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Mini Review

Redefining Prostate Cancer Diagnosis: The Global Discourse on Single PSA Cut-Off Level in Diverse Populations

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ABSTRACT

Controversy surrounds the use of Prostate Specific Antigen (PSA) as a definitive marker for identifying Prostate Cancer (PCa), despite its alarming incidence and mortality rates. This in-depth mini review examines recent published article and relevant literature analyzing the complex link between PCa and various risk factors. It also examines the potential of age-specific prostate-specific antigen reference intervals (ASRLs) as an alternative to a single PSA cutoff value. Our review uncovers that PCa is primarily rooted in advancing age and genetic predisposition (shared genes), with its impact further influenced by factors such as race, environmental conditions, lifestyle, and human development index. The existing studies suggest that ASRLs provide a viable alternative to overcome the limitations of relying on a single PSA cutoff value. Data from men belonging to different populations were analyzed for establishing ASRLs in accordance with the International Federation of Clinical Chemistry guideline. Spearman correlation analysis was used, with a significance threshold of P values<0.5. ASRLs were determined by utilizing the 95th percentile and PSA values within each 10-year age group, covering age groups 30-39, 40-49, 50-59, 60-69, 70-79 and ≥ 80 years. A positive correlation between PSA levels and age groups was observed. Furthermore, the review delves into the variation of PSA levels across different ethnicities. Synthesizing the findings, this review suggests that ASRLs may offer higher sensitivity compared to a single cutoff value, emphasizing the need for a nuanced approach to characterizing PSA based on both age and ethnicity.

Keywords: Age; Age-specific PSA; Healthy men; Prostate cancer; Prostate specific antigen; Genetic predisposition; Reference interval

INTRODUCTION

The rapid surge in Prostate Cancer (PCa) is a cause for concern for the entire human race. Over the course of several decades of monitoring, the increase in risk factors associated with this disease has been well-documented [1]. However, there is ongoing controversy regarding the use of single PSA cut-off values for diagnosing prostate cancer in both young and old men from diverse populations. PCa is the second most commonly diagnosed cancer affecting men population and the fifth leading cause of cancer-related deaths with 1,414,000 new cancer cases and 375,304 deaths globally in 2020. The pattern in incidence and mortality is alarming in men of African ancestry [2]. The incidence is currently increasing in adults under 50 years and in young men in most nations. Report noted that the burden of PCa is supposed to increase due to the aging population and economic growth [3]. Most men with prostate cancer will have unaffected overall survival due to the biologically indolent nature of the majority of the disease, even if treatment is required. It was estimated by 2000, that the percentage of PCa had reached 77.1% of all urological cases and was the most common and burdensome tumor in southeast Nigeria. A study documented that a mortality of PCa was high with 64% deaths in 2 years [4]. This may not signify an improvement in diagnosis and control of risk factors. Attempts at lowering this scenario require better diagnostic alternative for early detection and

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treatment. However, a study reported that African specific risk panels may require different screening approaches and treatment than standard practice in developed countries (Figures 1 and 2) [5].

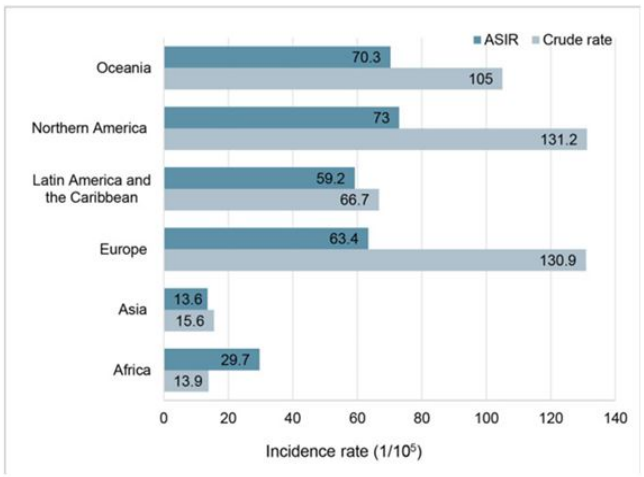

Figure 1: Incidence and mortality of prostate cancer in 2020 by continent. **Note:** ASIR: Age-Standardized Incidence Rate

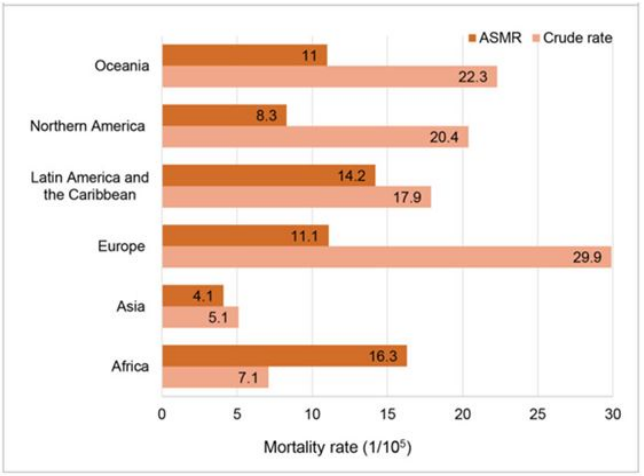

Figure 2: Incidence and mortality of prostate cancer in 2020 by continent. **Note:** ASMR: Age-Standardized Mortality Rate

Prostate cancer risks

There are still unknown factors specific to PCa in individuals of black race, although certain similarities have been observed between African-American and native African men. However, there are also disagreements, such as the belief that PCa is more prevalent among African-Americans compared to Africans. The comparison is challenging, particularly in terms of limited research on genetics in Africa. Nevertheless, it can be reasonably speculated that the occurrence of PCa in individuals of black race is influenced by shared genes, advancing age, family history and environmental and lifestyle factors. This speculation is supported by studies that have provided significant insights into the role of genetic variations in PCa risk. There are high-risk genes associated with prostate cancer, as well as genes with lower to moderate risk, which collectively account for over one-third of the risk of familial prostate cancer [6]. Therefore, identifying men with positive family history is important in curbing the incidence and mortality of prostate cancer. Additionally, prostate cancer is a polygenic disease with a significant hereditary component. Men who have a brother or father affected by prostate cancer have at least twice the risk of developing PCa compared to men without a family history and the risk further increases if the affected family member had an early onset of the disease. Furthermore, various lifestyle and dietary risk factors that may elevate the risk of cancer have been reasonably speculated, such as obesity, physical fitness and dietary patterns. The Human Development Index (HDI) has also shown to have an impact on the incidence and mortality of cancer [7].

Prostate cancer screening *via* PSA the current marker, has been used for decades and it is challenging to urologists. Controversy exists over PSA as a screening tool. This is due to its inability to discriminate between such men and those harboring lethal disease who will benefit most from identification and treatment. Prostate specific antigen is a glycoprotein in the Kallikren-like protease family with reduced chymotrypsin like enzyme activity. It is synthesized by all the epithelial cells of the prostate gland. It is organ-specific but not specific for prostate cancer as the levels are increased in benign prostate hypertrophy, acute prostatitis, urinary retention and infection, after digital rectal examination and after sexual activity [8]. The single cut-off of serum PSA level (0 ng/ml-4 ng/ml) is based on single study and limitations. It is old isotopic technology, non-appreciation of the diverse molecular form of PSA, the absence of standardization and lack of knowledge of co-variants of age. Report has questioned the use of traditional total PSA cut-off value of 0.4 ng/ml across all population and age. Studies also documented that ASRIs is better and should be used as alternative [9].

LITERATURE REVIEW

The following questions arise: 1) Is it really true that ASRIs is a better alternative to single PSA cut-off value? 2) Is it age dependent and population specific? The reasonable considerations found in literatures are as follows: PSA is influenced by age, race, diet and environment. It has an association with age related volume changes due to hyperplia of the prostate tissue. Report showed that age is a risk factor as susceptibility towards the disease increase with age. In a study conducted by Oesterling and colleagues, it was found that PSA values increased about 3.2% per year in 60 years old man [10]. Therefore, age specific is better in their age specific medium for young men and older age group. Nevertheless, serum PSA of 0 ng/ml-4 ng/ml was used as the basis for conducting prostate biopsy regardless of age. This finding was based study which had limitations on older technology which ignored the diverse molecular form of PSA and it's hardly a standard test.

In a recently published article by Okafor and colleagues, the hypothesis of susceptibility of prostate cancer association with age was explored in detail (Table 1) [11].

Table 1: Analysis of total serum prostate-specific antigen level (ng/ml) based on all six age groups distributions (total n=636).

Age (years)	N	Mean	Median	Minimum	Maximum	5th	25th	50th	75th	95th
30-39	182	0.46	0.22	0.00	3.21	0.00	0.01	0.22	0.69	1.94
40-49	145	0.86	0.42	0.00	3.52	0.00	0.15	0.42	1.41	2.52
50-59	163	1.39	1.06	0.00	4.7	0.00	0.39	1.06	2.30	3.52
60-69	83	2.0	2.1	0.01	4.51	0.03	0.80	2.1	2.97	4.38
70-79	54	3.90	4.15	0.27	7.0	0.27	2.20	4.15	4.83	6.95
80 and above	9	2.43	2.4	0.24	5.6	0.24	1.60	2.4	2.6	5.6

Note: tPSA: total Prostate-Specific Antigen; ng/ml=nanogram per mililiter

This shows the mean, median of serum PSA values in six categorized age groups. The 95th percentile PSA value in the 30-39 age group was the least at 1.94 ng/ml while the highest value of 6.95 ng/ml occur in the 70-79 age group. However, contrary to our expectation, the 95th percentile serum PSA value for the ≥ 80 age group stool sat 5.6 ng/ml, a lower value than that of 70-79 age group. The overall serum PSA level in the study was (0 ng/ml-6.95 ng/ml). The calculated 95th percentile serum total PSA value for each age group is designated in this study as the upper limit of the reference range while the lower limit is designated as 0 ng/mg (Figure 3) [12].

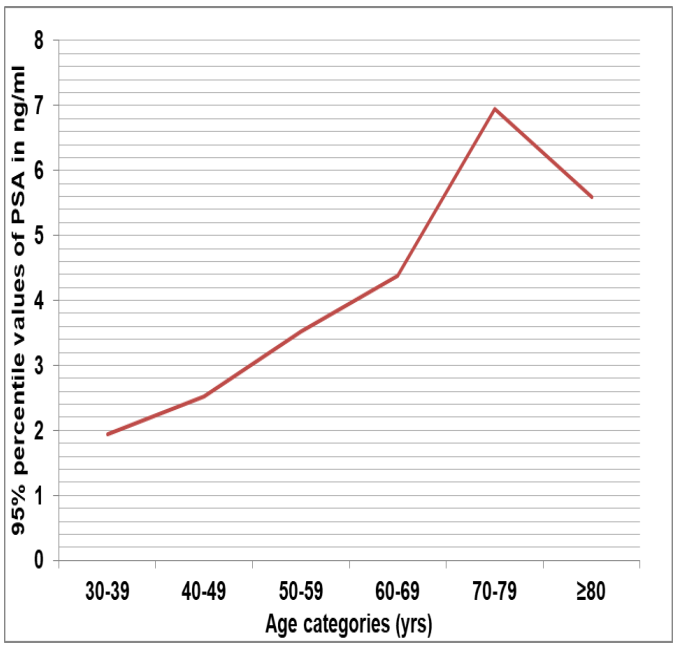

Figure 3: Correlation between 95th percentile values of PSA and age group categories. tPSA: total Prostate-Specific Antigen; ng/ml=nanogram per milliliter.

The data showed that the 95th percentile of serum PSA values for each 10 years age categories increased with age. PSA value demonstrated upward trend from the lowest age group of 30-39 years and peak at 70-79 years. Although, the work could not draw any conclusion from age groups >80 years because of the sample size, but supporting the finding is a positive and significant correlation between PSA values and subject age as shown in Figures 1 and 2 (Table 1) [13].

DISCUSSION

This mini review was conducted to highlight on the alarming incidence and mortality of prostate cancer and it also examines the potential of ASRLs as an alternative marker to a single PSA cutoff value in all ages and diverse population. An inappropriate diagnosis may result to wrong clinical decisions. Improvements in diagnosis, prevention and treatment are crucial for the overall enhancement of global health. The screening of PCa depends entirely on the use of single cut-off PSA which has appreciable limitations.

A recent article demonstrates that the 95th percentile of serum PSA values for each age group is a better alternative to a single PSA cutoff value and also noted that PSA value increases with age. This finding is supported by a positive and significant association between PSA values and participants' age, as depicted in Table 1 and Figure 3. These results align with a previous study conducted in Nigeria. Both studies indicate that a single serum PSA cutoff threshold cannot be universally applied across all age groups. Serum PSA levels are influenced by age, race, lifestyle, diet and environmental factors. Furthermore, PSA values are associated with age-related changes in prostate tissue volume due to hyperplasia [14].

Reports indicate that age is a risk factor, as susceptibility to diseases tends to increase with age. In a study by Oesterling and colleagues, it was observed that PSA values increased by approximately 3.2% per year in a 60-year-old man. Similarly, the study by Okafor and colleagues, which involved subjects of varying ages, revealed that PSA values were influenced by age, as evidenced by the stratification of results. PSA values exhibited an upward trend from the lowest age group of 30-39 years, peaking in the 70-79 years age group. Consequently, ASRLs are more appropriate for young men and older age groups [15].

However, it is worth noting that a serum PSA cutoff value of 0 ng/ml-4 ng/mL is commonly employed as the basis for prostate biopsy, regardless of age. This proposition is based on a single study, which has certain limitations and fails to consider the diverse molecular forms of PSA and the age-related co-variants [16]. PSA values obtained in recent published article were approximately three times higher than those reported by researchers in the western world [17]. However, values obtained from community-based recent article were lower than the findings of a hospital-based study in South-South Nigeria, possibly due to variations in population size, study design, inter-assay variation and verification bias [18].

Some scientists have suggested that PSA thresholds of 2 ng/ml-2.5 ng/mL should be used for individuals aged 40-49 years in African Americans, compared to 0 ng/ml-2.52 ng/mL in a recent Nigerian article [19]. Other studies have shown that serum PSA levels are higher in black than in Whites, Chinese, Indian and Japanese populations (Table 2). The similarity of elevated PSA values in both Nigerian studies, in comparison to traditionally accepted cutoff values, supports the influence of race on PSA values, with individuals of the same race exhibiting similar values while variations exist between age and race groups. We propose that ASRLs should be used as an alternative to singular PSA values. It is believed that by employing these threshold values which are lower for and high than 0 ng/ml-4 ng/ml in younger age and older age groups respectively, localized PCa can be detected early, leading to necessary interventions, reduced mortality and a decrease in unnecessary biopsies for patients with benign prostatic hyperplasia, without missing the presence of prostatic carcinoma. It has been proposed that using ASRLs sensitivity and specificity of PCa detection is enhanced in younger and older men respectively. We propose that a future multi-center community-based research should conducted to validate this finding [20].

Table 2: Age-specific reference intervals using the 95th percentile values of total PSA in diverse populations.

Studies	N	Age groups					
		30-39	40-49	50-59	60-69	70-79	≥ 80
Enugu Southeast Nigeria (community based)	636	0-1.94	0-2.52	0-3.52	0-4.51	0-6.95	0-5.6
Hospital-based study, Port Harcourt South-south Nigeria	476	0-1.60	0-4.93	0-6.93	0-7.80	0-9.69	0-13.30
African-American White men	471	-	0-2.5	0-3.5	0-4.5	0-6.5	-
European White men	1,160	0-1.78	0-1.75	0-2.27	0-3.48	0-4.26	0-2.64
Asian Chinese men	1,096	-	0-2.15	0-3.20	0-4.10	0-5.37	-
Indigenous Japanese men	345	-	0-2.0	0-3.0	0-4.0	0-5.0	-
South Indians men	583	0.9	1.3	1.48	1.6	2	2.47
Healthy Indian men	1,253	0.71	0.85	1.13	1.45	1.84	2.35

Note: n=number of participants; tPSA=total Prostate-Specific Antigen; ng/ml=nanograms per milliliter

CONCLUSION

The review confirms that serum PSA values increase with age and this cuts across all races, although, the rate of increase differs from race to race when compared to literature evidence. We suggest that redefining prostate cancer diagnosis with ASRLs, the global discourse on single PSA cut-off level in diverse populations will be minimized.

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CONFLICT OF INTEREST

No conflict of interest.

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