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Serum tumor necrosis factor alpha and C-reactive protein increase in breast cancer patients

Johnkennedy Nnodim[1*], Orji Somtochukwu M[2] and Ihionu Chukwudozie A[3]

[1]Department of Medical Laboratory Science, Faculty of Health Science, Imo State University Owerri, Imo State, Nigeria, [2]Department of Public Health, School of Health Technology, Federal University of Technology Owerri Imo State, Nigeria and [3]Dalzon Medical Diagnostics Limited, Plot 109 Ikenegbu Layout Owerri, Imo State Nigeria

Abstract: *Background:* Breast cancer is now the second most commonly cancer diagnosed in women and remains the leading cause of cancer death among females in less developed countries. Inflammation molecules liked C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) are suspected to be involved in breast carcinogenesis, The objective of this study was to determine the levels of serum tumor necrosis factor alpha and C-reactive protein in breast cancer patients. *Methods:* A case-control study was carried out involving 36 confirmed breast cancer patients within the ages of 45-60 years attending General Hospital Owerri and 36 apparently non breast cancer within the ages of 45-60 years served as control. Tumor necrosis factor alpha and CRP were determined by Enzyme-linked immunosorbent method. An independent students t- test was used to analyse the data. *Results:* The serum levels of TNF-α and CRP in breast cancer patients were significantly raised when compared with the control. *Conclusion:* Tumor necrosis factor alpha and high sensitivity C-reactive protein may be beneficial for diagnosis of breast cancer.

Keywords: Tumor necrosis factor alpha, CRP, Breast cancer, Owerri.

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide, with an estimated 1.7 million cases and 521,900 deaths in 2012. Breast cancer alone accounts for 25% of all cancer cases and 15% of all cancer deaths among females [1]. Obesity, lack of physical exercise, excessive drinking of alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, having children late or not at all, older age, and family history are risk factors for developing breast cancer among women [2].

It mainly forms in cells from the lining of milk ducts and the lobules that supply the ducts with milk [3]. Cancers developing from the ducts are known as ductal carcinomas, while those developing from lobules are known as lobular carcinomas [4]. In addition, there are more than 18 other sub-types of breast cancer [5]. Cancer occurs as a result of an interaction between a genetically susceptible host and an environmental factor. Normal cells divide as many times as needed and stop. They attach to other cells and stay in place in tissues. Cells become cancerous when they lose their ability to stop dividing, to attach to other cells, to stay where they belong, and to die at the normal time. Healthy cells will commit cell suicide that is programmed cell death when they are no longer needed. However, they are prevented from cell-self destruction by several protein clusters and pathways [6]. Sometimes the genes along these protective pathways are mutated in a way that turns them permanently on, rendering the cell incapable of committing suicide when it is no longer needed. This is one of the steps that leads to cancer in combination with other mutations [7].

Breast cancer is probably the most feared cancer in women because of its psychological impact. Nearly 1.3 million new cases are diagnosed every year globally [8-9]. More recently the incidence of breast cancer has been observed to be increasing geometrically in Nigeria. Breast cancer is now the second most commonly cancer diagnosed in women after cervical cancer in Nigeria. Chronic

inflammation is vital in various forms of cancer involving cancer initiation, promotion, progression, metastasis and clinical features. The relationship between cancer and the systemic inflammatory response could be due some possible mechanisms [10-11]. Firstly, tumor growth or invasion could induce tissue inflammation. Also, tumor necrosis and hypoxia or local tissue damage might activate an inflammatory response. Cancer cells themselves could increase production of inflammatory cytokines like TNF-α, CRP, IL-6 and IL-8 [12]. These inflammatory cytokines and chemokines interact with the immune vascular system and promote cancer growth, invasion, and metastasis [13-15].

TNF is mainly produced primarily by macrophages, but it is also synthesized by a broad variety of cell types like lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts, and neurons. Large quantities of TNF are released in response to lipopolysaccharide [16-18]. Tumor necrosis factor-alpha is a pleiotropic inflammatory cytokine. Most organs of the body appear to be affected by TNF-α[19]. C-reactive protein (CRP), a nonspecific marker of systemic inflammation. It is used to detect and monitor systemic inflammatory response in clinical practice and empirical research [20] Most studies suggested that CRP levels were higher in cancer cases than healthy subjects, and CRP levels for prediction of treatment efficacy and patients mortality with various types of cancer have been extensively reported [21]. Whereas whether elevated CRP levels share an identical value in predicting future cancer incidence remains uncertain [22].

A case–control study nested within the Nurses' Health Study (NHS) and the full cohort of the Women's Health Study (WHS), suggest that CRP, a nonspecific marker of inflammation, is modestly positively associated with breast cancer risk. One study with 1,241 breast cancer cases was conducted and found that increasing CRP levels were associated with a non-significantly decreased risk. There is scarcity of information in Owerri as regards the use serum tumor necrosis factor alpha and CRP in breast cancer diagnosis. This study was undertaken to determine the levels of serum tumor necrosis factor alpha and C-reactive protein in breast cancer patients.

Material and Methods

Research design: A case control study design was conducted in General Hospital Owerri from March, 2015 to September, 2015.

Subjects: A total of 36 confirmed breast cancer patients within the ages of 45-60 years attending General Hospital Owerri were involved in the study while 36 apparently healthy non breast cancer within the ages of 45-60 years served as control.

Blood Collection: In all subjects, 5ml of venous blood was collected into a non - anticoagulated tubes. The sample were spun in a Wisterfuge (model 684), centrifuge at 1000g for 10 minutes and the serum collected into a clean dry bijou bottle.

Biochemical Assay: Tumor necrosis factor alpha and C-reactive protein were determined by Enzyme-linked immunosorbent method.

Statistical analysis: The results were expressed as mean ± standard deviation. The statistical evaluation of data was performed by using independent students t- test. The level of significance was calculated at $p<0.05$.

Ethical clearance: Informed consent of the participants was obtained and was conducted in line with the ethical approval of the hospital.

Results

In this study the plasma TNF-α and CRP levels were higher in cases than controls ($p<0.05$) (table-1).

Table-1: The plasma TNF-α and CRP levels of the breast cancer and control subjects

Parameters	Breast cancer (n=36)	Control (n=36)	p value
TNF-α (Pg/ml)	162.53± 52.04*	130.51± 32.66	p<0.05
C-RP (ng/ml)	241.15 ± 26.37*	218.11± 39.25	p<0.05

*Significantly different from control at p<0.05

Discussion

In our case-control study we found the level of tumor necrosis factor-α (TNF-α) was significantly increased in breast cancer when compared with the control. This is in line with the work of Chaikate et al [22]. The increase in concentration of TNF-α is linked to inflammation resulting in heat, swelling, redness, pain and loss of function. TNF-α is a cell signaling protein that participates in systemic inflammation and is one of the cytokines that make up the acute phase reaction. It is synthesized mainly by activated macrophages, and other cell types which include CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons. The dysregulation of TNF synthesis has been implicated in a variety of human diseases like cancer [18].

Similarly, C-reactive protein was significantly increased in breast cancer patients when compared with the control. This is consistent with the work of Chaikate et al, [22]. The increase in C-reactive protein is a response to inflammation. It is an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells [21]. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells in order to activate the complement system via the C1Q complex. CRP is synthesized by the hepatic organ in response to factors released by macrophages and fat cells [22].

Inflammation is a mechanism that can remove the agent causing injury and initiate tissue repair by launching a well coordinated immune response [17]. The body responds to pathogen by inflammatory mechanism coordinated blood borne delivery to injured tissues of cells and soluble mediators. After the removal of the invading pathogen and wound healing, inflammation subsides. However, an unresolved inflammation on account of any failure in the precise control of the immune response can continue to perturb the cellular microenvironment, thereby leading to alterations in cancer-related genes [4].

One limitation of our study was other commonly measured inflammatory markers, such as interleukin-6, and adipokines, were not available; incorporating additional inflammatory markers may provide insight into the independent and joint effect of CRP and TNF-α with other inflammatory markers in breast cancer etiology.

Conclusion

The determination of tumor necrosis factor alpha and high sensitivity C-reactive protein may be valuable parameters for diagnosis of breast cancer.

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*All correspondences to: Dr. Nnodim Johnkennedy, Department of Medical Laboratory Science, Faculty of Health Science, Imo State University Owerri, Imo State, Nigeria. Email: johnkennedy23@yahoo.com