Research Article

Serum high sensitivity C-reactive protein in breast cancer patients

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ABSTRACT

Background: Breast cancer, second commonest malignancy in women is a multifactorial disease. Key role of chronic low grade inflammation has been linked with pathophysiology of breast cancer. High sensitivity C-Reactive Protein (hsCRP) is an acute phase reactant proinflammatory protein synthesized in hepatocytes. Present case control study was aimed with primary objective of estimation of serum hsCRP levels in newly diagnosed breast cancer patients and to correlate them with the staging of the disease.
Methods: We enrolled 60 newly histologically diagnosed cases of breast cancer and 60 healthy age matched controls. Demographic features, anthropometric measures were recorded. After overnight fast, blood samples were collected and analyzed for serum hsCRP levels.
Results: We observed significant differences between cases and controls in anthropometric parameters BMI and waist: hip (P <0.05) and hsCRP levels (P <0.001). Depending of the stage, serum hsCRP levels were associated with advanced stage. In stage I, association of hsCRP was not significant with disease while in stage II and III there was significant association. In stage IV patients with distant metastasis, serum hsCRP values were highly significantly raised compared to stage II and III. This suggests significant association of state of inflammation with stage of breast cancer.
Conclusion: Inflammatory component plays key role in all stages of tumourigenesis from initiation of the tumor, infiltration, local and systemic invasion. Estimation of hsCRP may be simple, inexpensive and useful tool for risk assessment, screening of high risk individuals and to predict outcome in diagnosed cases.

Keywords: Breast cancer, hsCRP, Low grade chronic inflammation

INTRODUCTION

Breast cancer, second commonest malignancy in women is a multifactorial disease. Clinical and epidemiological data suggest the role of hormones, genetic predisposition, environmental factors and obesity in causation of breast cancer. But now key role of chronic low grade inflammation has been linked with pathophysiology of breast cancer. Chronic inflammation has been implicated in the initiation and progression of malignancies.[1] C-reactive protein (CRP) is an acute phase reactant pentraxin protein synthesized in response to inflammation, infection and damage to tissues. It is produced in hepatocytes under the influence of cytokine Interleukin-6 from malignant lesion.[2]

Inflammatory pathways have been shown to be involved in tumor development, its invasion and distant metastasis also even if there is rare evidence of histological inflammation in patients of breast cancer.[3] Cancer related

inflammation has been identifies as seventh hallmark of cancer now.[4] Present study was aimed with primary objective of estimation of serum hsCRP levels in newly diagnosed breast cancer patients and to correlate them with the staging of the disease.

METHODS

Present case control study enrolled 60 new histologically diagnosed cases of breast cancer. 60 healthy age matched controls were selected after thorough breast examination and negative mammography results. Study was conducted as per the guidelines of institutional ethics committee and informed consents were obtained from all the participants. Cases with past history of hypertension, type 2 diabetes mellitus, cardiovascular diseases, malignancy, acute or chronic inflammatory disease were excluded from the study. Also women consuming anti-inflammatory drugs were eliminated from the study.

Demographic data related to age, family history of breast cancer, history of smoking, alcoholism, use of hormone therapy was recorded through standard questionnaire. For anthropometric measurements, body weight (kg), height (cm), waist circumference (cm) was recorded. Body mass index was calculated for all the subjects using formula Body weight (kg)/Height (m^2).

After confirmed histological diagnosis and thorough diagnostic work up, patients were staged according to TNM (tumor size, lymph nodes and metastasis) system.

After overnight fast, 3 ml venous blood samples were collected for biochemical assay. After clot formation, serum were separated and assayed for estimation of hsCRP. It was estimated by the method of chemiluminiscence immunoassay using Acculite CLIA microwells with Assay kits from Monobind INC, Lake forest, CA 92630 USA.

After compilation of data, statistical analysis was performed using the SPSS data analysis system. Demographic and biochemical data of all subjects was analyzed as mean ± SD and student't' test was applied to demonstrate the significance of different variables. P values less than 0.05 were considered as significant, less than 0.001 as highly significant and more than 0.05 as non-significant.

RESULTS

Out of 60 cases of breast cancer, 30 were in stage II, 12 in stage III, 14 in stage I and 4 in stage IV at the time of diagnosis. Patients' characteristics have been represented in the following Table 1.

We compared mean values of serum hsCRP stage wise (TNM) among all the cases. This characteristic has been shown in Table 2.

Table 1: Comparison of data among study participants.

Parameter	Cases Mean ± SD	Controls Mean ± SD
Age (years)	48.6 ± 12.5	44.3 ±9.3
BMI (kg/m^2)	23.5 ± 2.8	20.2 ± 2.4*
Waist circumference (cm)	92.4 ± 5.2	86.3 ± 3.5*
Waist : Hip	1.2 ± 0.4	0.92 ± 0.2*
Serum hsCRP (mh/dL)	4.2 ± 1.2	1.2 ± 0.8**

SD - Standard deviation, BMI - Body mass index, hsCRP - high sensitivity C-reactive protein, *P <0.05 Significant, **P <0.001 Highly significant.

Table 2: Stage wise distribution of patients and serum hsCRP levels.

Stage (TNM)	No. of patients	hsCRP Mean ± SD	P value
Stage I	14	1.34 ± 0.7	0.06
Stage II	12	2.62 ± 0.9	0.04*
Stage III	30	3.6 ± 1.4	0.0008**

*P <0.05 Significant, **P <0.001 highly significant.

DISCUSSION

In our study participants, we observed significant differences between cases and controls in anthropometric parameters BMI and waist: hip (P <0.05) and hsCRP levels (P <0.001). Depending of the stage, serum hsCRP levels were associated with advanced stage. In stage I, association of hsCRP was not significant with disease while in stage II and III there was significant association. In stage IV patients with distant metastasis, serum hsCRP values were highly significantly raised compared to stage II and III. This suggests significant association of state of inflammation with stage of breast cancer. Inflammatory component plays key role in all stages of tumourigenesis from initiation of the tumor, infiltration, local and systemic invasion.[6]

Cancer and inflammation are linked with each other in bidirectional way. Inflammation triggers development and progression of tumor, while tumor also induces inflammatory microenvironment.[7]

In a study from Tamil Nadu by Ravishankaran, CRP and IL- 6 levels were correlated positively with lymph node and distant metastasis and TNM stage.[8]

Various studies have shown the prognostic value of CRP in other malignancies like vulvar and gastroesophageal, hepatocellular, colorectal, renal and lung cancer.[9-11] Also it has been studied as a risk marker for the development of malignancies. But very few studies are there commenting on role of hsCRP in breast cancer patients. Allin et al. studied prognostic value of CRP in breast

cancer patients. They observed that patients with high CRP values at the time of diagnosis before administration of treatment had reduced and overall survival at the end of 7 years after follow up.[12]

Etiology of breast cancer is complex and multifactorial one. Its pathogenesis has been closely linked with inflammatory pathways. So state of low grade systemic inflammation should be investigated as risk factor in breast cancer along with routine modifiable and nonmodifiable risk factors. With this perspective we studied serum hsCRP levels in breast cancer patients. HsCRP, an acute phase reactant protein is a well-recognized and widely studied proinflammatory cardiac risk marker. But it has been widely studied as risk marker as well as prognostic parameter in various types of cancer. Various mechanisms have been proposed to explain link of chronic inflammation with breast cancer. Because of chronic state of low grade systemic inflammation, there is chronic activation of humoral immunity and infiltration of Th2 and innate cells.[11]

Patients with raised CRP levels have poor survival compared to those with normal values.[13]

Measurement of circulating C reactive protein by high sensitivity assay has been used in large prospective epidemiological studies to study its role as risk predictor. It has been reported to be associated with lung and prostate cancer. But Zhang et al reported no association of hsCRP with risk of breast cancer. In case of breast cancers, rarely inflammation is evident on histopathological examination.[14]

Also hsCRP has been studied widely and proved as a prognostic parameter after diagnosis of cancer. Hence estimation of hsCRP may be simple, inexpensive and useful tool for risk assessment, screening of high risk individuals and to predict outcome in diagnosed cases.

Patients of breast cancer are also at high risk of cardiovascular disease due to chemotherapy and radiation therapy. So it might be useful parameter to evaluate cardiac risk in these patients.

CRP lowering therapies might be proved to be useful for prevention and management of cancers. In future, large population based studies are needed to implicate addition of hsCRP test to current screening and staging methods.

CONCLUSION

State of chronic low grade inflammation also contributes to the development and progression of breast cancer. Although cardiovascular biomarker, hsCRP is now evolving as risk marker and prognostic parameter in patients of cancer also.

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