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Research Article

Serum Lipidomics Characterization of Breast Cancer Progression in a Transgenic Mouse Model of PyMT-Induced Breast Cancer

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Abstract

Background: Breast cancer is the most prevalent cancer in women worldwide. Notably, the identification of biomarkers can help to improve the efficiency of early breast cancer diagnosis and thus improve the survival rate of patients. Therefore, this study screened for such biomarkers with diagnostic significance through lipidomics.

Methods: Serum lipidomics analysis of MMTV-PyMT mice (n = 6) and their nontransgenic littermates (n = 6) was performed by ultrahigh-performance liquid chromatography coupled with mass spectrometry (UHPLC–MS). Univariate and multifactorial statistical analyses were used to screen for differential lipids between the groups combined with composition ratio analysis to evaluate diagnostic efficiency and reveal potential mechanisms and biomarkers of breast cancer.

Results: There were clear differences in the serum lipid profiles between the cancer and normal groups. In total, 13 differential lipids were selected by the criterion of $P < 0.05$. Triglycerides (TGs) were the major differential lipids with a ratio > 60%, indicating that these lipid metabolic pathways had evident disequilibrium, which could contribute to cancer formation.

Conclusion: To our knowledge, this is the first attempt to explore lipid biomarkers based on serum lipidomics with MMTV-PyMT mice to help with the early screening of breast cancer. Thirteen differential lipids can be used as potential diagnostic markers for breast cancer, with TGs being the main abnormal markers of cancer in serum.

Keywords: Breast cancer, Serum lipidomics, Biomarker, MMTV-PyMT mice

Background

Breast cancer is the most prevalent malignancy in women and is associated with the second highest number of cancer-associated deaths worldwide. The causes of breast cancer are complicated, but obesity is the most common risk factor [1,2]. With the rapid development of medical treatments, breast cancer has been well treated. Current clinical treatments for breast cancer include surgery, chemotherapy, hormone therapy, radiation therapy and immunotherapy [3]. The development and progression of breast cancer is a very complex multistep process involving reciprocal interactions of genes and environmental risk factors. Environmental factors, including diet, lifestyle and living environment, are receiving increasing attention. Blood lipids, used for both adipose and glucose transportation, and lipoproteins, used for membrane production, have been implicated in carcinogenesis through insulin resistance, inflammation, oxidative stress pathways, and the generation of signalling molecules in cancer cells.

Lipids are used for energy storage and metabolism and play an important role as signalling molecules for many cellular activities. The regulation of lipid metabolism, such as lipid uptake, synthesis and hydrolysis, is essential for maintaining intracellular homeostasis [4-6]. Cancer cells in the tumour microenvironment, which experience changes in nutrient supply during tumour progression, use lipid metabolism to support their rapid proliferation, survival, migration, invasion and metastasis. The association between lipids and lipoproteins with breast cancer has been determined. Ghahremanfard, et al. identified abnormally elevated lipid metabolism in breast cancer through the assessment of serum lipids in breast cancer patients. To date, most of the studies examining breast cancer cell lipid metabolism have focused on glucose and glutamine metabolism.

Lipidomics is a systematic approach that analyses the changes in lipid composition and expression in organisms based on high-throughput analysis techniques [7,8]. Currently, lipidomic analysis is generally performed by ultra-performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) [9]. This technique is characterized by its fast speed, high specificity, sensitivity, accuracy, stability and ability to simultaneously analyse multiple indicators. Thus, UHPLC–MS/MS has become one of the most important methods for the quantitative analysis of small molecule substances, including targets and their metabolites. Compared to traditional means of detection, advanced UPLC–MS/MS can help detect early pathological changes with greater sensitivity and accuracy [10]. Liu et al. found that by UPLC–MS/MS that triacylglycerols (TAGs) were the main disturbed lipid marker during colorectal cancer progression. The mammary-specific polyomavirus middle T antigen overexpression mouse model (MMTV-PyMT), first published in 1992, is the most commonly used genetically engineered mouse model (GEMM) for cancer research [11-13]. In particular, in breast cancer, the molecular and histological progression of the mammary lesions seen in MMTV-PyMT mice is similar to that of human mammary gland disease, making this model a valuable tool for cancer researchers to better understand tumour biology [11,14].

In this study, we performed a lipidomics study of serum samples from six MMTV-PyMT mice and six of their nontransgenic littermates by the UHPLC–MS/MS technique. By comparing the serum lipid profiles of the cancer and normal groups, we tried to identify the differential lipids and the potential mechanisms of the lipid metabolism pathways. Then, combined with trend change analysis of the differential lipids, the potential lipid markers for breast cancer diagnosis were evaluated and selected, which could provide a reference for the early screening of breast cancer.

Methods

Materials

A Q-Exactive Plus Mass Spectrometer (Thermo Scientific), a UHPLC Nexera LC-30A ultrahigh-performance liquid chromatograph (SHIMADZU), and a low temperature high speed centrifuge (Eppendorf 5430R) were used in this study. The chromatographic column was a Waters ACQUITY UPLC CSH C18 column (1.7 μm, 2.1 mm × 100 mm).Acetonitrile (Thermo Fisher), isopropanol (Thermo Fisher) and methanol (Thermo Fisher) were also used.

Sample preparation

An appropriate amount of serum sample was taken, and 200 μL of water was added to the sample before vortexing for 5 s. Subsequently, 240 μL of precooled methanol was added, and the mixture was vortexed for an additional 30 s. After that, 800 μL of MTBE was added, and the mixture was ultrasonicated for 20 min at 4 °C followed by standing for 30 min at room temperature. The solution was centrifuged at 14000 × g for 15 min at 10 °C, and the upper organic layer was retained and dried under nitrogen.

UHPLC–MS/MS method for lipid analysis

Reversed-phase chromatography was selected for LC separation using a CSH C18 column (1.7 μm, 2.1 mm× 100 mm, Waters). The lipid extracts were redissolved in 200 μL of 90% isopropanol/acetonitrile and centrifuged at 14000 × g for 15 min. Finally, 3 μL of sample was injected onto the system. Solvent A was acetonitrile–water (6:4, v/v) with 0.1% formic acid and 0.1 mM ammonium formate, and solvent B was acetonitrile–isopropanol (1:9, v/v) with 0.1% formic acid and 0.1 mM ammonium formate. The initial mobile phase was 30% solvent B at a flow rate of 300 μL/min. This solvent composition was maintained held for 2 min and then the proportion of solvent B was linearly increased to

100% over 23 min, followed by re-equilibration at 5% solvent B for 10 min.

Mass spectra were acquired with a Q-Exactive Plus in positive and negative modes. ESI parameters were optimized and preset for all measurements as follows: source temperature, 300 °C; capillary temperature, 350 °C, ion spray voltage, 3000 V; S-Lens RF level, 50%; and scan range of the instrument, m/z 200–1800.

Animal studies

Six- four-week-old female FVB/N-Tg MMTV-PyMT 634Mul/J transgenic mice obtained from the Southern Model Animal Center were used for the animal studies. Heterozygous MMTV-PyMT mice are routinely bred with nontransgenic FVB/n females. Six nontransgenic littermates were used as normal controls to construct a mouse model of spontaneous breast cancer with six MMTV-PyMT mice. All animals were housed under controlled temperature, humidity and lighting conditions within Xuzhou Medical University. All animal studies were approved and conducted under the oversight of the Animal Ethics Committee of Xuzhou Medical University and carried out in accordance with the Declaration of Helsinki.

Results

The formation of breast tumours in MMTV-PyMT mice

The development of breast cancer is a very complex process that involves modulation of the tumour microenvironment and metastasis, which is the main cause of cancer-associated death. Therefore, to truly explore the development of breast cancer in depth, it is necessary to model the dynamics of breast cancer in the human body. Therefore, in this study, we chose female FVB/N-Tg MMTV-PyMT 634Mul/J transgenic mice to simulate the changes in lipids caused by breast cancer in women. We bred FVB/N-Tg MMTV-PyMT 634Mul/J transgenic mice, and the female littermates were selected for genetic identification to verify the successful establishment of a spontaneous model of breast cancer (Figure 1A). Previous studies have shown that this model is characterized by multistep carcinogenesis, including hyperplasia at 4–5 weeks, carcinoma at 9–10 weeks, and advanced carcinoma at 12–13 weeks [15]. In this study, we chose mice with hyperplasia to observe the changes in breast cancer for early screening. We confirmed the occurrence and morphological changes of breast cancer by observing the H&E-stained images of PyMT tumours or normal mammary glands (Figure 1B) and measuring the tumour volume and tumour weight (Figure 1C-D). Finally, we used 200 µl of serum from 6 female FVB/N-Tg MMTV-PyMT 634Mul/J transgenic mice and 6 female nontransgenic littermates for lipidomic studies.

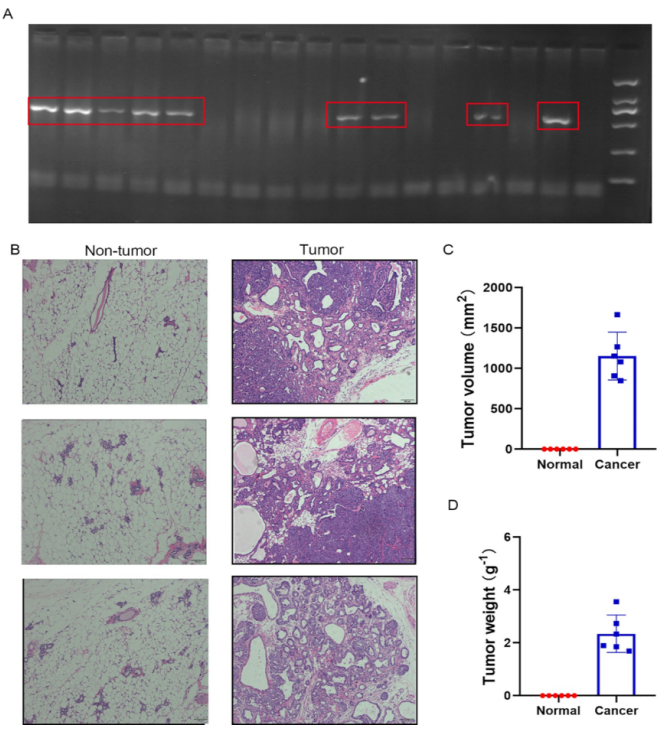

Figure 1: Validation of the MMTV-PyMT mouse model. (A) Verification of gene expression in neonatal mice by agarose electrophoresis. (B) H&E staining of PyMT tumours or normal mammary glands. Scale bar, 100 µm. (C-D) Description of the data analysis of tumour volume and tumour weight. Six mice were used for each group. Data are means ± SDs.

Lipidomics analysis

High reliability of the experimental quality control sample

A Pearson correlation analysis of the QC samples is shown in Figure 2A. A general correlation coefficient greater than 0.9 indicates a good correlation. The correlation coefficients of the QC samples were above 0.9, which indicated that the experiments were reproducible. The extracted ion peaks of all experimental samples and QC samples were analysed by PCA after Pareto scaling (Figure 2B). The results showed that the QC samples clustered closely together, indicating good reproducibility of the experiment. Hotelling's T2 test examines the samples by multivariate modelling and defines 95% or 99% confidence intervals. The results of Hotelling's T2 test are shown in Figure 2C. The QC samples were within the 99% confidence interval [16], indicating good reproducibility of the experiment. The multivariate control chart (MCC) is a multivariate statistical model based on the detected deviations in the QC samples and is a quality management tool for monitoring and judging the stability of the instrument. Each point in the MCC chart represents a QC sample,

and the x-axis is the sequence of all QC samples on the instrument. The points in the chart fluctuate up and down due to fluctuations in instrument status. Generally, the normal range is within plus or minus 3 standard deviations. The multivariate control chart for the QC samples of this project is shown in Figure 2D. The variations in the QC samples were within plus or minus 3 standard deviations, reflecting that the fluctuations of the instrument were within the normal range and that the data can be used for subsequent analysis. The smaller the relative standard deviation (RSD) of the ion peak abundance of QC samples, the better the stability of the instrument. RSD is an important indicator that reflects the quality of the data. In this experiment, the percentage of peak numbers with RSD ≤ 30% in the QC samples was above 80%, as shown in Figure 2E, indicating that the stability of the instrumental analysis system is good and that the data can be used for subsequent analysis.

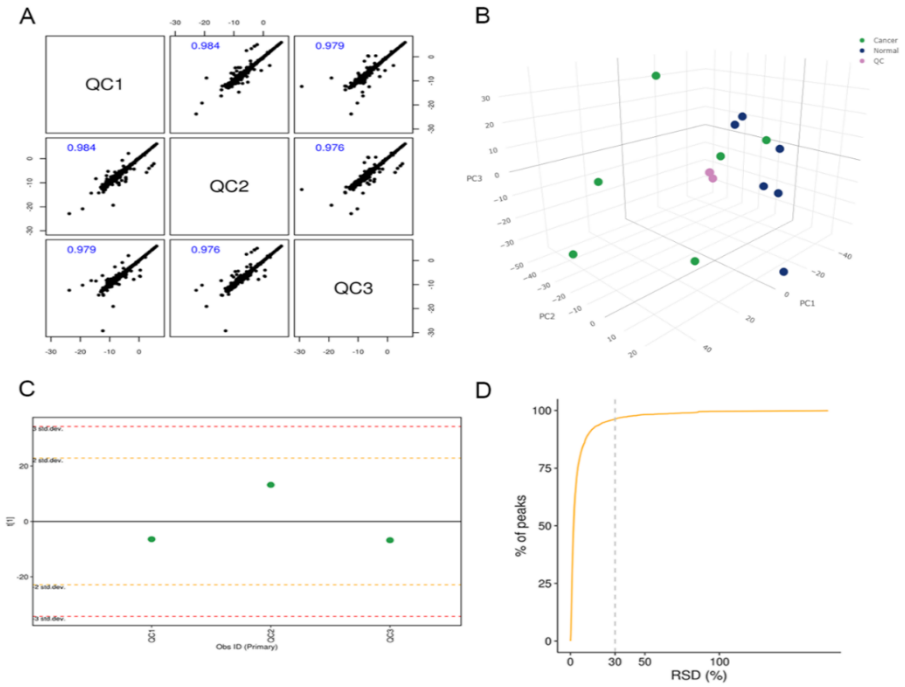

Figure 2: Experimental monitoring was performed in positive and negative ion modes. (A) QC sample correlation profiles. (B) PCA score plot for all samples and QC samples. (C) Hotelling's T2 test of the overall sample. (D) Multivariate control chart (MCC). (E) Plot of the relative standard deviation of the QC samples.

Identification of lipid compounds

The amounts of lipid compounds in the samples identified by the positive and negative ion patterns in this experiment are shown in Figure 3A. Lipid search was used to analyse the data obtained from the positive and negative ion patterns. Forty-five lipid subclasses were identified in positive and negative ion modes, and a total of 2691 lipid molecules were detected from both categories, as shown in Figure 3A.

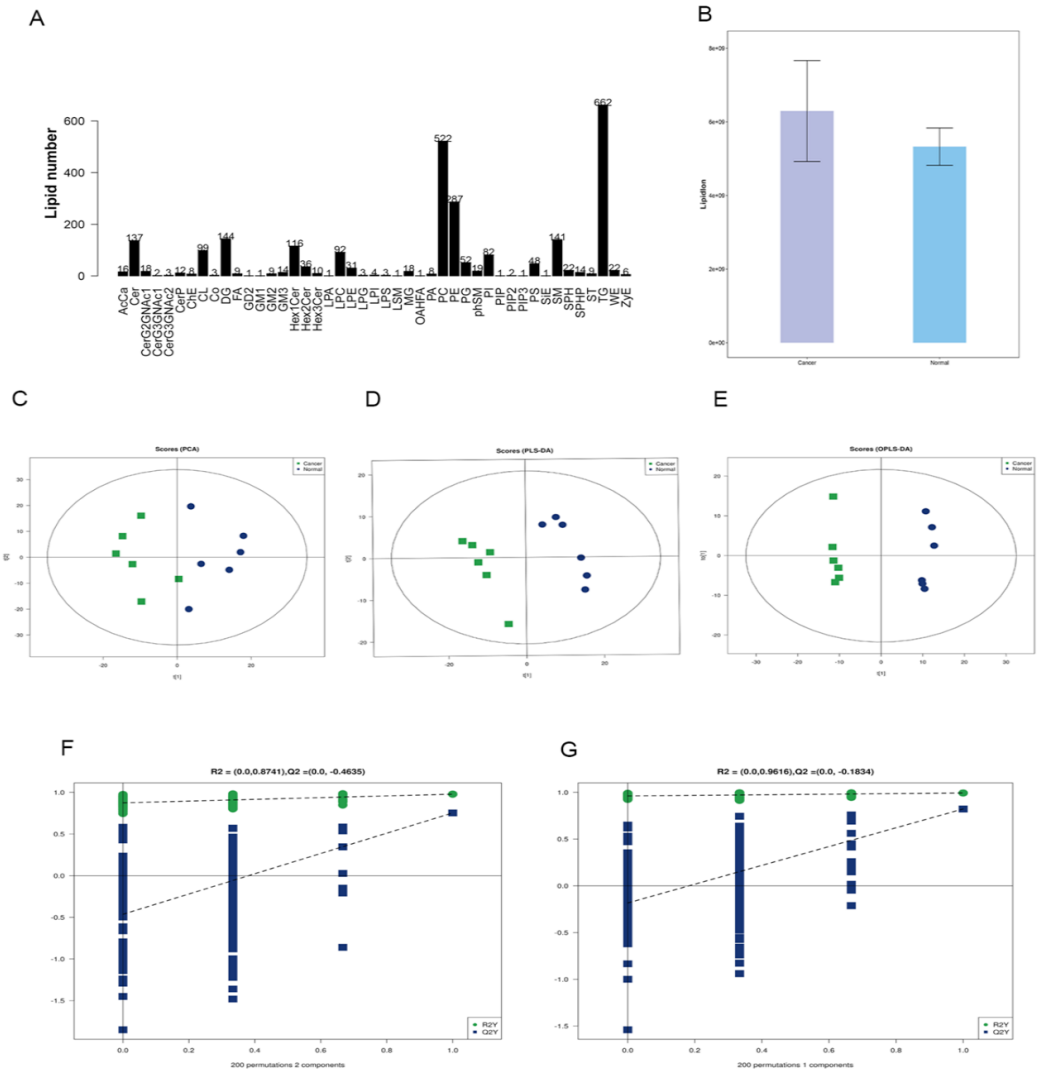

Figure 3: Multivariate data analysis of mouse serum metabolites based on UHPLC–MS/MS. (A) Statistical chart of the numbers of lipid subclasses and lipid molecules. (B) Significant differences in total lipid amounts between the cancer and normal groups. (C) PCA score chart of the cancer-normal group. (D) Partial least squares discrimination analysis (PLS-DA) plot. (E) Orthogonal partial least squares discrimination analysis (OPLS-DA) chart. (F) Permutation test chart for the PLS-DA model. (G) Permutation test chart for the PLS-DA model.

Breast cancer development caused disturbances in lipid metabolism

In this study, the contents of all the lipid molecules quantified in the same sample were summed to give the total lipid molecule content of that sample. Then, the total contents of samples from different groups were compared, and it was found that the lipid content in the cancer group was higher than that of the normal group, indicating that lipid metabolism promotes breast cancer. These results are shown in Figure 3B.

Principal component analysis (PCA) is an unsupervised data analysis method that linearly regroups all of the originally identified lipid molecules to form a new set of composite variables and simultaneously selects several composite variables from this group according to the problem being analysed. The chosen variables reflect as much information from the original variables as possible, thus achieving dimensionality reduction. Moreover, principal component analysis of lipids can also reflect the intergroup and intragroup variability of

samples in general. Analysis of the cancer and normal groups with the PCA model revealed that the two groups of samples showed specific trends of separation (Figure 2, 3C-D). Subsequently, a PLS-DA model was developed to show the differences and trends in the lipids between the control and model groups. This method used partial least squares regression to model the relationship between lipid expression and sample class to achieve prediction of the sample class. The samples in the model and control groups were significantly separated, indicating that lipid metabolism was significantly altered between the two groups (Figure. 3E). The R2Y and Q2 values of this PLS-DA model were higher than 0.6 (Figure 3F), indicating good reliability. Orthogonal partial least squares discriminant analysis (OPLS-DA) is a modified PLS-DA method that can filter out noise unrelated to the classification information and improve the resolution and validity of the model. Thus, we next performed OPLS-DA on the data and obtained the same conclusions as before (Figure 3G). Therefore, we determined that lipid metabolism can promote breast cancer.

Analysis of relative lipid expression in the serum of the cancer and normal groups

Lipid composition refers to the classes of lipids in a sample and their proportions. Lipid composition analysis is one of the main components of lipid data analysis. On the one hand, lipid composition is sample specific, and different types of samples, such as cell membranes, mitochondria, and endoplasmic reticulum, contain different lipid classes and proportions at steady state. On the other hand, under different treatment conditions or biological processes, the lipid composition changes accordingly, which in turn leads to alterations in the biophysical properties of the membrane and its functions. Overall, lipid composition analysis can be used to examine the major lipid composition and the range of content distribution of samples. By comparing the results from lipid composition analysis of the cancer group and the normal group, we found that the major lipid types were the same in both groups, but the proportion of TGs was the highest in the cancer group, while TGs ranked second in the normal group (Figure 4A). The dynamic range of content distribution allows the examination of the lipid molecules with the lowest and highest contents in each group of samples as well as the variations of lipid content across the range of samples. We further investigated the dynamic distribution range of lipid contents and found that the relative TG content was highest in the cancer group and much higher than that in the normal group (Figure 4B).

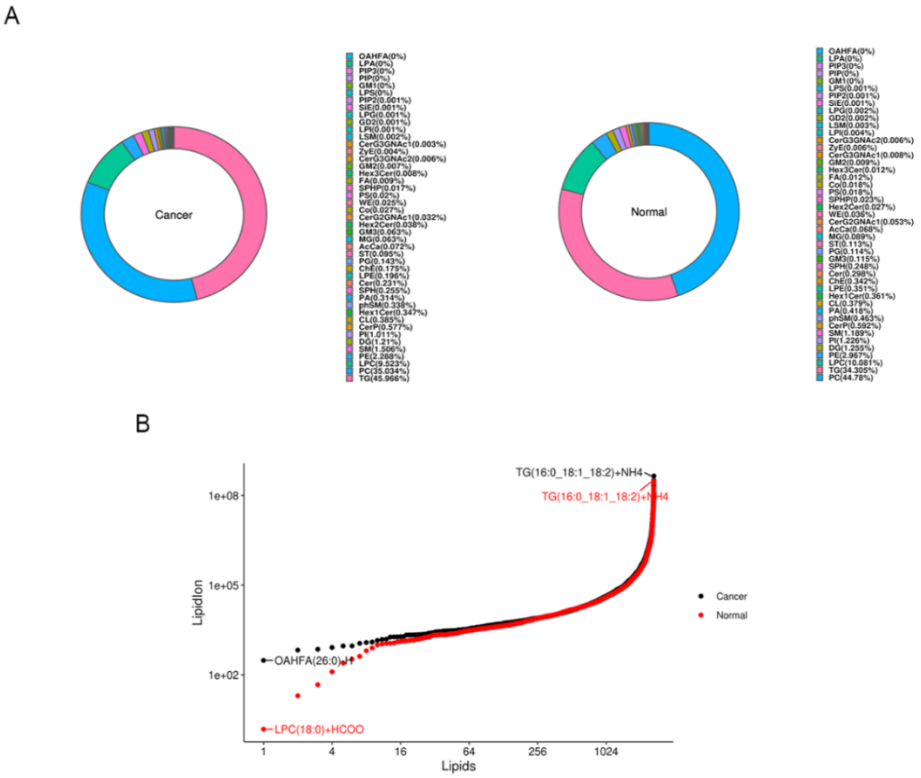

Figure 4: The proportion of TGs among the lipids was higher in the cancer group than in the normal group. (A) Plot of the percentages of 45 lipids in the cancer-normal group. (B) Dynamic distribution range of lipid contents in the cancer-normal group.

Screening and identification of diagnostic lipid biomarkers for breast cancer

Unlike polar metabolites such as amino acids and nucleotides, functional studies of lipids are mainly conducted on a subclass basis, and the biological functions of different lipid subclasses are somewhat different. Changes in the contents of lipid subclasses can reflect changes in lipid function. Therefore, by comparing the changes in the expression of lipid subclasses in different samples, we can screen out important subclasses that may be involved in relevant biological processes. In this study, we compared the changes in 45 lipid compounds in serum between the cancer and normal groups (Figure 5A-B), and we found that TGs changed significantly between these two groups (Figure 5 C-E).

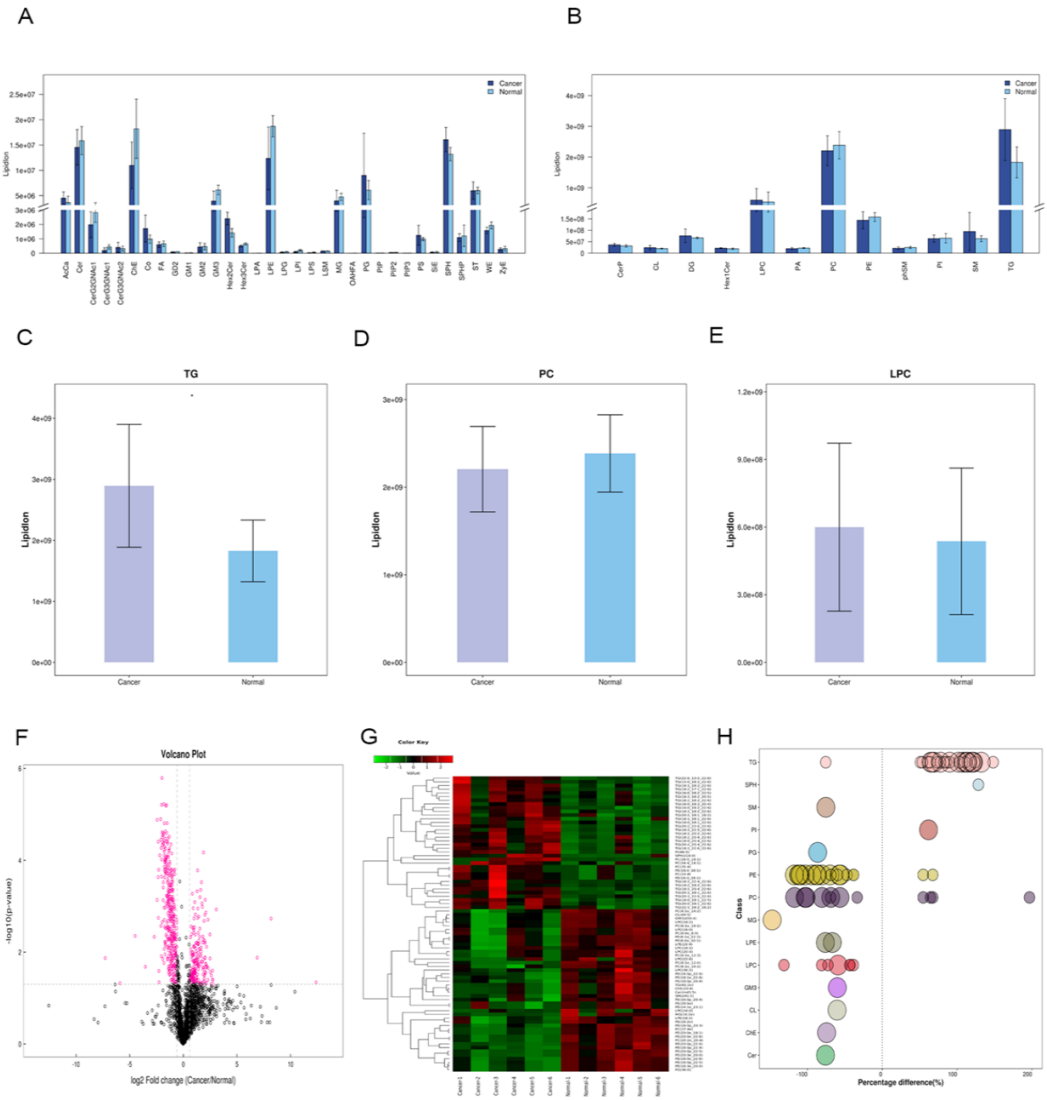

Figure 5: TGs promote the development of breast cancer. (A-B) TGs were the most significantly elevated of the 45 lipids in the cancer group compared with the normal group. (C-E) TG percentages were among the top three lipid percentages and had the most significant change. The results are shown as the means ± SEMs of 6 mice. *p<0.05 vs. control group. (F) Rose red dots are lipid molecules with FC > 1.5 or FC < 0.67, P value < 0.05. Differential lipid molecules screened by univariate statistical analysis. (G) Significantly different lipid (VIP>1, P value < 0.05) expression was used for hierarchical clustering of each group of samples. (H) Bubble size represents the significance of the difference, with smaller bubbles indicating significant differences (0.01<p value<0.05) and larger bubbles indicating highly significant differences (p value<0.01).

Univariate analysis can be used to visualize the significance of lipid changes between two samples, thus helping us screen potential marker lipid molecules (usually FC > 1.5 or FC < 0.67 and P value < 0.05 are used as screening criteria). We visualized the overall differential expression of lipid molecules in the groups with volcano plots, and the results showed that there were significantly differences in the lipid molecules (Figure 5F). To evaluate the rationality of the differential lipids as well as to more comprehensively visualize the relationship between samples and the differences in lipid expression patterns in different samples, we performed hierarchical clustering (HCC) on each group of samples using qualitatively significant differential lipid (VIP>1, P value < 0.05) expression, which assisted us in accurately screening for marker lipids and to investigate alterations to related metabolic processes (Figure 5G-H). The results again demonstrated that lipid metabolism was significantly different in the cancer and normal groups and that the TG content was significantly higher in the cancer group. In addition, we found 12 other lipids with significant differences between the cancer and normal groups (Figure S1A-L).

TG is an important therapeutic target and is closely related to other lipoproteins

Correlation analysis can help to measure metabolic proximities between significantly different lipids (VIP > 1, P value < 0.05) and is useful to further understand the inter-regulation of lipids during changes in biological state. Lipids with correlated expression may be involved in a common biological process; in addition, positively correlated lipids may indicate that they originate from the same synthetic pathway, while negatively correlated lipids may be catabolized for the synthesis of other lipids. In this study, we found that TGs are closely related to other lipids and can positively or negatively regulate some other lipids (Figure 6 A-C). Therefore, we think that TGs play a key role in the development of breast cancer and are clinically significant and poorly studied potential biomarkers.

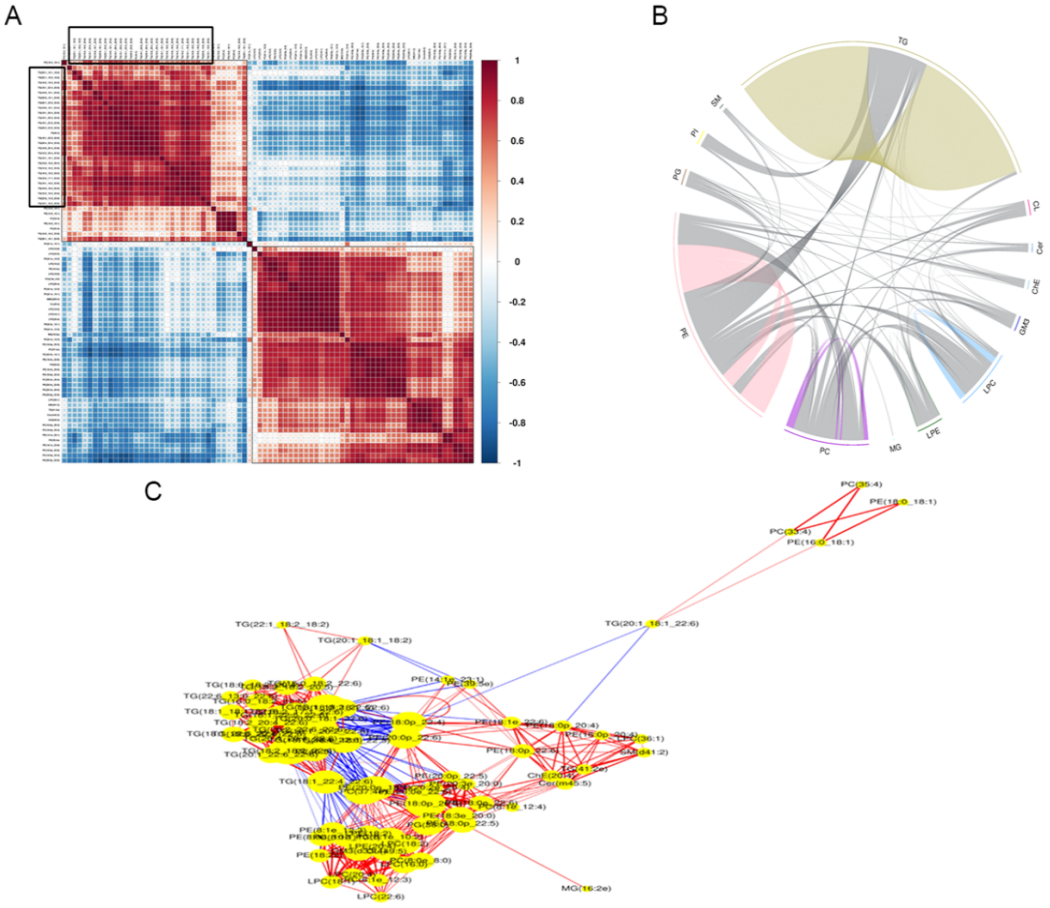

Figure 6: Analysis of the correlations of 45 differential lipids. (A) The correlation analysis results visualized in the form of a correlation clustering heatmap. (B) Chord diagrams showing correlations between lipid subclasses. (C) Network diagrams demonstrating the correlations between lipid molecules.

Discussion

Cancer screening, as part of routine health examinations, allows for the early detection and timely treatment of cancer [17]. Measuring circulating biomarkers is a minimally invasive and routinely used method that appears to be one of the most attractive and convenient ways to screen high-risk populations. Current screening methods focus on the analysis of genetic mutations, ctDNA or proteins in plasma or serum for early cancer diagnosis. However, the clinical application of lipidomic analysis in this area has not been clearly demonstrated.

Recent studies have reported modifications in lipid levels in the prognosis of different types of cancers [18-20]. For instance, the relationship between lipids and lipoproteins and breast cancer was determined [21]. An assessment of serum lipids in breast cancer patients by Ghahremanfard, et al. [22] revealed that elevated serum lipid levels may play an important role in the development of BC, which is in agreement with our lipidomics results in Figure 3B. Chen et al. identified a panel of plasma lipid species able to differentiate between early-stage breast cancer and benign lesions and act as relevant biomarkers for the early diagnosis of BC [23]. However, serum tumour markers have not been used in clinical trials; for example, CA15.3 and BR27.29 are not used for BC detection due to their low sensitivity [24-26].

In this study, serum lipid profiles were found to be significantly different between the cancer and normal groups. After an efficient and strict analysis, a total of 45 differential lipids were found between the groups, as shown in Figure 2A. TGs were the main lipid type among them, revealing that metabolic TG abnormalities could be involved in BC formation, as shown in Figure 5A-B.

Triglycerides (TGs) are the body's main source of stored energy and can be broken down according to the body's needs. Most tissues can use triglyceride breakdown products to supply energy, while the liver, fat and other tissues can also synthesize triglycerides and store them in adipose tissue [27-28]. Although TGs have many physiological functions, excess TGs can lead to altered fat cell function and increased blood viscosity, as well as an increased risk of disease [29,30]. Since cancer cells are rapidly proliferating cells, they rely on the continuous formation of phospholipids and sterols for membrane generation [31]. Unlike many normal human cells, tumour cells have the ability to synthesize fatty acids from scratch to meet the energy requirements of cell proliferation and improve the synthesis of all essential enzymes in these cells to achieve this goal; thus, metabolic signals may also determine that cells are carcinogenic [32,33]. The triglyceride/free fatty acid (TG/FFA) cycle is central to the generation of multiple signal transduction pathways that in turn control various metabolic, physiological, and signalling pathways in the cell [31]. Consistent with this, we found that TGs are closely related to other lipids and are of high research value in this study, as shown in Figure 6 A-C. Recent evidence indicates that lysophosphatidic acid, which is a byproduct of TG/FFA cycling, can activate NF-κB via the G protein-coupled receptor (GPCR) pathway. NF-κB is involved in the expression of the antiapoptotic proteins Bcl-2 and Bcl-xl in a variety of cells, linking the TG/FFA cycling operation to cell survival [34,35]. It has been shown that the combination of malonyl-CoA and the TG/FFA cycle leads to oncogenesis through interrelated metabolic and signalling pathways that allow cell proliferation [31]. However, whether TG/FFA cycling can influence the development of BC has not yet been reported, and this may be an important finding of this study that will be explored in depth in future studies. In addition to TGs, we found that 12 different lipids have potential diagnostic power for BC, as shown in Figure 6. In summary, in this study, we found that TGs were significantly different among serum lipids and could be a potential biomarker for the early diagnosis of breast cancer. These discoveries should provide a valuable reference for the early screening and carcinogenesis of BC.

Conclusion

To our knowledge, the present study is the first to explore lipid biomarkers for breast cancer based on serum lipidomics with MMTV-PyMT mice. In this study, we observed significant differences in the serum lipid profile between the cancer and normal groups in terms of TGs, and TGs were closely associated with other lipids. These results suggest that TGs could be used as potential biomarkers for breast cancer screening. Overall, this study provides new clues to the lipid metabolic pathways associated with breast cancer formation, and we will further validate our findings in future studies.

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Availability of data and materials: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interest: The authors declare that they have no competing interests

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