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Comparative study of significance of serum matrix metalloproteinase-13 (MMP-13) and carbohydrate antigen 15.3 (CA15.3) as an early tumor marker in female patients with breast cancer

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Abstract
Aim: To determine the usefulness of serum Matrix metalloproteinase-13 (MMP-13) along with Carbohydrate Antigen 15.3 (CA15.3) as an early tumor marker in female patients with breast cancer.
Method: The breast cancer patients were recruited from OPD/IPD of Surgery and Oncology department of SMS Hospital, and evaluated serum MMP-13 and CA15.3. Total 180 subjects were included in this study.90 breast cancer Patients were divided according to different stages and 90 control subjects also included.
Results: Serum MMP-13 and CA15.3 level raised significantly in breast cancer patients. Further increases with the advanced stage of the breast cancer.
Conclusion: Both MMP-13 and CA15.3 can be useful diagnostic tumor marker in breast cancer.

Keywords: MMP-13, CA15.3, Breast cancer

Introduction

Breast cancer is the most frequently diagnosed cancer disease in women worldwide, with an estimated one and a half million new cases each year and approximately half a million deaths per year [1]. Breast cancer is stage-biological process causing multiple genetic and epigenetic changes in the epithelial cells of the breast over a period of several years [2]. Female breast cancer has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths [3].

Matrix metalloproteinases are a family of endopeptidases that can degrade extracellular matrix proteins and promote cell invasion and metastasis [4]. The MMPs belong to proteasesmetzincin superfamily which are synthesized as pro MMP. MMP-13 (collagenase-3) is EC 3.4. 2422 the latest human collagenase. MMP-13 is expressed in a broad range of primary malignant tumors and it is emerging as a novel biomarker [5]. This enzyme exhibits preference toward cleavage of type II collagen, effectively completing the substrate spectrum of the collagenases. Collagenase-3 was first cloned from breast cancer tissue in 1994 [6]. MMP-13 expression has been regularly referred to in the literature as indicative of various cancerous processes including chondrosarcoma, breast cancer, head and neck tumors and melanoma [7]. MMP13 was first identified from overexpressing breast carcinomas [8].

CA 15.3 is a carbohydrate-containing protein antigen called mucin (MUC). Mucins are large transmembrane glycoproteins with extracellular domains formed of a highly O-linked glycosylated protein core consisting of a variable number of highly conserved 20-amino acid repeat units, classified into 7 families, MUC1 to MUC7, according to their genetic and biomolecular characteristics. CA 15.3 belongs to the MUC1 family.TheMUC1 gene is overexpressed in malignant breast tumors, allowing use of gene product CA 15.3 as tumor marker for breast cancer [9]. So, the aim of our study was to investigate the clinical significance of serum matrix metalloproteinase-13 along with CA15.3 levels in breast carcinoma by comparing its level with different stages of breast cancer and healthy controls.

Material &Method

The present case-control comparative study was conducted in the Department of Biochemistry, in association with the Department of Surgery and Oncology SMS Medical College and Attached group of Hospitals, Jaipur. Total 180 subjects here included in this study and divided into two groups as follows: Group 1 comprised of 90 Healthy Control & Group 2 comprised of 90 Breast cancer Patient. Patients were also divided according to different stages.

Inclusion Criteria

- Willingness to participate has included in this study and those who have given written consent.
- Female patients (age >20 years) diagnosed with breast cancer.
- All patients with operable breast lumps and recurrent breast lump in a previously operated case of carcinoma breast.

Exclusion Criteria

- Patients having other cancer, collagenopathy and all other diseases that affect the level of MMP-13.
- Previously diagnosed cases of breast cancer who is taking chemotherapy or radiotherapy.
- History of OCP & Pregnancy.
- Patients with benign breast diseases.

Venous blood sample was withdrawn for investigations taking all aseptic precautions. Serum was separated and investigated for MMP-13 and CA 15-3 by ELISA method [10].

Ethical approval and Informed consent

The Protocol was approved by institutional Ethics committee. Informed written consent was obtained from all study subjects.

Statistical Analysis

The data was analysed using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, means and standard deviations were calculated. The statistical tests applied for the analysis were one-way ANOVA with Post-Hoc Bonferoni test. The confidence interval and p-value were set at 95% and ≤ 0.05 respectively.

Results

Table 1: shows Serum MMP-13 and CA15-3 concentrations in breast cancer patients (case) and healthy controls groups. Both Serum MMP-13 and CA15-3 concentration were higher in breast cancer subjects as compared to controls.

Table 1: Serum MMP-13 (ng/ml) and CA15-3(U/ml) levels in breast cancer v/s healthy controls

Marker	Case	Control	P value
	Mean±SD	Mean±SD	
MMP-13(ng/ml)	72.54±42.88	6.26±1.66	<0.001
CA15-3(U/ml)	50.88±20.77	11.68±5.38	<0.001

Table 2: demonstrates serum MMP-13 and CA15-3 concentration in different stages of breast cancer. Both MMP-13 and CA15-3 concentration were higher in advanced stage of breast cancer. The results were highly significant. (p<0.001) (Figure 1).

Table 2: Serum MMP-13 and CA15-3 levels in different stages of breast cancer

Stage	N	MMP-13(ng/ml)	CA15-3(U/ml)
		Mean±SD	Mean±SD
I	15	27.87±15.61	37.82±10.47
II	25	34.51±15.68	40.15±12.98
III	25	82.03±11.42	46.24±14.08
IV	25	127.91±16.13	74.10±18.93
F value		222.27	29.44
P value		<0.001	

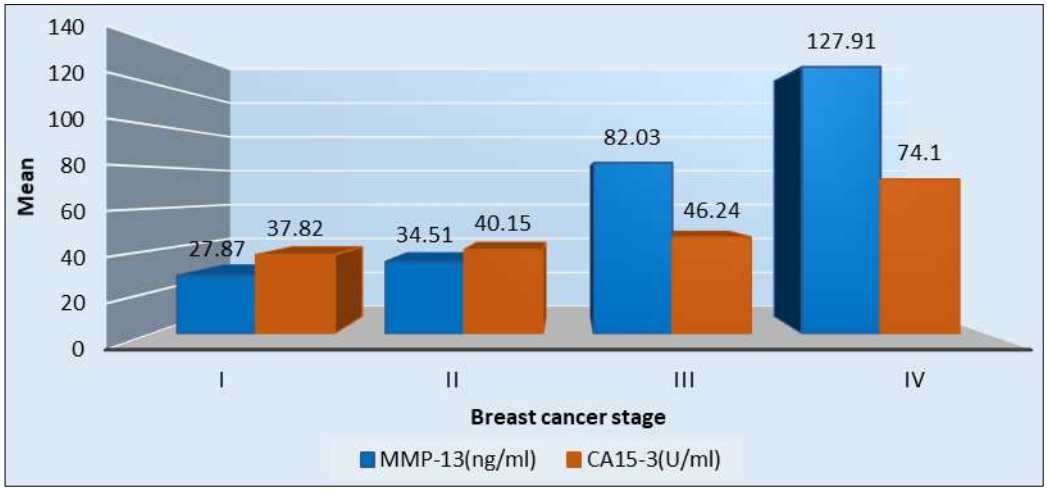

Fig 1: Serum MMP-13 and CA15-3 indifferent stages of breast cancer

Table 3 and 4: presents descriptive multiple (Intra groups) comparisons of serum MMP-13 and CA-15.3 in different stages (I, II, III, IV) of breast cancer respectively. Both MMP-13 and CA-15.3 concentration is significantly higher in advanced stage (IV) in breast cancer and the level increases further with metastasis.

Table 3: Multiple (Intra stages) Comparison of serum MMP-1 by Post Hoc- Bonferroni test

Dependent Variable	(I) Stagging	(J) Stagging	Mean Difference (I-J)	Std. Error	Sig.
MMP-13	I	II	-6.63667	4.81593	1.000
		III	-54.15679*	4.81593	.000
		IV	-100.04027*	4.81593	.000
	II	I	6.63667	4.81593	1.000
		III	-47.52012*	4.17071	.000
		IV	-93.40360*	4.17071	.000
	III	I	54.15679*	4.81593	.000
		II	47.52012*	4.17071	.000
		IV	-45.88348*	4.17071	.000
	IV	I	100.04027*	4.81593	.000
		II	93.40360*	4.17071	.000
		III	45.88348*	4.17071	.000

*=significant

Table 4: Multiple (Intra stages) Comparison of serum CA15-3 by Post Hoc – Bonferroni test

Dependent Variable	(I) Stagging	(J) Stagging	Mean Difference (I-J)	Std. Error	Sig.
CA 15.3	I	II	-2.32613	4.84729	1.000
		III	-8.41333	4.84729	.517
		IV	-36.27733*	4.84729	.000
	II	I	2.32613	4.84729	1.000
		III	-6.08720	4.19788	.904
		IV	-33.95120*	4.19788	.000
	III	I	8.41333	4.84729	.517
		II	6.08720	4.19788	.904
		IV	-27.86400*	4.19788	.000
	IV	I	36.27733*	4.84729	.000
		II	33.95120*	4.19788	.000
		III	27.86400*	4.19788	.000

*=significant

Discussion

Our study results depict that MMP-13 concentration was higher in breast cancer patients as compared with healthy control subjects and the level raised significantly in breast cancer patients with advanced stages. Our results are consistent with observation made by Kotepui M *et al*. [11] who observed MMP-13 expression was significantly greater in the cancerous breast tissues in comparison to those of normal breast tissues. It is explained by due to role of MMP-13 in breaking down type II collagen. MMP-13 contributes to the formation of a complex microenvironment that promotes malignant transformation in early stages of cancer. Most of the studies done at molecular level showed increased expression of MMP-13 in breast cancer [12]. Very few studies are available regarding its serum value. The increase in MMP-13 level in serum could be used as a diagnostic marker because in our study we have seen that the level of MMP-13 increases as the stage advances. This may be because in the process of breast cancer turning from low stage to advance stage, MMP13 will break down basement membranes of tissues and release of angiogenic factors to form an invasive carcinoma. This is in agreement with Nielsen *et al*. [13] Therefore MMP13 has tremendous potential to serve as a biological marker to assist in the clinical diagnosis of breast cancer.

CA15-3 concentration was also observed higher in breast cancer patients as compared with healthy controls and further increases with progression of advanced stages of breast cancer. Our results are in agreement with previous studies of Gioia D *et al*. [14] & Lee JS *et al*. [15] who also showed that serum concentrations of the CA15.3 are highly expressed in patients with breast cancer when compared with healthy controls. This may be because CA15.3 is the product of MUC-1 gene, and mucins which are aberrantly over expressed in many adenocarcinomas in an under-glycosylated form and then shed into circulation [16]. CA15-3 isan important diagnostic, prognostic indicator and good predictor for breast cancer.

Conclusion

Breast cancer is one of the most common and leading causes of cancer death among women worldwide. Early diagnosis of breast cancer can provide patients a wider range of therapeutic options as well as a higher success rate of therapy that lowers mortality. Quantitative analysis of tumor markers is the most convenient method to screen breast cancer. Our study results suggested that serum MMP-13 and CA15.3 can be useful serum tumor marker in patients with breast cancer. Serial determination of these markers may be beneficial for early detection of metastasis.

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