Features of the Metabolic Syndrome and Prostate Cancer in African-American Men

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BACKGROUND. Metabolic syndrome refers to a cluster of conditions that includes hypertension, dyslipidemia, central adiposity, and high blood glucose levels. Over the past decade, a growing body of literature suggests that metabolic syndrome may be associated with several different forms of cancer. Because prostate cancer risk is highest among African Americans, and these men, similarly, are more prone to developing specific features of the metabolic syndrome, including hypertension and type-2 diabetes, any relationships would have a significant impact on developing strategies for the primary prevention of prostate cancer.

METHODS. The Flint Men's Health Study is a community-based, case-control study of prostate cancer conducted exclusively among African Americans. Prostate cancer cases and controls completed an interviewer-administered questionnaire that asked about the respondent's history of high blood pressure and diabetes. All men also participated in a physical examination in which several measures of body composition, including waist circumference, were collected.

RESULTS. Hypertension was reported more commonly among men with prostate cancer (cases) compared with men in the control group (odds ratio [OR]. 2.4; 95% confidence interval [95% CI], 1.5–3.7), and cases were more likely to have a waist circumference >102 cm (OR, 1.8; 95% CI, 1.2–2.9). However, self-reported diabetes was not associated with prostate cancer risk. The men with prostate cancer also were more likely than controls to exhibit multiple syndrome characteristics (OR, 1.9; 95% CI, 1.2–3.0).

CONCLUSIONS. The current results indicated that features of the metabolic syndrome, specifically abdominal obesity and hypertension, are associated with prostate cancer in African-American men. This relationship, if it is proved causal, suggests that prevention or control of these conditions eventually may lead to a reduction in the incidence of prostate cancer in this high-risk minority group. ***Cancer* 2007;109:875–81.** © *2007 American Cancer Society.*

KEYWORDS: prostate cancer, African Americans, hypertension, diabetes, abdominal obesity.

In 1988, Reaven[1] described *Syndrome X* as a cluster of clinical conditions that serve as risk factors for cardiovascular disease. Over the next 2 decades, much has been written about Syndrome X, which is now commonly called the *metabolic syndrome*, and its central component, insulin resistance. A working definition of the metabolic syndrome was presented in the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATPIII]).[2] To be classified with metabolic syndrome, individuals must have ≥3 of the following 5 risk factors: 1) abdominal obesity (waist circumference >102 cm in men and >88 cm in women), 2) hypertriglyceridemia (triglycerides ≥150 mg/dL), 3) low

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high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men and <50 mg/dL in women), 4) high blood pressure (≥130/85 mm Hg), and 5) high fasting glucose (≥110 mg/dL). A recent report estimated that the metabolic syndrome is highly prevalent in the United States population and is present in nearly 25% of adults aged ≥20 years according to the working definition proposed by the ATPIII.[3]

It is recognized widely that certain racial and ethnic groups are predisposed to developing different features of the metabolic syndrome. Caucasians present most often with lipid abnormalities, including hypertriglyceridemia and low HDL cholesterol[3]; African Americans and Asians present with hypertension; whereas diabetes is diagnosed more frequently among Hispanics, Pacific Islanders, and Native Americans.[4] Abdominal obesity has increased drastically in all men over the past 40 years in the United States, regardless of race or ethnicity, and nearly 33% of adult men now have a waist circumference >102 cm (or approximately 40 inches).[5]

A number of recent reports have suggested that prostate cancer may be associated with features of the metabolic syndrome. Using data from a clinical study of men with prostate cancer in Sweden, Hammarsten and Hogstedt[6] observed that certain features of the metabolic syndrome, including both hypertension and obesity, were more common in men who had stage T3 cancer compared with men who had stage T2 cancers. In a prospective study of 16,209 Norwegian men, the presence of the multiple features of the metabolic syndrome was associated with an increased risk of being diagnosed with prostate cancer over a follow-up of 27 years. Men with measured values that placed them in the upper quartile for any 2 features of the metabolic syndrome were 1.23 times more likely to be diagnosed with prostate cancer (95% confidence interval [95% CI], 1.01–1.50). Men who exhibited any 3 features were 1.56 times more likely to be diagnosed prostate cancer compared with the rest of the cohort.[7] These data complement a number of studies in the literature that address the correlations between prostate cancer and metabolic syndrome,[8] body size,[9] insulin resistance,[10] and hypertension.[11]

Given the potential association between the factors that comprise the metabolic syndrome and prostate cancer and the public health importance of these conditions in African-American men, we set out to explore the potential correlations between abdominal obesity, hypertension, and diabetes and prostate cancer using data from the Flint Men's Health Study (FMHS), which is a community-based study of benign and malignant prostate disease in African-American men between ages 40 years and 79 years who reside in Genesee County, Michigan. The study represents 1 of the most comprehensive epidemiological datasets focusing uniquely on African-American men and the risk for prostate cancer.

MATERIALS AND METHODS

Participants

Data collection for the FMHS began in 1996 and concluded in 2002. Informed consent was obtained from study participants, and all protocols were approved by the Institutional Review Board at the University of Michigan Medical School. African-American men between ages 40 years and 79 years were identified from a probability sample with over sampling of men in older age groups. From the initial sample of 819 of eligible men, 730 men (89%) were willing to participate and completed the detailed, in-home, epidemiologic interview. Men who reported a history of prostate cancer or a prior operation on the prostate gland were considered ineligible for further study. In total, 379 men completed all aspects of the protocol, including providing a blood sample for a serum total prostate-specific antigen (PSA) measurement and undergoing a comprehensive urologic examination. Men who had an abnormal digital rectal examination and/or elevated total PSA concentration (≥4.0 ng/mL) were referred for prostate biopsy. Twenty men who subsequently were diagnosed with biopsy-confirmed prostate cancer were included in the study as cases, and the remaining 359 men were included in our control sample.

Prostate cancer case recruitment from the same community began in 1999 and was completed in 2002. Cases were identified by using the Genesee County Community-Wide Hospital Oncology Program registry, which includes the 3 hospitals for the county: Hurley Hospital, Genesys Regional Medical Center, and McLaren Regional Medical Center. Case participation in the study required 1) an interviewer-administered survey questionnaire, which gathered information identical to that of controls with respect to prostate cancer risk factors and medical conditions; 2) a review of the hospital and registry records for information on stage, grade, treatment, and prediagnosis PSA value; 3) anthropometric measurements; and 4) a blood sample. In total, 139 African-American men ages 40 years to 79 years who were residents of Genesee County and who had been diagnosed with prostate cancer completed all aspects of the case protocol. This number includes men who were identified either as a result of the initial recruit-

ment protocol or who were diagnosed with cancer between the initial survey and follow-up examination in 2002.

Metabolic Syndrome Features

The survey instrument that was administered to cases and controls included questions about socioeconomic status, occupation, health behaviors (including smoking and alcohol consumption), and family history of cancer. When appropriate, controls were asked to consider exposures and conditions prior to the interview, whereas cases were asked about the same exposures/conditions up until 1 year prior to diagnosis. Self-reported information also was used to assess prior medical history, including hypertension and diabetes. Men were asked a series of 3 questions to determine history of hypertension: 1) "Has a doctor ever told you that you have high blood pressure or hypertension?"; 2) "Do you have high blood pressure at the present time?"; and 3) "Do you have high blood pressure that is controlled by medication?" The last question was asked to avoid potential misclassification among men who did not report current high blood pressure because of antihypertensive medication use. Hypertension was defined as men reporting that they currently had high blood pressure or that they currently were using antihypertensive medication. Cases and controls also were asked, "Has a doctor ever told you that you have diabetes or high blood sugar?" For this report, height, weight, and waist measurements were obtained by trained health professionals.

Statistical Analysis

Crude associations between participant characteristics (age, smoking status, family history, body mass index [BMI], waist-to-hip ratio, and sedentary physical activity) and case-control status were tested by using a chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables (Table 1). Because age and smoking history were associated significantly with case-control status in this study, both factors were included in subsequent statistical models. Odds ratios (ORs) and 95% CIs were produced to quantify correlations between specific features of the metabolic syndrome (Table 2) and various combinations of features (Table 3) with case-control status by using logistic regression models. All tests and statistics were repeated after the exclusion of men who had insignificant cancers (defined as cases with biopsy and specimen Gleason scores $\leq$6, maximum tumor dimension $\leq$1 cm, localized tumor stage, and negative lymph node status) to evaluate any impact of detection bias.

TABLE 1
Baseline Characteristics of 498 African-American Men Participating in the Flint Men's Health Study*

Characteristic	Prostate cancer cases n = 139	Disease-free controls n = 359	P†
Mean age ± SD, y	67.4 ± 8.8	62.1 ± 10.1	<.001
Ever smoked, %	66.7	78.3	.016
Family history of prostate cancer, %	21.6	16.4	.179
Mean BMI ± SD, kg/m^2	28.5 ± 5.7	27.9 ± 5.9	.228
Sedentary, %‡	19.4	19.3	.990

SD indicates standard deviation; BMI, body mass index.
* These results exclude missing data.
† Associated either with the chi-square statistic or the Wilcoxon test.
‡ Participants were considered sedentary if they averaged <5 hours of light activity per day (with 1 hour of vigorous activity equal to 5 hours of light activity).

TABLE 2
Adjusted Odds Ratios and 95% Confidence Intervals Associated With Prostate Cancer According to Specific Features of the Metabolic Syndrome Among Participants in the Flint Men's Health Study

Variable	No. of men (%)		OR [95% CI]*
	Cases	Controls	
Abdominal obesity			
Waist circumference >102 cm	59 (42.8)	102 (28.5)	1.84 [1.17–2.91]
Waist circumference ≤102 cm	79 (57.2)	256 (71.5)	
High blood pressure†			
Yes	85 (61.2)	147 (41.1)	2.36 [1.49–3.73]
No	54 (38.8)	211 (58.9)	
Diabetes‡			
Yes	28 (21.7)	64 (17.8)	0.96 [0.55–1.68]
No	101 (78.3)	295 (82.2)	

OR indicates odds ratio; 95% CI, 95% confidence interval.
* Results exclude missing data: ORs were adjusted for age and smoking history.
† Based on self-report of current medical treatment for high blood pressure.
‡ Based on self-report of disease.

RESULTS

Data available from 498 African American men were included in this report, including 139 men with prostate cancer (cases) and 359 disease-free controls. Despite the strategy of over sampling control men in the older age groups, the cases were significantly older than the controls (67.4 years ± 8.8 years vs 62.1 years ± 10.1 years, respectively; $P < .001$) (Table 1). The men with prostate cancer, as expected, were more likely to report a family history of prostate cancer in a first-degree relative (father, brother, or son) compared with controls, although this difference did not reach statistical significance (21.6% vs 16.4%, respectively; $P = .18$). A greater proportion of controls compared with cases reported ever smoking

TABLE 3
Risk of Prostate Cancer in African American Men With Multiple Features of Metabolic Syndrome

Features of metabolic syndrome	No. of men (%)		Adjusted OR [95% CI]*
	Cases	Controls	
Exhibits all 3 features of metabolic syndrome	9 (7.0)	23 (6.4)	0.74 [0.28–1.91]
Exhibits any 2 of 3 features	50 (39.1)	83 (23.2)	1.76 [1.10–2.83]

OR indicates odds ratio; 95% CI, 95% confidence interval.
* Results exclude missing data: ORs were adjusted for age and smoking history.

cigarettes (78.3% vs 66.7%, respectively; $P = .016$). No significant differences were detected between prostate cancer cases and controls in BMI or sedentary behavior.

The data collected allowed us to examine 3 of the 5 key features of the metabolic syndrome in African-American men. The FMHS protocol did not collect information about lipid profile abnormalities. After adjustment for age and smoking history, African-American cases were 1.8 times more likely (95% CI, 1.2–2.9) to have a waist circumference >102 cm compared with controls (Table 2). Similarly, men who reported currently having high blood pressure or taking antihypertensive medications were significantly more likely to have been diagnosed with prostate cancer (adjusted OR, 2.4; 95% CI, 1.5–3.7). Nearly 20% of FMHS participants reported a diagnosis of diabetes; however, no association between diabetes and prostate cancer was detected in this study population. The removal of 35 men in the case group who had prostate cancer with low-risk features did not change the statistical significance of any of these results (data not shown).

Very few of our study participants (<10%) demonstrated all 3 features of the metabolic syndrome. Furthermore, we observed no differences in the likelihood of being diagnosed with prostate cancer between men who exhibited all 3 features compared with the other men. However, the presence of any 2 features (ie, abdominal obesity and hypertension, abdominal obesity and diabetes, or diabetes and hypertension) was associated significantly with a diagnosis of prostate cancer (adjusted OR, 1.8; 95% CI, 1.1–2.8). Of the 3 possible combinations of factors, abdominal obesity and hypertension exhibited the strongest association with prostate cancer (adjusted OR, 1.9; 95% CI, 1.1–3.3) (Fig. 1).

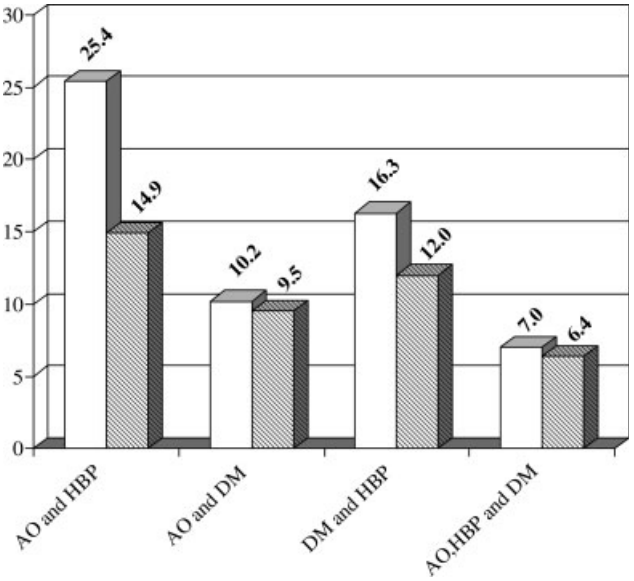

FIGURE 1. Combined features of the metabolic syndrome in African-American men with and without prostate cancer. The values are expressed as a percentage of the total number of either cases or controls. White bars indicate case data, and the hatched bars correspond to data from the control group. AO indicates abdominal obesity; DM, diabetes mellitus; HBP, high blood pressure.

DISCUSSION

African-American men have an approximately 1.6-fold greater chance of being diagnosed with prostate cancer compared with white men and a 2.4-fold greater chance of dying from the disease.[12] A significant amount of research has been completed over the last decade focusing on factors that may contribute to the disproportionate incidence and mortality from prostate cancer in this racial group. We have demonstrated that both abdominal obesity and hypertension are associated with an increased likelihood of being diagnosed with prostate cancer in African-American men. This observation, if it is confirmed as a causal relation, has important biologic and health-policy implications. Given the prevalence and modifiable nature of these features, control or prevention of these conditions may represent a sound strategy for the primary prevention of prostate cancer as well as cardiovascular disease in this high-risk minority group.

The link between specific features of the metabolic syndrome and prostate cancer risk focuses primarily on altered serum concentrations of insulin-like growth factors (IGFs) and associated binding proteins, sex steroid hormones, and sex-steroid binding globulin (SHBG).[13,14] It has been demonstrated that insulin resistance and hyperinsulinemia suppress the production of IGF binding protein 1 (IGFBP-1) and IGFBP-2 in the liver while increasing the production of IGF-1.[13] It has been reported that

IGF-1 contributes to the initiation and progression of prostate cancer through a number of mechanisms, including increased proliferation of both normal and neoplastic prostate cells and inhibition of apoptosis.[15–18] Increased insulin production also has been shown to inhibit the production of SHBG, resulting in higher concentrations of bioavailable testosterone and estradiol, which some have proposed also may promote the development and progression of prostate cancer. However, most current investigations of the direct relation between circulating testosterone and prostate cancer risk have not supported this hypothesis.[19,20] It is noteworthy that Hsing et al. observed a correlation between insulin resistance and prostate cancer among Chinese men that was independent of serum IGF, SHBG, and sex steroid hormone concentrations; this correlation suggests that there may be alternative mechanisms in prostate carcinogenesis, such as inflammation and oxidative stress, and further investigation is warranted.[10,21–23]

Our observations largely are consistent with previous studies in predominately Caucasian populations. However, not all investigations have consistently observed an association between features of the metabolic syndrome and prostate cancer risk. A recent study that used data gathered from the third National Health and Nutrition Examination Survey reported an increased prevalence of metabolic syndrome, as defined by the ATPIII, among all cancer survivors versus individuals without any history of cancer (258 per 1000 population vs 184 per 1000 population, respectively). However, metabolic syndrome was characterized less frequently among individuals who had a history of prostate cancer than among individuals without a history of prostate cancer.[24]

Of the three features of the metabolic syndrome that were measured in FMHS participants, hypertension was associated most strongly with prostate cancer risk. It has been shown that hypertension is associated with overall cancer mortality, but data supporting an association between high blood pressure and prostate cancer incidence are scant. Friedman[25] studied >58,000 men who were followed in the Kaiser Permanente Medical Care Program between 1964 and 1994 and identified 2297 men with prostate cancer that resulted in 464 deaths. No statistically significant association was observed between high blood pressure or resting heart rate and the subsequent diagnosis of prostate cancer. Fitzpatrick et al.[11] analyzed hypertension, heart rate, antihypertensive medication use, and the subsequent diagnosis of prostate cancer in a cohort of 2442 men from an observational study of adults aged ≥65 years. Although no association was detected in their study between high blood pressure and incident prostate cancer over 5.6 years of follow-up, the use of antihypertensive medications protected against the diagnosis of prostate cancer. In our study, we elected to use current reports of antihypertensive medication use in our definition of hypertension. It is worth noting that 11% of cases and 15% of controls in our study reported that they did not have high blood pressure because they were receiving medication for this condition. We do not have full medication histories and, thus, are unable to tease out potential associations with regard to specific classes of antihypertensive medications. Future research is needed in this area to explore more fully the potential associations between blood pressure elevation, use of antihypertensive medications, and prostate cancer diagnosis. Abdominal obesity was associated with prostate cancer among study participants. Although we observed that men with a larger waist circumference (>102 cm) were more likely to be diagnosed with prostate cancer, no correlation was observed between BMI and prostate cancer. This discrepancy in findings may highlight an important limitation in the use of BMI as a measure of obesity, in that it does not make any distinction between muscle and fat mass. BMI as a surrogate measure for obesity is particularly problematic among older individuals, because lean body mass generally is replaced by fat mass with increasing age. Waist circumference is considered a superior measure of the metabolic consequences of obesity and often is used in addition to BMI in epidemiologic investigations of anthropometric risk factors for disease.[26–28]

There are additional limitations in the current FMHS report that should be considered when interpreting these results. First, as mentioned above, serum analysis of HDL cholesterol and triglycerides was not performed among participants in the study; thus, evaluation for this investigation was limited to 3 of the 5 documented features of the metabolic syndrome: abdominal adiposity, hypertension, and diabetes. The guidelines set forth by the ATPIII require the presence of ≥3 criteria for a diagnosis of metabolic syndrome. Within those guidelines, coupled with the relatively low proportion of participants that exhibited all 3 indicators measured in the study, we were unable to properly determine the prevalence of metabolic syndrome in the study population. However, the 3 features that were evaluated independently in this study are highly prevalent in African Americans, so that prevention or control of these individual features potentially may have an impact on the incidence of prostate cancer in this population.

We acknowledge the presence of bias in this study that limits our ability to infer a causal relation between these features and prostate cancer risk. Because of the retrospective study design and the indolent progression of prostate cancer in most cases, we cannot establish firmly a temporal sequence between the onset of the conditions of interest and prostate cancer among the cases. In addition, reliance on self-reported information about the diagnoses of diabetes and hypertension introduces the potential for misclassification bias. However, prior studies indicated reasonable consistency and reliability in the reporting of these comorbidities, particularly among those reporting medication use to treat the condition.[29,30] Also, as mentioned above, there is the possibility of detection bias, in that prostate cancer may be more likely to be diagnosed among men who pursue regular medical care for the treatment of hypertension and/or diabetes. Recent findings published by Fowke et al suggest that the correlation observed in some studies between obesity and incident prostate cancer may be explained in part by increased frequency of physician examination and PSA testing associated with obesity-related conditions.[31] FMHS study controls were asked to report whether or not they had ever had a PSA test prior to their recruitment and testing as part of the study protocol. However, we did not detect a difference in the proportion of controls who reported prior prostate cancer screening between men who had a waist circumference >102 cm compared with men who had smaller waists (49% vs 43%, respectively; $P = .32$).

In conclusion, the current results suggest that hypertension and abdominal obesity are associated with prostate cancer among African-American men. The epidemic increase in the prevalence of obesity in the United States over the past few decades, coupled with the racial disparity in the incidence, treatment, and/or control of associated comorbidities, such as hypertension and diabetes, between African-American men and white men indicates that further study will be necessary to confirm these findings and should be considered a significant public health priority. The potential benefit would be observed not only by a reduction in the direct adverse health consequences of these conditions but also indirectly by potentially influencing the risk of prostate cancer in these men.

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