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Hyperlipoproteinemia (a) is associated with breast cancer in a Han Chinese population

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Abstract

To investigate the relationship between serum lipoprotein (a) (LP(a)) levels and breast cancer as well as the clinicopathologic characteristics of breast cancer in a Han Chinese population.

This study included 314 breast cancer patients, 51 patients with benign breast tumors, and 185 healthy control subjects. All study subjects were Han Chinese with similar socio-economic backgrounds, who were local residents of Zhoushan, Zhejiang, China or who had lived in Zhoushan for a long period of time. Serum concentrations of LP(a) were determined using a latex-enhanced immunoturbidimetric assay. Clinicopathological characteristics of patients were retrieved from medical records, which included the histopathological type, grade, stage, and molecular subtype of the disease, the expression of estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki67, and the level of reproductive hormones. Correlations between 2 groups were evaluated using the Spearman correlation analysis. Associations among ≥3 groups were interpreted using the Kruskal-Wallis H test or the logistic regression test.

Elevated serum LP(a) levels were detected in breast cancer patients compared with healthy control subjects, but no significant differences in LP(a) were detected between breast cancer and benign tumor or between benign tumor and healthy control. In breast cancer patients, serum LP(a) levels were inversely associated with HER2 expression, but they were not significantly correlated with any other clinicopathologic characteristics of breast cancer evaluated in this study.

Elevated serum LP(a) levels were associated with breast cancer in a Han Chinese population.

Abbreviations: Apoa = apolipoprotein(a), LDL = low density lipoprotein, LP(a) = lipoprotein (a).

Keywords: breast cancer, Han Chinese, HER2, lipoprotein (a)

1. Introduction

Breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer-related death in women worldwide.[1] While the breast cancer incidence in the United States increased slightly by 0.3% per year from 2012 to 2016,[2] the incidence in China has been growing more than twice as fast as the world's average since the 90s, and it is estimated to rise to a rate of over 100 cases per 100,000 women by 2021 if the trend continues.[3] This rapid increase in breast cancer is attributed to China's fast economic growth, the unique one-child policy, as well as a general lack of awareness about breast cancer in rural China, leading to delayed diagnosis and advanced stage of the disease at presentation.[3] It is recognized that early diagnosis and adequate medical intervention need to be imposed to improve patient outcome.

Breast cancer can result from environmental and hereditary risk factors. The environmental factors include unhealthy diet, drinking, smoking, obesity, exposures to toxicants or ionizing radiation, higher levels of certain hormones, and reproductive choices.[4,5] Approximately 5% to 10% of breast cancer have a hereditary cause, and most of these are accounted for by harmful mutations in 2 tumor suppressor genes: BRCA1 and BRCA2.[6,7] In clinical settings, it is well recognized that breast cancer is a heterogeneous disease with different histological presentations and treatment responses. To guide prognostication and treatment regimen, breast cancer is traditionally divided into 5 molecular subtypes: luminal A, luminal B, HER2, triple-negative/basal-like, and normal-like. With a new era of personalized medicine on the horizon, molecular techniques such as gene expression profiling have been used to characterize molecular signatures of the disease, as well as to identify new biomarkers for precise diagnosis and treatment.[8,9]

Lipoprotein (a) (LP(a)) is a modified type of low density lipoprotein (LDL), containing an additional protein called apolipoprotein(a) (apoa), which is covalently bound to apolipoprotein B-100.[10] Apoa is structurally similar to plasminogen, and it inhibits fibrinolysis by competing with plasminogen binding.[11] Moreover, LP(a) carries atherosclerosis-causing cholesterol and oxidized phospholipids that recruit inflammatory cells to vessel walls.[12] Numerous studies have identified LP(a) as

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a risk factor for atherosclerotic diseases such as myocardial infarction and stroke.[13,14] LP(a) is also implicated in malignancies,[15] but its functional role in cancer development in not clearly defined. Low LP(a) levels were linked to all-cause and cancer-related deaths in a Japanese cohort study[16,17]; however, elevated LP(a) levels were found to be associated with a number of malignancies in Chinese cohort studies.[18,19] These controversial findings suggest that the relationship between LP(a) and the risk of cancer may be related to the ethnicity of the patient cohort.

In the present study, we compared serum LP(a) levels among patients with breast cancer, patients with benign breast tumors, and healthy control subjects. We also examined the relationship between serum LP(a) levels and the clinicopathologic characteristics of breast cancer including the histopathological type, grade, stage, and molecular subtype of the disease and the expression of estrogen receptor (ER), progesterone receptor (PR), Ki67, and HER2. The relationship between LP(a) and reproductive hormone levels in breast cancer patients was also evaluated.

2. Materials and methods

2.1. Patients and healthy controls

This study included 314 patients with breast cancer, 51 patients with benign breast tumors (including mammobroblast and intraductal papilloma), and 185 healthy control subjects. The 314 breast cancer patients were admitted to the Breast Center of Zhoushan Hospital (Zhejiang, China) from 2015 to 2017. Breast cancer was confirmed by histopathological evaluation, and the patients had no major comorbidities. Patients who met any of the following criteria were exclude: a body weight of >30% above normal, uncontrolled diabetes, thyroid disorders, severe liver disease, familial hypercholesterolemia, prior diagnosis of malignant tumors, prior chemotherapy or radiotherapy, pregnancy. The clinicopathological characteristics of patients including the histopathological type, grade, stage, and molecular subtype of the disease, the expression of ER, PR, HER2, and Ki67, and the level of reproductive hormones were obtained from patient medical records. The 51 patients with benign breast tumors were randomly selected from patients admitted to Zhoushan Hospital in the same period (2015–2017). Benign breast tumor was confirmed by histopathological evaluation conducted independently by 2 senior pathologists. All study subjects underwent medical examinations at the Check-up Center of Zhoushan Hospital. All study subjects were Han Chinese with similar socioeconomic backgrounds, who were local residents of Zhoushan or who had lived in Zhoushan for a long period of time. All study subjects gave written informed consent. This study was approved by the Ethics Committee of Zhoushan Hospital (2017-051) and written informed consent was obtained from the patients.

2.2. Laboratory tests

Blood samples were collected in the morning after an overnight fast. Serum concentrations of LP(a) were determined using a latex-enhanced immunoturbidimetric assay kit from Meikang Biotech Co., Ltd. (Shanghai, China) following manufacturer's instructions. All biochemical tests were performed on a Beckman Coulter AU5800 clinical chemistry analyzer.

2.3. Statistical analysis

All data were interpreted using SPSS 22.0 (IBM Corp, Armonk, NY, USA) and SAS9.4 (STATISTICAL ANALYSIS SYSTEM, SAS Institute Inc, Raleigh, North Carolina, USA) software. Data not normally distributed are presented as median with interquartile range. Correlations between 2 groups were evaluated using the Spearman correlation analysis. Associations among ≥3 groups were interpreted using the Kruskal-Wallis H test or the logistic regression test. A P value $<.05$ was deemed statistically significant.

3. Results

3.1. Comparison of serum LP(a) levels among breast cancer, benign breast tumor, and healthy control

As shown in Fig. 1, patients with breast cancer, patients with benign breast tumors, and healthy control subjects showed median serum LP(a) levels of 163.95, 153.60, and 112.90 ng/mL, respectively. The Kruskal-Wallis H test revealed a statistically

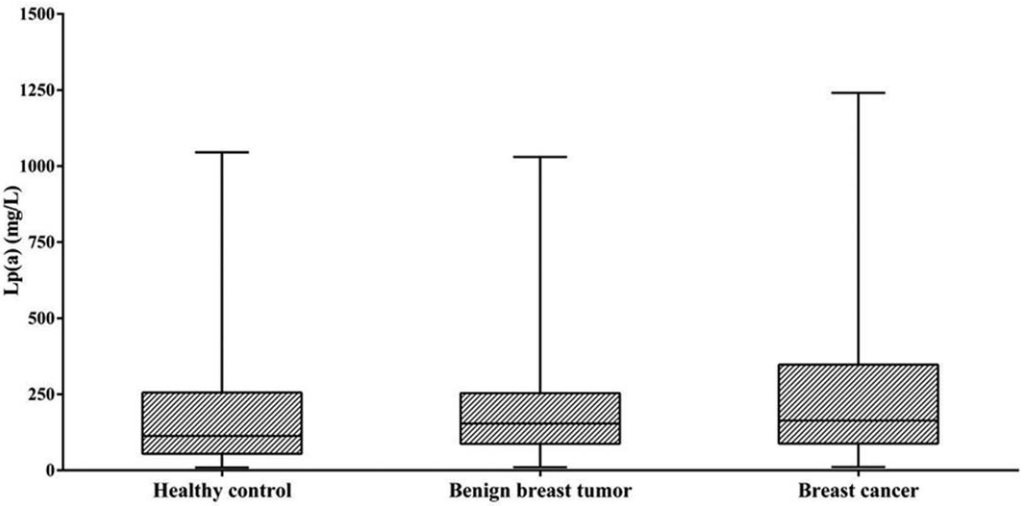

Figure 1. Serum LP(a) levels in patients with breast cancer or benign breast tumor and healthy controls.

Table 1

Serum LP(a) levels in breast cancer by various categories.

Classification	Number	Serum LP(a) level (median [25th–75th], ng/mL)	*H*	*P*-value
Histopathological type				
DCIS	39	172.20 (123.90–345.90)	4.154	.125
IDC	244	155.95 (82.18–328.58)		
Others	31	254.00 (64.00–523.00)		
PT				
PT0	26	167.65 (129.98–327.73)	7.698	.053
PT1	157	191.60 (107.65–406.25)		
PT2	119	142.20 (74.40–335.30)		
PT3	12	73.40 (52.68–205.00)		
PN				
PN0	207	178.00 (93.40–361.40)	6.724	.081
PN1	56	149.70 (81.23–372.15)		
PN2	30	123.45 (53.28–191.78)		
PN3	21	218.40 (77.90–455.15)		
Overall stage				
0	18	140.30 (96.70–266.58)	4.380	.223
I	115	194.80 (112.00–385.50)		
II	124	160.15 (82.73–365.55)		
III	57	133.40 (66.20–332.80)		
Grade				
1	24	125.10 (70.15–361.70)	0.859	.651
2	158	165.35 (82.78–360.25)		
3	52	146.50 (71.93–282.18)		
NA	80			
ER				
≤10	139	164.30 (89.20–361.10)	0.966	.617
10–50	45	(72.80–462.65)		
>50	127	166.40 (82.70–323.40)		
NA	3			
PR				
≤10	173	167.10 (87.35–365.95)	2.242	.326
10–50	76	169.15 (100.50–412.65)		
>50	62	155.85 (68.68–266.58)		
NA	3			
HER2				
Negative	145	188.10 (97.70–367.80)	7.972	.047
+	52	145.65 (70.20–419.35)		
++	61	198.80 (105.95–397.80)		
+++	53	126.20 (77.60–203.65)		
NA	3			
Ki67				
<20	193	164.30 (100.90–380.40)	2.664	.264
20–50	60	125.30 (71.60–304.95)		
≥50	57	196.80 (87.35–345.70)		
NA	4			
Molecular subtype				
Luminal-A	65	142.70 (65.75–290.40)	8.542	.074
Luminal-B (HER2 negative)	94	175.10 (114.08–409.53)		
Luminal-B (HER2 positive)	19	126.20 (63.10–248.20)		
HER2 overexpression	34	126.70 (82.60–190.73)		
Triple-negative	65	188.10 (90.65–389.05)		
NA	37			

DCIS = ductal carcinoma in situ, IDC = Invasive ductal carcinoma.

significant difference among the medians of the 3 groups ($H=14.318$, $P=.001$; Fig. 1). Further, rank-sum test showed that the median LP(a) level in breast cancer patients was significantly higher than that in healthy controls ($P=.00019$). However, no significant differences were detected between breast cancer and benign tumor or between benign tumor and healthy control ($P>.05$).

3.2. The relationship between serum LP(a) levels and the clinicopathologic characteristics of breast cancer

The 314 breast cancer patients enrolled in this study were categorized according to the histopathological type, grade, stage, and molecular subtype of the disease and the expression of ER, PR, HER2, and Ki67 (Table 1). Logistic regression analysis revealed that serum LP(a) levels were inversely associated with

Table 2

Differences in serum LP(a) levels between 2 breast cancer categories within a specific classification were analyzed using the Spearman correlation analysis.

	Model 1			Model 2		
Classification	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Histopathological type						
DCIS	1.000	Reference		1.000	Reference	
IDC	0.999	0.998–1.001	.403	0.999	0.998–1.001	.327
Others	1.001	1.000–1.003	.120	1.001	0.999–1.003	.144
PT						
PT0	1.000	Reference		1.000	Reference	
PT1	1.001	0.998–1.003	.597	1.000	0.998–1.003	.687
PT2	1.000	0.998–1.002	.857	1.000	0.998–1.002	.829
PT3	0.994	0.987–1.001	.092	0.994	0.987–1.001	.100
PN						
PN0	1.000	Reference		1.000	Reference	
PN1	0.999	0.998–1.001	.302	0.999	0.998–1.001	.271
PN2	0.998	0.995–1.000	.082	0.998	0.995–1.000	.061
PN3	1.000	0.998–1.002	.908	1.000	0.998–1.002	.893
Overall stage						
0	1.000	Reference		1.000	Reference	
I	1.001	0.999–1.004	.330	1.001	0.999–1.004	.324
II	1.001	0.998–1.003	.494	1.001	0.998–1.004	.436
III	1.000	0.997–1.003	.972	1.000	0.997–1.003	.981
Grade						
1	1.000	Reference		1.000	Reference	
2	1.001	0.999–1.003	.377	1.001	0.999–1.003	.257
3	1.002	0.999–1.004	.150	1.002	0.999–1.004	.130
ER						
≤10	1.000	Reference		1.000	Reference	
10–50	1.001	0.999–1.002	.273	1.001	0.999–1.002	.266
>50	1.000	0.998–1.001	.476	0.999	0.998–1.000	.183
PR						
≤10	1.000	Reference		1.000	Reference	
10–50	1.001	0.999–1.002	.365	1.001	0.999–1.002	.306
>50	0.999	0.998–1.001	.439	0.999	0.998–1.001	.306
HER2						
+++	1.000	Reference			Reference	
Negative	1.002	1.000–1.004	.016	1.002	1.000–1.004	.018
+	1.002	1.000–1.004	.109	1.002	1.000–1.004	.123
++	1.003	1.001–1.005	.015	1.003	1.001–1.005	.016
Ki67						
<20	1.000	Reference		1.000	Reference	
20–50	0.999	0.997–1.000	.145	0.999	0.998–1.001	.210
≥50	1.000	0.998–1.001	.606	1.000	0.998–1.001	.770
Molecular type						
Luminal-A	1.000	Reference		1.000	Reference	
Luminal-B (HER2 negative)	1.000	0.999–1.002	.644	1.001	0.999–1.002	.354
Luminal-B (HER2 positive)	0.999	0.996–1.001	.385	0.999	0.996–1.002	.454
HER2 overexpression	0.998	0.996–1.001	.133	0.999	0.996–1.001	.222
Triple-negative	1.000	0.999–1.002	.651	1.001	0.999–1.002	.507

DCIS = ductal carcinoma in situ, ER = estrogen receptor, IDC = Invasive ductal carcinoma; Model 1 = without age adjustment; Model 2 = with age adjustment; PR = progesterone receptor.

HER2 expression ($H = 7.972$, $P = .047$; Table 1), but they were not correlated with any other clinicopathologic characteristics mentioned above ($P > .05$, Table 1).

Differences in serum LP(a) levels between 2 breast cancer categories within a specific classification were interpreted using the Spearman correlation analysis. Compared with HER2-+++, HER2-negative and HER2-++ breast cancers exhibited significantly higher serum LP(a) levels (HER2-negative vs HER2-+++, $P = .016$ without age adjustment or .018 with age adjustment; HER2-++ vs HER2-+++, $P = .015$ without age adjustment or .016 with age adjustment; Tables 1 and 2). No significant differences were detected between any other 2 groups that were compared ($P > .05$, Table 2).

3.3. The relationship between serum LP(a) levels and serum reproductive hormone levels in breast cancer patients

The relationship between serum LP(a) levels and serum reproductive hormone levels including prolactin (Prl), estradiol (E2), progesterone (p), testosterone (tt), follicle-stimulating hormone (Fsh), and luteinizing hormone (Lh) in the 314 breast

Table 3

Correlation between serum LP(a) and serum reproductive hormones in breast cancer patients by Spearman correlation analysis.

Reproductive hormone	Spearman correlation coefficient (*r*)	*P*-value
Prl	−0.070	.507
E2	0.054	.607
p	0.111	.292
tt	−0.072	.500
Fsh	−0.002	.983
Llh	0.006	.963

E2 = estradiol; Fsh = follicle-stimulating hormone; Lh = luteinizing hormone; p = progesterone; Prl = prolactin; tt = testosterone.

cancer patients was interpreted using Spearman correlation analysis. No significant correlations between LP(a) and any of the above hormones were detected ($P > .05$; Table 3).

4. Discussion

Obesity and cholesterol are well recognized risk factors and prognostic markers for breast cancer.[20] Moreover, recent studies have implicated LDL in breast cancer pathogenesis. Plasma LDL-cholesterol levels at the time of diagnosis can predict breast cancer progression.[21] In addition, LDL was reported to promote breast cancer cell growth and invasion in vitro, and these pro-tumorigenic effects of LDL were mediated by upregulation of genes involved in pathways controlling cell proliferation and adhesion.[22] LP(a) is structurally very similar to LDL, but its functional role in breast cancer is currently unclear.

In the present study, we detected elevated serum LP(a) levels in breast cancer patients (n = 314) compared with healthy control subjects (n = 185). Considering that chemotherapy and radiotherapy can affect lipoprotein profiles of patients, including LP(a) levels,[23,24] we measured patient serum LP(a) levels before the initiation of any treatment. Our results were consistent with previous work of Kokoglu et al[25] who reported a positive association of LP(a) with breast cancer based on data from a much smaller sample size. These findings support a pro-tumorigenic function of LP(a) in breast cancer. However, in a Japanese cohort study, breast cancer patients showed a similar serum LP(a) level to non-cancer controls ($P = .89$).[16] These controversial data could be attributed to the ethnicity-dependence of LP(a) levels.[26] The functional role of LP(a) in breast cancer development requires further investigation.

In a Turkish cohort study, Kokoglu et al[25] reported a significantly elevated LP(a) level in stage IV breast cancer patients than Stage I group. In this study, we found no significant association between serum LP(a) levels and the histopathological type, grade, stage, or molecular subtype of breast cancer. This controversy may result from the much smaller sample size of the Turkish cohort study (only 18 stage I and 21 Stage IV patients enrolled) and/or the difference in patient ethnicity between the 2 studies (Han Chinese vs Turkish). 27-Hydroxycholesterol, a partial agonist of ER, has been reported to drive ER-positive tumor growth and metastasis in animal models of breast cancer.[27] In this study, we detected no significant association between LP(a) and the expression of ER, PR, or Ki67 in breast cancer patients. We also found no correlation between LP(a) and reproductive hormones including prolactin, estradiol, progesterone, testosterone, follicle-stimulating hormone, and luteinizing hormone. However, we detected a significant inverse association between serum LP(a) levels and HER2 expression in breast cancer. Specifically, HER2-negative and HER2-++ patients exhibited significantly higher serum LP(a) levels than HER2-+++ patients. HER2 overexpression occurs in 20% to 30% of breast cancer and is strongly associated with disease aggressiveness, reoccurrence, and poor prognosis.[28] The clinical significance of the association between LP(a) and HER2 warrants further investigation.

5. Conclusions

In summary, we detected significantly elevated serum LP(a) levels in breast cancer patients compared with healthy controls in a Han Chinese population. In addition, we found a significant inverse association between LP(a) and HER2 expression in breast cancer patients. These findings would help characterizing the molecular signatures of the disease, which would eventually facilitate the development of tailored therapy of breast cancer.

Author contributions

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