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Original Article

SERUM CA15-3 MEASUREMENT IN BREAST CANCER PATIENTS BEFORE AND AFTER MASTECTOMY

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Background: Much research is being carried out to find a tumor marker for early diagnosis of breast cancer when the lesion is still small. CA15-3, a glycoprotein, is one candidate with probable use as tumor marker in breast cancer.

Objective: We conducted this study to analyze the relationship between serum levels of CA15-3 and several variables including age, clinical stage, and the number of lymph nodes involved in breast cancer patients.

Methods: One hundred and thirty-six females including 39 normal controls, 54 patients with benign lesions, and 43 with malignant lesions entered this study. A second and third sample was obtained from patients who were diagnosed as having breast cancer, one week and one month postmastectomy, respectively. CA15-3 was measured by ELISA.

Results: The number of patients in the malignant group (6 out of 43) with elevated CA15-3 levels was higher than that in the normal controls (3 out of 39) and patients with benign lesions (1 out of 54). Forty percent of patients in stages II and III had a higher frequency of abnormal CA15-3 values, whereas 13% of those in stage I disease did so. One week after mastectomy, the mean ± SD serum CA15-3 was 18.3 ± 14.6 U/mL. However, a month later, the mean ± SD was 21.7±19.7 U/mL, which was approximately the same as the preoperative values (mean ± SD: 22.1 ± 25.6 U/mL). There was an abnormal elevation in CA15-3 values when ≥4 lymph nodes were involved. The correlation between the elevated CA15-3 values and the number of involved lymph nodes was significant ($P < 0.001$). Analysis of the CA15-3 values showed a sensitivity of 14.0% and a specificity of 92.3%. The positive and negative predictive values were 66.7% and 49.3%, respectively. The relative efficiency was 1.8%.

Conclusion: In this study, CA15-3 was found to have no value in the screening for early diagnosis of breast cancer. We observed a strong correlation between elevated CA15-3 levels and the progression of breast cancer.

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Keywords: Breast cancer • CA15-3 • prognosis • tumor markers

Introduction

Breast cancer is a well-known disease. Described by Egyptians, the reports of the disease date back to 3,000 B.C. A Persian physician, Democedes, is said to have cured the wife of the king Dariush. She suffered from a "tumor" in her breast, which was ulcerated and spread.[1]

Unfortunately, even after 5,000 years, the death toll for breast cancer has remained stable. Therefore, much research is being done to diagnose the cancer early when the lesion is still small. If diagnosed at an early stage, a surgical procedure can totally remove the tumor and the patient will be completely cured.

One area under intense research is a search for an ideal tumor marker. One of the features of an ideal tumor marker is being specific for that type of tumor. In other words, normal individuals or patients with benign lesions should not have detectable levels of that marker. The tumor marker

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should also be sensitive enough to detect tumors, while they are still small, i.e., in the early stages of the disease as well as during recurrences. Finally, these markers must be readily accessible through sampling of body fluids.[2] One group of tumor markers are the mucin-like glycoproteins, which are all defined by specific monoclonal antibodies (MAbs).

We decided to work on the tumor marker CA15-3. This tumor marker is a breast cancer-associated antigen, which is defined by two distinct MAbs. The antibodies bind DF_3 and 115D8 antigens. DF_3 antigen is found on the surface of human mammary cancer cells, whereas 115D8 antigen is found on the human milk fat globule membrane.[3] Both antigens are eventually released into the surrounding fluids. No previous survey has been done on CA15-3 in Iran. Therefore, we decided to conduct this study to analyze the potential uses of CA15-3 in early diagnosis of breast cancer patients among the Iranians.

Patients and Methods

CA15-3 can be quantified with monoclonal antibodies, using two different methods. The antigen level can be determined using radioimmunoassay based on a competitive binding principle or using a sandwich format with the ELISA method. Recently, ELISA has become the more popular method for evaluating the level of tumor marker in the serum. Nonetheless, the ELISA also has its drawbacks, known as the "hook effect". This is observed in certain samples where the tumor marker level is high, but a falsely low value is read.[4]

One hundred and thirty-six females were entered into this study. Five mL blood was collected from all females and transferred to the laboratory on ice. After the clotting, the blood samples were centrifuged. The serum was transferred to another tube and stored at -20˚C until use. CA15-3 was measured by ELISA (the Conc Ag Diagnostic kit) according to the manufacturer's instructions. Values ≥30 U/mL were considered abnormal.

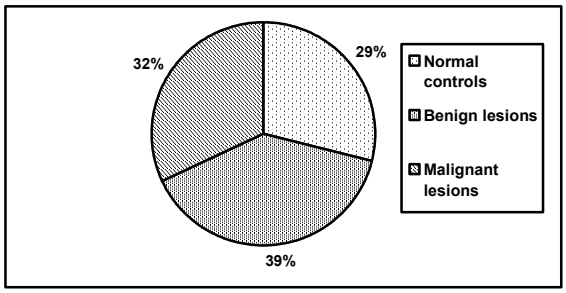

Figure 1. Three groups of patients and their percentages analyzed for CA15-3.

The patients in this survey were divided into three groups including 39 normal controls chosen from the laboratory personnel who showed no evidence of disease after a complete physical examination and laboratory work-up including a chest radiograph, liver function test, bone scan, mammography, etc.; 54 patients with benign lesions; and 43 patients with malignant lesions (Figure 1). Two more samples were taken from patients with diagnosed breast cancer who underwent mastectomy. The second sample was drawn one week and the third sample was drawn one month postoperatively. The patients with malignant lesions were further evaluated for their age, tumor size, lymph node involvement, and disease staging.

Results

The mean serum CA15-3 values are shown in Table 1. The mean in the normal group, in those

Table 1. The mean ± SD of CA15-3 level in the normal controls, benign lesions, and malignant lesions groups.

Group		Age	At presentation	Postoperative CA15-3 level		Tumor size
				1 week	1 month	
	Mean		18.63			
Normal controls	N		39			
	SD		7.36			
	Mean	35.02	12.85			
Benign lesions	N	51	54			
	SD	11.51	6.18			
	Mean	45.49	22.11	18.3	21.75	4.32
Malignant lesions	N	43	43			
	SD	11.19	25.63	14.59	19.65	34.60
Total	**Mean**	**39.81**	**17.47**	**18.30**	**21.75**	**4.32**
	SD	**12.46**	**15.87**	**14.59**	**19.65**	**4.60**

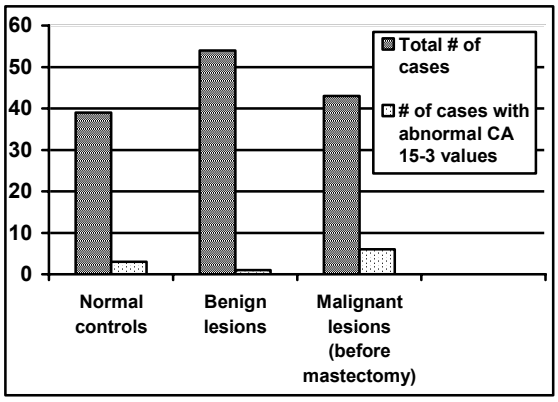

Figure 2. Number of abnormal CA15-3 in different groups of patients.

with benign lesions, and in patients with malignant lesions were all below the cut-off value. Nonetheless, abnormal CA15-3 values are observed in all three groups. With one or more patients in each group (Figure 2), after the clinical staging was performed, the premastectomy CA15-3 values were reevaluated according to the stage (Figure 3). It is apparent that the higher the disease stage, the higher is the frequency of abnormal CA15-3 values, when compared to those in stage I. The mean serum CA15-3 level slightly dropped one week after mastectomy. However, one month later, the value returned back to approximately the same preoperative value (Table 1).

In patients with malignant breast lesions, the age ranged from 27 to 66 years (mean ± SD: 45.5 ± 11.1). The tumor size in these patients ranged from one to 11 cm in diameter (mean ± SD: 4.3 ± 4.6). No correlation was found between CA15-3 marker level and the patient's age or tumor size. The number of lymph nodes involved ranged from one to ten nodes. There was no significant difference in CA15-3 level among the studied groups when 1–3 lymph nodes were involved. However, CA15-3

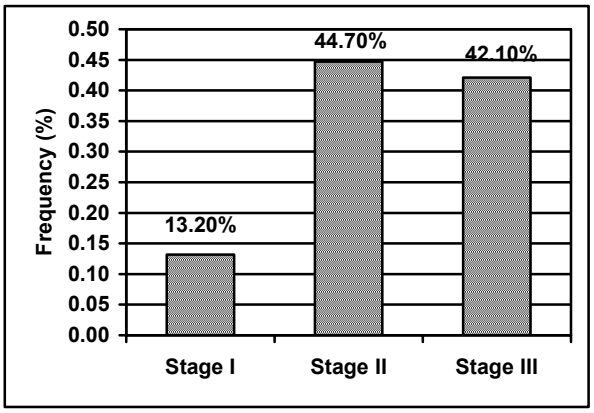

Figure 3. Frequency of elevated CA15-3 values in different stages of breast cancer.

Table 2. The sensitivity, specificity, positive and negative predictive values, and relative efficiency for CA15-3, as a test for early diagnosis of breast cancer.

Sensitivity for CA15-3	14.0%
Specificity for CA15-3	92.3%
Positive predictive value	66.7%
Negative predictive value	49.3%
Relative efficiency	1.81%

values increased in most cases when ≥4 lymph nodes were involved (Figure 3).

In our study, CA15-3 values, as a diagnostic test, had a sensitivity of 14.0% and a specificity of 92.3%. The positive and negative predictive values were 66.7% and 49.3%, respectively. The relative efficiency was only 1.8% (Table 2). A greater number of patients were in the malignant group (6 out of 43), as compared to the normal controls (3 out of 39), and patients with benign lesions (1 out of 54). Patients with stages II and III disease had a higher likelihood for having abnormal CA15-3 values, when compared to those with stage I disease.

Discussion

The mean serum CA15-3 values for normal controls, benign lesions, and patients with malignant breast lesions were all below the cut-off value of 30 U/mL. The mean ± SD value of CA15-3 for those with malignant lesions (22.1 ± 25.6 U/mL) was higher than that for those with benign breast lesions and the normal controls (12.9 ± 6.2 and 18.6 ± 7.4, respectively). No doubt, CA15-3 assay has no place in screening for early diagnosis of breast cancer. This was shown by the low sensitivity of the test (14.0%). The mean CA15-3 value between benign and malignant lesions was significant ($P < 0.05$) (Table 2).

One or more patients had elevated CA15-3 values in all three groups. However, the frequency of preoperative abnormal CA15-3 values for patients with cancer was approximately twice that observed in those in normal control group. After clinical staging, abnormally elevated CA15-3 levels were noted in 13.2% of stage I patients; whereas slightly over 40% of stages II and III patients had elevated levels (Figure 2). Therefore, CA15-3 assays could be a good marker for evaluating the progression of breast cancer.

Following mastectomy, CA15-3 levels were evaluated two more times. The results showed a slight drop in the mean CA15-3 value one week after mastectomy, which returned back to the pre-

operative level after one month. Since CA15-3 has a long half-life, a significant drop in CA15-3 antigen may not become obvious until three months after removal of the bulk mass of the tumor.[5] It is, therefore, recommended that patients with malignant lesions should be followed up for an extended period of time after mastectomy, so that the value of CA15-3 can be followed.

No correlation was found between the age of the patients and CA15-3 values. However, in another study,[6] a correlation was noted with the age of patients. In our study, there was also no correlation between the tumor size and CA15-3 levels.

There was an abnormal elevation in CA15-3 values, when ≥ 4 lymph nodes were involved. The correlation between the elevated CA15-3 values and the number of involved lymph nodes, as compared with the total number of lymph nodes, was significant ($P < 0.001$). This confirms that CA15-3 assays are valuable in evaluating the progression of the disease.

Elevated CA15-3 levels are more common in metastatic breast cancer patients than with other tumor markers (e.g., carcinoembryonic antigen [CEA]).[7] We noted a greater frequency of abnormal CA15-3 values in patients with malignant lesions than normal controls and patients with benign lesions. This finding is consistent with other reports.[8] CA15-3 has been shown to be elevated in 95% of cases where metastasis existed.[7] However, in our study only 4% showed an elevation in CA15-3. These values support the fact that CA15-3 is more valuable than CEA and is gradually replacing CEA in follow-up of patients with metastatic breast cancer.

Contrary to its low sensitivity value, the specificity of CA15-3 is high (92.3%). The specificity was shown to be 100% in another report.[9] Considering the fact that the early detection of cancer recurrence is of paramount importance, a study for an extended period of time is necessary to make a definite judgment on use of CA15-3.[10]

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