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RESEARCH ARTICLE

HAPTOGLOBIN PHENOTYPE, HP1-1: A POTENTIAL RISK FACTOR OF BREAST CANCER IN GHANAIAN WOMEN.

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Abstract

Background:- The haptoglobin phenotypes association with diseases is widely studied. However, association of the phenotypes with breast cancer especially in patients of African descents has received little attention.
Aim:- To determine the association of haptoglobin phenotypes with breast cancer among Ghanaian patients.
Methods:- A total of 63 women diagnosed with breast cancer and 54 female controls were recruited. The participants were between the ages of 20 and 60 years. Demographics and clinical parameters were collected. Polyacrylamide gel electrophoresis was used for haptoglobin phenotyping employing serum haemoglobin-supplementation method.
Results:- Hp 1-1 and HP 1 allele frequencies were high among patients. Hp 1-1 was strongly associated with breast cancer (OR = 3.09, CI = 1.32 – 7.24, p = 0.014) than Hp2-1 (OR = 2.1, CI = 0.88 – 4.58, p = 0.139) and Hp 2-2 (OR = 0.24, CI = 0.10 – 0.54, p = 0.0008). Most of the patients were traders (55.5%) and 22.2% were below the age 40 years. Blood pressure was elevated in patients than controls ($p < 0.05$) but difference was not significant when patients on chemotherapy was compared with those without treatment ($p > 0.05$). However, body mass index was significantly raised in patients and was independently affected by chemotherapeutic treatment but not age ($p < 0.001$).
Conclusion:- The strong association of haptoglobin phenotype, Hp 1-1 with breast cancer may suggests a critical role of the protein in disease prognosis.

Introduction:-

Breast cancer (BC) is rated high among cancers in women and found to be the leading cause of cancer related deaths globally. The aetiology of BC is not immediately known but factors including age, early stage at menarche, late age at first child birth, family history, oral contraception and increased age at menopause have been suggested to play a critical role (Babita *et al.,* 2014).Breast cancer incidence is high especially in the developing countries and late presentation to health facilities has been attributed to several factors (Clegg-Lamptey *et al.*,2009). In most cases, patients present the disease at the advanced stage and that poses a challenge to management leading to poor prognosis. Progression of BC has been associated with tumour microenvironmental alterations and is increasingly recognized as a major regulator (Jerby *et al.,* 2012). Identified biological signatures that influence tumour microenvironment in patients could be useful in the prediction of disease outcome.

Haptoglobin, an acute phase circulatory protein has been associated with many diseases including breast cancer (Awadallah and Atoum, 2004). Haptoglobin gene locus is highly polymorphic with two common co-dominant *HP1* and *HP2* alleles. The two alleles produce three distinct phenotypic presentations, Hp1-1, Hp2-1 and Hp2-2 (Sadrzadeh and Bozorgmehr, 2004) with occasional modified Hp2-1 (Hp2-1M) (Maeda, 1991). The effectiveness of physiological function depends on the phenotype and has been implicated in several diseases (Zhao *et al.*, 2007; Abdullah, 2009). The weak antioxidant property of Hp2-2phenotype has been implicated in several diseases (Quaye *et al.*, 2006; Vormittag *et al.*, 2005). However, Hp1-1 has been associated with breast cancer (Awadallah and Atoum, 2004). In cancers, the antioxidant/oxidant system is altered in favour of the later to sustain disease progression (Warburg, 1956). Reduced level of lipid peroxidation in serum of breast cancer patients has been reported, suggesting elevation or presence of effective antioxidants (Gerber *et al.*, 1996; Gonenc *et al.*, 2006).

To our knowledge no data exist on the association of haptoglobin phenotypes and breast cancer in Ghanaian patients. The aim of the study was to determine the prevalence of haptoglobin phenotypes and their association with breast cancer in Ghanaian patients.

Methodology:-

Study design:-

The study was a case-control study and was carried out from April to August, 2015.

Study site:-

Breast cancer patients were recruited from the Department of Surgery, Korle Bu Teaching Hospital, Accra-Ghana and controls from women group. The haptoglobin phenotyping was carried out at the Department of Biochemistry, Cell and Molecular Biology, Legon, University of Ghana.

Study population and sampling:-

Female patients diagnosed with breast cancer and apparently healthy female controls were recruited into the study. Clinical history, mammogram and histopathological investigations were the diagnostic procedures. Patients on chemotherapy, hormonal treatments and newly reported were recruited consecutively while the controls were recruited from a community using standard questionnaire. Patients diagnosed with other types of cancers were excluded from the study and all participants gave a written consent. The study was approved by the Protocol and Ethical Review Committee, School of Biomedical and Allied Health Sciences, University of Ghana.

Anthropometrical and blood pressure measurements:-

Height and weight of participants were taken and body mass index (BMI) calculated. Mercury sphygmomanometer with stethoscope were used to measure the blood pressure after allowing the participants to rest for 15-20 minutes on arrival. The blood pressure was taken twice with 2-5 minutes interval and the average was calculated. Other socio-demographic data collected include age, occupation and body surface area (BSA).

Sample preparation:-

About 5 ml of venous blood was collected from the arm of each participant and dispensed into serum gel separator tube. Blood sample in gel separator tubes were centrifuged and serum aliquoted into Eppendorf tubes. Serum was stored at -20°C for later use.

Determination of haptoglobin phenotypes:-

Serum haptoglobin phenotypes were determined by discontinuous polyacrylamide gel electrophoresis (PAGE) with haemoglobin-supplementation followed by 3,3,5,5-tetramethyl benzidine with o-dianisidine staining.

Statistical analysis:-

SPSS 20.0 version was used for the analyses. Means and standard deviations (Mean ± SD) were used to summarize all quantitative variables. Student's unpaired t-test was used to compare mean values. Chi square (χ^2) was used to comparison proportion and Odds ratio (OR) for association. $P < 0.05$ was considered statistically significant for all analyses.

Results:-

The comparison of the demographics and clinical parameters of the studied population is shown in Table 1. A total of 117 volunteers took part in the study and were made up of 63 breast cancer patients and 54 apparently healthy controls. The clinical parameters; systolic blood pressure (SBP), diastolic blood pressure (DBP) and body mass index (BMI) were significantly raised in the patients than the apparently healthy controls ($p < 0.05$). The occupation distribution between the patients and the apparently healthy control was not statistically significant ($p = 0.264$). In the current study, equal number of left and right breast cancers were presented. Body mass index strongly correlated with both systolic ($r = 0.366$, $p < 0.001$) and diastolic ($r = 0.296$, $p < 0.001$) blood pressure of the patients.

Table 1:- Socio-demographics and clinical parameters of the studied population.

Parameter	Breast Cancer Patients (N= 63)	Control (N = 54)	95% CI of mean diff.	p-value (t-test)
Age (yrs)	48.84 ± 10.58	42.26 ± 14.37	2.00 – 11.63	0.005*
BMI (kg/m^2)	30.13 ± 6.43	26.44 ± 5.53	-5.91 – (-1.47)	0.001*
SBP (mmHg)	133.25 ± 21.07	121.15 ± 15.91	5.18 – 19.04	0.001*
DBP (mmHg)	79.79 ± 11.70	74.37 ± 11.70	1.80 – 9.05	0.004*
BSA/m^2	1.83 ± 0.20	–	–	–
Occupation n (%):			χ^2	
Trader	35 (55.5)	36 (66.7)		
Civil servant	7 (11.1)	8 (14.8)		
Fashion industry	5 (7.9)	2 (3.7)	5.24	0.264
Unemployed	7 (11.1)	6 (11.1)		
Unskilled labour	9 (14.3)	2 (3.7)		

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, BSA = body surface area, *p - value is statistically significant.

Comparison of the clinical parameters between patients on chemotherapeutic treatment and those without treatment is presented in Table 2. Both blood pressures showed no significant difference ($p > 0.05$). Nevertheless, body mass index was significantly increased in patients on chemotherapy than the treatment naïve patients ($p < 0.05$) (Table 2).

Table 2:- Comparison of breast cancer patients receiving chemotherapy with patients without treatment.

Parameter	Chemotherapy treatment (n=19)	Patients without treatment (n) = 16)	95% CI of mean diff.	p-value
Age (yrs)	47.50 ± 7.26	49.16 ± 9.48	- 4.24 – 7.55	0.571
BMI (Kg/m^2)	32.50 ± 5.64	28.65 ± 4.34	- 7.28 – (-0.42)	0.029*
SBP (mmHg)	136.75 ± 22.67	134.47 ± 18.29	- 16.36 – 11.81	0.744
DBP (mmHg)	76.69 ± 10.76	136.75 ± 22.6	- 2.99 – 11.84	0.234

Patients on chemotherapy received had no other interventions. BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure *p - value is statistically significant.

The most frequent tumour stage and grade were T4 and grade II and 77 % of the patients were above 40 years (Table 3). The common treatments were chemotherapy (Cyclophosphamide, Adriamycin and 5-Fluorouracil) and hormonal treatments (Tamoxifen or Arimidex) while 25.4% were new cases.

Table 3:- Age-stratification of pathological descriptions and treatments of breast cancer patients.

Description	All N = 63	< 40yrears N = 14	>40years N = 49
Affected breast n (%):			
Left	29 (46.0)	7 (50.0)	22 (44.9)
Right	32 (50.8)	7 (50.0)	25 (51.0)
Both	2 (3.2)	0 (0.0)	2 (4.1)
Tumour stage n (%):			
T1< 2.0cm	2 (3.2)	0 (0.0)	2 (4.1)
2 < T2 < 5 cm	9 (14.3)	2 (14.3)	7 (14.3)
T3 ≥ 5 cm	13 (20.6)	3 (21.4)	10 (20.4)
T4>> 5 cm	32 (50.8)	8 (57.2)	24 (49.0)
Unknown	7 (11.1)	1 (7.1)	6 (12.2)
Tumour grade n (%):			
Grade I	15 (23.8)	3 (21.4)	12 (24.5)
Grade II	28 (44.4)	4 (28.6)	24 (49.0)
Grade III	17 (27.0)	7 (50.0)	10 (20.4)
Unknown	3 (4.8)	0 (0.0)	3 (6.1)
Treatment type n (%):			
Only chemo	19 (30.2)	3 (21.4)	16 (32.7)
MC	18 (28.6)	5 (35.7)	13 (26.5)
EC	5 (7.9)	1 (7.2)	4 (8.2)
Only excision	5 (7.9)	2 (14.3)	3 (6.1)
No therapy	16 (25.4)	3 (21.4)	13 (26.5)

n = frequency, chemo = chemotherapy, MC = mastectomy and chemotherapy, EC = excision and chemotherapy. Values are presented as frequency (percentage). Statistical significant was not determined due to the zero frequencies.

Distribution of Haptoglobin phenotypes among studied population

Table 4 shows the various Hp phenotypes among patients compared with controls. Hp 1-1 and Hp 2-1 were significantly expressed in patients than controls ($p < 0.05$) whiles Hp2-2 ($\chi^2 = 19.91$, $p < 0.001$) was less expressed in the patients.

Table 4:- Distribution of Haptoglobin phenotypes among studied population.

Subjects	Haptoglobin phenotypes (Hp) Hp 1-1	Hp 2-1	Hp 2-2	Hp 0	HP allele frequency HP 1	HP 2
Patients (N = 63) n (%)	26 (41.3)	23 (36.5)	12 (19.0)	2 (3.2)	0.61	0.39
Control (N = 54) n (%)	10 (18.5)	12 (22.2)	27 (50.0)	5 (9.3)	0.33	0.67
χ^2	10.50	4.71	19.91	2.22	14.63	14.63
P	< 0.005	< 0.05	< 0.001	> 0.05	< 0.001	< 0.001

N = sample size, n = phenotype frequency in the group

Hp 1-1 was significantly associated with breast cancer (OR = 3.09, CI = 1.32 – 7.24, p = 0.014) than Hp2-1 (OR = 2.1, CI = 0.88 – 4.58, p = 0.139) and Hp 2-2 (OR = 0.24, CI = 0.10 – 0.54, p = 0.0008). However, haptoglobin phenotypes distribution showed no changes in the clinical parameters within the patients ($p > 0.05$). Confounding analyses for BMI showed coefficients B = 6.391, $p < 0.001$, 95% CI = 3.381 – 9.402, for chemotherapy when adjusted for age, haptoglobin phenotypes and blood pressure. Chemotherapy, unadjusted for age did not alter much of its effect on BMI (B = 6.391, $p < 0.000$, 95 % CI = 3.516 – 9.367).

Discussion:-

Breast cancer (BC) is a common cancer among women and is a major cause of cancer-related deaths. Breast cancer association with haptoglobin phenotypes (Hp) is of great interest probably due to the poor prognosis of the disease and the variable antioxidant property of Hp phenotypes mediated by their respective molecular structures. Haptoglobin phenotype, Hp1-1 has far been associated with BC (Kaur *et al.*, 1984; Bartel *et al.*, 1985) and distribution of the phenotypes in a population was attributed to genetic and oxidative stress mechanism (Awadallah and Atoum, 2004). Furthermore, studies have also established strong association between Hp1-1 phenotype and other cancers (UGent *et*

al., 2011; Nada *et al.,* 2012). Conversely, a study reported no association between BC and Hp1-1 phenotype (Gast *et al.,* 2008).

In this current study, BC patients of African descents, were found to highly express theHp1-1 phenotype than the control group (Table 4) and was strongly associated with the disease. However, Hp2-2 phenotype was poorly expressed in the patients whereas the degree of association of Hp2-1 phenotype with BC was between that of Hp1-1 and Hp2-1 phenotypes. The role of Hp1-1 phenotype in the development or progression of BC is not immediately known. However, the molecule may affect the tumour microenvironmental changes. Highly expressed Hp1-1 phenotype in patients may contribute to the antioxidant/oxidant disturbance in patients mentioned several years ago (Warburg, 1956). This occurrence may however, also explain the reported reduced oxidative stress characterized by lower lipid peroxidation in breast cancer patients than the apparently healthy controls (Gonenc *et al.,* 2006). Lines of evidence have also shown association of overexpression of Hp1-1 with poor outcomes in oxidative stress-related disease (Quaye *et al*., 2000).

Patients also showed significantly elevated blood pressure (BP) and increased body mass index (BMI) (Table 1). Hypertension has strongly been associated with risk of BC and was pronounced in women with increased BMI (Largent *et al.,* 2006). Women under hypertension treatment were also reported to be at risk of developing BC (Largent *et al.,* 2010). Chemotherapy exposure has been reported to increase the risk of hypertension in patients (Fraema *et al.,* 2013). However, no significant difference was noticed in the clinical indices when patients receiving chemotherapy were compared with the treatment naïve patients (Table 2). Intriguingly, patients receiving chemotherapy were found to show increased body mass index compared to their counterparts and this supports recent work (Ricci *et al.,* 2014). Impact of increased body mass index on the health of breast cancer patients has received divergent views. Recently, increase in BMI of patients who were normal or underweight showed improved clinical outcomes in terms of pathological complete response (pCR) (Kogawa *et al*., 2015). In a different view, Chen et al., reported a negative impact of BMI on breast cancer treatment response in terms of pCR (Chen *et al.,* 2012).

In summary, high prevalence of Hp1-1 in breast cancer patients does not differ among Ghanaians and this may suggest a critical role in the disease prognosis. Most of the patients were above 40 years and showed elevated blood pressure which may not necessarily be attributed to chemotherapy. Increase in BMI of patients on chemotherapy compared to those without treatment may suggest a possible effect of chemotherapy treatment on BMI. Here, age of patients was not a confounding factor.

Conclusion:-

In conclusion, our study reports for the first time the prevalence of hatoglobin phenotypes in Ghanaian breast cancer (BC) patients and the association of Hp 1-1 phenotype with the disease. The study also provided additional evidence of the impact of chemotherapy on blood pressure and BMI of BC patients with age not being a contributing factor. Further studies to associate haptoglobin phenotypes with BC prognosis may provide baseline information for disease prediction and management.

Limitations of study:-

The cross-sectional study did not consider baseline information for blood pressure and body mass index (BMI) of the participants. Additionally, determination of the duration of the disease was a challenge since most patients reported at the health facility with advanced tumour.

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