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Age and Racial/Ethnic Disparities and Burden of Prostate Cancer: A Cross Sectional Population Based Study

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ABSTRACT

Objectives: The objective of this study was to examine the association of age and racial disparities in addition to obesity, dyslipidemia and diabetes and the burden of prostate cancer. **Methods:** The National Health and Nutrition Examination Survey (NHANES) data from 2001 to 2010 was used to examine the association between age and racial disparities in addition to obesity (body mass index), lipid and glycemic biomarkers and prostate cancer amongst adults in the United States. Data were analyzed for descriptive statistics and for differences using the t test, Chi-square test and ANOVA. A p value of <0.05 was considered statistically significant. **Results:** A total of 5,951 adults (40 yrs. and above) were included in this study. Sample mean age was 55.9 years, and 77% were non-Hispanic white. More participants (38%), older than 70 yrs. of age had PSA, total between 4-10 ng/ml and 9% had PSA total greater than 10 ng/ml, which was statistically significant (p<0.05). Similarly, participants younger than 50 yrs. of age had PSA ratio greater than 25% compared to participants older than 60 yrs. of age. These difference in PSA, total and free and PSA ratio was also statistically significant (p<0.05) There was two and half times higher odds of having high PSA, total and 10% odds of having greater than 25% PSA ratio with an increase in age and 20% greater chance of having higher PSA, total and 10% higher odds of having PSA ratio greater than 25%, if you were other than Mexican American such as Non-Hispanic white or black. **Conclusions:** Age and race/ethnicity found significantly associated with PSA levels. Role and impact of racial disparities and biomarkers discussed above in prostate cancer need further exploration.

Key words: Age disparities; racial disparities; prostate cancer risk; prostate cancer screening; prostate cancer

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INTRODUCTION

Prostate cancer is the most common cancer among men and the third leading cause of cancer death in the United States. About 161,360 new cases of prostate cancer are reported and about 26,730 deaths occur every year in the United States according to year 2017 estimates.[1] Worldwide in 2008, it was estimated that 9,13,000 men were diagnosed with prostate cancer, of which more than two-thirds of cases were diagnosed in developed countries.[2]

Several risk factors affecting men's risk of getting prostate cancer were reported in different studies.[3-9] Recent literature review revealed that many of these studies have focused on the impact of ethnicity, genetic predisposition, metabolic syndrome, obesity, and diabetes, and screening on prostate cancer.[3-9] A study conducted in England compared the incidence of cancer among six 'non-White' ethnic groups (Indian, Pakistani, Bangladeshi, Black African, and Black Caribbean, and Chinese).[3] This study concluded significantly higher incidence of prostate cancer among Africans and Caribbean Blacks compared to other groups, linking higher incidence to the genetic susceptibility. In another study by Lloyd *et al*., which has examined the risk of being diagnosed with, and dying from, prostate cancer among major ethnic groups, black men were twice more likely to be diagnosed with, and die from, prostate cancer compared to the White men suggesting the link of ethnicity with the incidence of prostate cancer.[4]

In a prostate cancer study conducted in China examining the genetic predisposition among a Chinese population using Chinese prostate cancer genome-wide association study (GWAS), researchers concluded that the top 10% of the population had two fold prostate cancer risk compared with men of the bottom 10%. The authors indicated these findings might be beneficial in the design of prostate cancer genetic risk screening.[5]

The association between metabolic syndrome and increased risk of prostate cancer among Chinese Han ethnic population was examined in a study by Zang *et al*.[6] This Study finding revealed significant association between metabolic syndrome and prostate cancer, suggesting management of metabolic syndrome might be beneficial in reducing progression of prostate cancer.[6]

In one Indonesian study, investigators evaluated obesity as a risk factor for prostate cancer.[7] Findings of this study demonstrated that various mechanisms that cause inflammation may also precipitates the development of prostate cancer further suggesting that the role of obesity in prostatitis is still unclear that it needs to be explored further.[7]

Similarly, the association between diabetes and prostate cancer was evaluated in another longitudinal study by Dankner *et al*.[8] Investigators in this study followed more than 1 million men for 11 years. Findings of this study concluded that the relationship between diabetes and prostate cancer is complicated and may vary across patient populations, further suggesting that it might be beneficial to consider diabetes as comorbidity in screening strategies for prostate cancer.[8]

Racial disparities in health outcomes are well documented and it is certainly true about a disease condition such as prostate cancer. Elimination of such disparities is one of two overarching goals of Healthy People 2010[1] and is the subject numerous Institute of Medicine (IOM) reports.[9,10] As the social demographics in the United States are continuously changing, it is important to understand the

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disparity in incidence rate, prognosis, and predictors among different ethnic populations for prostate cancer. The objectives of this study were to explore the burden of prostate cancer among different ethnicities and to examine the impact of age, obesity, lipid and glycemic markers on the risk of prostate cancer using a large population based survey.

METHODS

Study population

We analyzed the sample of adults 40 years and older who participated in National Health and Nutrition Examination Survey (NHANES), an ongoing population-based statistical survey to estimate the health status of the non-institutionalized civilian US population, based on interview, examination, and laboratory information from representative samples of US households. In-person interviews were conducted in sampled households, and subjects were invited to participate in medical examinations.[11] We aggregated NHANES data releases for 2001 through 2010 into a combined data set (NHANES 2001-2010) to increase sample size for greater estimator reliability (NHANES Analytic Guidelines).[12] Of 52,195 total participants who completed a home interview, 50,085 (96%) were examined. PSA levels were measured for 7,398 participants aged 40 years or older. Our study deemed for exemption status by the Institutional Review Board.

Study definitions

Hyperlipidemia was defined in accordance with "National Cholesterol Education Program-Adult Treatment Panel" (NCEP-ATP III) guidelines.[13] Individuals were considered hyperlipidemic, if they had Low-density lipoprotein (LDL) 130 mg/dl or higher; high-density lipoprotein (HDL) 40 mg/dl or lower and considered diabetic, if they had glycated hemoglobin (HbA1c) 7% or higher. National Cancer Institute (NCI) criteria were used for defining normal Prostate Specific Antigen (PSA) levels as, PSA, total (4 ng/ml), PSA, free (0.4 ng/ml) and PSA ratio (%).[14] An individual is considered diagnosed with prostate cancer, if he provided a positive response to the question, "Have you ever been told by a doctor or other health professional that you had prostate cancer? Body mass index, a measure of obesity defined as weight in kilograms divided by height in meters squared, was categorized according to clinical guidelines set by the National Institute of Health.[15]

STATISTICAL ANALYSIS

The statistical analyses for this study were performed using STATA, version 14 (STATA, College Station, Texas) a statistical software package that takes into account sample weighting and the complex, multistage probability sample design of NHANES.[16] Demographic characteristics were compared by age, race, education, BMI, lipid and glycemic markers using t test, chi-square test and ANOVA. For each age group and race/ethnicity mean PSA levels were calculated separately. Sampling weights were applied to take into account selection probabilities, over-sampling, non-response, and differences between the sample and the US adolescent male population. We estimated a multivariable logistic regression model incorporating covariates for age and race/ethnicity, education, HbA1c, total cholesterol, body mass index. A p value of <0.05 was considered statistically significant.

RESULTS

Our final study sample included 5,951 participants aged 40 years and older. The mean age of the total sample was 55.9 yrs, 77% were Non-Hispanic White and 44% with less than high school education. Ninety three percent participants had PSA total less than 4 ng/ml, 6% with PSA, free less than 0.10 ng/ml and 37% had PSA ratio less than 25% [Table 1]. Mean HbA1c level in sample was 5.7%, total cholesterol 198.9 mg/dl and BMI was 30.8. Very few participants knew if they were diagnosed with prostate cancer, took medicine for prostate cancer, or ever had surgery for prostate cancer [Tables 1 and 2].

Table 1: Participants demographic characteristics and biomarkers (N=5,951)

Age (yrs.)	%, (95%CI)
40-50	40.3 (38, 42.7)
51-60	27,8 (25.9, 29.8)
61-70	18.1 (16.9, 19.3)
71-80	11.7 (10.9, 12.6)
>80	2.1 (1.7,2.5)
Ethnicity	
Mexican American	6.2 (4.7, 8.0)
Other Mexican	3.2 (2.4, 4.3)
Non-Hispanic White	76.8 (73.7, 79.6)
Non-Hispanic Black	8.8 (7.5, 10.3)
Other	5.0 (1.7, 2.5)
Education	
Less than High School	43.9 (41.6, 46.2)
Some College	27.3 (25.8, 28.9)
College Graduate	28.9 (26.5, 31.3)
Body Mass Index (BMI)	
<18.4	0.7 (0.5, 1)
18.5-24.9	14.4 (13.0, 15.8)
25-29.9	30.3 (28.6, 32.3)
30-30.9	23.5 (21.4, 25.8)
>40	31.0 (28.0, 34.2)
PSA, total (ng/ml)	
<4 ng/ml	93.3 (92.6, 94.0)
4-10 ng/ml	5.5 (4.9, 6.2)
>10 ng/ml	1.1 (1.0, 1.4)
PSA, free (ng/ml)	
<0.10	6.1 (5.3, 7.0)
0.10-0.24	39.6 (38.1, 41.2)
≥ 25	54.3 (52.5-56.0)
PSA Ratio (%)	
<10	2.1 (1.7, 2.6)
10-20	18.4 (17.1, 19.9)
21-25	16.1 (15.0, 17.2)
>25	63.4 (61.8, 64.9)
Diagnosed with PC	377
Ever had prostate surgery	200
Was surgery for PC	191
Taken medicines for PC	110

Table 2: Mean levels of biomarkers and PSA for total sample

	Mean (95%CI)
Age (yrs.)	55.9 (55.4, 56.5)
HbA1c (%)	5.7 (5.7-5.8)
Total Cholesterol (mg/dl)	198.9 (197.2, 200.5)
BMI	29.1 (28.9, 29.4)
PSA, total (ng/ml)	1.5 (1.5, 1.6)
PSA, free (ng/ml)	0.4 (0.4, 0.4)
PSA Ratio (%)	30.8 (30.2, 31.5)

The mean PSA, free level among other Hispanic, Non-Hispanic black and Non-Hispanic Whites was 0.47 ng/ml, 0.46 ng/ml and 0.45 ng/ml, respectively little higher than that of Mexican American (0.37 ng/ml) [Table 3].

More participants (38%), older than 70 yrs. of age had PSA, total between 4-10 ng/ml and 9% had PSA total greater than 10 ng/ml. This difference in PSA, total was statistically significant. Similarly, participants younger than 50 yrs. of age had PSA ratio greater than 25% compared to participants older than 60 yrs. of age. These difference in

Table 3: Association between Mean PSA levels with Age groups and for Race/Ethnicity

	Mean PSA, total (ng/ml), 95%CI	PSA, free (ng/ml), 95%CI	PSA Ratio %, 95%CI
Age			
40-50	0.9 (0.9, 1.0)	0.3 (0.2, 0.3)	32.3 (31.5, 33.1)
51-60	1.3 (1.2, 1.3)	0.3 (0.3, 0.3)	30.7 (29.9, 31.5)
61-70	2.0 (1.9, 2.2)	0.5 (0.4, 0.5)	29.3 (28.2, 30.4)
71-80	2.8 (2.6, 3.1)	0.7 (0.7, 0.8)	31.0 (30.1. 32.0)
>80	3.6 (2.8, 3.5)	0.8 (0.7, 1.0)	30.6 (28.5, 32.7)
p-value	**0.000***	**0.000***	**0.000***
Ethnicity			
Hispanic American	1.4 (1.2, 1.5)	0.3 (0.3, 0.3)	28.5 (27.5, 29.6)
Other Hispanic	1.6 (1.2, 2.0)	0.4 (0.3, 0.4)	29.9 (27.4, 32.3)
Non-Hispanic White	1.5 (1.4, 1.5)	0.4 (0.4, 0.4)	31.4 (30.8, 32.1)
Non-Hispanic Black	1.8 (1.6, 2.0)	0.4 (0.4, 0.4)	30.0 (29.0, 31.0)
Other	1.5 (1.1, 1.9)	0.4 (0.3, 0.4)	32.6 (30.9, 34.2)
p-value	**0.100**	**0.010***	**0.001***

*Significant at p<0.05

Table 4: Association of age and race/ethnicity with PSA levels

	PSA, total (ng/ml), N			PSA, free (ng/ml), N)			PSA Ratio %, N			
	<4	4-10	>10	<0.10	0.10-0.24	>0.25	<10	10-20	20-25	>25
Age										
40-50	1,713	14	5	124	876	732	28	311	265	1,128
51-60	1,247	53	8	73	554	681	35	293	225	755
61-70	1,190	133	32	74	382	899	42	293	252	768
71-80	894	195	58	67	210	870	31	210	190	716
>80	178	58	16	17	37	198	8	44	47	153
p-value		**0.000***			**0.000***				**0.0002***	
Ethnicity										
Mexican American	932	56	17	60	406	539	26	230	182	567
Other Mexican	340	27	5	21	135	216	9	91	70	202
Non-Hispanic White	2831	267	58	201	1,079	1,876	67	560	76	2,016
Non-Hispanic Black	922	85	36	68	354	621	36	232	182	593
Other	197	18	3	5	85	128	6	38	32	142
p-value		**0.008***			**0.145**				**0.023***	

*Significant at p<0.05

PSA, total and free and PSA ratio was statistically significant (p<0.05) [Table 4].

Fifty eight percent of Non-Hispanic blacks and 56% of Non-Hispanic whites were obese compared to other race/ethnicities. Participants of age 60 and above were more obese compared to one that younger than 60 yrs. of age. These differences in BMI for age and race/ethnicity were statistically significant (p<0.05). Differences were also significant for HbA1 level and PSA, total; where 8% of the participants with HbA1c level more than 7% had PSA, total greater than 4 ng/ml. Ten percent of the participants with higher than 200 mg/dl total cholesterol had PSA, total greater than 4 ng/ml (p<0.05).

On logistic regression analysis, in both unadjusted and adjusted model, age was the significant predictor of high PSA, total, PSA, free and PSA ratio. Similarly, race/ethnicity, was found to be a significant predictor of PSA, total and PSA ratio, whereas, total cholesterol and BMI of PSA free level (p<0.05) [Tables 5 and 6]. There was two and half times higher likelihood of having high PSA, total and 10% higher likelihood of having greater than 25% PSA ratio with an increase in age and 20% greater chance of having higher PSA, total and 10% higher likelihood of having PSA ratio greater than 25%, if you were other than Mexican American such as Non-Hispanic white or black.

DISCUSSION

Given the significant impact of prostate cancer on men's health, researcher conducted survey to assess the knowledge of a group of men about prostate cancer.[17] Quantitative and qualitative data was collected about the participants' knowledge about the symptoms, disease prevention and the treatment of prostate cancer. Results of the study showed that the majority of the study sample did not have adequate knowledge about the symptoms of prostate cancer, prevention, and/or treatments. The authors concluded that there is an urgent need for health care professionals, employers, and policy makers to educate patients on prostate cancer to prevent the disease and enhance men's health.[17] Majority of the participants in our study were also unaware of their diagnosis of prostate cancer.

Our study findings are consistent with findings of a study by Lin *et al*. In this study, age was revealed as a significant factor of predicting Prostate Specific Antigen (PSA) levels when age-related reference levels for serum PSA was examined.[18] In a sample of 7803 healthy men, the serum PSA values were correlated with age, showing large increases among men older than 50 years. Increased serum PSA levels found with increased age among Taiwanese men, which are significantly different than ethnicities that are most often studied in the United States. In another study on prostate cancer among elderly men, authors argued that age is a critical prognostic factor that should be considered when making treatment decisions. Specifically, clinicians noted that PSA screening programs may result in over diagnosis of prostate cancer. Therefore, men who are older than 70 years may benefit from close monitoring and using alternative treatments to manage prostate cancer. Relationship between age, ethnicity, and PSA was explored in one Indonesian study.[19] A total of 1638 patients were enrolled in this study. Results of this study showed increased PSA levels with increase in age indicating that age is a prognostic marker of increased prostate cancer risk regardless of ethnicity.

Table 5: Age and other predictors of PSA levels (unadjusted and adjusted model)

	PSA, total		PSA, free		PSA Ratio	
			Unadjusted			
	OR (95%CI)	p- value	OR (95%CI)	p- value	OR (95%CI)	p- value
Age	2.5 (2.3, 2.8)	0.000*	1.1 (0.9, 1.2)	0.258	0.9 (0.9, 0.9	0.000*
Race/ethnicity	1.2 (1.0, 1.3)	0.025*	1.1 (1.0, 1.2)	0.214	1.1 (1.0, 1.2)	0.017*
			Adjusted			
Age	2.6 (2.3, 2.9)	0.000*	1.1 (1.0, 1.2)	0.144	0.9 (0.9, 0.9)	0.000*
Race/ethnicity	1.2 (1.0, 1.4)	0.042*	1.1 (0.9, 1.2)	0.357	1.1 (0.9, 0.9)	0.000*
Education	1.1 (0.9, 1.3)	0.252	1.1 (0.9, 1.3)	0.390	1.1 (1.1, 1.2)	0.247
HbA1c	1.0 (0.7, 1.4)	0.884	0.6 (0.4, 0.8)	0.002*	1.1 (0.9, 1.3)	0.596
Total Cholesterol	1.1 (0.9, 1.3)	0.462	0.9 (0.8, 1.1)	0.486	0.9 (0.8, 1.0)	0.102
BMI	0.9 (0.8,1.0)	0.063	1.0 (0.8,1.0)	0.580	1.1 (1,0, 1.1)	0.201

*Significant at p<0.05

Table 6: Race/ethnicity and other predictor of PSA levels (adjusted model)

	PSA, total		PSA, free		PSA Ratio	
	OR (95%CI)	p- value	OR (95%CI)	p-value	OR (95%CI)	p-value
Ethnicity	1.1 (1.0, 1.3)	0.046*	1.1 (0.9, 1.2)	0.329	1.1 (1.0, 1.2)	0.033*
Education	1.0 (0.8, 1.1)	0.730	1.1 (0.9, 1.3)	0.439	1.1 (1.0, 1.2)	0.180
HbA1c	1.3 (1.0, 1.8)	0.085	0.6 (0.4, 0.8)	0.004*	1.0 (0.8, 1.2)	0.902
Total Cholesterol	0.8 (0.7, 1.0)	0.013*	0.9 (0.8, 1.1)	0.344	0.9 (0.9, 1.0)	0.284
BMI	0.9 (0.8,1.0)	0.020*	1.0 (0.8,1.1)	0.556	1.1 (0.7, 1.5)	0.119

*Significant at p<0.05

In addition to age, results of this study revealed that ethnicity is also a significant factor to predict PSA levels. This finding was also validated in the study by Lim *et al*. that examined the association between ethnicity and PSA levels in a sample of 1054 men with no clinical evidence of prostate cancer.[20] This study revealed that baseline PSA level values differed among men based on their ethnicity. The authors concluded by recommending that ethnicity should be considered when evaluating serum PSA levels among a multiethnic patient population. In a study by Lim *et al.*, authors recommended that ethnicity, in addition to age, should be considered as a critical factor for the diagnosis and treatment of prostate cancer.

Studies have examined the association between diabetes and prostate cancer with varied results.[21-23] A study by Sarma *et al.*, epidemiological evidence was examined to support the inverse relationship between diabetes and prostate cancer.[22] The researcher postulated that screening-related factors might be the cause of this association. Patients with Type 2 diabetes might have reduced PSA and are less likely to seek health care services than patients without diabetes. Furthermore, patients with diabetes with low-grade disease are less likely to receive biopsy or prostate cancer treatment than those with high-grade. The author concluded that additional research is needed to confirm the underline cause of this inverse association.

Association between increased glycemic (HbA1c) levels with increased PSA levels, as observed in this study are in contrast to the findings of Jonasson *et al.*, where authors examined the relationship between poor glycemic control and reduced PSA among patients with Type 1 Diabetes.[23] A total of 25,476 patients with Type 2 Diabetes from the Swedish National Diabetes Register were included in this study. The researchers calculated the incidences of and hazard ratios (HR) for cancer among patients that were grouped based on their HbA1C. The HR for all cancer were 1.01 (0.98-1.04) per 1% unit increase in the HbA1C. The results of the study showed no associations between HbA1C and risks for all cancer among patients with Type 2 diabetes in contrast to findings of this study, where higher PSA, total was observed with HbA1c levels greater than 7%. The total PSA levels were measured in 639 men in the Epidemiology of Diabetes Interventions and Complications Trial (EDICT), the observational follow-up of participants in the diabetes Control and Complications Trial (DCCT). Findings of this study showed that decreased in PSA levels with HbA1C increase among participants with Type 1 Diabetes concluding that glycemic control has a direct impact on PSA levels.[22]

In a study to examine the association between obesity and PSA, a total of 35,632 Chinese men were surveyed and 13,084 were included in the analyses.[24] The participants were grouped based on their BMI (Body Mass Index) and PSA parameters were measured. Results of this research revealed that obesity was associated with lower PSA levels among Chinese men. The authors recommended that BMI and WC should be considered when PSA is used for PC screening. In this study, participants with BMI>30, showed higher PSA levels, however this difference was found not statistically significant.

The relationship between cholesterol levels and PSA was explored in several studies.[3-5] In a research study conducted among patients in Nigeria to examine the link between lipid characteristics and PSA, total cholesterol, triglycerides, HDL, and LDL and PSA levels were compared between the two groups.[25] The researchers indicated that, in addition to age, High PSA, total cholesterol, triglycerides, and LDL levels may be risk factors for prostate cancer. Suggesting, high HDL may prevent the onset of the disease.

In another study, the impact of statin drugs and cholesterol was assessed on PSA levels.[26] Authors analyzed data from the National Health and Nutrition Examination Survey (NHANES), where researchers compared the PSA levels among the statin users and nonusers. Results of the study suggested that the statin users who had lower cholesterol had lower PSA levels. In this study, participants with total cholesterol >200 mg/ml showed elevated PSA levels.

There are several limitations to this study. Our study used data of population based National Health and Nutrition Examination Survey (NHANES). As such, we could not measure the availability of insurance, use of diagnostic technologies, or time from symptom onset

to diagnosis. Nor could we measure the presence or absence of specific risk factors such as smoking or diet. Our measurement of demographic factors was limited to age, sex, race, and marital status. This study did not take into account whether there were differences by race in the underlying rate of cancer incidence. Efforts to prevent cancer through modification of risk factors such as smoking and diet are important. The need for risk-factor reduction, however, does not negate the need to focus on diagnosis at earlier stages as a mechanism to reduce disparities in cancer survival.

Non-Hispanic blacks, who are considered to be represented in the lower socioeconomic strata, are believed to have poor access to health care and preventive services than non-Hispanic whites. This further result in delayed diagnosis and presents with clinically advanced disease. Our study, which has used a large population-based data collected at individual-level found that non-Hispanic blacks were associated with the high risk of presenting with prostate cancer. Efforts to reduce prostate cancer mortality in African-Americans need to address the factors accounting for the racial disparity in clinical stage at diagnosis of prostate cancer. Risk of prostate cancer diagnosis and death stratified by the age and race/ethnicity provides patients, health care professionals and policy makers with useful information which can help them in deciding how to manage and minimize such risks. Higher than average risk of prostate cancer deaths among some groups should still be weighed against the harms of over diagnosis and overtreatment. The evidence for obesity, cholesterol levels, use of statins, presence of diabetes etc., are still important risk factors, however, these factors still needs be further investigations.

In conclusion, the non-Hispanic blacks and Whites had higher prostate cancer burden compared to their Mexican counterpart, as well there was higher likely hood of having increase risk of prostate cancer with advancing age. In the absence of clear primary prevention strategies for prostate cancer, understanding racial disparity in prostate cancer diagnosis and survival can offer some benefits to the health care professionals and the policy makers. Raising the awareness of prostate cancer among vulnerable population such as non-Hispanic blacks and implementing the awareness programs will provide a vehicle for earlier diagnosis and better outcome particularly for those at higher risk of prostate cancer.

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