Putative Risk Factors of Prostate Cancer in Unscreened Ghanaian Men

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Abstract

African countries with weak health systems and infrastructure are at risk of high incidence and mortality of prostate cancer. The absence of specific causative agents for prostate cancer calls for early detection strategies and the identification of susceptible factors. We undertook a community-based prostate-specific antigen screening of Ghanaian men to ascertain the association between putative risk factors and prostate cancer. Using an adjusted PSA cut-off we found a prostate cancer prevalence of 12.5% with most men diagnosed between 62–77 years (Mean; 69.50 ± 8.46). We found no statistically significant association between putative risk factors such as obesity, hypertension, intake of alcohol, and smoking with prostate cancer. However, we observed a significant association between age and occupation, and prostate cancer. Prostate cancer is a growing challenge in Ghanaian men. Detection with PSA offers diagnostic significance and may help in reducing the burden in men. Differences in genetic and environmental differences between populations call for a population-specific assessment of risk factors.

Introduction

Prostate cancer continues to be a global burden despite significant improvements in diagnostic and management approaches. Prostate cancer is the second frequent cancer seen in males and the sixth leading cause of male cancer deaths worldwide [1]. There are high incidence and mortality implications in Black men [2]. Genome-wide association delineates the high susceptibility in West African men [3]. Low and middle-income countries mostly in Africa with inherent weakened health infrastructure are predisposed to high incidence and mortality of diseases [4]. Ghana, a developing country is bedeviled with challenges of health and a general burden of disease [5]. Data from the World Health Organization show that non-communicable diseases including prostate cancer account for 43% of deaths in Ghana [6]. Even though epidemiological data on the burden of prostate cancer remain scanty, hospital-based studies suggest a high rate. Prostate cancer was the second cause of death in males in a 10-year autopsy review in Ghana [7]. Review of hospital registries reports that prostate cancer is the most common form of cancer in males [8, 9].

Reducing the incidence and mortality of diseases is dependent on; identification of causative agent(s), knowledge of risk factors, early detection, and therapeutic and preventive strategies. In the absence of a specific etiologic agent, risk factors such as age, obesity and hypertension, intake of alcohol, and smoking are indicated [10]. However, there are contrasting reports on the association of certain risk factors to prostate cancer [11]. Genetic and environmental differences between populations may account for the variations [12]. Therefore, the assessment of the putative factors of populations is not far-fetched. The introduction of the blood glycoprotein, Prostate-Specific Antigen (PSA) has provided significant improvements in the diagnosis and management of prostate cancer. Despite biases in PSA screening, the European Randomized Study of Prostate Cancer study involving 7408 participants showed a 21% reduction in risk to die of prostate cancer [13]. A comprehensive review for the US Preventive Task Force saw a decline in mortality from prostate cancer screening with PSA [14]. Despite the significant impact of PSA screening on populations, the same cannot be said in Ghana.
Information on community-based early detection of prostate cancer is scanty. We, therefore, undertook this study to assess the prevalence of prostate cancer in unscreened males in a Ghanaian population and ascertain the association between putative risk factors and prostate cancer. The findings demonstrate the prevalence of prostate cancer in an unscreened Ghanaian population and the need to develop appropriate early detection and awareness programs.

**Methodology**

2.1. **Participant Recruitment, Questionnaire and Anthropometric measurement**

Two hundred and ninety-six (296) men above 30 years were enrolled in the study in the community on a father's day celebration. Participants responded to open and closed-ended standardized questionnaires after agreeing to explained informed consent forms. Height in meters and weight in kilograms were measured with a Stadiometer two times and the average used for Body Mass Index calculation. Body mass index (BMI) was calculated as kilogram per meter square ($kg/m^2$). Obesity was classified by BMI according to international cut off points [15]. Obesity was defined as BMI greater than 30 $kg/m^2$. A tape measure was used to measure the waist circumference of study participants two times around the hipbones and the average used in the analysis. The blood pressure of participants was measured after the patients have been relaxed with a digital sphygmomanometer (Omron X3 Comfort, US).

2.2. **Biochemical measurement of total PSA**

Venous blood sample (5 ml) was drawn aseptically from each participant into serum separator vacutainer. Blood was centrifuged and the serum was aliquoted into 2.5 ml Eppendorf tubes. Using the classical sandwich Enzyme-Linked Immunosorbent principle (Human Diagnostics, Germany), serum samples were immobilized on a 96 well micro-titer plate coated with horseradish peroxidase-labeled mouse monoclonal antibody. The antigen-antibody complex was determined by adding TMB (3,3',5,5'-Tetramethylbenzidine) substrate to form a colored complex which was measured using a micro-plate reader (RT-2100C Microplate Reader, China).

2.3. **Case definition by total PSA thresholds**

We used a PSA threshold of >10 ng/ml as a case definition of prostate cancer, 4–10 ng/ml as prostate diseases, and 0–4 ng/ml as normal cases. The higher threshold was set to offset the biases that may be associated with PSA values. PSA values above 10 ng/ml have high specificity in prostate cancer diagnosis [16, 17].

2.4. **Statistical Analysis**

Data captured and analyzed on Statistical Social Sciences® (SPSS, Chicago, Illinois, USA) version 22. Mean ± standard deviation calculated, one-way ANOVA and Chi-square performed to determine statistical associations between risk factors and PSA. A p-value of $\leq 0.05$ considered statistically significant. Post hoc analysis used to determine the source of the statistical significance. Multiple logistic regression
models, adjusting for age, used to identify explanatory variables that predicted the odds of risk factors of prostate cancer.

2.5. Ethical Consideration

Ethics clearance from the Committee of Human Research and Ethics of the Kwame Nkrumah University Hospital, Kumasi, Ghana. Participants agreed to Informed consent forms. The study complied with the Helsinki Declaration of 1964, with revision in October 2008.

Results

Table 1 shows the socio-demographic and clinical characteristics of study participants. The majority of the 296 men in the study were in the age range of 62–77 years (47%), had no education (45.9%), were non-smokers (82.8%), and normal BMI. Prostate cancer was indicated in 12.5% of the population.
Table 1  
Socio-demographic and clinical characteristics of study participants

| Variable             | Frequency (N) | Prevalence (%) |
|----------------------|---------------|----------------|
| **Age (years)**      |               |                |
| 30–45                | 24            | 8.1            |
| 46–61                | 119           | 40.2           |
| 62–77                | 139           | 47             |
| 78–93                | 14            | 4.7            |
| **Occupation**       |               |                |
| None                 | 136           | 45.9           |
| Formal               | 42            | 14.2           |
| Informal             | 118           | 39.9           |
| **Smoking status**   |               |                |
| Yes                  | 59            | 17.2           |
| No                   | 245           | 82.8           |
| **Alcohol status**   |               |                |
| Yes                  | 168           | 56.8           |
| No                   | 128           | 43.2           |
| **BMI status (Kg/m²)** |             |                |
| <18.5 (Underweight)  | 10            | 3.4            |
| 18.5–24.9 (Normal)   | 137           | 46.3           |
| 25–29.9 (Overweight) | 88            | 29.7           |
| 30–34.9 (Obese)      | 43            | 14.5           |
| >35 (Morbid obese)   | 18            | 6.1            |
| **PSA status**       |               |                |
| 0–4 (Normal)         | 112           | 37.8           |
| 4–10 (Prostate disease) | 147       | 49.7           |
| >10 (Prostate cancer)| 37            | 12.5           |

N: total number of cases observed. Values are presented in frequency proportions (%)
Table 2 shows an association between age, obesity, and PSA status. Age was significantly associated with PSA status \((p < 0.001; \text{Chi-square (X}^2\text{) value} = 41.629)\). 11.6% of the prostate cancer patients were obese and there was no significant association between obesity and PSA status within all the parameters \((\text{Chi-square (X}^2\text{) value BMI} = 0.008)\).

### Table 2
**Association between age, obesity and PSA Status**

| Age group | PSA STATUS | Total | P-value |
|-----------|------------|-------|---------|
|           | 0–4 Normal | 4–10 Prostate Disease | >10 Prostate Cancer |
| 30–45     | 16 (66.7)  | 7 (29.2) | 1 (4.2) | 24 | < 0.001 |
| 46–61     | 58 (48.7)  | 56 (47.1) | 5 (4.2) | 119 |
| 62–77     | 35 (25.2)  | 79 (56.8) | 25 (18.0) | 139 |
| 78–93     | 3 (21.4)   | 5 (35.7) | 6 (42.9) | 14 |
| BMI status | Underweight | Normal | Overweight | Obese | Morbid obese |
|           | 5 (50.0)   | 4 (40.0) | 1 (10.0) | 10 | 0.944 |
| Normal    | 46 (33.6)  | 71 (51.8) | 20 (14.6) | 137 |
| Overweight| 37 (42.0)  | 42 (47.7) | 9 (10.2) | 88 |
| Obese     | 17 (39.5)  | 21 (48.8) | 5 (11.6) | 43 |
| Morbid obese | 7 (38.9)  | 9 (50.0) | 2 (11.1) | 18 |

\(\text{Chi-square (X}^2\text{) value for age} = 41.629; \text{Chi-square (X}^2\text{) value BMI} = 0.008\)

Table 3 examines the association between Clinical, Anthropometric, and PSA levels among study participants. Hypertension assessed by Diastolic blood pressure (DBP) and Systolic Blood Pressure were showed no association with prostate cancer risk indicated by PSA levels. Obesity as assessed by Waist Circumference and BMI was shown to be statistically insignificant when compared with PSA status.
Table 3
Clinical, Anthropometric and PSA levels among study participants

| Variables         | Normal (N = 112) | Prostate disease (N = 147) | Prostate cancer (N = 37) |
|-------------------|------------------|---------------------------|--------------------------|
| Age***            | 56.49 ± 10.24    | 62.14 ± 9.72              | 69.50 ± 8.46             |
| SBP ns            | 130.15 ± 18.60   | 130.63 ± 19.53            | 127.49 ± 16.02           |
| DBP ns            | 81.33 ± 11.52    | 81.14 ± 13.19             | 81.28 ± 10.08            |
| WC ns             | 90.75 ± 12.34    | 89.20 ± 11.73             | 86.92 ± 10.56            |
| BMI ns            | 26.09 ± 5.18     | 25.92 ± 5.13              | 25.80 ± 5.18             |
| PSA***            | 2.33 ± 0.94      | 6.42 ± 1.57               | 34.05 ± 3.06             |

Values are in mean ± standard deviation. *** mean values are statistically significant (p < 0.05); ns mean values are non-significant (p > 0.05). One-way Anova with Bonferroni Post hoc multiple comparism. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Table 4 represents the logistic regression of confounding factors associated with prostate cancer. There was no association between the intake of alcohol, smoking, and prostate cancer. Occupation is shown to be a good predictor of prostate cancer.

Table 4
Logistic regression of confounding factors associated with prostate cancer

| Variables in the Equation | β     | S.E.  | Wald | df | Sig. | Odd ratio | 95.0% Cl. for odd ratio |
|---------------------------|-------|-------|------|----|------|-----------|------------------------|
| Factors                   |       |       |      |    |      |           |                        |
| Step 1a                   |       |       |      |    |      |           |                        |
| Alcohol                   | 0.007 | 0.375 | 0.000| 1  | 0.984| 1.007     | 0.483 - 2.102          |
| Smoking                   | -0.309| 0.504 | 0.376| 1  | 0.540| 0.734     | 0.273 - 1.972          |
| Occupation                | 1.260 | 0.384 | 10.785| 1  | 0.001| 3.525     | 1.662 - 7.476          |
| Constant                  | -2.575| 0.374 | 47.315| 1  | 0.000| 0.076     |                        |

a. Variable(s) entered on step 1: Alcohol, Smoking, Occupation; β: regression coefficient; S.E.: standard error

Discussion
There is not enough community-based PSA screening program in Ghana and risk factors are largely undefined. We undertook a PSA screening program in an unscreened population and assessed some putative risk factors and their association with prostate cancer. The findings demonstrate the utility of PSA as a screening tool and a possible association of risk factors such as age, obesity, hypertension, alcohol intake, smoking, and occupation to prostate cancer.

In this community based study we observed 12.5% of the study population were positive for prostate cancer using relatively higher upper limit of PSA detection rate. Majority of the participants (49.7%) had other forms of prostate disease as assessed by PSA. Since there is not enough data on community based screening programs for prostate cancer in the community, we are unable to thoroughly examine our data with specific reference to similar studies. However, we found that a study by Arthur et al., 2006 [18] found exceedingly high (83.6%) prevalence rate amongst Ghanaian men attending a urology clinic at a tertiary hospital in Ghana. The high prevalence rate observed by Arthur et al., 2006 could be attributed to the low PSA detection rate of 4 ng/ml used as against ours of 10 ng/ml. We believe our decision of adjusting the PSA prostate cancer detection limit at 10 ng/ml is a better predictive value than 4 ng/ml since several studies have held that the chances of unwanted biopsies in using PSA detection limit of 4 ng/ml is high [16, 19]. Even-though we could not proof the veracity by biopsy diagnosis, we observed that an earlier study conducted in Ghanaian men of similar social characteristics which combined PSA measurement, digital rectal examination (DRE), and histopathology found a prevalence rate of 16.0% consistent with our data [20]. In the Hsing et al study, 2014, 7.0% were confirmed as prostate cancer by histopathology, a figure consistent with our reported prevalence rate at a cut-off 10 ng/ml. A recent review of hospital-based registry in the study population have reported a prostate cancer incidence of 10.5% per 100,000 men [21]. These findings agreeing with our findings demonstrate the diagnostic utility of adjusted PSA cut-off of 10 ng/ml in an unscreened population. Our mean PSA of 34.05 ± 3.06 ng/ml further supports the use of adjusted PSA value detecting for prostate cancer since PSA values above 25 ng/ml have been shown to correlate with aggressive prostate cancer [22]. Due to the biases in estimating for PSA, we recommend an adjustment of the PSA values to 10 ng/ml as prostate cancer indicative to forestall unwarranted biopsies. Persons below the adjusted cut-off must be balanced with other indicative symptoms suggested by the International Prostate Cancer Symptom Score and referral to hospitals for diagnostic monitoring.

The concept of age as a risk factor of prostate cancer is time-honored. However, inter-racial and population-based differences of age defined risk groups call for population-specific determination. Prostate cancer was highly detected in the age range of 62–77 years with a mean age of 69.50 ± 8.46 years in the population (Table 2, 3). We found a strong association between age and prostate cancer (Table 3, p < 0.05). We further show that prostate cancer is highly detected above 45 years with PSA. This outcome is consistent with previous hospital and community-based studies in Ghanaian populations. Arthur and colleagues in community-based cross-sectional studies found more prostate cancer within the age range of 66–70 years even at a low PSA detection rate of 4 ng/ml [18]. Simlarly, review of prostate cancer detected by biopsy and PSA reported a high peak in the age range of 60–69 years with a mean age of 65.4 years [23]. In a large cohort of 1,037 men, when was PSA was combined with Digital rectal examination as diagnostic tools for prostate cancer, most of the men diagnosed of prostate cancer were
found within the ages 70–74 year [20]. The study of Hsing and colleagues [20] supports our findings of the chance of detecting prostate cancer using PSA at the age of 69.50 ± 8.46. Another study in Ghanaian men which determined the nomogram for predicting the probability of the positive outcome of prostate biopsies among Ghanaian men also found high frequency within the age range of 70–79 years [24]. We, therefore, agree to the widely held view that prostate cancer is a disease of adult males. However, our finding of detecting prostate cancer at 45 years could be relevant within the view of contradictory statements on the age detection rate of prostate cancer in different settings. The European Association of Urology adopts an early age of 40 years [25] whiles the United States Preventive Services Task Force recommends 50 years [26]. We assert that the ability of our adjusted PSA cut off point of 10 ng/ml for prostate cancer to pick prostate cancer at an early age of 45 years in the study setting could be informative. Our data could support the view of a recent review study which suggested increasing high incidence of prostate cancer in younger men [27]. Our report feeding into reported low knowledge and awareness of prostate cancer risk in Ghana [28, 29] call for the introduction an aggressive mass screening program to accurately detect the early detection age in the study setting.

Obesity is a growing burden in Ghana with attributions to non-communicable diseases [30]. Assessed by BMI > 30 kg/m² we observed that, 14.5% of the participants were obese which agreed to the high prevalence of obesity in Ghana [30]. However, there was no significant association between obesity and prostate cancer. A similar finding by Asare and colleagues [31] in Ghanaian men attending Urology Clinic also found no significant association between obesity assessed by BMI and prostate cancer. Furthermore, a Nigerian prostate cancer detection study also found no significant association of obesity and prostate cancer [32]. In a large US population, it has been also found that obesity is not associated with prostate cancer [33]. However, a recent study in Ghanaian men assessing abdominal obesity as a risk factor to prostate cancer contradicts our finding [34]. However, the lower cut-off PSA detection limit of 2.5 ng/ml used in their study could account for the association of obesity with prostate cancer. This is because several studies have predicted the biases associated with using lower nomogram for predicting prostate cancer. Furthermore, since the study did not delineate biological or sociological reasons to their findings we may have to be in the loop requiring more robust detection regime to ascertain whether obesity is a risk factor to prostate cancer in Ghanaian men.

Even though hypertension is a major risk factor in many cancers, an association with prostate cancer is undefined. In our search for comparative literature, we did not obtain data of studies that assess the risk of hypertension in the Ghanaian population. However, there are reported meta-analysis and systematic reviews linking hypertension as a risk factor to prostate cancer [35, 36]. We, however, found no significant association between hypertension and prostate cancer. This finding is consistent with a study in Finnish men where hypertension decreased the risk of prostate cancer [37]. Generally, the pathophysiology of hypertension is complex involving several metabolic and signaling mechanisms. More studies are needed to delineate the role of hypertension in prostate cancer pathology.

Furthermore, even though alcohol is carcinogenic the risk to prostate cancer is largely unresolved. Epidemiological studies have reported contrasting outcomes on the risk of alcoholism to prostate cancer.
In this current study we report of no association of alcohol intake with prostate cancer. This finding of ours is compatible with a prospective study in the United States, which also observed no association between consumption of alcohol and prostate cancer [38]. Similarly, Demoury and colleagues also showed no significant association between lifetime in-take of alcohol and prostate cancer in Canadian men [39]. Even though there is yet unresolved biological justification between alcohol consumption and prostate cancer, reports of dose-dependent risk abound. A 30-year prospective cohort of Finnish men indicated that heavy consumption of alcohol increased risk to prostate cancer [40]. A meta-analysis of literature also supported the dose-dependent risk of alcohol intake and prostate cancer [41]. We did not explore the possibility of dose-dependent intake of alcohol in the study population; however, our finding wage into the debate on the risk of alcohol intake to prostate cancer.

With respect to smoking we found low prevalence of smoking amongst the participants. This finding contradicts earlier comprehensive review of smoking prevalence in Ghana, which reported high incidence in older men [42]. We agree with the reasoning put forth by Nketiah and colleagues [43] that factors such as religion, level of income, educational status, and public health could account for the low prevalence in the study population. Furthermore, we showed no association of smoking and prostate cancer (OR, 1.007; CI 95%). This finding contradicts systematic and meta-analysis of smoking and prostate cancer which report of an association [44, 45]. Risk of smoking to prostate cancer is a life course activity where the frequency and habit of smoking over some time account for its risk to prostate cancer [46]. The risk of smoking to prostate cancer is dose-dependent where heavy smokers have a risk [47]. The limitation of not assessing the frequency of smoking over a period as well as the dose of smoking may have influenced our outcome. However, we do not consider smoking as a major risk factor to prostate cancer.

Occupational exposure characterized by formal and informal work was significantly associated with prostate cancer. Men within the informal working group were more in the study than men with the formal occupation. The finding contradicts the study of the Ghana prostate study, which found a high association of prostate cancer amongst men in formal occupation [48]. The study agrees to studies that have associated informal work such as farming, construction as posing a high risk to prostate cancer [49, 50]. Even though we did not isolate specific occupation and its association with prostate cancer, we can infer that since most of the general population in the study setting are into farming and strenuous activity-based work, physical activity may play a role.

In conclusion, we observe that prostate cancer is highly detectable in an unscreened Ghanaian population. Prostate-specific antigen estimation with adjusted prostate cancer detection rate of 10 ng/ml may provide an improved approach to screening prostate cancer in unscreened men above 45 years. Exploratory studies are required to ascertain the impact of risk factors such as obesity, hypertension, smoking, and alcohol intake on prostate cancer. Older men and informal occupations may serve as risk factors for prostate cancer amongst Ghanaian men.

Declarations
Declaration of interests

The authors of this research article declare no competing interests.

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Conflict of Interests

There is no conflict of interest associated with this research.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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