

Effects of Breast Cancer and Mastectomy on Fibrinolytic Activity in African Women

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ABSTRACT

Reduced blood fibrinolytic activity (FA) has been postulated in cancer. It is good to know if this is also the case in Africans with breast cancer. Africans are known to possess enhanced fibrinolysis. This study was designed to assess the effect of breast cancer on fibrinolytic activity and the effect of mastectomy on fibrinolysis in African women.

Sixty histo-pathologically proven breast cancer patients aged 25 - 45 years were compared with 50 healthy age-matched controls. Plasma fibrinogen levels and euglobulin lysis time (ELT) were estimated in breast cancer patients and the controls.

Patients with breast cancer had significantly increased fibrinogen levels euglobulin lysis time ($P < 0.001$) compared with controls. There was significant mean difference between pre and post-mastectomy fibrinogen and euglobulin lysis time values ($p < 0.05$). Progressive significant decrease in fibrinogen levels and euglobulin lysis time values ($P < 0.05$) were observed over the weeks studied respectively. African women with breast cancer have defective fibrin clearing which could predispose them to thrombotic diathesis and early mastectomy may be beneficial. We suggest that fibrinolytic components may be a prognostic marker for breast cancer. (*Afr J Reprod Health* 2006; 10[3]:114-119)

RÉSUMÉ

Effets du cancer du sein et de la mammectomie sur l'activité fibrinolytique chez les femmes africaines. L'activité fibrinolytique du sang réduite (AF) a été postulée dans le cancer. Il faut bien savoir si c'est le cas chez les Africains atteints du cancer du sein. On reconnaît chez les Africains une fibrinolyse exaltée. Cette étude a été menée pour évaluer l'effet du cancer du sein sur l'activité fibrinolytique et l'effet de la mammectomie sur la fibrinolyse chez les femmes africaines. Soixante femmes atteintes du cancer du sein et qui sont âgées de 25 - 45 ans dont les cas ont été confirmés histopathologiquement ont été comparées à cinquante femmes de mêmes âges qui n'étaient pas atteintes, servant des cas témoin. Le niveau du fibrinogène du plasma et le temps de lyse engloblines (TLE) ont été calculés chez les patientes atteintes du cancer du sein et chez les femmes témoin. Les femmes atteinte du cancer du sein ont eu des niveaux élevés du fibrinogène et du temps de lyse engloblines ($P < 0,001$) par rapport au groupe témoin. Il y a eu une différence moyenne importante entre la pre et la post mammectomie du fibrinogène et des valeurs du temps de lyse ($p < 0,05$). Au cours des semaines étudiées respectivement, nous avons remarqué une baisse significative progressive dans les niveaux du fibrinogène et dans les valeurs du temps de lyse ($p < 0,05$). Les femmes africaines qui sont atteintes du cancer du sein ont une dépuraton de la fibrine qui les dispose à la diathèse thrombotique et une mammectomie précoce peut être salutaire. Nous suggérons que les éléments fibrinolytiques peuvent être un indice pronostique pour le cancer du sein. (*Rev Afr Santé Reprod* 2006; 10[3]:114-119)

KEY WORDS: *Fibrinolytic activity, Fibrinogen, Breast cancer, mastectomy*

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Introduction

The suggestion that patients with cancer may develop thrombotic diathesis was first made over a century ago.^{1,2} This is as a result of changes in the properties of the blood. Further studies postulated that the coagulative power of carcinoma is an effective aid to their spread.^{3,4} The fact that venous invasion by tumor is associated with overlying thrombus is well recognized. It has been reported that most malignant tumours possess both thromboplastic and fibrinolytic properties.⁵ Zackarski et al noted that tumour cells have the potential for the activation of blood coagulation.⁶ The role of fibrinolytic enzymes in cancer is thought to be involved in proteolytic degradation of the extracellular matrix, one of the steps involved in invasion and metastasis. Increase in these enzymes in colon and breast tumours, appears to be a general phenomenon, since it has also been found in endometrium and brain.⁷ It has now been established by several studies that fibrinolytic components are strong independent prognostic marker in breast cancer.^{8,9}

Previous study from our laboratory has shown that there is evidence of induction of platelet in African women with breast cancer.¹⁰ In Nigeria, breast cancer ranks as one of the commonest malignancies in women.¹¹⁻¹³ Globally, cancers of the breast account for 25% of female cancers and 18% of deaths from cancer in Nigeria.¹⁴ Previous studies indicated that the incidence of breast cancer in Nigeria is about 33.6 per 100,00.^{14,15} With worldwide increase in incidence of the disease as a result of the changing population profile particularly in the developing countries, breast cancer is likely to be a major public health problem in Nigeria in this millennium.¹⁶ To date, no study has examined the haemostatic and in some cases fibrinolytic enzymes response in African breast cancer patients. In an attempt to address this neglect, we examined the fibrinolytic activity and its significant relationship to thrombotic episodes in Nigerian

breast cancer patients at premastectomy and postmastectomy periods.

Materials and Methods

Patients: Sixty women age range 25 - 45 years (means \pm SD of 32.1, \pm 4.5 years) recently diagnosed as having breast cancer were studied. The diagnosis was made from histology of biopsy specimen of breast tissue. Patients were selected from among referral cases after physical examination at a cancer out patient clinic of the University of Benin Teaching Hospital.

Fifty normo-tensive volunteers in apparently good health were included in the study as controls. The controls had a mean age of 32.00 \pm 5.21 years (range 30 - 45 year). The patients and controls were not taking contraceptive pills or on any hormonal therapy and there were no history of haemostatic disorders. Both the patients and the controls group gave informed consent.

Method: Nine mls of venous blood was withdrawn with minimal stasis on the day of collection into a plastic tube containing 1ml citrate anticoagulant. Clear plasma was separated by centrifugation at 2,500g for 30 minutes in a refrigerated centrifuge and kept at 4°C until tested the same day. The plasma fibrinogen level was measured by the clot weight method of Ingram¹⁷. The euglobulin lysis time (ELT) was determined by the method of Haugie¹⁸. The test is based on the precipitation of euglobulin fraction in citrated plasma in acid medium. Nine and half mls of acetic acid was added to 0.5ml of test plasma. The mixture was mixed and incubated at 4°C for 30 minutes. The supernatant was removed by inverting the centrifuge tube over filter paper to obtain the euglobulin fraction. The euglobulin fraction was reconstituted with 0.5ml borate buffer solution and 0.5ml of warmed 0.025M calcium chloride for the euglobulin fraction to form euglobulin clot. The time taken for the clot to lyse is euglobulin lysis time in minutes (ELT). The ELT was expressed as fibrinolytic activity

unit in terms of plasminogen activator (PA) derived from the formula $106/T2$ where T is the euglobulin lysis time in minutes.¹⁹

Statistical Analysis

Data, using the epi info statistical software were expressed as mean \pm standard deviation (SD) and student's t- test was used for comparison. Differences were considered significant at an error probability of P less than 0.05. The correlation between fibrinogen concentration and euglobulin lysis time was determined using the Pearson's correlation.

Results

The levels of fibrinogen concentration, euglobulin lysis time in minutes (ELT) and plasminogen activator (PA) in the control group and in patients are shown in Table 1. Fibrinogen levels were

significantly higher ($P < 0.001$) in patients with breast cancer as compared with controls.

Concomitantly ELT and PA were significantly increased and decreased in cancer patients ($P < 0.001$) respectively.

Figure 1: shows the changes in plasma fibrinogen levels weekly over five weeks of study. The mean difference between pre and post mastectomy after 4 weeks was significantly decreased ($P < 0.05$). There was significant decrease in fibrinogen levels ($P < 0.05$) from the first week of therapy and over the five weeks of study.

Figure 2: shows the progressive changes of ELT over five week's of study. There were consistent significant decrease ($P < 0.05$) between first and second week of treatment while there was no change between pre and 2nd week of treatment. After the second week of treatment there was consistent fall in ELT. The mean

Table 1: The levels of fibrinogen concentration and Fibrinolytic activity in normal and women with breast cancer

	Controls (50)	Breast Cancer Patients (60)	P-value
Euglobulin lysis time (min). (ELT)	142.62 \pm 33.48	281.00 \pm 83.00	0.001
Plasminogen activator (PA)	49.16 \pm 3.40	12.66 \pm 2.99	0.001
Fibrinogen (g/l)	2.61 \pm 0.39	6.80 \pm 1.23	0.001

P < 0.05 not significant. PA = plasminogen activator

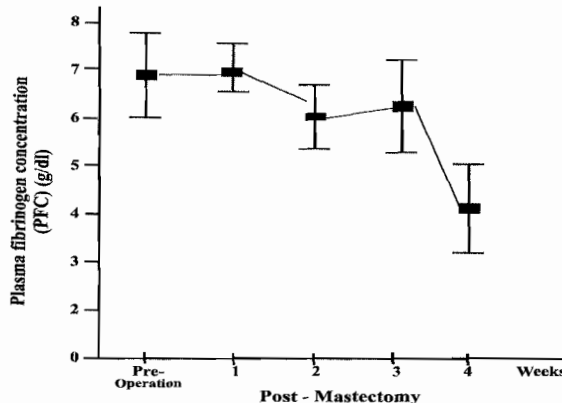


Figure 1: Pre and post mastectomy, Plasma fibrogen concentration at weekly measurement of newly diagnosed Breast cancer patients.

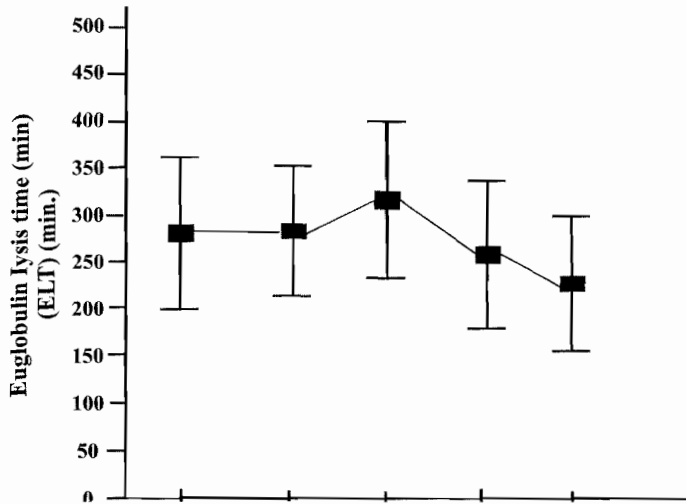


Figure 2: Pre and post mastectomy. Euglobulin lysis time at weekly measurement of newly diagnoses Breast cancer patients

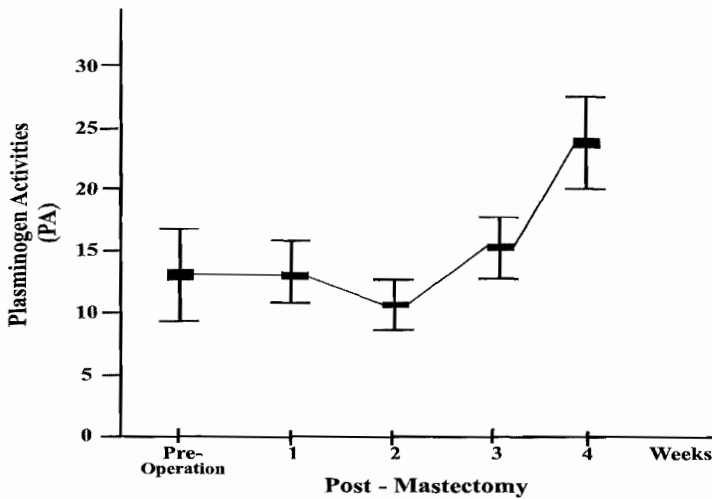


Figure 3: Pre and post mastectomy Plasminogen Activity at weekly assessment of newly diagnosed breast cancer patients.

difference between pre and post mastectomy after 4 weeks of study was significant ($P < 0.05$).

Figure 3: shows the changes in the plasminogen activity over five weeks duration. There was progressive significant increase ($P < 0.05$) weekly after initial drop on the 2nd week of therapy. The difference between pre and post

mastectomy plasminogen activity were significant ($P < 0.05$) after four weeks of treatment.

The correlation analysis showed that ELT in patients with breast cancer had a significant positive correlation with plasma fibrinogen ($r = 0.8315, P < 0.001$). (Fig.4)

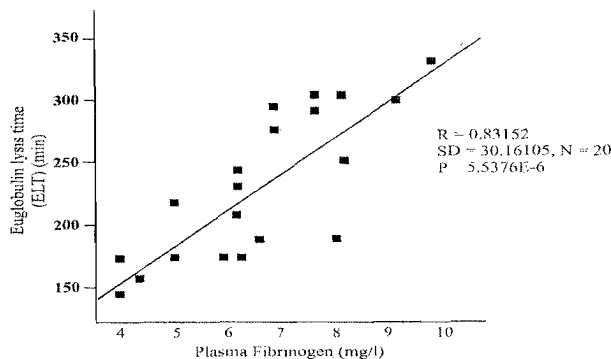


Figure 4: Correlation between Plasma Fibrinogen and Euglobulin lysis time

Discussion

Carcinoma of the breast is as common in middle aged women of developing countries as in women of developed countries.² Thrombotic diathesis in cancer has been shown to be due to changes in blood properties¹ and its spread has been implicated in the coagulative power.^{3,4}

In this study, euglobulin lysis time (ELT) and plasma fibrinogen were significantly higher in cancer patients compared with controls. The significant increase in ELT signifies decreased fibrinolytic activity (Figures 2 and 3) implying that cancer patients could be predisposed to defective fibrin formation. This fibrin- thrombin formation coupled with increased fibrinogen concentration could lead to thromboembolic complications and hyper coagulable state in African women with breast cancer. The decrease in fibrinolytic activity could be due to the presence of fibrinolytic inhibitors such as urokinase as well as plasminogen activator inhibitor PA1-1. These inhibitors have been shown to be of prognostic significance.⁹

In women who had mastectomy, the pre mastectomy mean values of ELT and fibrinogen levels were significantly higher compared with post-mastectomy values (Figure 1 & 4). The ELT dropped consistently over the period of study after a slight increase on the second day with similar changes in fibrinogen levels. These changes may constitute a protective measure against

possible development of thrombin-fibrin formation and consequently guiding against thromboembolic complication during treatment. The use of fibrinolytic components as prognostic factors for tumor relapse and survival has now been established by several studies.^{9,10} Urokinase and, in some cases PA1-1, are strong independent prognostic markers in breast cancer.^{9,10}

The increases in plasma fibrinogen levels in cancer patients are significant in that it may affect the plasma viscosity.¹⁹ The global effect of plasma fibrinogen on blood viscosity could lead to blood flow resistance, all of which will enhance hypercoagulable state. The increased plasma fibrinogen levels in cancer may be as a result of tumour cells potentials for the activation of blood coagulation and induction of platelet aggregation production as well as acute phase reaction²⁰ all of which will enhance further hypercoagulation state^{6,7}. The plasma fibrinogen levels of newly diagnosed breast cancer patients were statistically significant ($P < 0.05$) and progressively decreasing over four weeks of study after mastectomy. There was a linear significant positive correlation between euglobulin lysis time (ELT) and plasma fibrinogen ($r = 0.8315$; $p < 0.001$) (figure 4). This study strongly shows that haemostatic and haemorheological parameters could be useful tools for early assessment of malignancy, which exhibits the characteristics of chronic inflammation.

The use of fibrinolytic components for prognostic purposes might be of great importance for the adaptation of therapy for each individual cancer patient⁹.

We conclude that African women with breast cancer may be predisposed to thrombosis and thrombo-embolic complications but early detection and mastectomy could reduce the mortality and morbidity rate. Fibrinolytic components measurement could also be of prognostic significance. However the findings in the present study are limited by the fact that the effects of blood transfusion and chemotherapy on fibrinolytic activity in breast cancer patients were not studied. It is suggested that further studies that will analyze all the variables that affect fibrinolytic activity in breast cancer patients be carried out.

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