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Oxidative Stress in Ghanaians Presenting with Prostate Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Authors WKBAO, CKGS and IA designed the study and wrote the protocol. Authors IA and WKBAO performed the laboratory assays. Author CKGS performed the clinical evaluation. Authors IA, CKGS and WKBAO drafted the manuscript. All authors reviewed the manuscript for its intellectual content and effected corrections. All authors read and approved the final manuscript for publication.

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ABSTRACT

Introduction: The latest estimates of global cancer incidence show that prostate cancer has become the second most common cancer among men in the world. A number of reports have linked oxidative stress to prostate cancer. Although oxidative stress has been found to be much prevalent among the Ghanaian population, no data exist on its prevalence among prostate cancer patients in Ghana. This study therefore sought to investigate oxidative stress in Ghanaians presenting with prostate cancer.
Methods: This cross-sectional study was conducted at the out-patient department of the department of surgery, Komfo Anokye Teaching Hospital, Kumasi, between the period of November, 2010 and April, 2012. In all, one hundred and twenty four (124) adult males (87 case

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subjects and 37 control subjects) aged at least forty two years were enrolled.
Results: Malondialdehyde, an oxidative stress marker, and uric acid were significantly raised whereas the measured antioxidant (vitamin C) was significantly reduced among the prostate cancer patients compared to the controls. The indication is that oxidative stress with reduced antioxidant levels is common in prostate cancer patients.
Conclusion: Oxidative stress may have a significant role in prostate cancer. Based on the findings, it may seem reasonable to propose that therapeutic regimens aimed at beefing up the antioxidant defences could help offer some degree of protection for prostate cancer patients against oxidative stress.

Keywords: Prostate; cancer; oxidative; antioxidant; malondialdehyde; peroxidation; polyunsaturated; phospholipid.

1. INTRODUCTION

Prostate cancer (PCa) is gradually taking a centre stage around the globe with a dreadful epidemiology. The latest estimates of its global incidence for instance, has it that prostate cancer has become the second most common cancer among men in the world, accounting for about 11.7% of new cancer cases overall, which constitutes 19% of all cancers in developed countries and 5.3% in developing countries [1]. In Europe for instance, an estimated 2.6 million new cases of cancer are diagnosed each year. Out of this, prostate cancer alone constitutes about 11% [2]. It has also been reported that PCa also accounts for about 9% of all cancer deaths among men within the European Union [3].

The global PCa burden is predicted to reach 1.7 million new cases and 499,000 new deaths by the year 2030 [4]. In Ghana, about 921 new cases are reported every year with as many as 758 PCa deaths being reported annually [5]. Numerous studies on oxidative stress have been done in Ghana and across the African continent involving varying age groups. To the best of our knowledge however, none of them involved PCa. Currently, PCa is the second most common cancer and the sixth leading cause of cancer deaths among men in the world. Global incidence of PCa is on the ascendancy. Annually, about 899,100 new cases of PCa are reported worldwide, 39,600 for Africa and 13,300 for West Africa. It is also estimated that every year, about 258,100 PCa deaths are reported worldwide for which 28,000 and 10,700 occur in Africa and West Africa respectively This dreadful disease also has a number of horrendous complications including sexual, urinary and bowel dysfunction as well as bone pain. It has been reported that quite a preponderant proportion of PCa patients do experience significant reduction in their quality of life due to physical pain, mental anguish as well as economic hardship [4].

Despite its precarious nature, a number of biological processes including oxidative stress which were previously thought to be somewhat innocuous or pose indirect and long term harmful effects to the human body are now being reported to be associated with this dreadful disease. Oxidative stress is an end result of lipid peroxidation (a reaction whereby molecular oxygen is incorporated into poly-unsaturated fatty acids (PUFA) to produce lipid peroxides). It has been reported that lipid peroxidation mediated by free radicals is considered to be the major mechanism of cell membrane destruction and cell damage [6]. It has been reported that oxidative stress is characterized by disequilibrium between oxidant and antioxidant forces in favour of oxidation, and that the lipid peroxidation process, initiated by the reaction of free radicals with polyunsaturated fatty acids [7] is used as a marker of oxidant force.

Cell membranes generally, are made up of lipid bilayers and thiol containing proteins. The unsaturated lipid component and thiol containing proteins of the cell membranes are susceptible to free radical attack. Oxygen radicals usually react with these polyunsaturated fatty acid residues in phospholipids giving rise to the production of a plethora of products, many of which are reactive toward proteins and DNA. It has been reported that lipid peroxidation appears to be a major source of endogenous DNA damage in humans that may contribute significantly to cancer and other genetic diseases linked to lifestyle and dietary factors [8].

Antioxidants are compounds that dispose, scavenge and suppress the formation of free radicals, or oppose their actions [9]. Free radicals are formed in both physiological and pathological conditions in mammalian tissues [10]. Defense

mechanisms of the body however, play an important role in the formation of antioxidants - putting up a remarkable attempt to minimize the damage, as an adaptation to stressful situations. Malondialdehyde (MDA) is a naturally occurring product of lipid peroxidation and is used as an indicator of oxidative stress in cells and tissues. It has been reported that MDA reacts with amino groups on proteins and other biomolecules to form a variety of adducts, including adducts with DNA bases that are mutagenic and carcinogenic [11]. This study was therefore conducted to investigate oxidative stress in Ghanaians presenting with prostate cancer.

2. MATERIALS AND METHODS

2.1 Study Area and Site

The study was conducted at Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana. KATH is the second largest hospital in the country and serves as the main referral hospital for the Ashanti, Brong-Ahafo and the three northern regions. It is affiliated to the medical school of Kwame Nkrumah University of Science and Technology and also has the accreditation for postgraduate training by the West African College of Surgeons in surgery, obstetrics and gynaecology, otorhinolaryngology, ophthalmology and radiology. The urology department falls under the department of surgery [12].

2.2 Study Design

This cross-sectional study was conducted at the out-patient unit of the department of surgery, Komfo Anokye Teaching Hospital, Kumasi, between the period of November, 2010 and April, 2012. Prior to the study, ethics approval was sought from the Kwame Nkrumah University of Science and Technology (KNUST) School of Medical Science/KATH Committee on Human Research Publications and Ethics (CHRPE). In all, one hundred and twenty four adult males comprising 87 case subjects and 37control subjects aged at least forty two years were enrolled. The sample size was selected by convenience because of the scarcity of prostate cancer patients available at the time of the study. The participation of the respondents was voluntary and informed consent was obtained from each of them. Smokers were excluded from the study, since the constituents present in cigarette are potential sources of oxidative degradation of membrane lipids. Medical history and biodata for the prostate cancer patients and the control subjects was solicited with a self-designed questionnaire. It contained the following: name, age, occupation, place of residence as well as family prostate cancer history.

2.3 Case and Control Groups

The case group comprised those who presented with the clinical signs and symptoms and were diagnosed of prostate cancer at the outpatient department of the department of surgery, Komfo Anokye Teaching Hospital, Kumasi. The diagnosis of prostate cancer was through biopsy work-up and histological examination. Based on their Gleason scores, the prostate cancer cases were classified into mildly aggressive (5-6), moderately aggressive (7) and highly aggressive (8-10). The Gleason score is the sum of the two most common patterns (grades 1-5) of tumour growth found. The Gleason score ranges from 2 to 10, with 2 being the least aggressive and 10 the most aggressive. The control subjects were healthy normal adult males without prostate cancer.

2.4 Collection of Samples

Venous blood specimens were collected from the study participants between 7 am and 11 am under aseptic conditions, at the Komfo Anokye Teaching Hospital, Kumasi, Ghana. About 10 mL of blood was drawn from every study participant, 8 mL and 2 mL were dispensed into vacutainer plain-gel tubes and fluoride tubes respectively. The blood samples were then transported to the biochemistry laboratory at Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana within an hour. The blood samples were centrifuged together with the ones in fluoride tubes at 4000 r.p.m for 10 minutes. Sera and plasma obtained were separated and the concentrations of the various parameters such as malondialdehyde (MDA), prostate specific antigen (PSA), vitamin C, alkaline phosphates (ALP), uric acid as well as creatinine determined. The serum MDA and plasma vitamin C concentrations were determined within four hours.

2.5 Determination of Serum MDA Concentration

2.5.1 Principle and method

Malondialdehyde (MDA) levels were determined by the MDA Thiobarbituric acid (TBA) test which is the colorimetric reaction of MDA and TBA in acid

solution. MDA, a secondary product of lipid peroxidation, reacts with thiobarbituric acid (TBA) to generate a red coloured product, which was detected spectrophotometrically at 535 nm. This method is a fast, sensitive and low cost method that can be used to indicate the extent of lipid peroxidation in a variety of systems [13].

A volume of 0.5 ml of the patient's serum sample was added to 2.5 ml of 20% trichloroacetic acid (TCA). Then 1 ml of 0.67% thiobarbituric acid (TBA) was added to the mixture. The resulting mixture at this point was then boiled in a water bath (at temperature of 100℃ for 30 minutes). The hot mixture was then allowed to cool using iced water bath and the sample was then extracted with 4 ml n-butanol and centrifuged at 4000 r.p.m for 10 minutes. The absorbances of supernatant were measured at 535 nm and the results were expressed as µmol L^{-1}, using the extinction coefficient of 1.56 x 10^5 L mmol cm^{-1}.

Abs = **CεL**
Therefore, C = **Abs/εL**
Abs = absorbance of the test sample
C = concentration of the test sample
ε = extinction coefficient
L = light path (1 cm).

2.6 Determination of Vitamin C Concentration

2.6.1 Principle and method

Ascorbic acid (vitamin C) in plasma is oxidized by Cu (II) to form dehydroascorbic acid, which reacts with acidic 2, 4 dinitrophenylhydrazine to form a red dihydrazone which is measured at 520 nm [14]. Ascorbic acid concentrations were determined within 4 hours. The reagents used for the assay included: Ascorbic acid standard, 5% Trichloroacetic acid (TCA) DTC – a mixture of (0.4 g thiourea, 0.05 g $CuSO_4.5H_2O$ and 3 g of 2, 4 dinitrophenylhydrazine in 4.5 mol/L H_2SO_4) as well as 65% H_2SO4.

To 0.5 ml of the test plasma an amount of 0.5 ml of distilled water and 1 ml of 5% TCA were added. The resulting mixture was then thoroughly mixed and centrifuged at 500 g for 15 minutes. Then, 1 ml of the supernatant obtained was treated with 0.2 ml of DTC (which is a mixture of 0.4 g thiourea, 0.05 g $CuSO_4.5H_2O$ and 3 g of 2, 4 dinitrophenylhydrazine in 4.5 mol/L H_2SO_4) and the resulting mixture was incubated in a water bath at 37℃ for 3 hours. Then, 1.5 ml of 65% sulphuric acid (H_2SO_4) was added to the mixture which was thoroughly mixed. The resulting solution was then allowed to stand at room temperature for another 30 minutes. The standard and the test were then read against the blank at 520 nm and concentration of test determined using the following formula [14].

$$T_{conc} = (T_{abs}/S_{abs}) \text{ X } S_{conc}$$

T_{conc} = Concentration of the test sample
T_{abs} = Absorbance of the test sample
S_{abs} = Absorbance of the standard
S_{conc} = Concentration of the standard

2.7 Determination of Serum Total PSA

Prostate specific antigen (PSA) levels were determined using Mindray MR-96A ® semi-automated immunoassay Analyzer ®, China. The principle and method adopted for the determination of serum total PSA was based on ELISA (Enzyme-Linked Immunosorbent Assay).

25 µL each of the patient's serum and calibrator were pipette and dispensed into two separate microtitre wells. Then, 100 µL of the conjugate reagent was added to each of both wells. The microtitre wells were covered with adhesive strip, then mixed by votexing and incubated at room temperature (20℃ -25℃) for half an hour. The wells were then washed 5 times using the washed solution. 100 µL of the substrate reagent was added to each of both wells and incubated at room temperature for 15 minutes. Then, 100 µL of the stop reagent was also added to each of both wells. The resulting mixtures were thoroughly mixed. The absorbance of the calibrator and each of the test serum were then measured using the Mindray MR-96A microplate reader (China) and the corresponding PSA concentrations were displayed on the screen.

2.8 Biochemical Assays

The biochemistry investigations were performed with Selectra E ® Chemistry Analyzer and parameters determined include alkaline phosphatise and uric acid. The methods adopted for the determination of uric acid and alkaline phosphatase was predetermined by the reagent manufacturer ELITech reagents (Vital Scientific N.V, AC Dieren, Netherlands).

2.9 Statistical Analysis

Data were entered on Microsoft Excel. Graph Pad Prism version 5.00 for windows was used for the statistical analysis (Graph Pad software, San Diego California USA). One-way ANOVA and

Fisher exact test were used for comparison of variables proportions and one-way ANOVA used to test differences in means for continuous variables. The results are expressed as Mean ± SD. A level of $P < .05$ was considered as statistically significant.

3. RESULTS AND DISCUSSION

The current study assessed the level of oxidative stress among both the PCa population as well as the controls by the measurement of MDA (oxidative stress marker) and Vitamin C (antioxidant marker) as well as uric acid. In Addition, Gleason scores were also ascertained for each of the PCa patients and a range of 5 to 9 obtained with a mean score of 7.56±1.13 corresponding to moderately aggressive cancer. Based on their Gleason scores, the prostate cancer cases were classified into mildly aggressive (5-6), moderately aggressive (7) and highly aggressive (8-10). The Gleason score is the sum of the two most common patterns (grades 1-5) of tumour growth found. The Gleason score ranges from 2 to 10, with 2 being the least aggressive and 10 the most aggressive. Almost half (49.4%) of the prostate cancer patients had highly aggressive PCa whereas 41.4% and 9.2% had the moderate and mild PCa respectively (Fig. 1).

Among all the PCa groups, only the highly aggressive PCa group were significantly older than the control subjects ($P = .003$). The mean concentrations of prostate specific antigen (PSA) in all the PCa groups were significantly higher than the control group ($P < .001$). The highest concentration of ALP was observed among the highly aggressive PCa group (484.3±242.5 $\mu molL^{-1}$; $P < .001$) (Table 1).

The mean levels of MDA and uric acid among the PCa patients were significantly increased compared to the control ($P < .001$). Conversely, the mean levels of vitamin C were significantly higher among the control group compared to the PCa patients ($P < .001$) (Table 2). This result is similar to that reported by Ozmen et al. [15] in Turkey. Though statistically insignificant, the MDA level in our study was highest among the highly aggressive PCa patients followed by the moderately and mildly aggressive PCa patients (8.7±3.3 $\mu molL^{-1}$, 8.5±2.9 $\mu molL^{-1}$ and 8.0±2.7 $\mu molL^{-1}$ respectively). It is possible that PCa patients with higher aggressiveness of the disease were subjected to higher levels of oxidative stress and that may possibly explain why the MDA levels were observed to increase with increasing Gleason score [16]. However, the highest and least levels of vitamin C were observed among the moderately aggressive and mildly aggressive PCa populations respectively. Unlike their study which used high performance liquid chromatography (HPLC) for the measurement of both MDA and vitamin C, colorimetric and spectrophotometric procedures were used in our study for MDA and vitamin C measurement. However, the highest and least levels of vitamin C were observed among the moderately aggressive and mildly aggressive PCa populations respectively.

Unlike their study which used high performance liquid chromatography (HPLC) for the measurement of both MDA and vitamin C, colorimetric and spectrophotometric procedures were used in our study for MDA and vitamin C measurement. Though both methods used in the current study are sensitive, accurate and specific, HPLC is known to be superior in terms of the above mentioned indices. It is likely that PCa patients in both studies may have been subjected to indifferent states or levels of oxidative stress and that may possibly explain the similarity of both studies' findings. It has been reported that in the course of PCa, imbalance of oxidant-antioxidant processes occur and that oxidative stress usually occurs when there is an imbalance between extreme production of reactive oxygen species and insufficient antioxidative defences, including superoxide dismutase (SOD), catalase (CAT), vitamins (C,E), ß-carotene and glutathione (GSH) [16].

Contrary to our study's findings, reduced level of uric acid among PCa patients has been reported by Yossepowitch et al. [17]. Compared to control subjects in their study, patients with localized prostate cancer had no difference in oxidative stress indices, whereas those with metastatic disease had an increased malondialdehyde concentration ($P < 0.05$) but a decreased uric acid concentration ($P < 0.04$). In their study, it was reported that subjects with the metastasized PCa had an increased malondialdehyde concentration but a decreased uric acid concentration compared to increased concentrations of both malondialdehyde and uric acid observed among the PCa population in this study. Though statistically insignificant, the highest malondialdehyde levels in our study were observed among the highly aggressive PCa patients followed by the moderately and mildly aggressive PCa patients. It could be possible

that PCa patients with fastest growth of the disease tumour were subjected to highest levels of oxidative stress and that may possibly explain why the malondialdehyde levels were observed to increase with increasing Gleason score [17], [18]. Both studies also used Thiobarbituric acid (TBA) test for the measurement of malondialdehyde and this in addition to similar disease patterns may have played a key role for the similar malondialdehyde results.

The uric acid levels among our PCa patients were significantly higher compared to the controls. Among the PCa patients, the highest uric acid levels were observed among the highly aggressive PCa group (694.5±478.5 µmolL^{-1}) followed by the mildly aggressive (574.6±204.9 µmolL^{-1}) and moderately aggressive PCa patients (470.7±256.2 µmolL^{-1}). Generally, uric acid can act as either a pro-oxidant or antioxidant and it's likely that the uric acid levels measured in our study was acting as a pro-oxidant [19]. It has been reported that uric acid is increased by alcohol consumption and other dietary factors, age, etc. [20]. The PCa patients in both studies were of similar age. However, PCa patients with alcohol consumption were not excluded from our study. Besides, their dietary data were not collected to help ascertain the influence of diet on the uric acid levels. It is therefore possible that alcohol consumption and dietary factors may have also contributed to the elevated levels of uric acid observed among the PCa patients.

Uric acid is the final enzymatic product in the degradation of purines in humans and higher primates. It is derived exclusively from the oxidation of xanthine and hypoxanthine by xanthine oxidase. It has been hypothesized that the ability of uric acid to provide a primary defense against human cancer is based on its capacity to scavenge singlet oxygen, its capacity to inhibit lipid peroxidation, as well as its high serum concentration in humans [21]. The protective antioxidant properties of uric acid for instance, have been identified in many different organ systems [22]. Nonetheless, studies have also reported that increased serum urate, the dominant monosodium form of uric acid at physiological pH, was found to exhibit strong statistical association with increased premature cancer death in both men and women, and thus acting as a pro-oxidant. This therefore suggests a rather more complex role of uric acid in cancer biology than that of a general antioxidant [22].

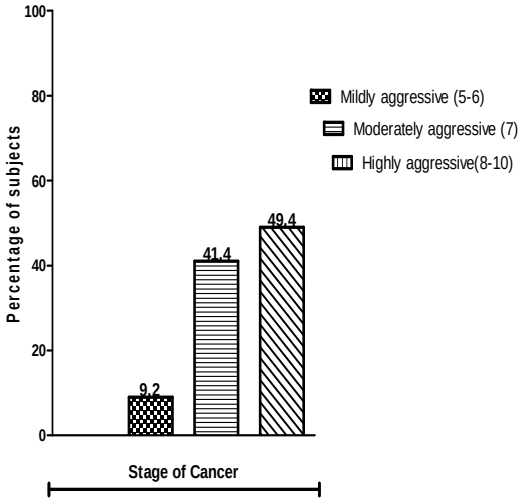

Fig. 1. Distribution of aggressiveness of prostate cancer based on Gleason score

Table 1. Age and biochemical characteristics of the study population classified by Gleason score

Parameter	Control (n=37)	Prostate cancer cases			
		Mildly aggressive (n=8)	Moderately aggressive (n=36)	Highly aggressive (n=43)	*P* value
Age (years)	62.49±8.4	60.3±5.2	63.78±7.3	68.1±7.8**	.003
PSA (ngmL^{-1})	1.726±0.9	32.9±16.1**	29.11±25.7***	37.4±28.8***	< .001
ALP (µmolL^{-1})	268.1±64.5	285.0±64.9	324.5±178.8	484.3±242.5$^{***\#\ ŧŧŧ}$	< .001

PSA: Prostate specific antigen. ALP: Alkaline phosphatase. CRE: Creatinine. Data are presented as mean±SD. One way ANOVA used to test mean differences between groups (prostate cancer cases vs. control; ¥ mildly aggressive vs. moderately aggressive; # mildly aggressive vs. highly aggressive; ŧ moderately aggressive vs. highly aggressive) *P < .05. **P < .01. ***P < .001. ŧP < .05. ŧŧP < .01. ŧŧŧP < .001*

Table 2. Oxidative stress markers among study population stratified by Gleason score

Parameter	Control (n=37)	Prostate Cancer Cases			
		Mildly aggressive (n=8)	Moderately aggressive (n=36)	Highly aggressive (n=43)	*P* value
MDA ($\mu molL^{-1}$)	3.2±0.9	8.0±2.7***	8.5±2.9***	8.7±3.3***	< .001
VIT C ($\mu molL^{-1}$)	30.4±7.8	10.0±3.8***	12.9±6.4***	11.4±7.5***	< .001
UA ($\mu molL^{-1}$)	293.4±66.5	574.6±204.9	470.7±256.2	694.5±478.5***ǂ	< .001

MDA: Malondialdehyde. VIT C: Vitamin C. UA: Uric acid. Data are presented as mean±SD. One way ANOVA used to test mean differences between groups (prostate cancer cases vs. control; ¥ mildly aggressive vs. moderately aggressive; # mildly aggressive vs. highly aggressive; ǂ moderately aggressive vs. highly aggressive) *P < .05. **P < .01. ***P < .001. ǂP < .05. ǂǂP < .01. ǂǂǂP < .001*

4. CONCLUSIONS

It has been established by this study that increased lipid peroxidation (oxidative stress) with reduced antioxidant levels are common in PCa patients. Malondialdehyde, an *in vivo* oxidative stress indicator, and uric acid were significantly increased among the PCa groups compared to the control whereas the measured antioxidant (vitamin C) was significantly reduced among the PCa patients. Therefore oxidative stress may have a significant role in prostate cancer as other studies have reported. Meanwhile, based on the findings, it may seem reasonable to propose that therapeutic regimens aimed at beefing up the antioxidant defences could offer some degree of protection for PCa patients against oxidative stress.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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