Article

J. Biol. Regul. Homeost. Agents. 2024; 38(10): 5957–5963
https://doi.org/10.23812/j.biol.regul.homeost.agents.20243810.475

Association of Serum CA15-3, CA125, and TPS Levels with Clinicopathological Factors in Patients with Breast Cancer

Yingjie Li[1], Luyao Zhou[1], Zhidong San[1], Peng Zhou[1,*]

[1]The Second Department of General Surgery, First People's Hospital of Yongkang, 321300 Jinhua, Zhejiang, China
*Correspondence: zhoupengsci2022@163.com (Peng Zhou)
Submitted: 21 March 2024 Revised: 23 April 2024 Accepted: 5 May 2024 Published: 1 October 2024

Background: Breast cancer, the most common cancer, is the leading cause of cancer-related deaths among women globally. To effectively reduce mortality, it has become a hot topic to find prognostic indicators that are highly correlated with poor prognosis of breast cancer in early stages. Therefore, this study aimed to explore the levels of serum cancer antigen 15-3 (CA15-3), cancer antigen 125 (CA125), and tissue polypeptide specific antigen (TPS) in individuals with breast cancer and to elucidate the relationship between these markers and clinicopathological factors, as well as their impact on disease prognosis.

Methods: This study included 140 subjects diagnosed with breast cancer (breast cancer subgroup), 120 subjects with breast cancer benign lesions (breast benign disease subgroup), and 120 healthy controls (control subgroup). The clinical data and blood samples were collected from all study subjects. Furthermore, the serum levels of CA15-3, CA125, and TPS were evaluated using corresponding enzyme linked immunosorbent assay (ELISA) kits. The correlation between serum indexes and clinicopathological factors was analyzed. Additionally, the 3-year survival rate of breast cancer patients was assessed using the Kaplan-Meier method.

Results: A statistically significant difference was observed in the serum CA15-3, CA125, and TPS levels across three subgroups: breast subgroup, benign breast disease subgroup, and control subgroup ($p < 0.05$), with higher levels observed in the breast subgroup followed by benign breast disease subgroup. Furthermore, their levels were correlated with pathological type, tumor node metastasis classification tumor node metastasis (TNM) stage, lymph node metastasis, and histological grade ($p < 0.05$, $p < 0.001$). Moreover, these markers were identified as independent risk factors for breast cancer using multivariate Logistic regression analysis ($p < 0.05$). The probability of survival of breast cancer subjects in high CA15-3 level subgroup, high CA125 level subgroup and high TPS level subgroup was notably lower than that in low level subgroup, which was shown by Kaplan-Meier analysis ($p < 0.05$).

Conclusion: The serum levels of CA15-3, CA125, and TPS are significantly elevated in subjects with breast cancer, and their expression levels are correlated with pathological type, TNM stage, lymph node metastasis, and histological grade. These tumor markers can be used as predictors of breast cancer prognosis.

Keywords: breast cancer; cancer antigen 15-3; cancer antigen 125; tissue polypeptide specific antigen; clinicopathological factors; prognosis

Introduction

According to epidemiological study [1], the worldwide incidence and mortality rate of female breast cancer were reported as $46.3/10^5$, in 2018. Furthermore, these rates continue to rise annually, posing significant health challenges globally. The morbidity and mortality of female breast cancer in China are relatively lower than the global ratio. However, China has the highest total number of cases due to its large population [2,3]. Compared to advanced breast cancer, early breast cancer has a greater chance of radical cure, a longer survival time, and a better prognosis [4]. Therefore, the early diagnosis, treatment, and prognosis evaluation of breast cancer are crucial.

Additionally, research has found that prognostic markers are differentially expressed in malignant and benign lesions [5]. Moreover, compared to malignant tumors, benign breast tumors like breast nodules and fibroadenomas seldom metastasize or recur and can be effectively treated through specific therapies. These observations highlight the importance of prognostic markers in determining and implementing subsequent treatment approaches, providing valuable insights for ongoing therapeutic interventions. Serum tumor markers are crucial in differentiating malignant tumors and predicting disease outcomes. Furthermore, they are minimally invasive, rapid, and reproducible, and widely used in clinical practice [6,7].

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

This study examined the serum levels of common breast cancer tumor markers, such as cancer antigen 15-3 (CA15-3), cancer antigen 125 (CA125), and tissue polypeptide specific antigen (TPS), to assess their correlation with clinicopathological factors and their impact on patient survival. This investigation revealed increased expressions of these markers in the serum of breast cancer subjects, suggesting their significance as indicators for clinical efficacy and prognosis [7–9]. Based on this analysis, the serum levels of CA15-3, CA125, and TPS were compared among breast cancer patients, those with benign breast lesions, and healthy control subjects. While evaluating their prognostic value, the correlation between these markers and the clinicopathological factors of breast cancer was explored, particularly in the context of early breast cancer.

Materials and Methods

Design and Procedures

In this retrospective study, a subgroup of breast cancer patients was compared with a subgroup of individuals with benign breast cancer and a control subgroup to evaluate serum levels of CA15-3, CA125, and TPS, to assess the relationship between these serum indexes and clinicopathological factors, and to examine the 3-year survival outcomes of the subjects. The breast cancer subgroup included 140 subjects diagnosed with breast cancer, the benign disease subgroup comprised 120 subjects diagnosed with benign breast lesions, and the control subgroup contained 120 healthy individuals. All study participants provided informed consent for inclusion in the study. The study design adhered to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of First People's Hospital of Yongkang City, China (approval number: 2018-2-16).

Setting and Participants

This study assessed the suitability of the participants based on the predetermined criteria. The inclusion criteria were as follows: (1) Age range of 30–75 years. (2) Confirmation of breast cancer through biopsy or surgical pathology. (3) Those who did not undergo any anti-tumor therapy before surgery. However, the exclusion criteria of this study included: (1) Study subjects presented with significantly abnormal heart, liver, or kidney functions. (2) Pregnant or lactating women. (3) Subjects with incomplete clinical data. (4) Those who were not diagnosed with breast cancer.

Measures

Data Collection

We collected data on the age, menstrual status, pathological type, tumor size, tumor node metastasis (TNM) stage, lymph node metastasis, histological grading, and other relevant parameters of the study subjects.

Evaluation of Serum CA15-3, CA125, and TPS Levels

Fasting elbow vein blood (4 mL) was collected from all preoperative subjects in the morning. Following centrifugation of the blood samples at 2062 ×g for 10 minutes, the supernatant was carefully transferred to a frozen tube and stored at –80 °C.

The serum levels of CA15-3 (PC108, Beyotime, Shanghai, China), CA125 (DCA125, R&D Systems, Shanghai, China) and TPS (EKN50047, Biocompare, South San Francisco, CA, USA) were assessed using enzyme linked immunosorbent assay (ELISA). For this purpose, 100 µL of serum or 100 µL PBS for blank was added to the plate and incubated at 37 °C for 90 minutes. The plates were washed 3 times with phosphate buffer solution tween (PBST) to remove unbound proteins and then incubated with 10 µg/mL biotin lectin for 1 hour at room temperature. After washing 6 times with PBST, streptavidin-HRP was added to bind to biotin lectin. After 6 additional washes, tetramethyl benzidine (TMB) solution was added for 10 minutes in the dark to develop color, and the reaction was terminated with HCL. Finally, the optical density (OD) of each well was determined at 450 nm using a microplate reader (Victor X4, Perkin Elmer, Waltham, MA, USA). However, each experiment was replicated three times to calculate the average of the experimental results.

Follow-up of the Study Subjects

All breast cancer patients were followed up for 3 years through outpatient reexamination and telephone calls, with the occurrence of the subject's death being the end point.

Data Statistics

Statistical analysis was conducted using SPSS software (version 22.0, IBM, Armonk, NY, USA), and the measurement data with normal distribution and uniform variance were expressed through ($\bar{x}\pm$s). The *t*-value test was used to compare the two subgroups, and F-value test was used for multi-subgroup comparison. Independent prognostic factors of breast cancer were analyzed utilizing multivariate Logistic regression. Moreover, the survival rate of the breast cancer patients was analyzed employing the Kaplan-Meier method, and the findings were compared using the log-rank test. A p-value < 0.05 was considered statistically significant.

Results

Baseline Data

The mean ages of the breast cancer subgroup, breast benign disease subgroup, and control subgroup were (55.34±8.59) years, (56.02±9.34) years, and (55.19±9.49) years, respectively. In terms of age, there was no notably difference ($p > 0.05$).

Table 1. Serum levels of CA15-3, CA125, and TPS among study subjects.

Category	n	CA15-3 (U/mL)	CA125 (U/mL)	TPS (U/L)
Breast cancer subgroup	140	62.58±12.58*#	108.52±14.51*#	120.13±20.18*#
Benign breast disease subgroup	120	18.75±4.35*	36.12±6.13*	48.22±7.88*
Control subgroup	120	14.66±3.12	15.33±3.46	36.53±5.22
F		1399.00	3413.00	1533.00
p		<0.001	<0.001	<0.001

Note: Compared to the control subgroup, * $p < 0.05$; Compared to the benign breast disease subgroup, # $p < 0.05$. CA15-3, cancer antigen 15-3; CA125, cancer antigen 125; TPS, tissue polypeptide specific antigen; F, Equality of Variances; *p*, *p*-value.

Serum Levels of CA15-3, CA125, and TPS

The serum levels of CA15-3, CA125, and TPS were significantly elevated in the breast cancer subgroup compared to the benign breast disease and control subgroups ($p < 0.001$). Furthermore, compared to the control subgroup, the serum levels of CA15-3, CA125, and TPS were higher in subjects with benign breast lesions ($p < 0.05$). The serum levels of CA15-3, CA125, and TPS are shown in Table 1.

Correlation between Serum Levels of CA15-3, CA125, TPS and Clinicopathological Factors of Breast Cancer

There was no association between serum levels of CA15-3, CA125, and TPS and patient age, menstrual status, and tumor size in subjects with breast cancer ($p > 0.05$). However, these tumor markers significantly correlated with pathological type, TNM stage, lymph node metastasis, and histological grade ($p < 0.05$, $p < 0.001$). Furthermore, compared to the intraductal carcinoma subgroup, TNM stage I–II stage subgroup, subgroup without lymph node metastasis, and histological grade I–II grade subgroup, the serum levels of CA15-3, CA125, and TPS were substantially higher in the invasive ductal carcinoma subgroup, TNM stage III–IV stage subgroup, lymph node metastasis subgroup, and histological grade III grade subgroup ($p < 0.05$). The correlation of tumor markers with clinicopathological factors is presented in Table 2.

Risk Assessment of Breast Cancer

Based on the findings presented in Tables 1,2, multivariate analysis (Table 3) was conducted to assess the correlation between elevated levels of CA15-3, CA125, and TPS and breast cancer risk. High levels of CA15-3, CA125, and TPS were observed as risk factors for breast cancer ($p < 0.05$).

The Correlation between Serum CA15-3, CA125, and TPS Levels and Breast Cancer Prognosis

The serum levels of CA15-3, CA125, and TPS were divided into high-level and low-level subgroups based on median values of 43.35, 67.45, and 85.8, respectively. The 3-year survival of breast cancer patients was assessed utilizing the Kaplan-Meier method. We observed that study subjects with low levels of CA15-3 (n = 70), CA125 (n = 70), and TPS (n = 70) exhibited substantially high probability of survival compared to those in the high CA15-3 (n = 70), high CA125 (n = 70), and high TPS (n = 70) subgroups ($p < 0.05$). The correlation between serum tumor marker levels and the prognosis of breast cancer is shown in Figs. 1,2,3.

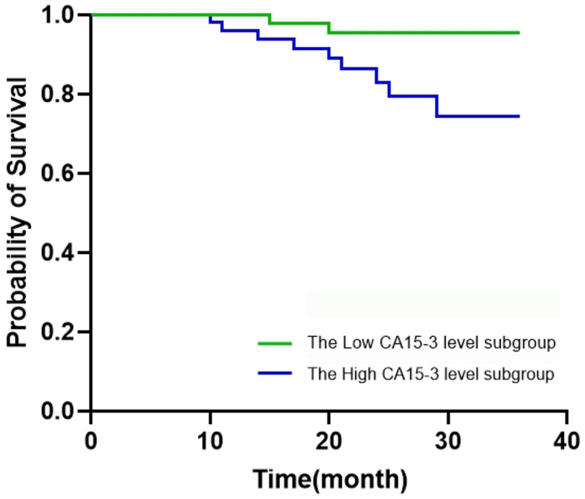

Fig. 1. Survival curve of high CA15-3 level subgroup and low CA15-3 level subgroup ($c^2 = 5.665$, $p = 0.017$).

Discussion

With the growth of aging, the change of lifestyle and the increase of work pressure, breast cancer has become a significant threat to women's lives and health globally [10]. In 2000, there were about 1.05 million women with breast cancer in the world, which increased to 2.09 million in 2018. The cumulative risk of disease and death from 0 to 74 years old was up to 5.03% and 1.41%, respectively [11]. The incidence of breast cancer has been associated with age, diet, life style, and family history, highlighting the significance of women's participation in breast cancer screening [12]. Imaging examination (such as breast X-ray, ultrasound, MRI) is the main method for clinical diagnosis

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Table 2. Association between serum levels of CA15-3, CA125, TPS and clinicopathological factors of breast cancer patients.

Factors	n	CA15-3 (U/mL)			CA125 (U/mL)			TPS (U/L)		
		$\bar{x}\pm s$	t	p	$\bar{x}\pm s$	t	p	$\bar{x}\pm s$	t	p
Age										
≤50 years old	71	60.66±14.12	1.863	0.065	106.87±10.88	1.380	0.170	117.57±19.78	1.543	0.125
>50 years old	69	64.56±10.3			110.22±17.22			122.77±20.1		
Menstrual status										
Menopause	76	60.78±13.76	1.880	0.062	106.48±10.67	1.845	0.067	117.39± 19.39	1.782	0.077
Premenopausal	64	64.73±10.51			110.95±17.64			123.40±20.45		
Pathological type										
Intraductal carcinoma	43	54.63±10.22	5.514	<0.001	104.16±10.19	2.425	0.017	113.90±15.10	2.495	0.014
Invasive ductal carcinoma	97	66.11±11.83**			110.46±15.61*			122.90±21.39*		
Tumor size										
≤5 cm	75	60.77±13.85	1.859	0.065	106.56±10.72	1.746	0.083	117.34± 19.52	1.778	0.078
>5 cm	65	64.67±10.43			110.79±17.55			123.36±20.29		
TNM stage										
I–II stage	94	60.63±13.15	2.700	0.008	106.69±11.30	2.184	0.031	117.47±17.91	2.287	0.024
III–IV stage	46	66.57±10.05*			112.27±18.82			125.59±23.04		
Lymph node metastasis										
No	81	60.76±13.58	2.048	0.042	106.47±10.61	2.001	0.047	117.25±18.82	2.017	0.046
Yes	59	65.09±10.42*			111.35±18.10*			124.09±21.11*		
Histological grade										
I–II grade	79	60.72±13.71	2.032	0.044	106.37±10.70	2.026	0.045	117.17±19.05	2.007	0.047
III grade	61	65.00±10.34*			111.29±17.83*			123.95±20.78*		

* means $p < 0.05$, ** means $p < 0.001$. TNM, tumor node metastasis.

Table 3. Multivariate analysis of risk factors for breast cancer.

Variables	B	S.E.	Wald	Sig.	EXP (B)	95% CI for EXP (B)	
						Lower	Upper
TPS	0.038	0.010	13.603	0.000	1.039	1.018	1.060
CA15-3	0.044	0.016	6.981	0.008	1.044	1.011	1.079
CA125	0.063	0.005	135.454	0.000	1.065	1.054	1.077
Menstrual status	0.486	0.799	0.370	0.543	1.625	0.340	7.775
Constant	–4.985	0.446	124.716	0.000	0.007		

B, B value; S.E., standard error; CI, confidence interval; EXP (B), exponent of B.

of breast cancer, combined with breast tissue biopsy for diagnosis, but the examination cost is high, it needs a simple and easy way to assist diagnosis, treatment, and prognosis [13,14].

The abnormal expression of serum tumor markers is associated with tumorigenesis, serving as a guide for diagnosing, treating, and predicting the prognosis of malignant tumors [15]. Common serum tumor markers such as CA15-3, CA125, and TPS are frequently used in clinical settings. CA15-3 is a high molecular glycoprotein normally found only on the surface of mammary epithelial cells in low levels within the bloodstream. However, in the case of breast cancer, CA15-3 is overexpressed in breast cancer cells, leading to abnormally increased serum levels. The severity of breast cancer is linked to its elevated serum levels [16,17]. CA125 is predominantly distributed on the surface of mesothelial cells. Usually, due to the barrier of basement membrane, CA125 cannot enter the blood normally, and the serum concentration is low. Once malignant change occurs, the cells expressing CA125 will depolarize and CA125 will enter the blood circulation, and the serum content will increase [18,19]. Previous research [20] has shown that CA125 has significant diagnostic value for breast cancer, endometrial cancer, and ovarian cancer, and it can also predict the patient's metastasis. TPS mainly reflects the division and proliferation of tumor cells, indicating high expression in malignant tumor tissues and serum [21]. Our findings revealed that the levels of serum CA15-3, CA125, and TPS in breast cancer subgroup were significantly higher compared to those in the benign breast disease subgroup and control subgroup. These observations indicate that the abnormal expression of serum CA15-3, CA125, and TPS in the breast cancer patients may be correlated with the occurrence and progression of breast can-

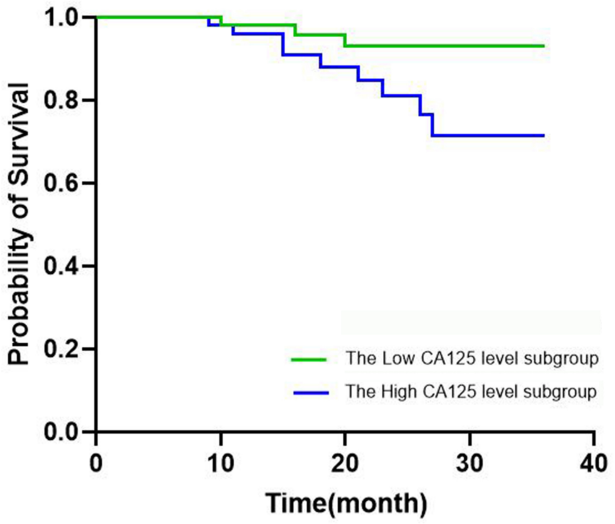

Fig. 2. Survival curve of high CA125 level subgroup and low CA125 level subgroup (c^2 = 4.370, p = 0.037).

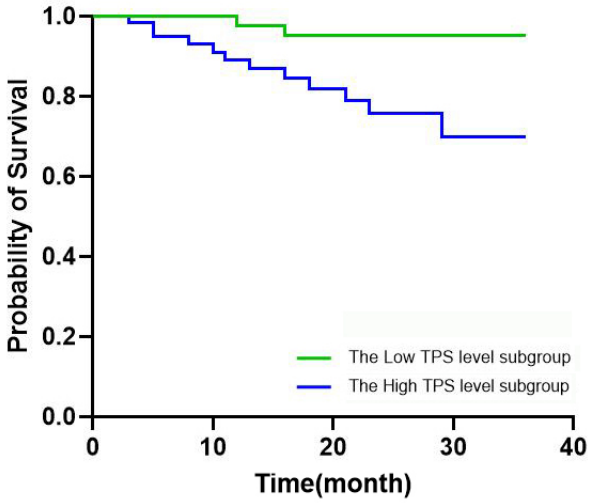

Fig. 3. Survival curve of high TPS level subgroup and low TPS level subgroup (c^2 = 7.608, p = 0.006).

cer. Several studies [22–24] have confirmed that the serum CA15-3, CA125, TPS levels in breast cancer patients are increased, and the postoperative expression level is reduced, which can be used as diagnostic and therapeutic monitoring indicators for breast cancer.

CA15-3, CA125, and TPS are typical prognostic markers for breast cancer; however, few studies have investigated their relationship with clinicopathological factors. Furthermore, our study demonstrated that serum CA15-3, CA125, and TPS levels were not correlated with age, menstrual status, or tumor size, but were associated with pathological type, TNM stage, lymph node metastasis, and histological grade. Previous studies [25,26] have reported that age and menopause are important factors in the incidence of breast cancer, the older the age, the higher the risk of disease. Compared to premenopausal women, the prevalence rate of postmenopausal women increased by 50%. However, there was no obvious correlation with the serum tumor markers, that is, the severity of the disease. Compared to intraductal carcinoma, invasive ductal carcinoma has stronger ability to destroy basement membrane, metastasize and invade, and its condition is more serious and complex, so the serum CA15-3, CA125 and TPS levels are higher [27]. Previous reports [28–30] have indicated the significance of serum CA15-3, CA125, and TPS in scoring clinical staging, histological grading, recurrence, and breast cancer metastasis. CA15-3 has certain clinical value for postoperative recurrence and metastasis of breast cancer. The more metastatic lesions and the wider the scope, the higher the level of CA15-3. CA125 is an ovarian associated antigen, which is highly expressed in ovarian cancer patients, but CA125 has certain application value in the diagnosis of breast cancer. The level of TPS can reflect the activity of tumor division and proliferation [31]. After tumor cell division, a large amount of TPS is released into the blood. In the active stage of proliferation, serum TPS is highly expressed, which fully indicates the biological status of the tumor. The higher levels of these markers lead to more severe disease progression. After adjustment for menstrual status, multivariate Logistic regression analysis showed high CA15-3, CA125, and TPS levels as independent risk factors for the prognosis of breast cancer, suggesting their use as prognostic indicators. A study conducted by Wang *et al*. [32] has shown that the combined evaluation of serum tumor markers, specifically CA15-3, CA125, TPS, and carcinoembryonic antigen (CEA) can predict postoperative lymph node metastasis in breast cancer patients, guiding clinical treatment decision and prognosis evaluation. This 3-year follow-up study demonstrated that the survival probability of the low CA15-3 level subgroup, low CA125 level subgroup and low TPS level subgroup was significantly improved. These findings indicate that serum CA15-3, CA125, and TPS can be used as prognostic indicators for breast cancer. However, this study also has some limitations due to the sensitivity of prognostic markers to decrease significantly with longer follow-up, the sample size will be expanded for further study.

Conclusion

In summary, elevated serum levels of CA15-3, CA125, and TPS in breast cancer patients are correlated with pathological type, TNM stage, lymph node metastasis, and histological grading. These markers can also provide a reference for the prognosis of subjects.

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

PZ, YJL and LYZ designed the research study. YJL and ZDS performed the research. LYZ and ZDS provided help and advice on the ELISA experiments. LYZ and YJL analyzed the data. YJL drafted this manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of First People's Hospital of Yongkang City, China (approval number: 2018-2-16). All study participants provided informed consent for inclusion in the study.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018; 68: 394–424.

[2] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, *et al*. Cancer statistics in China, 2015. CA: A Cancer Journal for Clinicians. 2016; 66: 115–132.

[3] Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K, *et al*. Global patterns of breast cancer incidence and mortality: A population-based cancer registry data analysis from 2000 to 2020. Cancer Commun (Lond). 2021; 41: 1183–1194.

[4] Morey BN, Gee GC, von Ehrenstein OS, Shariff-Marco S, Canchola AJ, Yang J, *et al*. Higher Breast Cancer Risk Among Immigrant Asian American Women Than Among US-Born Asian American Women. Preventing Chronic Disease. 2019; 16: E20.

[5] Murray GI, Burke MD, Ewen SW. Glutathione localisation in benign and malignant human breast lesions. British Journal of Cancer. 1987; 55: 605–609.

[6] Luthra S, Chandran U, Diergaarde B, Becich M, Lee AV, Neumann CA. Expression of reactive species related genes is associated with patient survival in luminal B breast cancer. Free Radical Biology & Medicine. 2018; 120: 170–180.

[7] Ibrahim J, Peeters M, Van Camp G, Op de Beeck K. Methylation biomarkers for early cancer detection and diagnosis: Current and future perspectives. European Journal Of Cancer. 2023; 178: 91–113.

[8] Allarakha A, Gao Y, Jiang H, Wang PJ. Prediction and prognosis of biologically aggressive breast cancers by the combination of DWI/DCE-MRI and immunohistochemical tumor markers. Discovery Medicine. 2019; 27: 7–15.

[9] Zhao J, He J, Zhong L, Huang Y, Zhao Y. Production of aptamers by cell-SELEX and their applications in cancer biomarker identification. Discovery Medicine. 2020; 29: 159–167.

[10] Song X, Liang B, Wang C, Shi S. Clinical value of color Doppler ultrasound combined with serum CA153, CEA and TSGF detection in the diagnosis of breast cancer. Experimental and Therapeutic Medicine. 2020; 20: 1822–1828.

[11] Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, Moradi-Kalbolandi S, *et al*. Breast cancer: Biology, biomarkers, and treatments. International Immunopharmacology. 2020; 84: 106535.

[12] Zhang X, Dong X, Guan Y, Ren M, Guo D, He Y. Research progress on epidemiological trend and risk factors of female breast cancer. Cancer Research on Prevention and Treatment. 2021; 87–92.

[13] Ahern TP, Broe A, Lash TL, Cronin-Fenton DP, Ulrichsen SP, Christiansen PM, *et al*. Phthalate Exposure and Breast Cancer Incidence: A Danish Nationwide Cohort Study. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2019; 37: 1800–1809.

[14] Fortner RT, Sisti J, Chai B, Collins LC, Rosner B, Hankinson SE, *et al*. Parity, breastfeeding, and breast cancer risk by hormone receptor status and molecular phenotype: results from the Nurses' Health Studies. Breast Cancer Research: BCR. 2019; 21: 40.

[15] Sutton EJ, Dashevsky BZ, Oh JH, Veeraraghavan H, Apte AP, Thakur SB, *et al*. Breast cancer molecular subtype classifier that incorporates MRI features. Journal of Magnetic Resonance Imaging: JMRI. 2016; 44: 122–129.

[16] Rao S, Smith DA, Guler E, Kikano EG, Rajdev MA, Yoest JM, *et al*. Past, Present, and Future of Serum Tumor Markers in Management of Ovarian Cancer: A Guide for the Radiologist. Radiographics: a Review Publication of the Radiological Society of North America, Inc. 2021; 41: 1839–1856.

[17] Tang S, Wei L, Sun Y, Zhou F, Zhu S, Yang R, *et al*. CA153 in Breast Secretions as a Potential Molecular Marker for Diagnosing Breast Cancer: A Meta Analysis. PloS One. 2016; 11: e0163030.

[18] Svobodova S, Kucera R, Fiala O, Karlikova M, Narsanska A, Zedníková I, *et al*. CEA, CA 15-3, and TPS as Prognostic Factors in the Follow-up Monitoring of Patients After Radical Surgery for Breast Cancer. Anticancer Research. 2018; 38: 465–469.

[19] Fang C, Cao Y, Liu X, Zeng XT, Li Y. Serum CA125 is a predictive marker for breast cancer outcomes and correlates with molecular subtypes. Oncotarget. 2017; 8: 63963–63970.

[20] Chen Y, Gao SG, Chen JM, Wang GP, Wang ZF, Zhou B, *et al*. Serum CA242, CA199, CA125, CEA, and TSGF are Biomarkers for the Efficacy and Prognosis of Cryoablation in Pancreatic Cancer Patients. Cell Biochemistry and Biophysics. 2015; 71: 1287–1291.

[21] Zhang M, Cheng S, Jin Y, Zhao Y, Wang Y. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer.

Biochimica et Biophysica Acta. Reviews on Cancer. 2021; 1875: 188503.

[22] Hadoussa M, Ayari J, Azaiez MB, Dhief R, Balti M, Hadoussa S, Haddaoui A. Clinical interest of the tumor marker CA15-3 in the early detection of breast cancer recurrence. European Journal of Cancer. 2018; 92: S27–S28.

[23] Miceli R, Cao C, Maolanon NN, Jacobs R, Wu J, Orlandi R. Plasma Profile of Immune Determinants Predicts Pathological Complete Response in Locally Advanced Breast Cancer Patients: A Pilot Study. Clinical Breast Cancer. 2022; 22: 705–714.

[24] Namura M, Tsunoda H, Kobayashi D, Enokido K, Yoshida A, Watanabe T, *et al*. The Loss of Lymph Node Metastases After Neoadjuvant Chemotherapy in Patients With Cytology-proven Axillary Node-positive Primary Breast Cancer. Clinical Breast Cancer. 2019; 19: 278–285.

[25] Braithwaite D, Miglioretti DL, Zhu W, Demb J, Trentham-Dietz A, Sprague B, *et al*. Family History and Breast Cancer Risk Among Older Women in the Breast Cancer Surveillance Consortium Cohort. JAMA Internal Medicine. 2018; 178: 494–501.

[26] Reiner AS, Sisti J, John EM, Lynch CF, Brooks JD, Mellemkjær L, *et al*. Breast Cancer Family History and Contralateral Breast Cancer Risk in Young Women: An Update From the Women's Environmental Cancer and Radiation Epidemiology Study. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2018; 36: 1513–1520.

[27] Winton LM, Nodora JN, Martinez ME, Hsu CH, Djenic B, Bouton ME, *et al*. Factors associated with surgical management in an underinsured, safety net population. Surgery. 2016; 159: 580–590.

[28] Fan Y, Chen X, Li H. Clinical value of serum biomarkers CA153, CEA, and white blood cells in predicting sentinel lymph node metastasis of breast cancer. International Journal of Clinical and Experimental Pathology. 2020; 13: 2889–2894.

[29] Barry JD, Koch TJ, Cohen C, Brigati DJ, Sharkey FE. Correlation of immunohistochemical markers with patient prognosis in breast carcinoma: a quantitative study. American Journal of Clinical Pathology. 1984; 82: 582–585.

[30] Seale KN, Tkaczuk KHR. Circulating Biomarkers in Breast Cancer. Clinical Breast Cancer. 2022; 22: e319–e331.

[31] Jelski W, Mroczko B. Biochemical Markers of Colorectal Cancer - Present and Future. Cancer Management and Research. 2020; 12: 4789–4797.

[32] Wang W, Xu X, Tian B, Wang Y, Du L, Sun T, *et al*. The diagnostic value of serum tumor markers CEA, CA19-9, CA125, CA15-3, and TPS in metastatic breast cancer. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2017; 470: 51–55.