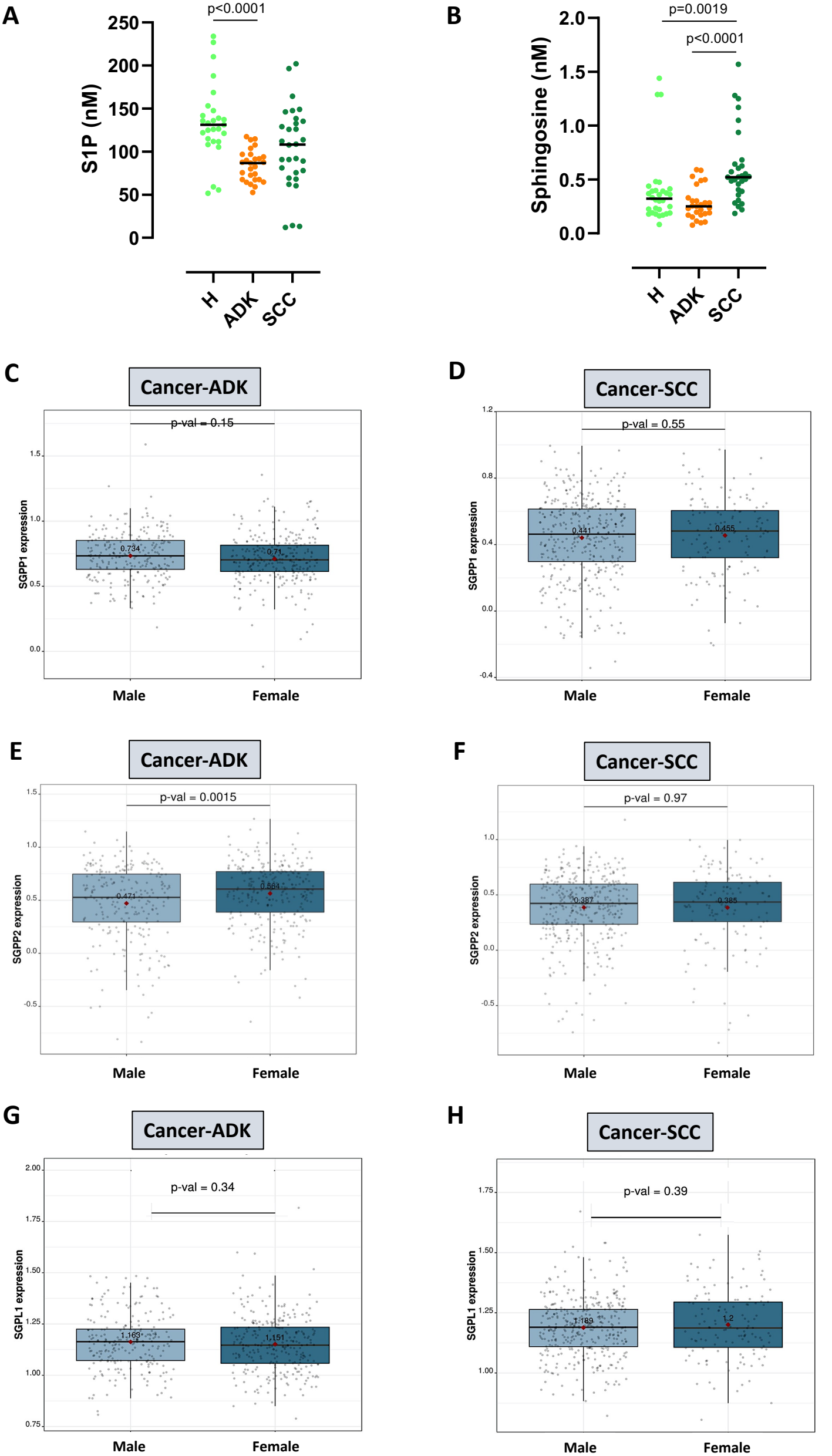
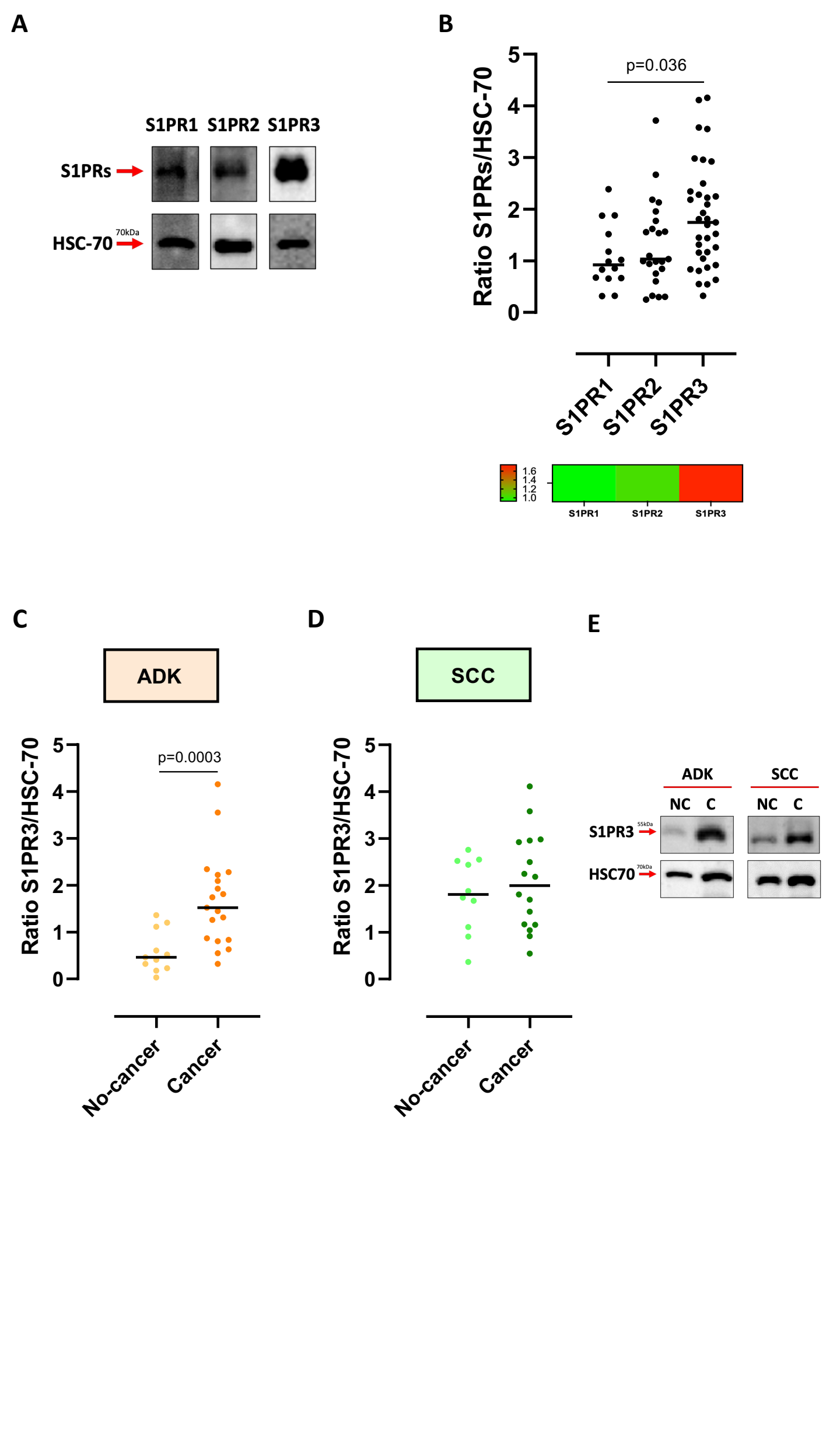


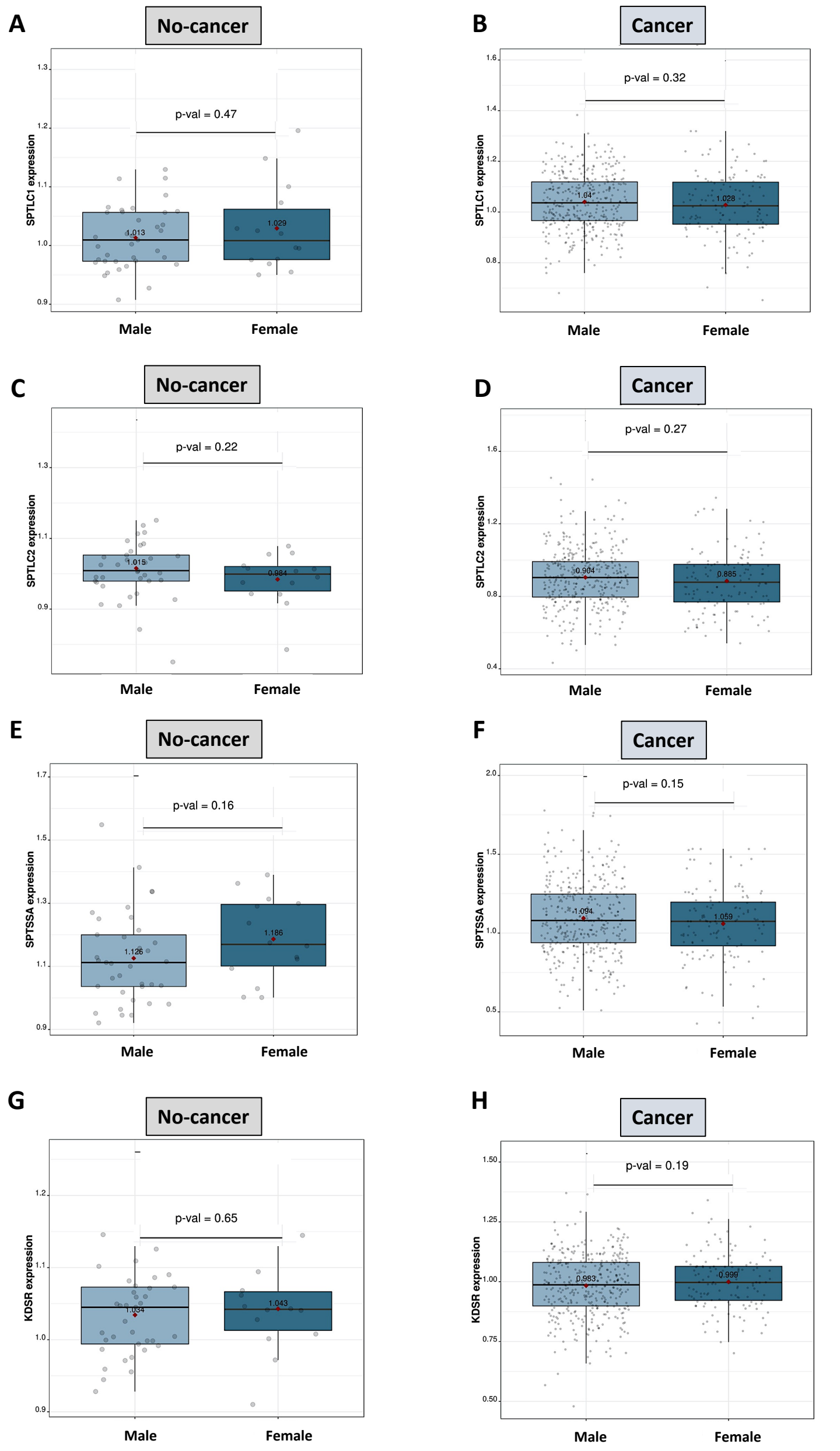
Supplementary Figure S1

Supplementary Figure S1. S1P (**A**) and sphingosine (**B**) quantification in plasma of H (n=27), ADK (n=37) and SCC patients (n=30), by means of LC-MS/MS. Statistical differences were assessed by means of One-way ANOVA followed by Dunn's post hoc test. H: healthy; ADK: lung adenocarcinoma; SCC: lung squamous cell carcinoma. Transcripts quantification of sphingosine-1-phosphate phosphatase 1 and 2 (SGPP1 and SGPP2) in cancerous lung tissues of ADK (**C** and **E**, male=240; female n=277) and SCC (**D** and **F**, male=371; female n=130) patients. Transcripts quantification of sphingosine-1-phosphate lyase 1 (SGPL1) in cancerous lung tissues of ADK (**G**, male=240; female n=277) and SCC (**H**, male=371; female n=130) patients. Data were from RNAseq TCGA_LUAD_2016, for lung adenocarcinoma patients, and TCGA_LUSC_2016 dataset, for lung squamous cell carcinoma patients. A comparative analysis of transcripts with default parameters was performed by means of Lung Cancer Explorer (LCE) tool .



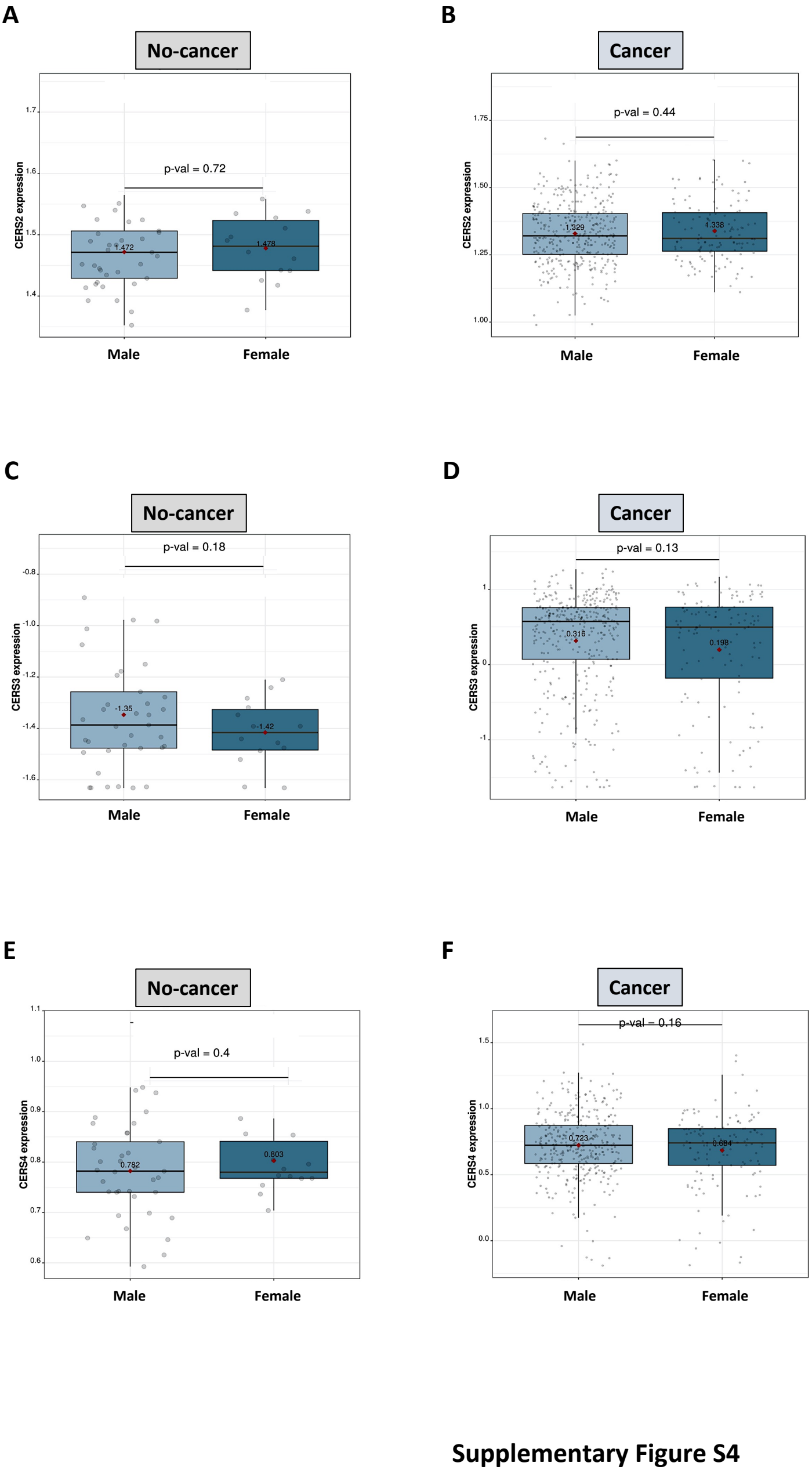
Supplementary Figure S2

Supplementary Figure S2. Expression of S1PRs on lung cancerous tissues. S1PR3 (55kDa; n=35) was over-expressed in lung cancerous tissues, compared to S1PR1 (44kDa; n=14) and S1PR2 (40-50kDa; n=23). HSC70 was used as loading control (**A** and **B)** . Data are represented as scatter dot plots indicating the median. Statistical differences were assessed by means of One-way ANOVA followed by Dunn's post hoc test. Western blotting analysis showed a higher expression of S1PR3 (55kDa) in cancerous lung tissues of ADK patients (Cancer, n=19) compared to non-cancerous lung tissues (No-cancer, n=11) (**C**), while cancerous (Cancer, n=16) and non-cancerous (No-cancer, n=10) lung tissues of SCC patients had similar expression of S1PR3 (**D**). **E)** Representative blot for S1PR3 expression in non-cancerous (NC) and cancerous (C) tissues of ADK and SCC patients. The quantitative analysis was performed by ImageJ software. Data are represented as scatter dot plots indicating the median. Statistical differences were assessed by means of two-tailed Mann-Whitney U test. S1PR1: sphingosine-1-phosphate receptor 1; S1PR2: sphingosine-1-phosphate receptor 2; S1PR3: sphingosine-1-phosphate receptor 3; HSC70: Heat shock cognate protein 70; ADK: lung adenocarcinoma; SCC: lung squamous cell carcinoma.



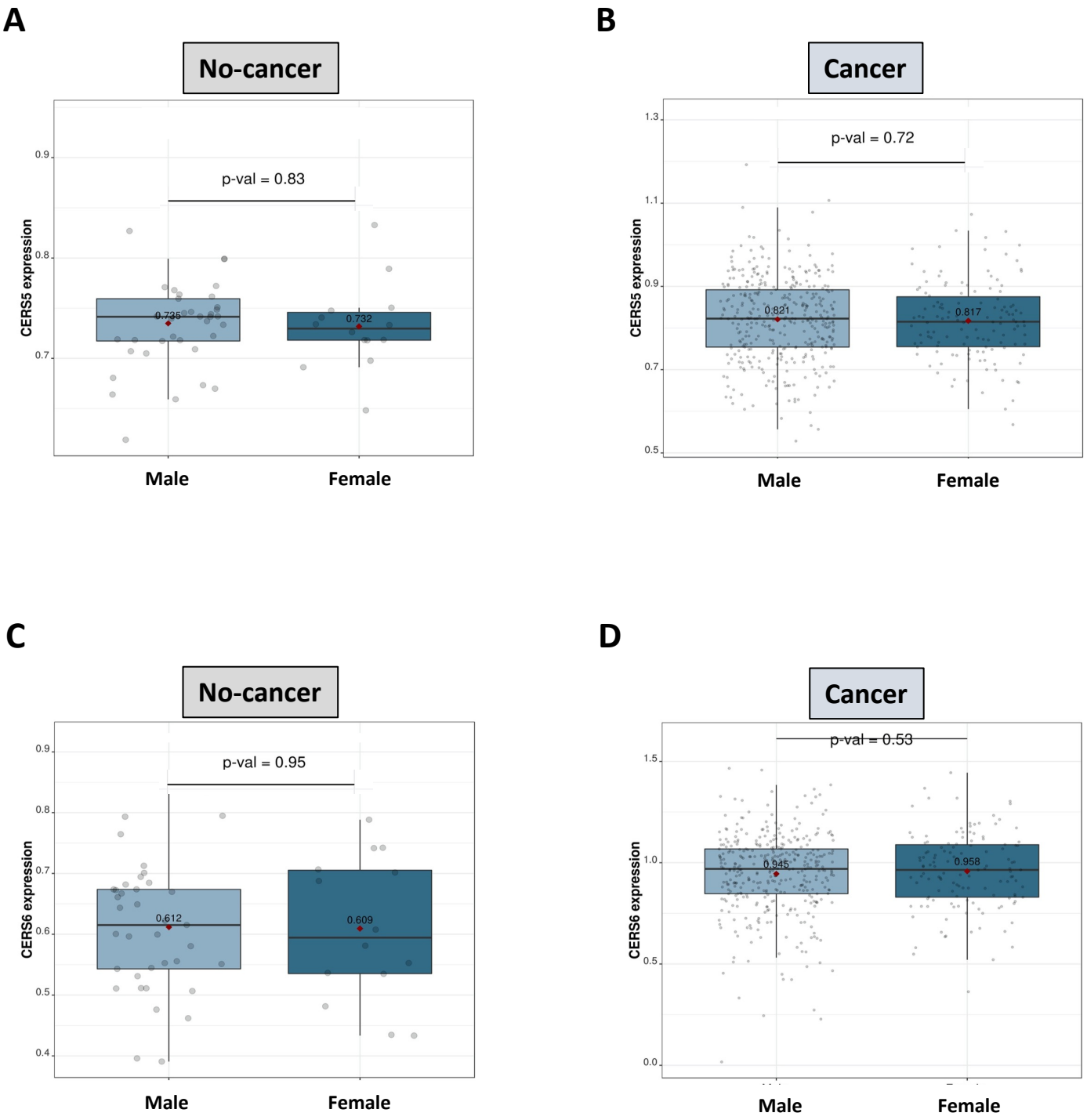
Supplementary Figure S3

Supplementary Figure S3. Expression of S1P metabolic enzymes involved in the first two steps of *de novo* synthesis. Transcripts expression of the S1P *de novo* synthesis enzymes in non-cancerous (No-cancer, male n=37, female n=14) and cancerous (Cancer, male n=371, female n=130) lung tissues of SCC patients from TCGA_LUSC_2016 dataset. Serine palmitoyl transferase (SPT) subunits: Serine palmitoyl transferase long chain base subunit 1 and 2 (SPTLC1 and 2) and serine palmitoyl transferase small subunit A (SPTSSA) (**A-F**); 3-ketodihydrosphingosine reductase (KDSR) (**G-H**). A comparative analysis of transcripts with default parameters was performed by means of Lung Cancer Explorer (LCE) tool.

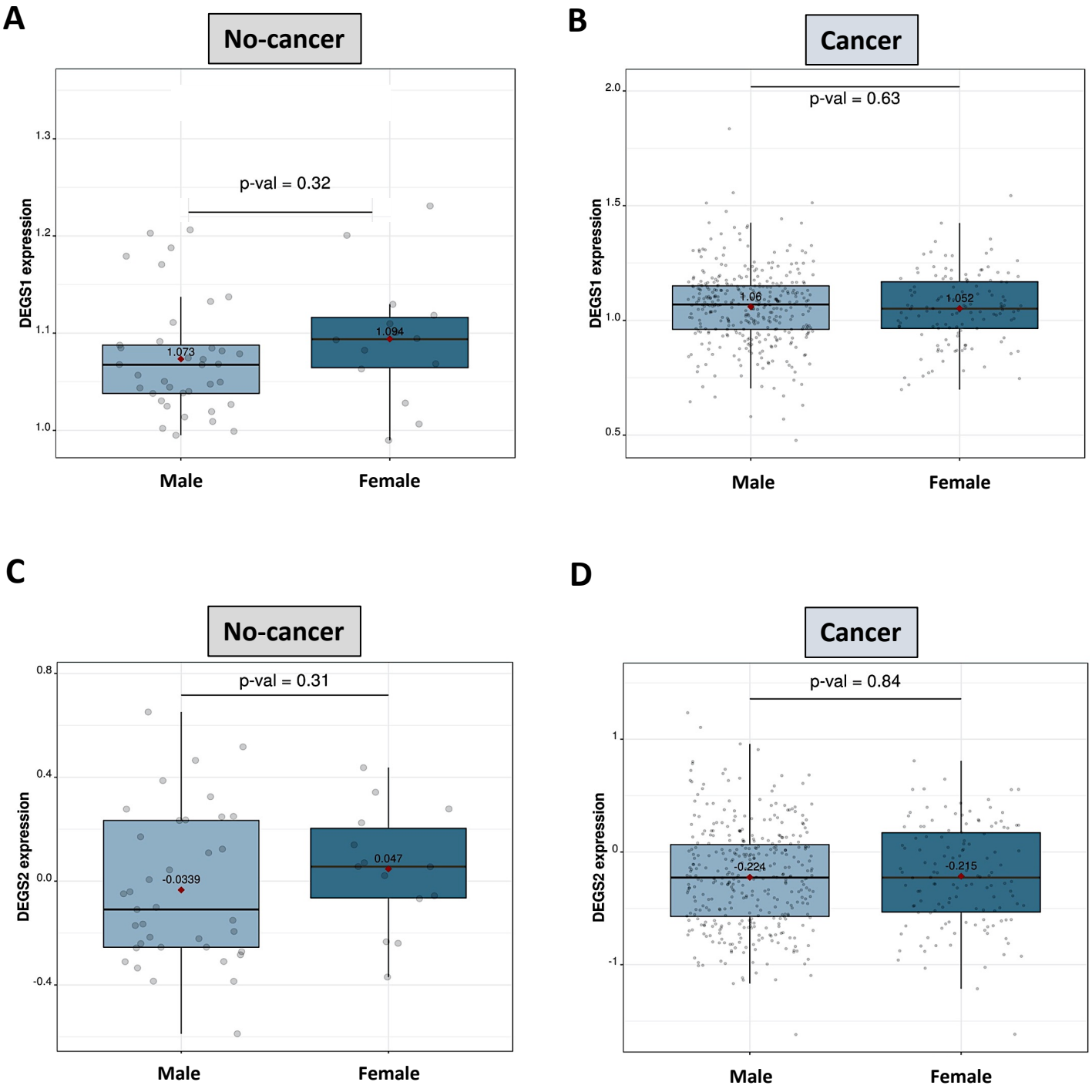


Supplementary Figure S4

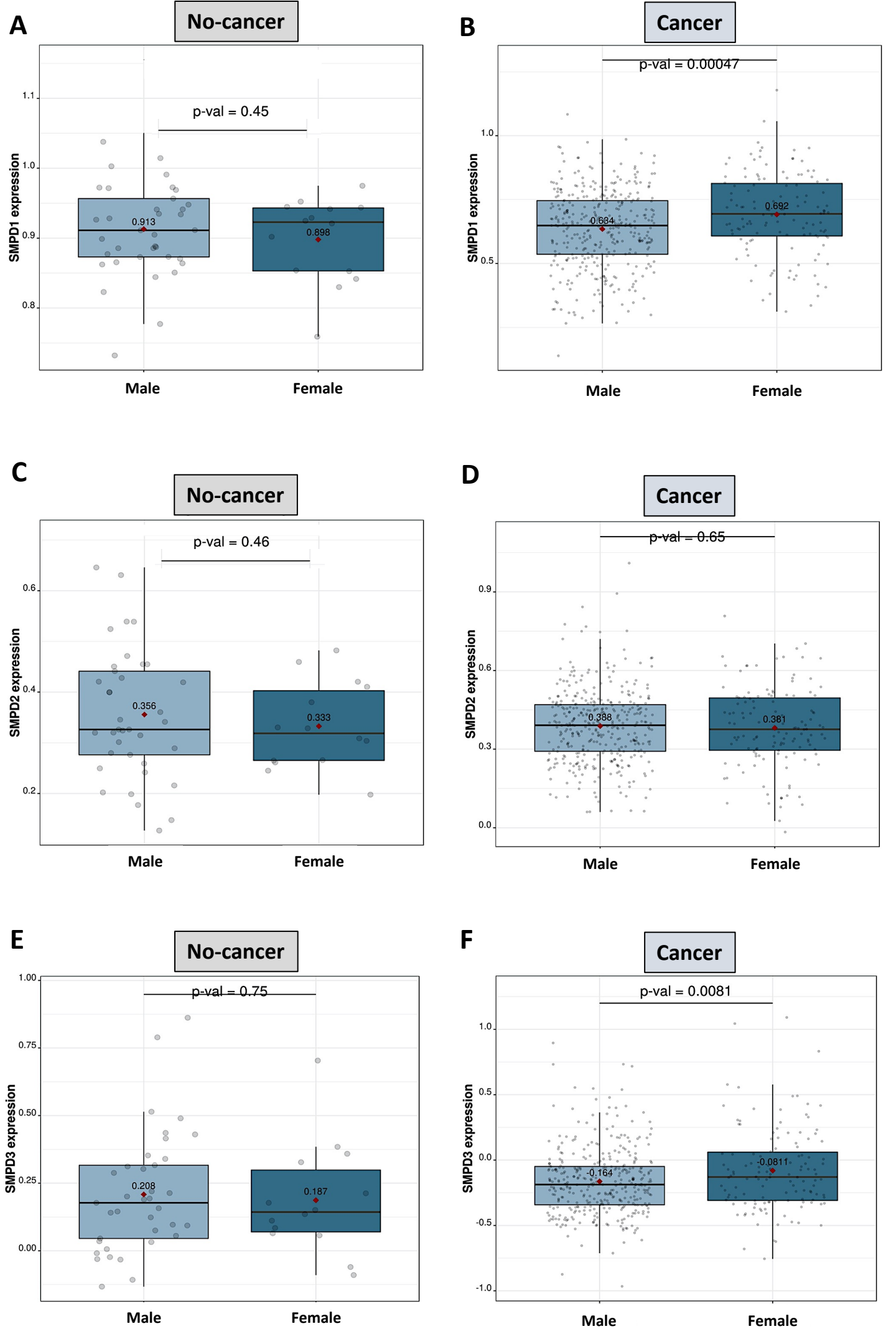
Supplementary Figure S4. Expression of S1P metabolic enzymes producing dihydroceramide starting from dihydrosphinganine. Transcripts expression of the S1P *de novo* synthesis enzymes in non-cancerous (No-cancer, **A**, **C** and **E**, male n=37, female n=14) and cancerous (Cancer, **B**, **D** and **F**, male n=371, female n=130) lung tissues of SCC patients from TCGA_LUSC_2016 dataset: ceramide synthase 2 (CERS2, **A** and **B**), 3 (CERS3, **C** and **D**) and 4 (CERS4, **E** and **F**). A comparative analysis of transcripts with default parameters was performed by means of Lung Cancer Explorer (LCE) tool.



Supplementary Figure S5. Expression of S1P metabolic enzymes producing dihydroceramide starting from dihydrosphinganine. Transcripts expression of the S1P *de novo* synthesis enzymes in non-cancerous (No-cancer, **A** and **C**, male n=37, female n=14) and cancerous (Cancer, **B** and **D**, male n=371, female n=130) lung tissues of SCC patients from TCGA_LUSC_2016 dataset: ceramide synthase 5 (CERS5, **A** and **B**) and 6 (CERS6, **C** and **D**). A comparative analysis of transcripts with default parameters was performed by means of Lung Cancer Explorer (LCE) tool.

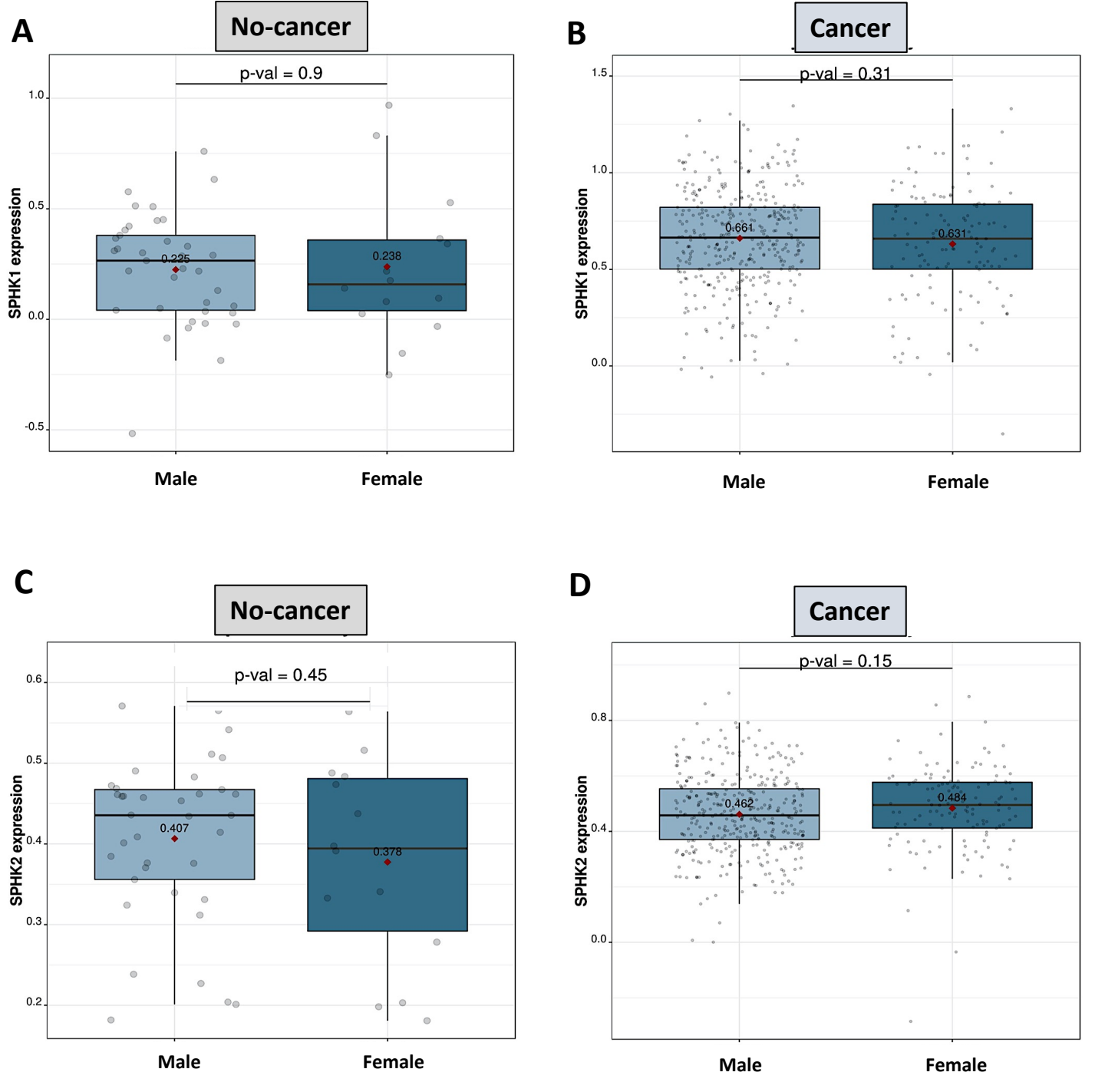


Supplementary Figure S6. Expression of S1P metabolic enzymes producing ceramide starting from dihydroceramide. Transcripts expression of the S1P *de novo* synthesis enzymes in non-cancerous (No-cancer, male n=37, female n=14) and cancerous (Cancer, male n=371, female n=130) lung tissues of SCC patients from TCGA_LUSC_2016 dataset. Dihydroceramide desaturase 1 (DEGS1, **A** and **B**) and 2 (DEGS2, **C** and **D**). A comparative analysis of transcripts with default parameters was performed by means of Lung Cancer Explorer (LCE) tool.



Supplementary Figure S7

Supplementary Figure S7. Expression of S1P metabolic enzymes involved in the sphingomyelin hydrolysis. Transcripts expression of the sphingomyelin-dependent S1P synthesis enzymes in non-cancerous (No-cancer, male n=37, female n=14) and cancerous (Cancer, male n=371, female n=130) lung tissues of SCC patients from TCGA_LUSC_2016 dataset. Sphingomyelinase 1 (SMPD1, **A** and **B**), 2 (SMPD2, **C** and **D**), and 3 (SMPD3, **E** and **F**). A comparative analysis of transcripts with default parameters was performed by means of Lung Cancer Explorer (LCE) tool.



Supplementary Figure S8. Expression of S1P metabolic enzymes. Transcripts expression of the sphingosine kinase 1 (SPHK1) (**A** and **B**), sphingosine kinase 2 (SPHK2) (**C** and **D**) in non-cancerous (No-cancer, male n=37, female n=14) and cancerous (Cancer, male n=371, female n=130) lung tissues of male and female SCC patients from TCGA_LUSC_2016 dataset. A comparative analysis of transcripts with default parameters was performed by means of Lung Cancer Explorer (LCE) tool.

Supplementary Table S1. Healthy subjects informations. H: healthy.

Healthy Subjects	Sex	Age (years)
H1	Female	68
H2	Female	75
H3	Female	69
H4	Female	76
H5	Female	42
H6	Female	60
H7	Female	67
H8	Female	82
H9	Female	73
H10	Female	77
H11	Female	41
H12	Female	35
H13	Male	53
H14	Male	59
H15	Male	66
H16	Male	67
H17	Male	55
H18	Male	33
H19	Male	49
H20	Male	78
H21	Male	63
H22	Male	61
H23	Male	59
H24	Male	59
H25	Male	46
H26	Male	49
H27	Male	53

Supplementary Table S2. Non-small cell lung cancer (NSCLC) patients informations. LC: lung cancer; ADK: lung adenocarcinoma; SCC: lung squamous cell carcinoma.

NSCLC patients	Sex	Histotype	Age (years)
LC1	Female	ADK	72
LC2	Female	ADK	67
LC3	Female	ADK	73
LC4	Female	ADK	59
LC5	Female	ADK	68
LC6	Female	ADK	57
LC7	Female	ADK	54
LC8	Female	ADK	63
LC9	Female	ADK	44
LC10	Female	ADK	62
LC11	Female	ADK	62
LC12	Female	ADK	75
LC13	Male	ADK	66
LC14	Male	ADK	71
LC15	Male	ADK	42
LC16	Male	ADK	80
LC17	Male	ADK	83
LC18	Male	ADK	69
LC19	Male	ADK	66
LC20	Male	ADK	79
LC21	Male	ADK	66
LC22	Male	ADK	75
LC23	Male	ADK	56
LC24	Male	ADK	41
LC25	Male	ADK	49
LC26	Male	ADK	59
LC27	Male	ADK	58
LC28	Female	SCC	67
LC29	Female	SCC	63
LC30	Female	SCC	68
LC31	Female	SCC	40
LC32	Female	SCC	55
LC33	Female	SCC	77
LC34	Female	SCC	35
LC35	Female	SCC	49
LC36	Female	SCC	69
LC37	Female	SCC	35
LC38	Female	SCC	59
LC38	Female	SCC	82
LC40	Female	SCC	27
LC41	Female	SCC	70
LC42	Female	SCC	48
LC43	Male	SCC	45
LC44	Male	SCC	54
LC45	Male	SCC	57
LC46	Male	SCC	52
LC47	Male	SCC	69
LC48	Male	SCC	42
LC49	Male	SCC	53
LC50	Male	SCC	49
LC51	Male	SCC	40
LC52	Male	SCC	50
LC53	Male	SCC	43
LC54	Male	SCC	50
LC55	Male	SCC	55
LC56	Male	SCC	35
LC57	Male	SCC	72