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CIRCULATING TUMOR MARKERS OF BENIGN AND MALIGNANT BREAST DISORDERS IN LIBYA

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ABSTRACT

Background: Breast cancer is most common malignant disorder in Libyan females. Breast cancer is the most dreadful disease in terms of quality of life, though heart disease is a more common cause of mortality here. Benign and malignant breast disorders are very common in Libyan women like other Arab countries particularly younger individuals than western world. An increase in the incidence of cancers has been reported in the Arab countries [1]. This could be explained by the attribution of various factors such as the robust epidemiological control of infectious diseases, increase in the average life span of the general population, higher socio-economic status, smoking, higher incidence of hepatitis B and C, and food fads socio-economic status. Breast cancer is one of the leading cancers, causing higher rate of morbidity and mortality comparable to that of other developed countries, however, with an earlier age of onset [2]. 26% of all cancers are breast cancers in Libyan women as per the Benghazi cancer registry. [3]. Almost a decade ago, Singh and Al-Sudani [4] demonstrated that breast cancer is one of the top ten cancers responsible for higher mortality in Libya. In another study conducted between 1981 and 1985 [5], breast cancer was the most frequent tumor (29.8%) in females and the majority of these patients were of a younger age group (72.3% below 50 years). Almost all the patients selected for our study were multiparous and were exposed to breast-feeding [6]. A recent literature review by Najjar and Easson [6] provided evidence that the average age of onset of breast cancer in Arab women is 48 years and is almost a decade sooner than their western counterparts and this warrants effective screening and management strategies [7]. The present study is a case control study of tumour markers CA 125, CA 15-3 and Carcino Embryonic Antigen (CEA) in serum of patients suffering from benign and malignant breast disorders in Libya.

Materials and methods: There are 12 cases of carcinoma of breast patients with age group ranging from 30 – 55 years of age, 10 cases of benign breast disorders i.e., Fibroadenosis with age group ranging from 18 to 50 years retrieved from department of surgery, 7th October Hospital, Benghazi, Libya and there are 12 cases of age matched controls free from both malignant and benign disorders of breast were included in this study. Venous sampling was done to the patients, all the patients and controls were measured serum CA125, CA15-3and CEA levels by authenticated methods by using Cobas E 411 analyser. Statistical analysis was done by using SPSS software by using Mann-Whitney and Wilcoxon tests.

Results: There is no significant rise of CA 125 in benign (p=0814) and malignant (p= 0.676) disorders of breast when compared to controls. CA 15-3 was significantly high in patients suffering from breast cancer (p= 0.019) when compared to controls and also very significantly high when (p= 0.003) compared with patients with benign breast disorders. The level of CA 15-3 was not significantly high in patients with benign breast disorders (p=0.186) when compared to controls. The level of CEA was significantly high in patients of breast cancer when compared to patients of benign breast (p=0.009) disorders and (p=0.017) controls. The level of CEA is not significantly in high patients of benign breast disorders (p=0.634) when compared to controls.

Conclusion: The present study showing high levels CA 15-3 and CEA only in malignant disorders of breast may be useful as diagnostic and prognostic markers. CA 125 has not shown any significance in this study proving that it is not an important marker in malignant breast disorders.

KEYWORDS :

Introduction

Breast cancer is the second most common type of cancer after lung cancer (10.4% of all cancer incidence, including both genders) and the fifth most common cause of cancer death.[1] Further, this condition is a significant health problem among Libyan women, with an incidence of 18.8 new cases per 100,000 women per year.[2] The patients are often

younger than in Europe, and follow the pattern common in Middle East and North Africa (MENA).[3] A recent literature review by Najjar and Easson[3] provided evidence that the average age of onset of breast cancer in Arab women is 48 years and is almost a decade sooner than their western counterparts and this warrants effective screening and management strategies.[4] Further, most of the patients present with advanced disease,[2,5] indicating a diagnostic delay.

Early detection of breast cancer is quintessential for appropriate management when tumor burden is still low and also when patients are most likely to respond to adjuvant therapy. Recently, concentration of serum tumor markers has been used to detect tumor activity.[6] A tumor marker is a biochemical indicator of presence of a tumor,[7] and can be detected in blood, urine, other body fluids and also tissues.[6,8] Tumor markers are either produced by tumor cells themselves or by the body in response to these cells. Since these substances are released into the circulation, they can be measured in the blood. However, these markers are not the primary diagnostic tools for cancer. They can be used only to support the diagnosis.[9] and also to evaluate the progression of the disease after initial chemotherapy and radiotherapy to monitor subsequent treatment strategies.[10]

However, the key advantages of tumor markers are that they provide a minimally invasive, cost-effective source of information which would aide in monitoring the course of the disease, determine prognosis, and planning the treatment.[6]

Tumor markers showing evidence of utility in breast cancer and recommended for use in clinical practice are CA 15-3, CA 27.29, Carcinoembryonic antigen (CEA), Estrogen receptor (ER), Progesterone receptor (PR), Human epidermal growth factor receptor 2 (HER2), Urokinase plasminogen activator (uPA), Plasminogen activator inhibitor 1 (PAI-1) and multiparameter assays for gene expression. Few other markers which could be used for screening of breast cancer since they did not demonstrate adequate evidence supporting routine use in clinical practice are P53, cathepsin D, cyclin E and nestin.[6]

The present study is a case control study of tumour markers CA 125, CA 15-3 and Carcino Embryonic Antigen (CEA) in serum of patients suffering from benign and malignant breast disorders in Libya.

Materials and methods

This was a case-control study conducted between 2013 to2014. Ethics committee clearance was obtained from University of Benghazi Ethics Committee. A total of 149 subjects were included in the study. The case records of a total of 76 cases of carcinoma breast in the age group ranging from 30 – 55 years and 22 cases of benign breast disorders i.e., Fibroadenosis in the age group ranging from 18 to 50 years were retrieved from the department of surgery, 7th October Hospital, Benghazi, Libya. Fifty two age matched subjects free from both malignant and benign disorders of breast were included as controls in this study. Venous blood samples was drawn from all the cases and controls. Informed Consent was obtained from all study participants. Serum CA125, CA15-3 and CEA levels were measured by authenticated methods using Cobas E 411 analyser. Statistical analysis was done by using SPSS software by using Mann-Whitney and Wilcoxon tests.

All participants were asked to fill in a Lifestyle questionnaire and interview, included information containing questions regarding reproductive history, obtained by questionnaire on ages at menarche, menopause, and first birth; parity; and family history of breast cancer. Breast Cancer-risk factors, medical history, exogenous hormone use and menopausal Status were also assessed. In addition, anthropometric measurements (e.g. height, weight) were recorded. The height and weight were measured and obesity was defined as body mass index (BMI) of $\geq$ 30 kg/ m^2, where BMI was calculated by dividing the weight in kilograms on height in meters squared.

Results

Serum CEA: The level of serum CEA was very significantly high in the carcinoma breast group when compared to controls (p=0.000) and group with benign breast disorders (p=0.001). The level of CEA was not significantly high in patients with benign breast disorders (p=0.540) when compared to controls.

Serum CA 15-3: The observed values of the serum CA 15-3 levels (mean ± S.D) in the carcinoma breast, benign breast disorders and control groups were 28.1±24.6, 11.9±4.4 and 14.1±6.5 respectively. Serum CA 15-3 was very significantly high in patients suffering from breast cancer (p= 0.000) when compared to controls, and very significantly high (p=0.000) when compared with subjects with benign breast disorders. The level of CA 15-3 was not significantly high in subjects with benign breast disorders (p=0.644) when compared to controls.

Serum CA19-9: Serum CA19-9 level was significantly high in the carcinoma breast group when compared to controls (p=0.003) and group with benign breast disorders (p=0.008). However, there was no significant increase in the serum CA 19-9 in the group with benign breast disorders compared to controls (p=0.647).

Serum CA 125: Serum CA 125 (mean ± S.D) in the carcinoma breast, benign breast disorders and control groups were 17.1±15.1, 13.4±10.4 and 14.2±10.4 respectively. There was no significant increase in the serum CA 125 levels in the groups with carcinoma breast and benign breast disorders when compared with controls (p=0.215 and 0.825 respectively).

Summary of results are shown in table 1.

Table 1: Serum tumor marker levels in the study population

	Carcinoma Breast	Benign Breast Disorders	Controls	P Value
	n=74	n=21	n=52	
CEA (ng/ml)	3±2.8	1.3±0.5	1.6±0.7	0.000
CA15-3 (U/ml)	28.1±24.6	11.9±4.4	14.1±6.5	0.000
CA19-9 (U/ml)	14±13.9	6.6±6.1	7.9±7.5	0.003
CA125 (U/ml)	17.1±15.1	13.4±10.4	14.2±10.4	0.342

Discussion

In our study, we analysed the serum levels of four biomarkers, CEA, CA 15-3, CA 19-9 and CA 125 in subjects with benign and malignant breast disorders and in controls.

Carcinoembryonic antigen belongs to a family of related cell surface glycoproteins and contains 45–50% carbohydrates. It is a single polypeptide chain consisting of 641 amino acids, with lysine at its N-terminal position. It is the most frequently used tumor marker in clinical practice for colorectal, gastrointestinal, lung and breast cancer. In breast cancer, serum CEA levels are associated with metastatic disease, and the circulating levels of CEA are directly proportional to the size of both primary and metastatic tumor.[6] However, CEA alone is nonspecific for diagnosis of breast cancer,[11,12] and should be considered complementary to CA 15-3 in detecting recurrence of breast cancer.[13] Therefore, serum CEA, CA 15-3 and the clinicopathological assessments should be performed and correlated for proper diagnosis in patients with metastatic breast cancer.[6] Evidence suggests that high levels of serum CA 15-3 (e.g. 150 U/ml) and/or serum CEA (e.g. 120 ng/ml) in patients suspected to have only localized disease suggests the presence of underlying metastatic disease.[12] In our study, the serum CEA were significantly elevated in the cases with carcinoma breast compared to those with benign breast disorders (p=0.001) and the controls (p=0.000), but not in the group of carcinoma breast compared to controls. Similar to our results, Hayes et al.[14] and Norum et al.[15] found a significant elevation in the serum levels of CEA in patients with breast cancer than in the controls.

CA 15-3 is one of the most recommended tumor markers which has shown evidence of clinical utility in breast cancer. It is a carbohydrate-containing protein antigen called mucin (MUC), and belongs to the MUC1 family. Although the exact physiological functions of MUC1 proteins are not understood completely, it has been postulated to reduce cell-to-cell interaction and also inhibit tumor cell lysis.[16] It has been observed that the MUC1 gene is overexpressed in malignant breast tumors and therefore CA 15-3 can be used as tumor marker for breast cancer.[17] Further, this marker is more useful in assessing the disease prognosis as well as monitor the treatment efficacy because its serum concentration and the proportion of patients with elevated CA 15-3 values tend to increase with the severity of the disease and/or size of the tumor.[18] Darlix et al.[19] opine that serum CA 15-3 level is an independent prognostic factor in metastatic breast cancer patients.

In our study, the serum CA 15-3 concentration was very significantly

high in cases suffering from breast cancer when compared with controls (p=0.000) and cases of benign breast disorders (p=0.000). These results are in agreement with the Hayes et al.[14] and Gion et al.[20] who reported a highly significant difference between the patients suffering from breast cancer and the control. The result obtained in our study confirms that CA 15-3 is a sensitive tumor marker for the evaluation and monitoring of patients with breast cancer as demonstrated previously.[21,22]

CA 19-9 is a tumor marker closely associated with invasion and metastasis of many malignancies, similar to CEA. This marker is of great clinical value for the diagnosis and prognosis of pancreatic cancer,[23] and also in gastrointestinal cancers.[24-26] However, there is paucity of data on its role in carcinoma breast. Zhao et al.[27] demonstrated that CA 19-9 is an unreliable marker to predict breast cancer. However, in our study, we observed serum CA19-9 level was significantly elevated in the carcinoma breast group when compared to controls (p=0.003) and group with benign breast disorders (p=0.008). However, no significant increase was observed in the serum CA 19-9 in the group with benign breast disorders compared to controls (p=0.647).

Cancer antigen 125 (CA 125) is a tumor marker commonly used in ovarian cancer but may also be elevated in the metastatic phase of other malignancies.[28] Studies have shown that the levels of CA 125 are increased in up to 84% of metastatic breast patients.[29,30] Further, the CA 125 levels seem to depend on the site of metastasis. In the study by Yerushalmi et al.,[31] when bone metastasis was the solitary site of disease, CA 125 was normal in 73% of patients. On the contrary, when multiple metastases were found at first relapse, 65% of patients had increased CA 125 levels. According to the researchers, this was probably because CA 125 is mainly produced by mesothelial cells and hence, is more likely to be increased in cases of abdominal and pleural metastases.[32,33] However, in our study, we did not observe a significant elevation in the serum CA125 concentrations in the carcinoma breast cases when compared with the cases with benign breast disorders and the controls.

Conclusion

Carcinoma breast is a major problem among Libyan women, especially because of lack of early diagnosis. Tumor markers may have a role in aiding the diagnosis and assessing prognosis of this condition. Although previously it has been observed that CEA, CA 15-3 and CA 125 are complementary to one another as diagnostic and prognostic tools for breast cancer, according to the results of our study, serum CA 15-3 and CEA are important markers in malignant breast disorders but not serum CA 125. We also observed that CA 19-9 may have a role in breast cancer. However, ours was a retrospective study, and the sample size in our study was very small, and these results need to be replicated in a larger population to confirm the findings.

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