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(54) **Title:** METHODS FOR DETECTING OR MONITORING CANCER USING LPE AS A MARKER

(57) **Abstract:** A method of detecting a cancer, such as ovarian cancer, in a test subject including (a) determining the amount of a lysophosphatidyl ethanolamine in a sample of a bodily fluid taken from the test subject, and (b) comparing the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject to a range of amounts of the lysophosphatidyl ethanolamine found in samples of the bodily fluid taken from a group of normal subjects of the same species as the test subject and lacking the cancer, such as ovarian cancer, whereby a change in the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid from the test subject indicates the presence of the cancer, such as ovarian cancer.

METHODS FOR DETECTING OR MONITORING CANCER USING LPE AS A MARKER

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 USC 119(e) of U.S. provisional application Serial No. 61/002,282 filed November 7, 2007, U.S. provisional application Serial No. 61/002,989 filed November 14, 2007 and U.S. provisional application Serial No. 61/066,331 filed February 20, 2008, the entire contents of all of which provisional applications are incorporated by reference herein.

BACKGROUND OF THE INVENTION

Field of the Invention

Methods for detecting a cancer, such as ovarian cancer, are disclosed herein. Also discussed herein are methods for monitoring a cancer, such as ovarian cancer. More particularly, disclosed herein are methods for detecting ovarian cancer in a test subject by determining the amount of a lysophosphatidyl ethanolamine ("LPE") in a sample of a bodily fluid taken from the test subject. The methods discussed herein are particularly useful as a screening test for ovarian cancer.

Background Information

Ovarian cancer is one of the deadliest cancers for women, due to its high fatality rate. In the United States in 2007, it was estimated that 22,430 women would be diagnosed with ovarian cancer and 15,280 women would die of ovarian cancer. Unfortunately, heretofore, only 25% of ovarian cancer patients were diagnosed at stage I. Most of the patients were

diagnosed at an advanced stage, stage III or IV, at which the 5-year survival rate decreases to 20 to 25% from 95% at stage I.

Presently, the most commonly used biomarker for diagnosing ovarian cancer is CA-125, a group of surface glycoproteins with uncertain biological function. Although CA-125 is elevated in 82% of women with advanced ovarian cancer, it has very limited clinical application for the detection of early stage disease, exhibiting a positive predictive value of less than 10%. The addition of physical examination by diagnostic ultrasound improves the positive predictive value to 20%, which is still too low to meet the requirement for cancer detection. Developing a clinical test to diagnose ovarian cancer with high sensitivity and specificity at the early stage has become the most urgent issue in battling this refractory disease.

Frequently, the detection of cancer depends upon the detection and inspection of a tumor mass, which has reached sufficient size to be detected by physical examination. The detection of molecular markers of carcinogenesis and tumor growth can solve many of the problems associated with the physical examination of tumors. Samples taken from the patient for screening by molecular techniques are typically blood or urine, and thus require minimally invasive techniques. Thus, they can be used on a regular basis to screen for cancers. In addition, because molecular markers may appear before the tumor reaches a detectable size, it is possible to detect cancers at very early stages in the progression of the disease.

Biomarkers identified from serum proteomic analysis for the detection of ovarian cancer are discussed in Z. Zhang et al., Cancer Research, 64, 5882-5890, August 15, 2004.

Methods for detecting a cancer associated with elevated concentrations of lysophospholipids have been described in US 2002/0123084 and US 2002/0150955.

USP 6,500,633 discloses a method of detecting carcinomas by measuring the level of a glycerol compound, such as glycerol-3-phosphate, in a plasma, serum or urine specimen from a patient.

US 2007/0196875 (inventors: Lian Shan and Stanley L. Hazen) discloses a method for detecting ovarian cancer using plasmenyl-PA as a marker.

US 2008/0020472 (inventors: Lian Shan and Lorelei D. Davis) discloses a method for detecting ovarian cancer using plasmenyl-PE as a marker.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a non-invasive method for detecting a cancer, such as ovarian cancer, in a test subject.

It is another object of the present invention to utilize a molecular marker for the screening and diagnosis of a cancer, such as ovarian cancer.

It is a further object of the present invention to provide a non-invasive method to monitor the presence of a cancer, such as ovarian cancer, over time.

The above objects, as well as other objects, advantages and aims, are satisfied by the present invention.

The present invention concerns a method of detecting a cancer (for example, ovarian cancer) in a test subject comprising:

(a) determining the amount of a lysophosphatidyl ethanolamine in a sample of a bodily fluid taken from the test subject, and

(b) comparing the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject to a range of amounts found in samples of the bodily fluid taken from a group of normal subjects of the same species as the test subject and lacking the cancer (for example, if the bodily fluid taken from the test subject is serum, then the

bodily fluid taken from each member of the group of normal subjects will also be serum), whereby a change in the amount (such as a lower amount) of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject indicates the presence of the cancer (for example, ovarian cancer).

The present invention further concerns a method for monitoring a cancer (for example, ovarian cancer) in a test subject over time comprising:

(a) determining the amount of a lysophosphatidyl ethanolamine in a sample of a bodily fluid taken from the test subject at a first time,

(b) determining the amount of the lysophosphatidyl ethanolamine in a sample of the bodily fluid taken from the test subject at a second time (for example, if the bodily fluid in step (a) is serum, then the bodily fluid in step (b) will also be serum), which is later than the first time,

(c) comparing the amounts of the lysophosphatidyl ethanolamine in each of step (a) and step (b) to determine whether there has been an increase or a decrease in the amount of the lysophosphatidyl ethanolamine in a sample of the bodily fluid taken from the test subject at the later time relative to the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject at the first time, whereby a decrease from the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject at the later time indicates the presence of, or worsening of, the cancer (for example, ovarian cancer), or an increase from the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject at the later time indicates an absence, or improvement of, the cancer (for example, ovarian cancer).

BRIEF DECRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the levels of 18:0 lysophosphatidyl ethanolamine ("18:0 LPE") in plasma samples from ovarian cancer patients and patients without ovarian cancer ("healthy controls").

Fig. 2 is a graph showing the levels of 18:1 lysophosphatidyl ethanolamine ("18:1 LPE") in plasma samples from ovarian cancer patients and patients without ovarian cancer ("healthy controls").

Fig. 3 is a graph showing the levels of 18:2 lysophosphatidyl ethanolamine ("18:2 LPE") in plasma samples from ovarian cancer patients and patients without ovarian cancer ("healthy controls").

Fig. 4 is a graph showing the levels of 16:0 lysophosphatidyl ethanolamine ("16:0 LPE") in plasma samples from ovarian cancer patients and patients without ovarian cancer ("healthy controls").

Fig. 5 is a graph showing the levels of 20:4 lysophosphatidyl ethanolamine ("20:4 LPE") in plasma samples from ovarian cancer patients and patients without ovarian cancer ("healthy controls").

Fig. 6 is a graph showing the levels of 22:6 lysophosphatidyl ethanolamine ("22:6 LPE") in plasma samples from ovarian cancer patients and patients without ovarian cancer ("healthy controls").

DETAILED DESCRIPTION OF THE INVENTION

Applicants have discovered that the lipid lysophosphatidyl ethanolamine ("LPE") can be used in the methods disclosed herein for detecting a cancer, such as ovarian cancer, and monitoring a cancer, such as ovarian cancer, in a test subject.

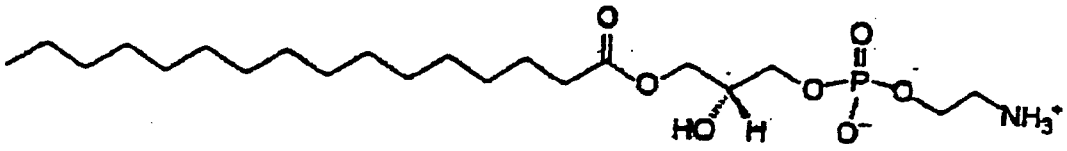
Non-limiting examples of the lysophosphatidyl ethanolamine that can be used in the methods disclosed herein include the following: 18:0 LPE, 18:1 LPE, 18:2 LPE, 16:0 LPE, 22:6 LPE and 20:4 LPE.

The molecule weights, chemical names and structures for 16:0 LPE, 18:0 LPE, 18:1 LPE, 18:2 LPE, 20:4 LPE and 22:6 LPE are as follows:

16:0 LPE

mw 453.55

1-Palmitoyl-2-Hydroxy-*sn*-Glycero-3-Phosphoethanolamine



18:0 LPE

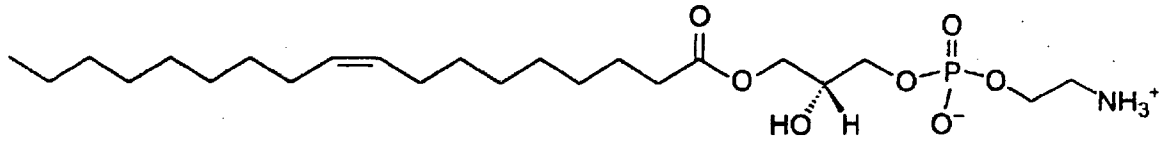
mw 481.61

1-Stearoyl-2-Hydroxy-*sn*-Glycero-3-Phosphoethanolamine

18:1 LPE

mw 479.59

1-Oleoyl-2-Hydroxy-*sn*-Glycero-3-Phosphoethanolamine



18:2 LPE

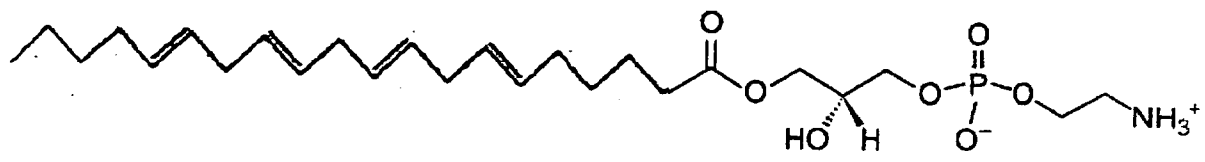
mw 477.58

1-linoleoyl-2-Hydroxy-*sn*-Glycero-3-Phosphoethanolamine

20:4 LPE

mw 501.59

1-Arachidonoyl-2-Hydroxy-*sn*-Glycero-3-Phosphoethanolamine



22:6 LPE

mw: 525.60

1-Docosahexaenoeyl-2-Hydroxy-*sn*-Glycero-3-Phosphoethanolamine

In an embodiment of the invention, an amount of a lysophosphatidyl ethanolamine ("LPE) found in a sample of a bodily fluid taken from a test subject is compared to the amount of the LPE found samples taken from normal subjects of the same species as the test subject lacking a cancer (for example, ovarian cancer) (e.g., if the test subject is a human, then the normal subject is a human who does not have the cancer (for example, ovarian cancer)). Thus, the amount of a LPE taken from a test subject, e.g., a female, is determined, and a range of amounts of LPE taken from normal females, e.g., lacking ovarian cancer, is obtained. A lower amount of the LPE found in the sample of the bodily fluid taken from the test subject when compared to a range of amounts of the LPE in samples of the bodily fluid taken from a group of normal subjects of the same species as the test subject and lacking the cancer (for example, ovarian cancer), indicates the presence of the cancer (for example, ovarian cancer).

The amount of the LPE detected in the sample taken from a test subject may be measured by first extracting lipids as described in detail infra. The amount of the LPE is then quantified using standard procedures, such as mass spectroscopy, gas chromatography, HPLC, NMR or other approaches.

In addition to the direct measurement of the LPE by extraction, antibodies, such as monoclonal antibodies reactive with the LPE can be used in an assay to detect the amount of the LPE. For example, anti-LPE antibodies may be labeled using standard procedures and used in assays including radioimmunoassay (RIA), both solid and liquid phase, fluorescence-linked assays or enzyme-linked immunosorbent assays (ELISA), wherein the antibody is used to detect the presence and amount of the LPE.

The test subject can be a eukaryotic organism, preferably a vertebrate, including, but not limited to, a mammal, a bird, a fish, an amphibian or a reptile. Preferably, the subject is a mammal, most preferably a human. The bodily fluid includes, but is not limited to, plasma, serum, urine, saliva, ascites, cerebral spinal fluid or pleural fluid. Preferably, the bodily fluid is plasma or a serum which is obtained from a whole blood specimen from the test subject.

The methods disclosed herein can be used to detect, screen or monitor for a broad range of cancers at an early stage. Such cancers include gynecological cancers, including ovarian cancer, breast cancer, cervical cancer, uterine cancer, endometrial cancer, peritoneal cancer, fallopian tube cancer and vulva cancer. Other cancers that can be detected, screened or monitored according to the methods disclosed herein include, but are not limited to, testicular cancer, colon cancer, lung cancer, prostate cancer, bladder cancer, kidney cancer, thyroid cancer, stomach cancer, pancreatic cancer, brain cancer, liver cancer, ureter cancer, esophageal cancer and larynx cancer. The methods disclosed herein are preferably directed to detecting ovarian cancer.

The methods disclosed herein are non-invasive and require only a bodily fluid specimen, such as a blood specimen from the test subject (patient). Thus, such methods are particularly useful for screening patients who have not been previously diagnosed as having ovarian cancer. Such patients include women at elevated risk by virtue of a family history of the disease, premenopausal women with anovulatory cycles and postmenopausal women.

The methods disclosed herein include a screening test for identifying within a risk population, a subject population with a greater propensity for developing ovarian cancer.

The methods disclosed herein can provide a number of benefits. First, the methods provide a rapid and economical screen for large numbers of subjects to promote early diagnosis of ovarian cancer, which can result in improved quality of life and better survival rates for patients.

Using the methods disclosed herein for prognosis, the medical professional can determine whether a subject having ovarian cancer in the early stages requires therapy or does not require therapy. This could also identify subjects who may not benefit from a particular form of therapy, e.g., surgery, chemotherapy, radiation or biological therapies. Such information could result in an improved therapy design for obtaining better responses to therapy.

The methods disclosed herein can also be used to identify patients for whom therapy should be altered from one therapeutic agent to another. This could obviate the need for "second look" invasive procedures to determine the patient's response to the therapy and facilitate decisions as to whether the particular type of therapy should be continued, terminated or altered.

Because cancers may recur in a significant number of patients with advanced cancers, early detection and continued monitoring over time using the methods disclosed herein can identify early occult (i.e., "hidden") recurrences prior to symptoms presenting themselves.

In addition, methods disclosed herein will facilitate distinguishing benign from malignant tumors. Masses in the ovary can be initially detected using procedures such as ultrasound or by physical examination. Thereafter, the methods disclosed herein can be used to diagnose the presence of a cancer (for example, ovarian cancer). This could obviate the

need for surgical intervention, and/or identify subjects for whom continued monitoring is appropriate, resulting in improved early detection and survival for ovarian cancer patients.

Examples

The present invention will now be described in the context of the following non-limiting examples.

Example 1: Quantitative Determination of LPE Levels in Human Plasma

(a) Extraction of LPE from Human Plasma

LPE in plasma was extracted using a modified Bligh-Dyer method, which follows the following procedure: First mix 200 pmol 14:0 LPE with 200 µl plasma. The mixture was vortexed and 2 ml 2:1 (v:v) methanol-chloroform was added. The mixture was vortexed again and kept at room temperature for 10 minutes. Then it was centrifuged at 4000 rpm at 10 °C for 10 minutes. The top liquid layer was transferred into another tube and dried under nitrogen. The dried pellet was dissolved in 200 µl 100 mM ammonium acetate in methanol and centrifuged at 9000 rpm for 5 minutes. 50 µl of the supernatant was injected and analyzed by LC/ESI/MS/MS.

(b). LC/ESI/MS/MS Analysis of LPE

LC/ESI/MS/MS analysis of LPE species was performed using a Quattro Micro mass spectrometer (Micromass, Altrincham, U.K.) equipped with an electrospray ionization (ESI) probe and interfaced with a Shimadzu SCL-10Avp HPLC system (Shimadzu, Tokyo, Japan). Lipids were separated with a Betabasic-18 column (20×2.1 mm, 5 µm, Thermo Electron, Waltham, MA), protected by a Betabasic 18 pre-column (10×2.1 mm, 5 µm, Thermo Electron, Waltham, MA). 1mM ammonium acetate aqueous solution was used as mobile phase A and 1 mM ammonium acetate in methanol was used as mobile phase B. The flow

rate was 200 µl/minute. The gradient used was as follows: the column was first equilibrated with 50% B (50% A), followed by a linear change from 50% B (50% A) to 100% B (0% A) in the first 4 minutes. The gradient was kept at 100% B in the following 8 minutes. In the following 4 minutes, the gradient was changed back to 50% B (50% A) to re-equilibrate the column. Mass spectrometric analyses were performed online using electrospray ionization tandem mass spectrometry in the negative multiple reaction monitoring (MRM) mode. The MS parameters are: capillary voltage, 3.0 KV; cone voltage, 35 V; source temperature, 100 °C; desolvation temperature, 350 °C; flow rate of desolvation gas, 500 L/hr; flow rate of cone gas, 50 L/hr; mass resolution of both parent and daughter ions, 15.0; multiplier, 650. The MRM transitions used to detect LPE were the mass to charge ratio (m/z) for their molecular anion M^- and their corresponding daughter ion (collision energy 25 eV).

(c) Levels of LPE

The levels of 16:0 LPE, 18:2 LPE, 18:1 LPE, 18:0 LPE, 20:4 LPE and 22.6 LPE were determined in a negative MRM mode. The MRM transitions used to detect them were the mass to charge ratio (m/z) for their molecular anion M^- and their corresponding daughter ion (collision energy 25 eV).

Example 2: Data Analysis

Data analysis was done using the student t-test and the peak area ratio of analyte to internal standard was determined. The results are shown in Fig. 1 to Fig. 6.

Forty (40) plasma samples were collected. Among them were twenty (20) stage III ovarian cancer patients and twenty (20) healthy controls. The LPE data are expressed as peak area ratio of the LPE and its internal standard, 14:0 LPE. The results are shown in Table 1 below and in Figs. 1 to 6.

Table 1. Levels of 16:0 LPE, 18:2 LPE, 18:1 LPE, 18:0 LPE, 20:4 LPE, 22:6 LPE, their corresponding standard deviation, and p value of ovarian cancer patients related to healthy controls

	Ovarian Cancer		Healthy control		p value
	LPE level	Standard Deviation	LPE level	Standard Deviation	
16:0 LPE	0.359	0.095	0.490	0.160	<0.01
18:2 LPE	0.472	0.212	0.853	0.426	<0.01
18:1 LPE	0.285	0.128	0.568	0.379	<0.01
18:0 LPE	0.382	0.100	0.403	0.162	<0.01
20:4 LPE	0.123	0.037	0.147	0.052	0.10
22:6 LPE	0.0138	0.0067	0.0164	0.0068	0.23

WHAT IS CLAIMED IS:

1. A method of detecting a cancer in a test subject comprising:

(a) determining the amount of a lysophosphatidyl ethanolamine in a sample of a bodily fluid taken from the test subject, and

(b) comparing the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid from the test subject to a range of amounts of the lysophosphatidyl ethanolamine found in samples of said bodily fluid taken from a group of normal subjects of the same species as the test subject and lacking the cancer, whereby a change in the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid from the test subject indicates the presence of the cancer.

2. The method of claim 1, wherein the test subject is a human.

3. The method of claim 2, wherein the cancer is ovarian cancer.

4. The method of claim 3, wherein, in step (b), the change in the amount is a lower amount.

5. The method of claim 4, wherein the bodily fluid is plasma.

6. The method of claim 5, wherein the lysophosphatidyl ethanolamine is selected from the group consisting of 18:0 LPE, 18:1 LPE, 18:2 LPE, 16:0 LPE, 22:6 LPE and 20:4 LPE.

7. A method for monitoring a cancer in a test subject over time comprising:

(a) determining the amount of a lysophosphatidyl ethanolamine in a sample of a bodily fluid taken from a test subject at a first time,

(b) determining the amount of the lysophosphatidyl ethanolamine in a sample of the bodily fluid taken from said test subject at a second time, which is later than the first time,

(c) comparing the amounts of the lysophosphatidyl ethanolamine in each of step (a) and step (b) to determine whether there has been an increase or a decrease in the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject at the later time relative to the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject at the first time, whereby a decrease from the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject at the later time indicates the presence of or worsening of the cancer, or an increase from the amount of the lysophosphatidyl ethanolamine in the sample of the bodily fluid taken from the test subject at the later time indicates an absence or improvement of the cancer.

8. The method of claim 7, wherein the test subject is a human.

9. The method of claim 8, wherein the cancer is ovarian cancer.

10. The method of claim 9, wherein the lysophosphatidyl ethanolamine is selected from the group consisting of 18:0 LPE, 18:1 LPE, 18:2 LPE, 16:0 LPE, 22:6 LPE and 20:4 LPE.

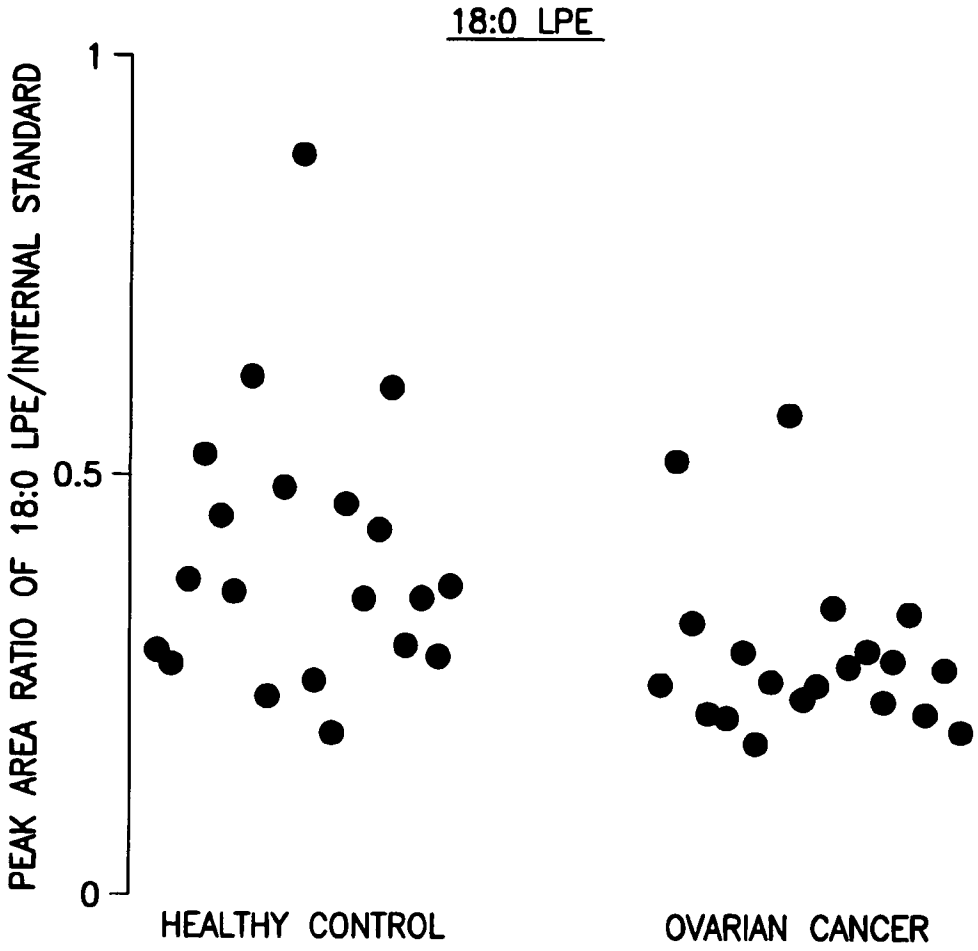

18:0 LPE
PEAK AREA RATIO OF 18:0 LPE/INTERNAL STANDARD
1
0.5
0
HEALTHY CONTROL
OVARIAN CANCER

FIG. 1

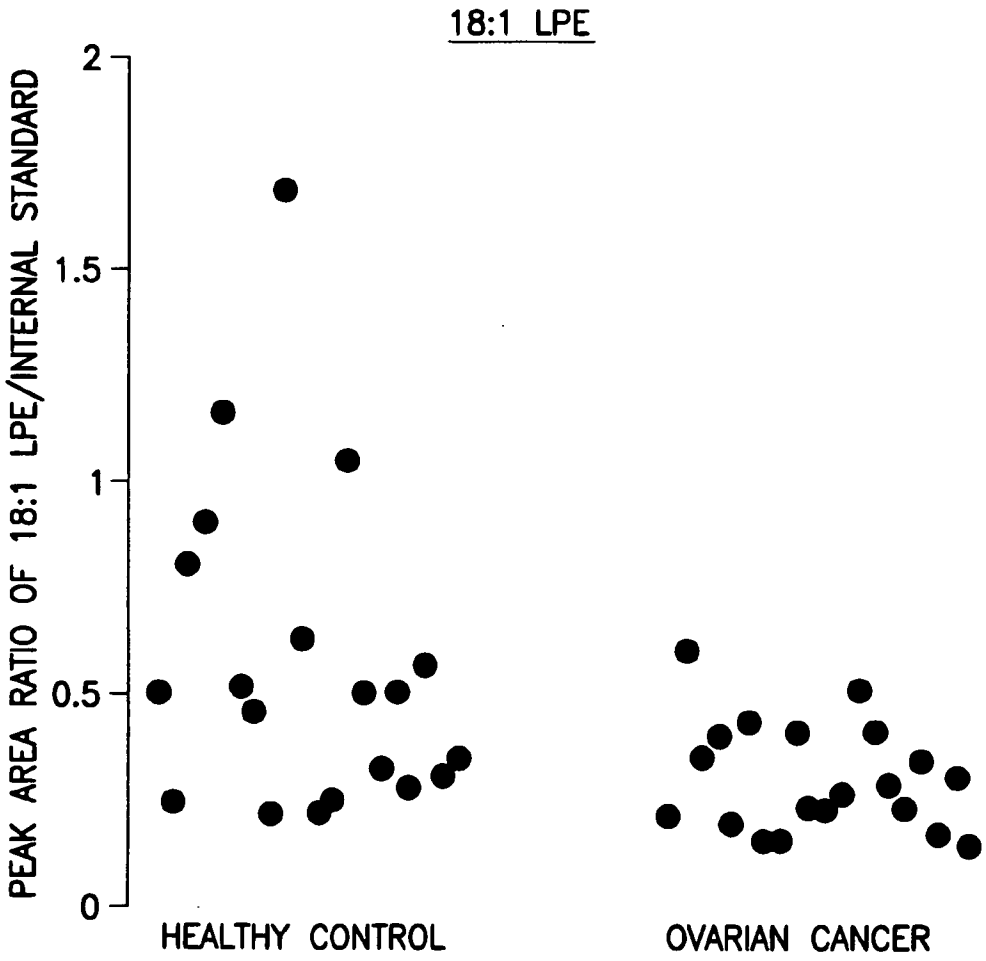

18:1 LPE
PEAK AREA RATIO OF 18:1 LPE/INTERNAL STANDARD
2
1.5
1
0.5
0
HEALTHY CONTROL
OVARIAN CANCER

FIG.2

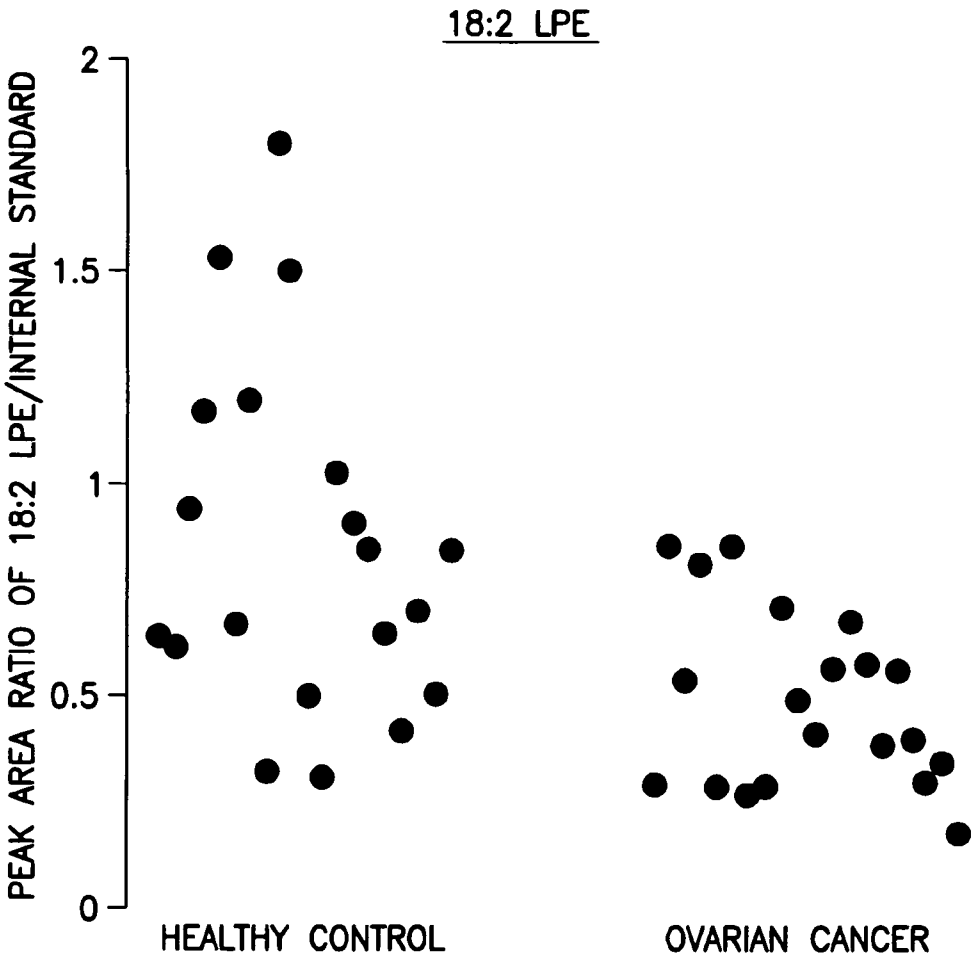

18:2 LPE
PEAK AREA RATIO OF 18:2 LPE/INTERNAL STANDARD
2
1.5
1
0.5
0
HEALTHY CONTROL
OVARIAN CANCER

FIG.3

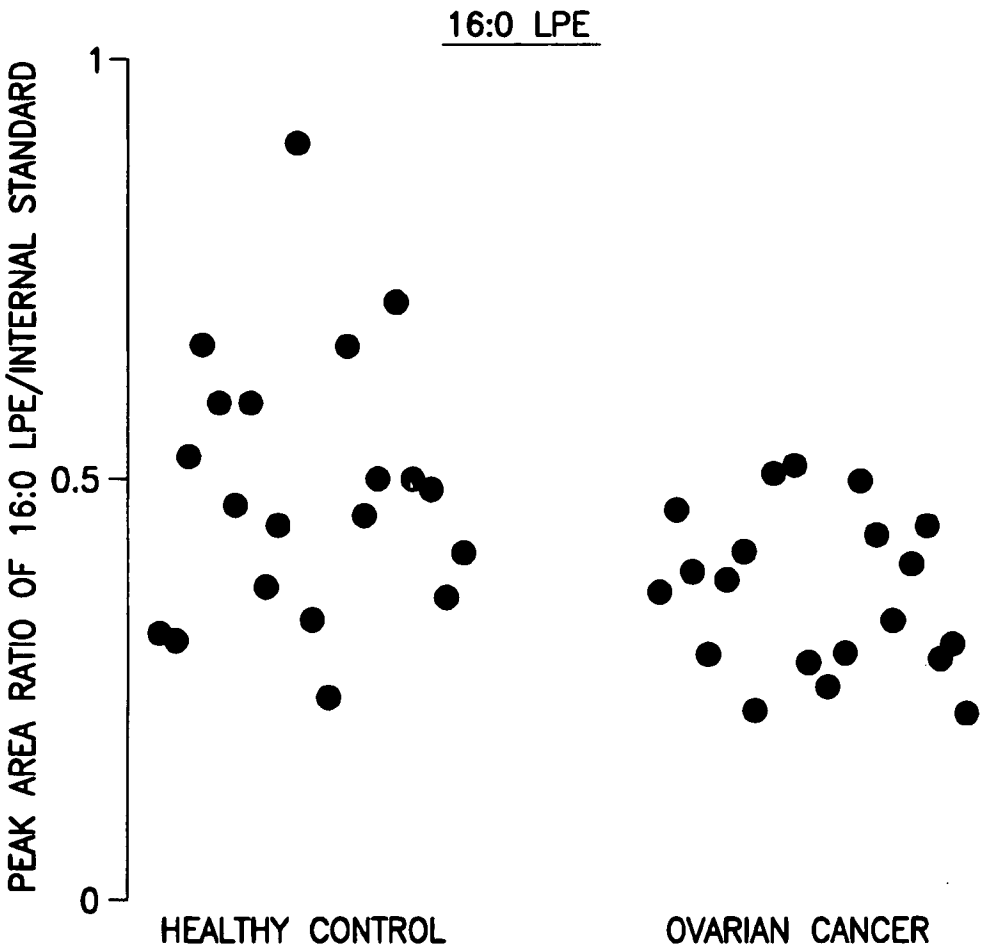

16:0 LPE
PEAK AREA RATIO OF 16:0 LPE/INTERNAL STANDARD
1
0.5
0
HEALTHY CONTROL
OVARIAN CANCER

FIG.4

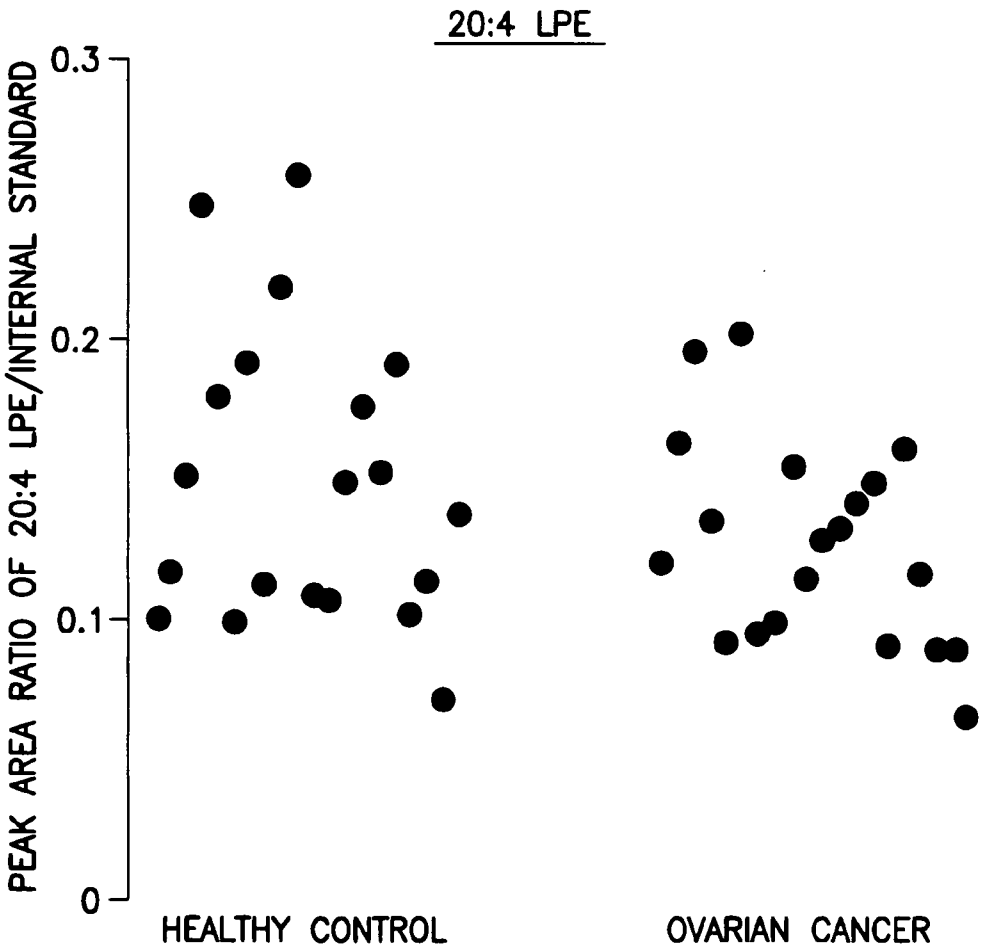

20:4 LPE
PEAK AREA RATIO OF 20:4 LPE/INTERNAL STANDARD
0.3
0.2
0.1
0
HEALTHY CONTROL
OVARIAN CANCER

FIG.5

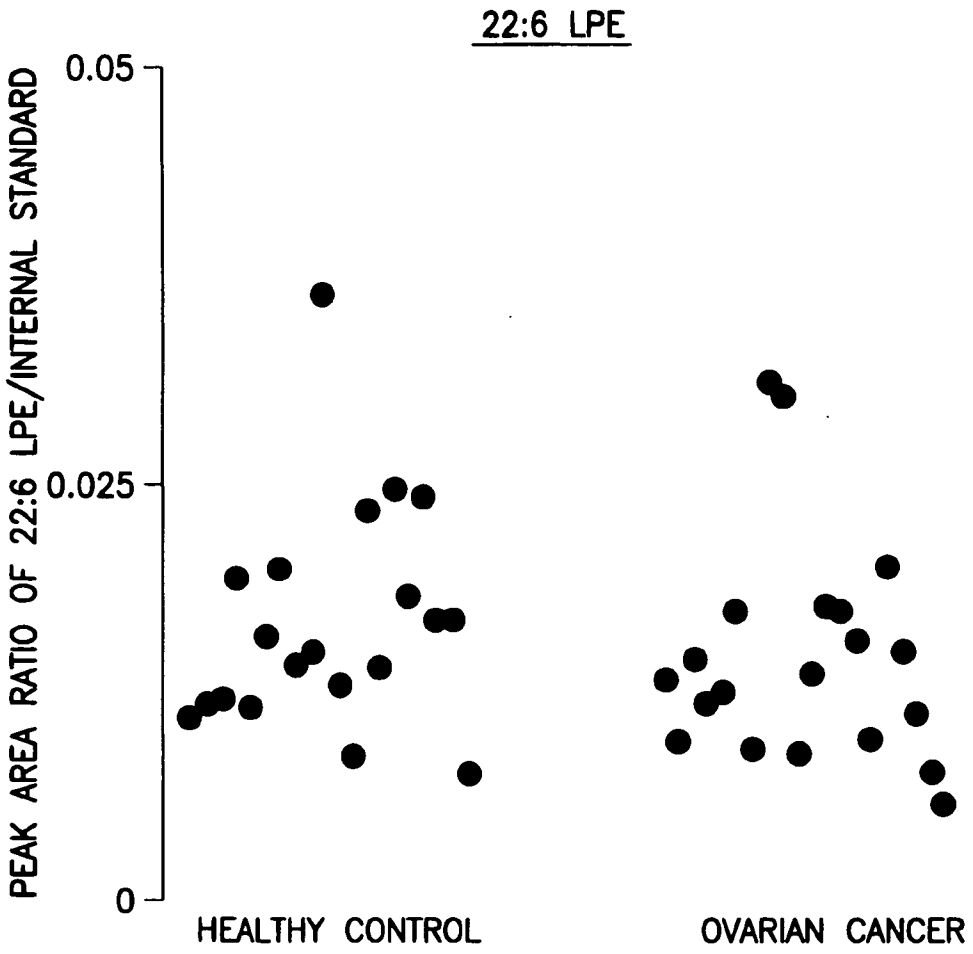

22:6 LPE
PEAK AREA RATIO OF 22:6 LPE/INTERNAL STANDARD
0.05
0.025
0
HEALTHY CONTROL
OVARIAN CANCER

FIG.6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/12491

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/574; C12Q 1/28 (2008.04)
USPC - 435/7.23, 28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 435/7.23, 28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/195.15; 436/536; 530/388.8 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST(DB=PGPB,USPT,USOC,EPAB,JPAB), Google(lysophosphatidyl ethanolamine, plasmenyl-PA, Plasmalogens, lysophosphatidylethanolamine), Google Scholar(lysophosphatidylethanolamine ovarian cancer, 22:6 LPE)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0137541 A1 (MILLS et al.) 15 July 2004 (15.01.2004) Abstract; para [0006], [0009]-[0012], [0017], [0025], [0027]-[0028], [0062]-[0078]	1-3
Y		4-10
Y	NOGUCHI et al. Identification of p2y9/GPR23 as a Novel G Protein-coupled Receptor for Lysophosphatidic Acid, Structurally Distant from the Edg Family. THE JOURNAL OF BIOLOGICAL CHEMISTRY, July 2003, Vol 278, No 28, pp. 25600-25606, pg 25600, right col, para 1, ln 6-12	4-10

☐ Further documents are listed in the continuation of Box C. ☐

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Date of the actual completion of the international search	Date of mailing of the international search report
5 January 2009 (05.01.2009)	13 JAN 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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