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ORIGINAL ARTICLE

Analysis of risk factors related to breast cancer metastasis: a retrospective nested case-control study

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Summary

Purpose: *To explore the laboratory indexes related to breast cancer metastasis, so as to provide scientific basis for the control of breast metastasis.*

Methods: *A retrospective cohort-based nested case-control study was used to screen 732 breast cancer patients recorded in the First and the Third Hospitals of Jilin University's electronic medical record system between January 2008 through December 2015 without metastasis at admission. Those with subsequent metastasis were classified as the metastasis group and those without metastasis as the control group. The suspected confounders were matched by propensity score matching, then univariate analysis was conducted, and the variables with statistical significance were included in multivariate conditional logistic regression analysis.*

Results: *A total of 86 patients were matched in the transfer group and 315 in the control group, with a total sample size of 401.In univariate analysis, fasting plasma glucose (FPG), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP) and direct bilirubin (DBIL) in two groups were statistically different ($p<0.05$), multiple conditional logistic regression showed that FPG (OR=1.335) and ALP (OR=1.016) were factors related to breast cancer metastasis.*

Conclusions: *For breast cancer patients, the higher FPG and ALP levels may be associated with metastasis. Therefore, daily monitoring and control of these indicators may be helpful for the control of cancer metastasis.*

Key words: *breast cancer, metastasis, laboratory indexes, risk factors*

Introduction

Breast cancer is considered as one of the most common cancers in females. This disease is the leading cause of cancer-related death in 103 countries [1]. A systematic review and meta-analysis showed that the age standardized rate of breast cancer for women of eastern Mediterranean region countries from 1998 to 2019 had an upward trend [2]. The incidence of breast cancer in North Africa was higher at 29.3 per 100.000 than Sub-Saharan Africa (SSA) at 22.4 per 100.000 [3].It was estimated that the age-standardized incidence rate will increase to 85 per 100.000 women aged 35–69 by 2021 in China [4].

According to a related study, nearly 12% of breast cancer patients eventually spread beyond the breast to other parts of the body [5], including the lymph nodes, lung, liver, brain and so on. As we all know, if the patients develop distant metastases, the survival decreases greatly [6], which will affect the patients' quality of life and impose a huge economic burden on relatives and society.

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A large number of studies has demonstrated that serum lipid parameter, hepatic biochemical indexes, renal function indexes, FPG and other indicators were related to distant metastasis of breast cancer. A cohort study found that as FPG levels rose, the risk of distant metastases increased [7]. Accumulating evidence suggested that elevated cholesterol and its metabolites accelerated breast cancer development and progression [8-10]. According to past studies, triglycerides (TG) were significantly higher in patients with metastasis than those without. Moreover, for the breast cancer patients with a higher level of serum TG, the distant metastasis rate was higher [11,12]. The relationship between renal function indexes and breast cancer metastasis had been rarely reported. Serum trace elements played an important role in breast cancer with distant metastasis, such as cupric ion, zinc ion and so on [13,14]. Previous experiments on mice suggested that bile acid metabolism seemed to have an effect on cholesterol metabolism [15], which may play an indirect role in breast cancer metastasis. Akram Yazdani et al found that ALP was one of independent prognostic factors associated with bone metastases [16]. Several studies have shown that ALP was a predictor of breast metastasis and was proved to be related to prognosis [17-19].

Our research further explored the relationship between various indicators and breast cancer metastasis. Because the indicators are convenient and easy to obtain, the monitoring and control of relevant indicators can provide a scientific basis for controlling or preventing breast cancer metastasis.

Methods

Study design and patients

We screened 732 breast cancer patients diagnosed in the First and the Third Hospitals of Jilin University's electronic medical record system between January 2008 through December 2015. The deadline for follow-up was set on December 31, 2018 to ensure that each patient was followed for at least 36 months, which is helpful to accurately assess the status of metastasis. The inclusion criteria were: (1) patients with clinically diagnosed primary breast cancer; (2) age 18 years or older; (3) patients without lymph nodes or distant metastases. The exclusion criteria were: (1) missing laboratory data in case records; (2) patients had other cancers at the same time or a history of cancer. Breast cancer with metastases prior to the follow-up deadline was recorded as metastatic, and controls were selected from other patients without metastases. All the inpatients recruited in the study were informed on admission that their electronic medical records might be used for scientific research. They had signed the informed consent form which was approved by the ethics committee of the School of Public Health, Jilin University.

Demographic and clinical variables

Age, treatment received (radiation or chemotherapy), smoking history, drinking history, family history and previous history were recorded. Smoking at least one cigarette per week for more than 12 months was defined as smoking; alcohol consumption referred to drinking at least once a month and continuously drinking for more than 6 months; Family history referred to whether a person had breast cancer or other cancers in their immediate family, and previous history referred to diseases related to the indicators studied, such as coronary heart disease, diabetes, hypertension and so on. Liver function, kidney function, FPG, ion (serum ion indexes) blood lipid and other indicators were recorded and analyzed as retrospective nested case-control study.

Propensity score matching methods

Six possible confounders including age, smoking history, drinking history, chemotherapy or radiotherapy, family history, and previous history were matched. The caliper value was set at 0.02 and the method was nearest neighbor matching with a ratio of 1:4.

Statistics

Statistical software SPSS24.0 and R (v4.0.3) were used for data analysis. Independent sample T-test was used for the baseline data conforming to normal distribution, otherwise, Mann–Whitney U test was used. Single factor analysis of the relationship between laboratory indicators and breast cancer metastasis was performed using logistic regression analyses. $P<0.05$ was statistically significant. Variables with statistical significance in univariate analysis were included in multivariate conditional logistic regression to obtain influencing factors related to breast cancer metastasis.

Results

Baseline characteristics

Among 732 subjects, 86 patients in the metastasis group and 315 in the control group were successfully matched. Only 4 patients in the me-

Table 1. Sample sizes before and after matching

Subsamples	*All*		*Matched*		*Unmatched*		*Discarded*	
	Control	*Treated*	*Control*	*Treated*	*Control*	*Treated*	*Control*	*Treated*
(all cases)	642	90	315	86	327	4	0	0

tastasis group were not matched (Table 1). Before the propensity score matching, univariate analysis was performed on the factors to be matched, indicating that there was statistically significant difference between the two groups in smoking history ($p<0.05$), while there was no difference in other factors. However, in order to avoid ignoring the mixed influence of these factors, they were also matched. It can be seen that after matching, there was no statistical difference in smoking history between the two groups ($p>0.05$) and all variables were comparable (Table 2).

Univariate analysis

The variables with more than 20% missing values were not included in the analysis, and a total of 21 variables including FPG, ALP and so on were included; the relationship between the two groups was tested using binary logistic regression analysis for the data before matching and single-factor conditional logistic regression for matched data as shown in Table 3. $P<0.05$ was considered statistically significant. In total population, after single factor logistic regression, the concentration of FPG, high-density lipoprotein cholesterol (HDL-C), ALP and serum creatinine (Scr) were statistically associated with breast cancer metastasis. The odds ratio (OR) and 95% confidence interval (CI) were 1.173[1.005,1.368], 0.397[0.191,0.823], 1.012[1.003,1.021] and 0.973[0.947,1.000], respectively. After adjusting for age, smoking history, drinking history, previous history, family history and chemotherapy or radiotherapy, FPG, GGT, ALP and DBIL were statistically significant with OR (95%CI) of 1.369[1.093,1.715], 1.015[1.003,1.027], 1.018[1.006,1.029] and 1.284[1.010,1.632].

Multivariate conditional logistic regression analysis

FPG, GGT, ALP and DBIL were included in the multivariate conditional logistic regression analysis ($p<0.05$) with the method of 'Enter'. The results showed that the concentration of FPG and ALP were statistically related to the outcome (Table 4). Their OR(95% CI) were1.335[1.057,1.686] and 1.016[1.003,1.028].

Discussion

Our study showed HDL-C and Scr may be influenced by smoking, alcohol consumption, family history and previous history. After matching these factors, there was no difference between the two groups. In univariate analysis, GGT was observed to the associated with breast cancer metastasis. According to previous studies, the possible mechanism of increasing level of GGT of patients with metastasis may be hepatocellular damage and biliary obstruction [20]. Elevated levels of GGT have also been found in patients with liver metastases from breast cancer [21]. As for DBIL, there were almost no related studies revealing that DBIL was a biomarker for poor prognosis

Table 2. Basic characters in study population

Characteristics	*Before matching*				*After matching*			
	Non-metastatic (n=642,87.7%)	*Metastatic (n=90,12.3%)*	*x^2 or T value*	*p value*	*Non-metastatic (n=315,78.6%)*	*Metastatic (n=86,21.4%)*	*x^2 or T value*	*p value*
Smoking history							1.527	0.217
no	613 (95.5)	80 (88.9)	5.560	0.018	302 (95.9)	79 (91.9)		
yes	29 (4.5)	10 (11.1)			13 (4.1)	7 (8.1)		
Drinking history								
no	637 (99.2)	90 (100.0)	-	1.000	315 (100.0)	86 (100.0)	-	-
yes	5 (0.8)	0 (0.0)			0 (0.0)	0 (0.0)		
Chemotherapy or radiotherapy							0.033	0.856
no	39 (6.1)	7 (7.8)	0.389	0.533	20 (6.3)	5(5.8)		
yes	603 (93.9)	83 (92.2)			295 (93.7)	81 (94.2)		
Family history							0.466	0.495
no	608 (94.7)	86 (95.6)	0.008	0.930	310 (98.4)	83 (96.5)		
yes	34 (5.3)	4 (4.4)			5 (1.6)	3 (3.5)		
Previous history							0.150	0.698
no	543 (84.6)	76 (84.4)	0.001	0.974	276 (87.6)	74 (86.0)		
yes	99 (15.4)	14 (15.6)			39 (12.4)	12 (14.0)		
Age(year)	50±9	50±11	0.035	0.972	50±10	50±11	0.063	0.950

Table 3. Univariate analysis of the influencing factors of breast cancer metastasis

	Before matching		*After matching*	
	OR (95%CI)	*p value*	*OR (95%CI)*	*p value*
FPG (mmol/L)	1.173 [1.005,1.368]	0.043	1.369 [1.093,1.715]	0.006
TBA(μmol/L)	0.972 [0.917,1.030]	0.331	0.938 [0.872,1.009]	0.086
LDL-C (mmol/L)	0.965 [0.729,1.276]	0.801	1.073 [0.774,1.489]	0.671
HDL-C (mmol/L)	0.397 [0.191,0.823]	0.013	0.460 [0.209,1.015]	0.054
TC (mmol/L)	0.834 [0.664,1.048]	0.119	0.889 [0.682,1.158]	0.383
TG (mmol/L)	0.960 [0.796,1.159]	0.672	0.998 [0.798,1.248]	0.988
GGT (U/L)	1.001 [0.993,1.008]	0.878	1.015 [1.003,1.027]	0.017
ALP (U/L)	1.012 [1.003,1.021]	0.007	1.018 [1.006,1.029]	0.003
Serum sodiumion(mmol/L)	1.044 [0.948,1.150]	0.379	1.018 [0.913,1.135]	0.753
Serum chloride ion(mmol/L)	0.950 [0.872,1.034]	0.232	0.928 [0.846,1.018]	0.112
Serum potassiumion(mmol/L)	0.682 [0.325,1.433]	0.312	0.740 [0.337,1.623]	0.452
Serumcalcium ion(mmol/L)	2.565 [0.383,17.198]	0.332	7.828 [0.910,67.338]	0.061
TBIL (μmol/L)	1.032 [0.977,1.089]	0.258	1.053 [0.993,1.118]	0.084
DBIL (μmol/L)	1.183 [0.951,1.473]	0.132	1.284 [1.010,1.632]	0.041
BUA (μmol/L)	1.002 [0.998,1.005]	0.355	1.003 [0.999,1.006]	0.163
BUN (mmol/L)	0.924 [0.784,1.089]	0.344	0.909 [0.753,1.098]	0.323
AST (U/L)	0.993 [0.975,1.012]	0.484	1.002 [0.982,1.022]	0.865
IBIL(μmol/L)	1.001 [0.982,1.021]	0.920	1.074 [0.993,1.163]	0.076
Scr (μmol/L)	0.973 [0.947,1.000]	0.046	0.974 [0.946,1.003]	0.083
ChE (U/L)	1.000 [1.000,1.000]	0.092	1.000 [1.000,1.000]	0.091
ALT(U/L)	0.996 [0.985,1.006]	0.415	1.004 [0.991,1.017]	0.568

Table 4. Multivariate conditional logistic regression analysis of laboratory indicators and breast cancer metastasis

Variables	*B*	*SE*	*Wald*	*p value*	*OR*	*95% CI for OR*
FPG (mmol/L)	0.289	0.119	5.889	0.015	1.335	[1.057,1.686]
GGT (U/L)	0.007	0.007	1.008	0.315	1.007	[0.994,1.020]
ALP (U/L)	0.016	0.006	6.210	0.013	1.016	[1.003,1.028]
DBIL (μmol/L)	0.218	0.128	2.931	0.087	1.244	[0.969,1.597]

in breast cancer. Our multivariate analysis also showed this variable was not associated with breast cancer metastasis.

Our results showed FPG may be the risk factor of breast cancer metastasis (OR=1.335, p<0.05). According to previous studies, it has been proven that hyperglycemia was associated with the incidence of breast cancer and a statistically significant risk of breast cancer existed in women having elevated FPG levels [22,23]. A study found for breast cancer patients, the diabetic group was easier to suffer lymph nodes metastasis than the non-diabetic group [24]. Furthermore, a cohort study conducted with 1261 women in Milan has found that the group of all other glucose quintiles had higher risks of distant metastasis than the lowest one [7]. Recent research on breast cancer treatment showed that diabetes and high FPG level may be related to the non-response of neoadjuvant chemotherapy in breast cancer patients, which may confirm this correlation that we found [25]. Generally, cancer cells are featured by high rates of glucose uptake and glycolytic metabolism. Therefore, high circulating glucose may provide an environment conducive to the malignant clones so as to promote the initiation and progression of cancer [26]. The molecular mechanism of glucose metabolism in tumor cells has been studied by Macheda et al [27], who have shown that overexpression of facilitating glucose transporter (GLUT) proteins like GLUT1 and/or GLUT3 were related to increased glucose transport in malignant cells. As for the factors that have played an important role in the regulation of glucose transporter expression in breast cancer, hypoxia and estradiol and epidermal growth factor were verified [27,28]. The induction of oxidative

stress was another mechanism by which glucose could induce cancer progression. Oxidative stress reaction may lead to stimulation of inflammatory signaling pathways. In the end, genomic instability and disruption of normal mechanisms of cellular signaling happened [29]. The previous study indicated that metabolic syndrome including high blood glucose was a strong risk factor for breast cancer in females, particularly in subjects 55 years of age. High glucose or diabetes may lead to hepatic inflammation, oxidative stress, and a lipid peroxidation response, which would cause liver damage, even liver cancer. But the mechanisms associated with breast cancer development were currently poorly understood [30]. Rothman et al reported that fasting glucose levels depended on the hepatic and renal gluconeogenesis and others found that counter-regulatory hormones such as adrenal hormones could stimulate gluconeogenesis, which suggests that we need to explore the role of these hormones on the effect of glucose in breast cancer [31,32]. Besides, it has been found that the negative effects of high BMI and high blood glucose in breast cancer were confined to sex hormone-positive cancers. As we know, high glucose levels may be mediated by insulin. However, one review reported that glucose was not the key driver of cancer growth and progression for those with obesity, metabolic syndrome or diabetes, which suggests that more studies should be conducted to further investigate the effect of FPG on breast cancer metastasis [33].

Our study results revealed ALP may be the risk factor of poor prognosis of breast cancer, which means the causal relationship between them needs to be further studied. A previous study indicated that neoplastic metastasis of the liver made localized intra-hepatic cholestasis so as to increase the concentration of serum ALP [34]. As for breast cancer, there are studies that support our conclusions. A study of women in India showed elevated serum ALP may help predict the prognosis of breast cancer, which may offer a useful diagnostic tool to monitor disease progression [35]. The progressive increase in the serum ALP activities with breast cancer was an indication of metastasis. In studies of bone metastasis prognostic factors in breast cancer, ALP and its isoenzymes (especially the bone-specific AP [B-AP]) was found to be one of the independent prognostic factors, which was consistent with our results though our outcome variables didn't indicate the specific site of metastasis [16,35,36]. Besides, tartrate-resistant acid phosphatase 5b (TRACP 5b) activity related with B-AP may be an indicator of bone metastasis for breast cancer patients according to a related research [37]. Many researchers have found that the abnormal increase of markers related to bone resorption and bone formation indicates the possibility of bone metastasis in breast cancer, which indirectly indicates that monitoring ALP level may be helpful for the early prevention of breast cancer metastasis [38,39].

Strengths and limitations

Regarding strengths, the study was a retrospective nested case-control study using propensity score matching, which aimed to equalize the possible confounding factors between the case and control groups. As for limitations, the first one, as an observational study rather than an experimental one, it was hard for us to avoid confounding bias. Then, some confounding effects had not been ruled out, such as breast cancer stage, tumor type and so on.

Conclusions

In conclusion, we found that FPG and ALP values were associated with metastasis of breast cancer. They were risk factors of breast cancer metastasis, and it may be more likely to metastasize in breast cancer patients with higher levels. This suggests that we may monitor their levels and control their increasing trend to reduce the incidence of breast cancer metastasis and improve the quality of life.

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Abbreviations

FPG: fasting plasma glucose, TBA: total bile acid, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TC: total cholesterol, TG: triglyceride, GGT: gamma-glutamyl transpeptidase, ALP: alkaline phosphatase, TBIL: total bilirubin, DBIL: direct bilirubin, BUA: blood uric acid, BUN: blood urea nitrogen, AST: aspartate aminotransferase, IBIL: indirect bilirubin, Scr: serum creatinine, ChE: cholinesterase, ALT: alanine aminotransferase

Conflict of interests

The authors declare no conflict of interests.

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