these alterations to the lipid profile and

226 other metabolic changes, such as increase of ketone bodies⁸, suggest that the metabolic profile of
227 ovarian cancer patients resemble a diabetic phenotype.

228

229 Sphingolipids, especially Cers, have been linked to the development and progression of cancer²⁵, but
230 results appear vary depending on the type of tumor.²⁶ Cers are considered to have anti-cancer
231 properties, to act as second messengers for cell apoptosis²⁵ and to modulate cell growth.²⁷ Another
232 sphingolipid, sphingosine-1-phosphate (S1P), has opposing cellular effects to Cers.²⁶ The role of
233 sphingolipid metabolism in ovarian cancer has been investigated in a recent study in which 74 women
234 with HGSOC were found to have significantly elevated plasma and tissue concentrations of C16-Cer,
235 C18:1-Cer and C18-Cer compared to those of healthy controls²⁸, which is in line with our results.
236 The researchers speculated that the increased amounts of Cers would be associated with particularly
237 aggressive epithelial ovarian cancer cases and that the increased Cer concentrations would lead to
238 increased conversion to S1P, as they found an elevated S1P concentration in tumor tissue. However,
239 congruent with our data, elevation of S1P could not be observed in blood.

240

241 Buas et al. have shown reduction of all measured TAGs in the plasma of ovarian cancer patients.⁷
242 However, in a lipidomic analysis of low and highly aggressive ovarian cancer cell lines, TAGs
243 increased dramatically along aggressiveness of the cells and were assumed to be the largest source of
244 cellular energy.²⁹ In a mouse model of HGSOC, compared to healthy mice, the serum levels of
245 LPE(16:0) and PIs were decreased, while TAG(55:7) was significantly increased at early-stage cancer
246 development.³⁰ On the other hand, decreased levels of TAGs in epithelial ovarian cancer patients
247 have been shown to predict early recurrence of cancer.³¹ In our study, only the concentrations of
248 TAGs with longer fatty acid chains were increased or not altered, while those TAGs with short fatty
249 acid chains were decreased. Our former study proposed that this result could be explained by genetics

250 via low expression of the *ABCD1* gene⁹ which is associated with transport of long-chain fatty acids
251 into the peroxisome for β -oxidation.³²

252

253 Phospho- and sphingolipids are the most studied lipids in regard to the pathogenesis of ovarian
254 cancer.³³ In 2004, it was shown that plasma levels of lysophospholipids varied between healthy
255 controls and ovarian cancer patients, as well as pre- and postoperatively.³⁴ Moreover, in a pathway
256 analysis, glycerophospholipid (LPCs and PCs) metabolism was a main dysregulated pathway in the
257 pathogenesis of ovarian carcinoma.³⁵ Alteration of LPC levels may be caused by the binding and
258 activation of specific cell surface G protein-coupled receptors (GPCRs), which can activate cell
259 growth and proliferation.³⁶ Altered LPCs and lysophosphatidylethanolamines (LPEs) contribute to
260 genetic instability and cancer initiation via enhanced phospholipase A2 (PLA2) activity³⁷ and
261 inflammation.³ Phospholipids are needed in cancer cells to generate the cellular membrane and
262 maintain membrane integrity.³ A large metabolic profiling study³ of 448 plasma samples from
263 epithelial ovarian cancer patients identified 53 specific metabolites that distinguished early- and late-
264 stage ovarian cancer with an AUC of 0.88. These metabolites included LPCs and LPEs which were
265 elevated in localized ovarian cancer but reduced in metastasized ovarian cancer. A potential
266 explanation for the reduced levels of LPCs and LPEs in advanced cancer could be that rapidly
267 proliferating tumors consume more phospholipids in their attempt to maintain membrane integrity,
268 leading to an exhaustion of substrates.³⁰ Also lysophosphatidic acid (LPA) has been purported to be
269 a possible biomarker because some studies have shown LPA to be elevated in plasma samples of
270 ovarian cancer patients.^{34,38}, but we could not confirm this as we did not monitor LPAs in our
271 lipidomic method.

272

273 Borderline ovarian tumors have low malignant potential and elevated mitotic activity without stromal
274 invasion. They commonly occur in younger women compared to ovarian cancer patients and have

275 lower recurrence rates.³⁹ Denkert et al. found significantly different metabolite levels (including
276 metabolites from glycerolipid metabolism and free fatty acids) in borderline ovarian tumor tissues
277 compared to invasive ovarian carcinomas using gas chromatography/time-of-flight mass
278 spectrometry.²⁰ However, they had only nine borderline tumors in their study. Based on the present
279 study, lipid metabolism in borderline ovarian tumors differs from that in invasive cancers. The Charité
280 cohort had more borderline ovarian tumors (N=18) than the Finnish cohort. These samples were
281 mainly serous epithelial tumors. Significant differences were observed only for occasional
282 plasmalogens as compared to benign controls.

283

284 In the Charité cohort, the results were evaluated by menopausal status. Greater alterations in Cer
285 d16:1, d18:0 and d18:1 were observed in postmenopausal women. However, in some PC lipids,
286 premenopausal changes were stronger. A serum lipidomics study of ovariectomized healthy rats
287 showed that Cers and phospholipids increased in response to estrogen deficiency while TAGs
288 decreased, which was contrary to earlier studies.⁴⁰ Our study lacks data on possible hormone
289 replacement or hormone therapy in the Charité premenopausal group. The samples from the Finnish
290 cohort were postmenopausal with no current hormone therapy.

291

292 Our study had some limitations. First, changes in lipoprotein levels can at least partly explain the
293 overall decrease of lipids among cancer patients, but unfortunately, we did not have lipoprotein levels
294 available from the patients. Neither did we have the information on BMI, which may also affect lipid
295 levels. Second, in the Finnish cohort, the sample sets contained both serum and plasma samples,
296 which may affect the lipid levels. However, it is worth noting that the lipid changes were consistent
297 with the two other data sets, and thus, it can be assumed that the difference does not significantly
298 affect the results. Moreover, the logistic regression models developed in the Charité cohort showed
299 high AUC values in the Finnish cohort, which also supports the validity of the results. Third, there

300 was an age imbalance in the cohorts, as the Charité cohort patients were older than the controls.
301 However, the results were consistent with the Finnish cohort, where the controls were older than the
302 patients. This finding and our previous age-adjusted lipidomic analyses⁹ suggest that age does not
303 explain the differences in lipid metabolism observed in ovarian cancer patients. Fourth, the blood
304 samples were not collected during a fasting condition, which may affect the results. However, it is
305 worth noting that there were no differences between groups and that it is expected that fasting samples
306 might have given a better separation between the ovarian cancer patients and the subjects with benign
307 disease.

308

309 We have shown that blood lipidomic changes occur in several patient cohorts and already at the early-
310 stage ovarian cancer, but intensify with the progression of the disease. Many of the lipid changes are
311 similar in patients with serous, mucinous and endometrioid ovarian carcinoma, suggesting that
312 rewiring of lipid metabolism is an integral part of ovarian carcinogenesis. The results provide an
313 excellent basis for further development of diagnostics and the future investigations should also
314 explore the potential of exploiting the altered ovarian cancer lipid metabolism for therapeutic
315 purposes.

316

317 **Additional information**

318 **Ethics approval and consent to participate**

319 All patients gave their informed consent to the study, and the investigation was approved by the local
320 Ethical Committees of Charité, Oulu and Tampere University Hospitals. The study was performed in
321 accordance with the Declaration of Helsinki.

322 **Availability of data and materials' statement**

323 The datasets generated during and/or analysed during the current study are available for non-
324 commercial use from the corresponding author on reasonable request.

325 **Conflict of interest**

326 MH and KMK are employed by Zora Biosciences Oy, which holds patent disclosures for diagnostic
327 tests of ovarian cancer using small molecules, including lipids. JUM reports grants and personal fees
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332 **Authorship**

333 JUM, EIB, UP, JS, RJN and HK conducted patient enrollment and clinical work. KMK performed
334 lipidomic mass spectrometry experiments, and MH statistical analyses. RJN, MH and JUM wrote the
335 manuscript. All authors have revised and approved the manuscript.

336

337 Supplementary information is available at the British Journal of Cancer's website.

338

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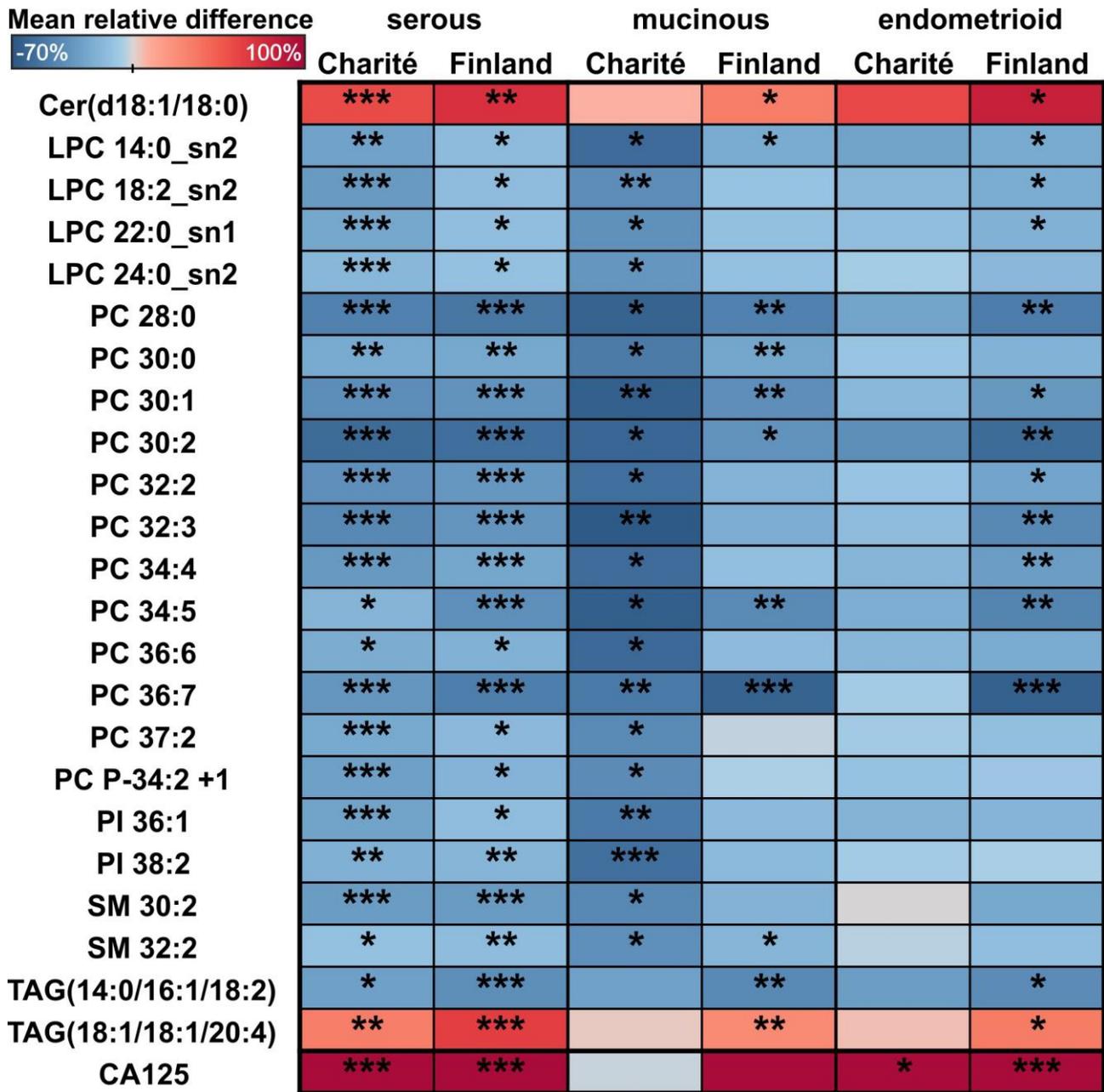
437 **Figure 1.** Heatmap showing lipidomic changes in early- (I/II) and late-stage (III/IV) ovarian cancer
438 patients. In addition, the results are shown in pre- and postmenopausal patients of all stages. The
439 difference is calculated relative to controls. The color scale (from -70% to 100%) is adjusted
440 according to the lipids, in cancer patients CA 125 showed mean elevation higher than 100%. ***,
441 $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$. Charité study had 60 premenopausal controls and 17 cancer cases as
442 well as 48 postmenopausal controls and 42 cancer cases.

Mean relative difference



	Charité		Finland		Charité: menopause	
	I&II	III&IV	I&II	III&IV	pre	post
CE 14:0		*	**	***		
CE 16:2		*	*	***		*
Cer(d16:1/24:0)		*	***	***	*	*
Cer(d18:0/18:0)		**		**		**
Cer(d18:0/20:0)		*	**	***		
Cer(d18:1/18:0)		***	*	***	*	***
Cer(d18:1/24:1)		***		*		
Cer(d18:2/24:0)		*	**	*		
Cer(d20:1/24:1)		***		*	*	*
Glc/GalCer(d16:1/24:0)	**	**		*	*	***
Glc/GalCer(d18:1/26:0)		*	**	*		**
LPC 14:0_sn2	**	**	***	*	**	**
LPC 18:2_sn2	**	***	**	*	**	***
PC 28:0	*	***	***	***	***	**
PC 30:0	*	***	***	***	**	*
PC 30:1	*	***	***	***	**	**
PC 30:2	**	***	***	***	***	***
PC 32:2	*	***	***	***	***	**
PC 32:3	*	***	***	***	***	**
PC 33:3		**	**	**	*	
PC 34:3a		***		*	*	**
PC 34:3b		**	*	**		
PC 34:3c		***	*	*	*	**
PC 34:4	*	***	**	***	***	*
PC 34:5		**	***	***	*	
PC 36:6		***	*	**	**	
PC 36:7	*	***	***	***		**
PC 37:2	**	***		*	***	**
PC O-34:2	*	***		**	*	***
PC P-34:2 +1	***	***		*	***	***
PE O-34:1	*	***		**		***
PI 36:1	***	**	**	*	*	***
PI 38:2	**	**	**	*	*	**
SM 30:2		***	**	**	*	***
SM 37:2	**	***		*	**	**
TAG(14:0/16:1/18:2)		**	***	*	***	
TAG(16:1/16:1/16:1)		*	**	*		
TAG(18:1/18:1/20:4)		***	***	***	*	*
TAG(18:1/18:1/22:6)		***	*	*	*	
CA125	***	***	***	**	**	***

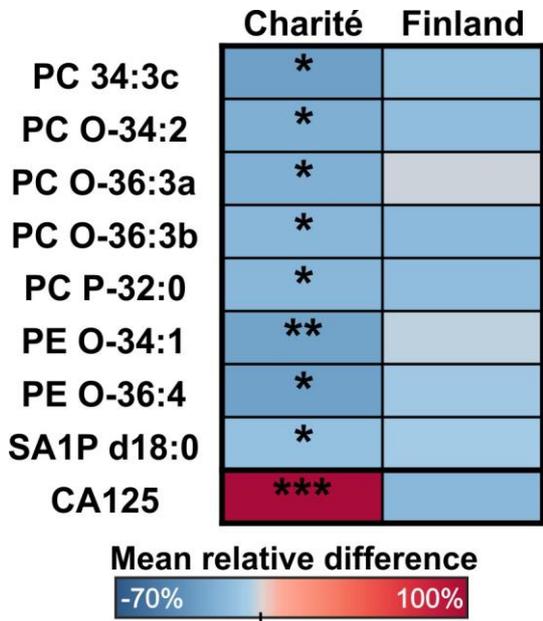
444 **Figure 2.** Heatmap showing lipidomic changes in ovarian cancer patients with different histological
 445 subtypes as compared to control subjects. The color scale (from -70% to 100%) is adjusted according
 446 to the lipids, in some of the analyses CA 125 showed elevation higher than 100%. ***, p<0.001; **,
 447 p<0.01; *, p<0.05.



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450 **Figure 3.** Heatmap showing lipidomic changes in patients with borderline tumors as compared to
 451 control subjects. The color scale is adjusted according to the lipids (from -70% to 100%), CA 125
 452 showed elevation higher than 100% in the Charité cohort. ***, p<0.001; **, p<0.01; *, p<0.05.



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456 **Table 1.** Clinical characteristics of the study cohorts. For age, the values represent median and interquartile
 457 range and p-values in the comparison against the control group are denoted as follows: ***, p<0.001; **,
 458 p<0.01; *, p<0.05; N.S., not significant.

		Charité	Finland	Charité discovery	
Malignant		62	76	152	
Age		57 (50-72)***	58 (51-64)*	59 (50-67)***	
Histology	serous	41	29	147	
	mucinous	6	18		
	endometrioid	9	14	5	
	other	6	15		
Stage	I&II	26	52	8	
	III&IV	33	22	133	
	NA	3	2	11	
Sample	serum	62	22	152	
	plasma		54		
Borderline		18	7		
Age		51 (44-57) N.S.	63 (56-67) N.S.		
Histology	serous	13	5		
	mucinous	2	2		
	other	3			
Stage	I&II	12	7		
	III&IV	3			
	NA	3			
Sample	serum	18	7		
Benign		109	82	98	
Age		49 (40-58)	62 (56-69)	41 (31-55)	
Diagnosis	other	7	2	43	
	uterine fibroid	7	1	25	
	cyst	4	9	1	
	cystic teratoma	12	8	5	
	functional cyst	22			
	inclusion cyst	3			
	endometrioid cyst	5			
	non-ovarian cyst		4		
	cystadenoma	32	2	4	
	mucinous cystadenoma		3	2	
	cystadenofibroma	7	10	2	
	serous cystadenoma		34	3	
	Brenner tumor	1	2	1	
	fibroma/thecoma		5		
	fibroadenoma		1		
	incomplete abortion			5	
	adnexitis			5	
	endometriosis	9	1	2	
	Sample	serum	109	82	98

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Table 2. AUC values with 95% confidence intervals for the logistic regression models. As comparison, the models are shown also for CA 125 alone or CA 125 as binary variable dichotomized by the clinically used 35 U/mL cut off value.

Variable1	Variable 2	Charité			Finland		
		All	Stage I/II	Stage III/IV	All	Stage I/II	Stage III/IV
CA125 / Glc/GalCer(d18:1/26:0)	Cer(d18:1/24:1) / LPC 14:0_sn2	0.93 (0.89-0.96)	0.87 (0.80-0.94)	0.98 (0.96-1.00)	0.76 (0.68-0.85)	0.74 (0.64-0.83)	0.93 (0.84-1.00)
Cer(d18:1/24:1) / LPC 14:0_sn2	CA125 / PC 37:2	0.93 (0.89-0.96)	0.87 (0.81-0.94)	0.98 (0.95-1.00)	0.76 (0.68-0.85)	0.73 (0.64-0.83)	0.95 (0.89-1.00)
Cer(d20:1/24:1) / LPC 14:0_sn2	CA125 / PC 37:2	0.92 (0.87-0.96)	0.85 (0.77-0.93)	0.98 (0.95-1.00)	0.77 (0.68-0.85)	0.74 (0.64-0.83)	0.95 (0.90-1.00)
Cer(d18:1/24:1) / LPC 14:0_sn2	CA125 / PI 38:2	0.92 (0.89-0.96)	0.87 (0.81-0.94)	0.97 (0.94-1.00)	0.77 (0.69-0.85)	0.75 (0.66-0.84)	0.95 (0.88-1.00)
CA125	TAG(18:1/18:1/22:6) / LPC 14:0_sn2	0.91 (0.86-0.96)	0.83 (0.73-0.92)	0.98 (0.96-1.00)	0.78 (0.70-0.86)	0.75 (0.66-0.84)	0.89 (0.77-1.00)
TAG(18:1/18:1/22:6) / LPC 14:0_sn2	CA125 / PC 37:2	0.91 (0.86-0.96)	0.83 (0.74-0.91)	0.98 (0.96-1.00)	0.78 (0.70-0.86)	0.75 (0.66-0.84)	0.88 (0.73-1.00)
TAG(18:1/18:1/22:6) / LPC 14:0_sn2	CA125 / PC P-34:2 +1	0.91 (0.86-0.96)	0.83 (0.75-0.92)	0.98 (0.96-1.00)	0.78 (0.70-0.86)	0.75 (0.66-0.84)	0.89 (0.75-1.00)
TAG(18:1/18:1/22:6) / LPC 14:0_sn2	CA125 / SM 37:2	0.91 (0.86-0.95)	0.83 (0.73-0.92)	0.98 (0.96-1.00)	0.78 (0.70-0.86)	0.75 (0.66-0.84)	0.91 (0.80-1.00)
Cer(d20:1/24:1) / LPC 14:0_sn2	CA125 / PI 38:2	0.91 (0.87-0.96)	0.85 (0.76-0.93)	0.97 (0.94-1.00)	0.78 (0.70-0.86)	0.76 (0.67-0.85)	0.95 (0.88-1.00)
TAG(18:1/18:1/22:6) / PC 30:0	CA125 / PC 30:0	0.90 (0.85-0.95)	0.82 (0.73-0.91)	0.98 (0.95-1.00)	0.79 (0.72-0.87)	0.77 (0.68-0.85)	0.91 (0.78-1.00)
CA125		0.90 (0.84-0.95)	0.81 (0.71-0.90)	0.97 (0.94-1.00)	0.72 (0.62-0.81)	0.67 (0.57-0.78)	0.95 (0.91-1.00)
CA125 (35 U/mL cut-off)		0.80 (0.73-0.86)	0.69 (0.59-0.80)	0.89 (0.84-0.94)	0.71 (0.64-0.79)	0.68 (0.60-0.76)	0.91 (0.87-0.95)

463

464 Abbreviations
465
466 AC, Acylcarnitine
467 CE, cholesterylester
468 Cer, ceramide
469 DAG, diacylglycerol
470 Gb3, globotriasoylceramide
471 Glc/GalCer, glucosyl/galactosylceramide
472 LacCer, lactosylceramide
473 LPC, lysophosphatidylcholine
474 LPC O, alkyl-linked lysophosphatidylcholine
475 LPC P, alkenyl-linked lysophosphatidylcholine
476 LPE, lysophosphatidylethanolamine
477 LPE O, alkyl-linked lysophosphatidylethanolamine
478 LPE P, alkenyl-linked lysophosphatidylethanolamine
479 PC, phosphatidylcholine
480 PC O, alkyl-linked phosphatidylcholine
481 PC P, alkenyl-linked phosphatidylcholine
482 PE, phosphatidylethanolamine
483 PE O, alkyl-linked phosphatidylethanolamine
484 PE P, alkenyl-linked phosphatidylethanolamine
485 PG, Phosphatidylglycerol
486 PI, phosphatidylinositol
487 S1P, sphingosine-1-phosphate
488 SA1P, sphinganine-1-phosphate
489 SM, sphingomyelin
490 TAG, triacylglycerol
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Supplementary Table S1. Number of lipids and the mean coefficient of variation (CV) for all the analyzed lipid classes.

Lipid class	Number of lipids	CV
AC	8	15 %
CE	21	24 %
Cer d16:1	8	26 %
Cer d18:0	7	36 %
Cer d18:1	9	25 %
Cer d18:2	9	27 %
Cer d20:1	4	22 %
DAG	18	29 %
Gb3	4	41 %
Glc/GalCer	22	29 %
LacCer	10	28 %
LPC	40	11 %
LPC P/LPC O	13	11 %
LPE	11	12 %
LPE P/LPE O	2	13 %
PC	70	20 %
PC P/PC O	46	23 %
PE	23	27 %
PE P/PE O	15	30 %
PG	4	23 %
PI	19	19 %
S1P/SA1P	4	9 %
SM	41	16 %
TAG	42	11 %

Supplementary Table S2. Lipids that showed consistent alteration in all three and were significant in at least two study cohorts.

Lipid class	Lipid name	Charité		Finland		Charité Discovery		
		Change (%)	p-value	Change (%)	p-value	Change (%)	p-value	
CE	CE 14:0	-10,5	0,113	-22,3	1,2E-05	-22,3	4,1E-06	
	CE 14:1	-13,0	0,247	-28,2	1,5E-04	-22,0	4,7E-05	
	CE 16:2	-11,8	0,060	-20,7	3,3E-04	-21,1	2,0E-07	
	CE 18:0	-9,8	0,113	-10,8	0,020	-26,7	4,9E-10	
	CE 18:2	-9,9	0,028	-2,1	0,568	-21,9	7,2E-10	
Cer d16:1	Cer(d16:1/23:0)	-7,0	0,300	-28,5	2,6E-06	-24,9	5,7E-04	
	Cer(d16:1/24:0)	-17,7	0,027	-30,2	6,0E-07	-29,3	6,1E-08	
	Cer(d16:1/26:0)	-15,7	0,055	-18,7	0,003	-17,1	0,004	
Cer d18:0	Cer(d18:0/18:0)	36,1	0,001	45,0	0,044	49,7	5,7E-05	
	Cer(d18:0/20:0)	28,2	0,023	58,2	4,1E-04	22,0	0,018	
	Cer(d18:0/23:0)	-8,8	0,158	-20,4	0,001	-17,4	0,004	
Cer d18:1	Cer(d18:1/18:0)	56,2	2,9E-06	52,5	1,9E-04	71,4	7,2E-12	
	Cer(d18:1/20:0)	15,9	0,027	24,4	0,027	39,7	9,9E-08	
	Cer(d18:1/24:0)	-4,4	0,570	-13,6	0,002	-11,9	0,009	
	Cer(d18:1/24:1)	18,8	0,003	6,9	0,477	30,5	1,1E-06	
Cer d18:2	Cer(d18:2/18:0)	28,0	0,005	20,7	0,063	26,2	5,2E-04	
	Cer(d18:2/23:0)	-10,9	0,190	-17,9	7,8E-04	-18,5	5,6E-04	
	Cer(d18:2/24:0)	-13,4	0,105	-20,8	9,9E-05	-22,4	1,1E-05	
	Cer(d18:2/26:0)	-10,7	0,298	-9,8	0,037	-14,2	0,040	
Cer d20:1	Cer(d20:1/24:1)	29,1	6,8E-04	13,5	0,126	43,9	2,1E-07	
DAG	DAG(14:0/18:1)	-24,0	0,203	-23,5	9,6E-04	-39,1	6,9E-04	
Gb3	Gb3(d18:1/24:0)	-16,8	0,011	-7,7	0,788	-23,1	8,6E-05	
Glc/GalCer	Glc/GalCer(d16:1/20:0)	-21,6	0,011	-25,1	0,001	-16,8	9,7E-04	
	Glc/GalCer(d16:1/22:0)	-19,0	0,015	-29,5	4,2E-05	-23,4	1,5E-05	
	Glc/GalCer(d16:1/23:0)	-22,8	0,003	-22,5	0,008	-19,3	3,8E-04	
	Glc/GalCer(d16:1/24:0)	-26,9	4,5E-04	-25,8	0,013	-23,1	5,0E-06	
	Glc/GalCer(d18:1/20:0)	-15,4	0,019	-6,7	0,845	-19,7	9,2E-05	
	Glc/GalCer(d18:1/22:0)	-18,8	0,001	-11,2	0,752	-25,9	2,6E-07	
	Glc/GalCer(d18:1/23:0)	-19,4	0,003	-15,9	0,081	-23,8	7,8E-07	
	Glc/GalCer(d18:1/24:0)	-17,2	0,002	-19,7	0,047	-24,2	4,7E-07	
	Glc/GalCer(d18:1/26:0)	-16,3	0,016	-23,7	0,002	-21,0	9,4E-05	
	Glc/GalCer(d18:2/20:0)	-19,9	0,003	-11,7	0,587	-23,3	1,7E-04	
	Glc/GalCer(d18:2/22:0)	-19,2	0,002	-19,6	0,022	-17,9	5,0E-04	
	Glc/GalCer(d18:2/23:0)	-22,2	0,003	-20,5	0,012	-21,6	5,2E-05	
	Glc/GalCer(d18:2/24:0)	-17,1	0,002	-17,5	0,088	-23,9	4,8E-08	
	LacCer	LacCer(d16:1/16:0)	-3,9	0,495	-12,8	0,016	-21,1	5,3E-05
LPC	LPC 14:0_sn1	-31,2	1,9E-05	-13,7	0,001	-19,1	0,002	
	LPC 14:0_sn2	-34,0	3,1E-05	-21,0	3,4E-05	-30,3	2,3E-05	
	LPC 18:2_sn1	-32,0	1,1E-05	-5,0	0,147	-29,7	1,9E-07	
	LPC 18:2_sn2	-33,4	2,9E-06	-12,8	0,004	-34,7	2,3E-12	
	LPC 20:0_sn1	-24,5	6,2E-05	-2,7	0,308	-16,6	0,003	
	LPC 20:0_sn2	-25,2	9,9E-06	-6,9	0,085	-14,6	0,011	
	LPC 20:2_sn2	-25,4	6,7E-06	-7,0	0,067	-16,4	3,2E-05	
	LPC 20:3_sn2	-19,0	0,003	-2,6	0,226	-24,4	1,4E-06	
	LPC 22:0_sn1	-27,2	1,6E-07	-13,3	0,004	-28,7	6,3E-10	
	LPC 24:0_sn1	-21,0	3,4E-06	-10,0	0,015	-28,7	1,5E-12	
	LPC 24:0_sn2	-19,0	2,0E-05	-11,6	0,007	-28,9	2,3E-13	
	LPC O	LPC O-20:0	-19,6	0,001	-6,0	0,095	-15,5	7,1E-04
		LPC O-22:0	-15,6	0,007	-6,6	0,074	-25,3	4,8E-11
		LPC O-22:1	-22,3	3,7E-04	-5,3	0,113	-17,5	0,002
LPC O-24:1		-15,3	0,019	-6,1	0,093	-17,8	8,2E-05	
LPC O-24:2		-25,3	5,5E-05	-8,5	0,203	-33,0	1,2E-08	
LPE	LPE 18:2_sn1	-37,7	5,8E-06	-1,3	0,288	-40,1	1,5E-11	
	LPE 18:2_sn2	-37,2	1,8E-06	-4,0	0,191	-35,4	4,6E-10	
LPE P	LPE P-16:0	-9,9	0,013	-23,3	1,5E-07	-12,4	0,197	
	LPE P-18:0	-13,2	0,005	-12,8	9,4E-05	-7,8	0,382	
PC	PC 28:0	-47,2	5,5E-06	-47,8	2,7E-07	-59,0	1,5E-15	
	PC 30:0	-26,4	0,001	-25,1	2,1E-05	-43,4	4,0E-15	
	PC 30:1	-39,4	2,1E-04	-34,6	1,2E-06	-52,1	2,4E-13	
	PC 30:2	-57,6	4,2E-08	-48,2	4,5E-07	-61,4	2,1E-14	

	PC 31:1	-14,8	0,311	-23,8	0,002	-36,9	1,9E-08
	PC 32:1	-12,2	0,795	-15,0	0,016	-29,0	1,9E-06
	PC 32:2	-38,0	8,7E-07	-26,7	1,9E-06	-52,5	4,0E-19
	PC 32:3	-42,9	1,1E-05	-34,3	2,9E-07	-58,5	4,2E-17
	PC 33:2	-18,0	0,010	-7,8	0,098	-35,6	6,9E-13
	PC 33:3	-23,3	0,021	-23,4	1,9E-04	-42,0	4,2E-11
	PC 34:2	-15,9	0,001	-5,8	0,198	-28,6	4,5E-10
	PC 34:3a	-22,1	5,0E-04	-14,2	0,010	-37,9	9,7E-14
	PC 34:3b	-19,2	0,025	-17,5	0,001	-35,8	3,9E-12
	PC 34:3c	-25,4	0,002	-21,8	0,010	-44,1	1,2E-13
	PC 34:4	-35,4	1,3E-05	-22,1	4,5E-05	-52,1	5,6E-16
	PC 34:5	-28,0	0,006	-39,4	2,9E-08	-41,3	1,4E-05
	PC 35:2a	-16,5	0,036	-0,4	0,931	-26,3	2,6E-06
	PC 35:2b	-16,1	0,006	-2,9	0,413	-28,1	1,1E-09
	PC 35:3a	-26,7	1,3E-05	-5,9	0,151	-39,8	3,1E-15
	PC 35:3b	-17,1	0,019	-4,5	0,206	-35,9	2,0E-09
	PC 36:1	-16,3	0,033	-9,5	0,038	-12,5	0,053
	PC 36:2	-22,6	7,2E-05	-7,7	0,103	-35,1	2,0E-13
	PC 36:3a	-30,8	3,2E-07	-3,8	0,280	-36,0	2,2E-14
	PC 36:3b	-14,6	0,040	-4,9	0,186	-29,2	1,9E-08
	PC 36:5a	-16,9	0,030	-10,6	0,097	-32,1	1,4E-07
	PC 36:6	-28,8	7,7E-04	-20,3	7,5E-04	-46,4	2,0E-09
	PC 36:7	-32,8	9,3E-04	-52,7	1,6E-13	-27,4	2,1E-05
	PC 37:1	-16,8	0,004	-5,1	0,300	-20,5	4,6E-06
	PC 37:2	-26,5	2,6E-05	-11,7	0,022	-36,3	6,0E-13
	PC 37:3	-13,5	0,031	-2,2	0,432	-30,4	7,4E-09
	PC 38:0	-10,9	0,049	-5,9	0,106	-29,1	5,0E-11
	PC 38:3	-19,4	0,007	-3,0	0,262	-30,6	1,5E-09
	PC 38:5b	-4,4	0,564	-19,6	0,002	-16,1	0,003
	PC 38:6a	-28,1	9,3E-05	-9,9	0,051	-35,0	2,6E-10
	PC 38:6b	-33,2	1,3E-06	-5,8	0,446	-38,0	7,1E-13
	PC 40:8	-22,0	0,004	-7,7	0,051	-33,4	6,8E-10
PC P	PC P-34:2	-29,8	2,3E-06	-12,7	0,035	-33,3	2,7E-13
PC O	PC O-32:1	-17,6	0,011	-3,4	0,490	-31,3	7,1E-10
	PC O-34:1	-13,4	0,012	-0,2	0,968	-22,2	1,2E-08
	PC O-34:2	-29,9	1,0E-05	-12,6	0,031	-39,7	6,7E-17
	PC O-36:1	-10,2	0,075	-9,8	0,026	-27,6	1,5E-07
	PC O-36:2b	-27,1	4,4E-06	-2,1	0,924	-36,3	4,2E-14
	PC O-36:3a	-28,9	4,8E-07	-4,6	0,424	-38,7	4,8E-16
	PC O-36:3b	-22,1	1,5E-04	-0,2	0,644	-33,2	4,7E-13
	PC P 36:2a	-25,8	1,0E-04	-9,0	0,235	-26,8	6,2E-08
	PC P-32:0	-17,6	0,001	-6,8	0,214	-20,2	8,1E-07
	PC P-32:1	-16,2	0,018	-11,7	0,159	-21,4	1,6E-05
	PC P-34:1	-13,8	0,039	-3,2	0,815	-13,9	3,6E-04
PE	PE 34:3	-19,1	0,328	-19,5	0,009	-49,7	8,1E-07
	PE 36:2	-10,7	0,326	-17,1	0,010	-37,9	1,5E-06
	PE 36:3a	-31,0	0,005	-3,9	0,359	-53,8	2,0E-07
	PE 36:3b	-44,6	0,003	-5,4	0,674	-54,7	3,9E-08
	PE 36:5	-6,4	0,700	-25,9	4,1E-05	-26,5	0,023
	PE 38:3	-9,7	0,583	-10,6	0,042	-40,4	6,8E-07
	PE 38:5b	-7,2	0,995	-23,5	1,0E-04	-36,9	1,6E-04
PE O	PE O-34:1	-25,6	3,8E-05	-11,7	0,030	-12,4	0,047
	PE O-36:4	-35,9	1,3E-05	-2,6	0,148	-49,1	4,9E-11
	PE O-38:5	-35,4	3,0E-06	-0,2	0,419	-38,5	1,3E-09
	PE O-38:6	-22,7	0,001	-4,2	0,259	-16,2	0,044
PG	PG 34:1	-2,6	0,870	-13,6	0,024	-22,9	0,011
	PG 36:2	-5,5	0,740	-16,6	0,007	-25,6	3,5E-04
PI	PI 32:0	-22,0	0,181	-19,6	0,005	-49,6	3,0E-04
	PI 34:1	-18,7	0,050	-7,2	0,163	-31,3	4,7E-04
	PI 34:2	-17,6	0,016	-4,1	0,371	-31,3	6,4E-06
	PI 36:1	-30,7	4,1E-05	-16,7	0,001	-40,1	3,8E-07
	PI 36:3a	-42,8	1,4E-08	-1,9	0,195	-51,5	9,9E-10
	PI 36:3b	-27,7	2,1E-04	-3,8	0,223	-39,6	3,0E-09

	PI 38:2	-25,1	2,7E-04	-16,1	0,002	-40,5	3,5E-07
	PI 38:3a	-23,5	4,9E-04	-4,8	0,104	-33,8	1,6E-09
	PI 38:3b	-23,7	0,007	-3,9	0,458	-13,3	0,050
S1P	S1P d16:1	-10,2	0,045	-14,2	1,6E-04	-20,0	1,4E-08
	S1P d18:1	-3,7	0,333	-9,3	0,001	-19,3	1,3E-07
	S1P d18:2	-11,3	0,007	-2,0	0,396	-29,3	1,2E-13
SA1P	SA1P d18:0	-6,4	0,126	-11,0	5,6E-04	-24,8	5,3E-13
SM	SM 30:2	-29,3	1,2E-04	-24,5	2,5E-04	-35,8	2,2E-11
	SM 31:1	-9,3	0,158	-11,3	0,033	-24,7	1,2E-07
	SM 32:1	-3,4	0,615	-9,8	0,004	-17,3	7,4E-06
	SM 32:2	-14,4	0,006	-13,7	9,7E-04	-28,0	3,3E-11
	SM 36:0	27,8	0,012	40,0	0,008	6,9	0,288
	SM 37:2	-24,7	4,2E-05	-9,5	0,069	-34,8	1,4E-13
	SM 39:1	-8,9	0,203	-16,5	1,7E-04	-27,5	1,3E-10
	SM 40:2b	-10,0	0,044	-7,9	0,021	-27,3	4,5E-12
	SM 44:2	12,6	0,035	13,1	0,041	5,0	0,304
TAG	TAG(14:0/16:0/18:1)	-21,2	0,112	-31,0	6,4E-06	-37,3	1,0E-04
	TAG(14:0/16:0/18:2)	-16,3	0,318	-31,2	1,7E-05	-36,5	2,3E-04
	TAG(14:0/16:1/18:1)	-23,5	0,085	-30,4	1,1E-05	-44,3	1,5E-04
	TAG(14:0/16:1/18:2)	-28,1	0,009	-35,5	1,7E-05	-50,9	2,4E-06
	TAG(14:0/17:0/18:1)	-1,9	0,555	-20,4	0,004	-22,6	0,045
	TAG(14:0/18:0/18:1)	-17,5	0,166	-29,4	4,4E-05	-44,4	1,7E-04
	TAG(14:0/18:2/18:2)	-26,4	0,010	-23,0	0,013	-47,7	3,3E-06
	TAG(14:1/16:0/18:1)	-18,9	0,528	-30,3	1,9E-05	-35,4	0,005
	TAG(14:1/16:1/18:0)	-11,6	0,860	-23,7	0,001	-28,7	0,016
	TAG(14:1/18:0/18:2)	-12,7	0,391	-14,0	0,008	-25,3	0,014
	TAG(14:1/18:1/18:1)	-9,6	0,408	-15,7	0,009	-33,0	1,2E-04
	TAG(16:0/18:1/18:1)	18,4	0,002	3,0	0,780	9,2	0,037
	TAG(16:1/16:1/16:1)	-19,3	0,207	-26,7	5,2E-04	-43,7	5,2E-05
	TAG(16:1/16:1/18:0)	-19,2	0,108	-27,6	2,5E-05	-40,5	6,6E-05
	TAG(18:1/18:1/20:4)	30,3	0,003	40,5	9,7E-07	28,4	6,7E-06
	TAG(18:1/18:1/22:6)	52,8	6,0E-04	28,6	0,004	54,9	5,4E-08