Metabolic Syndrome Is Associated with Aggressive Prostate Cancer Risk Regardless of Race

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Research Article

Keywords: Prostate Carcinoma, Insulin Resistance Syndrome, Outcomes, Black Race, Prevention.

Posted Date: February 17th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1135975/v1

Abstract

Purpose

A recent meta-analysis suggested a link between Metabolic Syndrome (MS) and high-grade prostate cancer (PC), though few black men were included. We tested the link between MS and PC risk in a population of black and white men undergoing prostate biopsy. We hypothesized MS would be linked with aggressive PC, regardless of race.

Methods

Among men undergoing prostate biopsy at the Durham Veterans Affairs Hospital, we abstracted history of or treatment for hypertension (≥130/85 mmHg), dyslipidemia (HDL<40 mg/dL), hypertriglyceridemia (≥150 mg/dL), diabetes/impaired fasting glucose (fasting glucose≥100ml/dL), and obesity (waist circumference ≥40 inches) in the year prior to biopsy. Biopsy grade group (GG) was categorized as low (GG1) or high-grade (GG2-5). Multinomial logistic regression was used to examine MS (3-5 components) vs. no MS (0-2 components) and risk of high-grade and low-grade vs. no PC adjusting for key confounders. Interactions between race and MS were tested.

Results

Of 1,051 men (57% black), 532 (51%) had MS. Men with MS were older, more likely to be non-black, and had larger prostate volumes (all p≤0.011). On multivariable analysis, MS was associated with high-grade PC (OR=1.73, 95%CI 1.21-2.48, p=0.003), but not overall PC (OR=1.17, 95%CI 0.88-1.57, p=0.29) or low-grade (OR=0.87, 95%CI 0.62-1.21, p=0.39). Results were similar in black and non-black men (all p-interactions>0.25).

Conclusion

Regardless of race, MS was associated with aggressive PC, but not overall PC risk. If confirmed in other studies, our data suggest that prevention of MS may reduce the risk of developing aggressive PC in both black and non-black men.

Introduction

Metabolic Syndrome (MS) prevalence is increasing and is a serious public health problem worldwide.[1, 2] In the US, MS affects more than one-third of adults.[1] MS consists of a diagnosis of at least three of the following five risk factors: increased abdominal obesity, dyslipidemia (high triglycerides and high HDL cholesterol), hypertension, and abnormal glycemic status.[3] Given obesity, a MS component, is linked with multiple cancers,[4] it is plausible MS may also be associated with cancer development and progression. Indeed, MS has been linked with numerous cancers, including increased PC risk.[5] A recent meta-analysis of 130,000 men found that MS is associated with increased PC incidence,[6] though the overall increased risk was modest. However, not all individual studies were consistent with some finding MS was associated with *lower* PC risk[7, 8] Nonetheless, the meta-analysis found MS was strongly linked with high-grade PC (OR=1.89, p<0.0001).[6]

Importantly, nearly all studies evaluating MS and PC risk focused on White, European, or Asian men.[9–11] Whether results differ by race and specifically whether MS is linked with PC among black men, who have one of the highest PC incidence and mortality rates in the world, is limited.[12] To date, few studies examined the link between MS and PC in Black men.[12, 13]

To evaluate the link between MS and PC risk across different races, we analyzed a case-control study of black and non-black (predominantly white) men undergoing prostate biopsies at the Durham Veterans Affairs (VA) Medical Center (DVAMC) in Durham, North Carolina. We choose an equal access healthcare setting to minimize potential effects that access to care may have on our results. Given obesity, which is one of the components of MS, is linked with lower PSA,[14] but larger prostate sizes,[15] it is noteworthy that all men in this biopsy cohort had data available on PSA and prostate volume to adjust for in the analyses to account for potential differences between men with and without MS. Furthermore, obesity and insulin resistance have been recognized as the leading contributors in MS, which in turn is associated with the production of various pro-inflammatory cytokines which may promote genomic instability and a greater risk of cancer development.[16] Likewise, in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) clinical trial, high cholesterol levels, another MS component, were associated with high-grade PC but not overall nor low-risk PC.[17] Based upon the recent meta-analysis[6] and our understanding we were unlikely to be powered to detect a very small increase in total PC incidence, we a priori hypothesized that MS would be linked with aggressive PC regardless of race, but not overall PC incidence.

Methods

Study Design

Data were obtained from an ongoing case-control study of veterans undergoing prostate biopsy for concerns about PC at the DVAMC. The study was approved by the institutional review board and written informed consent was obtained from all subjects. Subjects were recruited between January 2007 and July 2018 from the urology clinic. Eligible subjects were men with no prior PC history undergoing a prostate biopsy because of abnormal PSA and/or suspicious digital rectal exam (DRE) as clinically indicated. For men with multiple biopsies performed at the DVAMC, we only used data from their initial biopsy at the DVAMC. Of 2279 eligible subjects, 1322 consented to participate (58% response rate). We excluded 249 subjects due to missing PSA, DRE, prostate volume, MS data, or grade group, and 22 active surveillance biopsies as these subjects would have been diagnosed with PC, resulting in 1051 men.

MS was defined as three or more of the following: dyslipidemia, hypertriglyceridemia, diabetes/impaired fasting glucose, hypertension, and abdominal obesity. Dyslipidemia was defined as HDL <40 mg/dL in the year prior to biopsy. Hypertriglyceridemia was defined as triglycerides ≥150 mg/dL or prescription drugs to treat high triglycerides in the year prior to biopsy. Diabetes was defined as fasting glucose >100ml/dL, prescription of an anti-diabetic agent, or diagnosis of diabetes in the medical record in the year prior to biopsy. Hypertension was defined as two blood pressure measurements where systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg within the year prior to biopsy. Waist circumference was measured by trained personnel and obesity was defined as waist circumference ≥40 inches. Race was self-reported as black, white, Asian/Pacific Islander, or American Indian/Alaska Native. As <1% of patients were races other than black or white, race was grouped as black or non-black with 99% of the non-black men being white. Prostate volume was measured at biopsy via transrectal ultrasound. Biopsy grade was categorized as low-grade (grade group 1) or high-grade (grade group 2-5).

We tested the association between MS (categorical, no: 0-2 vs. yes: 3-5 components), demographic and clinical variables using chi-squared for categorical variables and Wilcoxon rank sum for continuous variables. Variables included age (continuous), year (continuous), race (black vs. non-black), baseline PSA (continuous), DRE (normal vs. abnormal) and pre-study prostate volume (continuous). In an exploratory analysis, we examined variables by both MS and race using chi-squared or Kruskal-Wallis tests.

Logistic regression was used to examine the association between MS and PC risk versus no PC. Multinomial logistic regression was used to examine the association between MS and risk of low-grade PC (GG 1) versus no PC and high-grade PC (GG 2-5) versus no PC. The number of MS components was also tested in the above models as a continuous variable. Multivariable models were adjusted for age, year of consent, race, log-transformed baseline PSA, DRE, and log-transformed prostate volume. The interaction between race and MS in adjusted analyses was also tested and models were stratified by race. In secondary analyses, the association between each individual MS component and PC risk and grade was examined in separate univariable and multivariable models, and interactions were tested between race and each component. As a sensitivity analysis, we then repeated all analyses defining low-grade PC as GG 1-2 and high-grade PC as GG 2-5.

Significance was defined as $P<0.05$. All analyses were performed using SAS 9.4 (SAS Institute; Cary, NC).

Results

Baseline characteristics

Among 1051 men, 532 (51%) had MS and 519 (49%) did not. Having MS was associated with older age, non-black race, and larger prostate volume (Table 1, all $p\leq0.011$). There was no association between MS with PSA or DRE.

Black men were younger at biopsy, had higher PSA, fewer suspicious DREs, and higher rates of overall cancer (all $p\leq0.015$; Supplementary Table 1). Non-black men with MS had the largest prostate volumes, while black men without MS had the lowest prostate volumes ($p<0.001$).

MS and PC outcomes

While MS was not associated with overall PC (52% vs. 55%, p=0.27), MS was associated with PC grade (p=0.005, Table 1). Specifically, men with MS were less likely to have low-grade (20% vs. 28%) and more likely to have high-grade PC (32% vs. 27%) or no PC (48% vs. 45%).

On unadjusted analyses, MS was not associated with overall PC (OR=0.87, 95%CI 0.68-1.11, p=0.26) or high-grade PC (OR=1.10, 95%CI 0.83-1.46, p=0.52, Table 2). However, MS was associated with *lower* odds of low-grade PC (OR=0.65, 95%CI 0.48-0.89, p=0.003). On multivariable analysis, MS was associated with increased odds of high-grade PC (OR=1.73, 95%CI 1.21-2.48, p=0.003; Table 2), but not overall (OR=1.17, 95%CI 0.88-1.57, p=0.29) or low-grade PC (OR=0.87, 95%CI 0.62-1.21, p=0.39). When low-grade was treated as the reference, MS was associated with increased odds of high-grade PC vs. low-grade PC (OR=2.00, 95%CI 1.38-2.89, p<0.001).

'Table 1: Demographic characteristics by metabolic syndrome (MS)'			
	No MS (N=519)	MS (N=532)	p value
Age at biopsy			0.011[1]
Median	63	64	
Q1, Q3	59, 67	60, 68	
Year			0.057[1]
Median	2011	2011	
Q1, Q3	2009, 2016	2009, 2016	
Race			<0.001[2]
Non-black	184 (35%)	265 (50%)	
Black	335 (65%)	267 (50%)	
PSA level, ng/ml			0.64[1]
Median	5.9	5.8	
Q1, Q3	4.5, 8.6	4.6, 8.2	
Prostate volume, ml			<0.001[1]
Median	39.0	43.0	
Q1, Q3	27.3, 54.5	31.3, 62.1	
DRE			0.65[2]
Not suspicious for cancer	384 (74%)	387 (73%)	
Suspicious for cancer	135 (26%)	145 (27%)	
Hypertension	399 (77%)	496 (93%)	
Hypercholesterolaemia	70 (13%)	355 (67%)	
Hypertriglyceridemia	55 (11%)	338 (64%)	
Diabetes	60 (12%)	274 (52%)	
Obesity (waist≥ 40 inches)	186 (36%)	467 (88%)	
Biopsy had cancer (yes/no)			0.27[2]
No Cancer	232 (45%)	256 (48%)	
Cancer	287 (55%)	276 (52%)	
PC Grade			0.005[2]
No cancer	232 (45%)	256 (48%)	
Low-grade (grade group 1)	146 (28%)	105 (20%)	
High-grade (grade group 2-5)	141 (27%)	171 (32%)	
[1]Wilcoxon [2]Chi-Square			

Table 2. Univariable and multivariable OR and 95% CIs for the association between metabolic syndrome and risk of prostate cancer

	All prostate cancers			Low-grade PC			High-grade PC		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Univariable									
No metabolic syndrome	Ref.	-	-	Ref	-	-	Ref.	-	-
Metabolic syndrome	0.87	0.68-1.11	0.26	0.65	0.48-0.89	0.003	1.10	0.83-1.46	0.52
Continuous	0.90	0.83-0.99	0.039	0.80	0.71-0.90	<0.001	1.00	0.89-1.12	0.96
Multivariable*									
No metabolic syndrome	Ref.	-		Ref.	-		Ref.	-	
Metabolic syndrome	1.17	0.88-1.57	0.29	0.87	0.62-1.21	0.39	1.73	1.21-2.48	0.003
Continuous	1.03	0.92-1.16	0.63	0.91	0.79-1.04	0.15	1.20	1.04-1.39	0.011
*Adjusted for age, year, race (white, black, others), log transformed PSA, DRE, and log transformed TRUS.									
Interaction between race and MS, p=0.37 for all cancer, p=0.91 for low-grade, p=0.25 for high-grade									

On univariable analysis, greater number of MS components (as a continuous variable) was associated with lower odds of overall PC (OR=0.90 per MS component, 95%CI 0.83-0.99, p=0.039; Table 2) and lower odds of low-grade PC (OR=0.80 per MS component, 95%CI 0.71-0.90, p<0.001). Number of MS components was not associated with high-grade PC versus no PC. On multivariable analysis, greater number of MS components was associated with increased odds of high-grade PC (OR=1.20 per MS component, 95%CI 1.04-1.39, p=0.011). Associations with overall and low-grade PC in crude analyses were attenuated and no longer significant after multivariable adjustment.

Interaction testing

We tested the interaction between race and number of MS components in adjusted analyses and found no significant interactions for estimating PC risk (p=0.37 for all cancer, p=0.91 for low-grade PC, p=0.25 for high-grade PC). When stratified by race (Supplementary Table 2), results were generally similar in non-black and black men, although slightly stronger in non-black men, though as noted there were no significant interactions. The association between MS and high-grade PC was stronger in non-black men (OR=2.41, 95%CI 1.33-4.36, p=0.003) and did not reach statistical significance in black men (OR=1.44, 95%CI 0.91-2.29, p=0.12), though again the interaction test was null (p=0.25).

Individual MS components

On univariable analysis, there was a trend for obesity, hypertriglyceridemia, dyslipidemia, hypertension, and diabetes (in separate models) to be associated with lower odds of low-grade PC (OR range 0.62-0.86), but only obesity, hypertriglyceridemia, and dyslipidemia reached significance (Table 3). The ORs for the individual MS components and risk of high-grade PC were not consistent and ranged from 0.84 to 1.33. On multivariable analysis, ORs for all MS components were all <1 for low-grade PC (range 0.80 to 0.91) but none were significant. In contrast, ORs for each MS component were all >1 for high-grade PC (range 1.17 to 1.55), but only obesity reached significance. All interactions between individual components and race for predicting overall or low/high-grade PC were not statistically significant (p≥0.18, Table 3).

Table 3
Univariable and multivariable OR and 95% CIs for the association between metabolic syndrome components and risk of prostate cancer

Metabolic syndrome component	All prostate cancers			Race interaction	Low-grade PC			Race interaction	High-grade PC			Race interaction
	OR	95% CI	P		OR	95% CI	P		OR	95% CI	P	
Univariable												
Obesity	0.76	0.59-0.98	0.032		0.62	0.46-0.85	0.003		0.90	0.67-1.21	0.48	
Hypertriglyceridemia	0.88	0.69-1.14	0.34		0.72	0.52-0.99	0.046		1.03	0.77-1.38	0.82	
Dyslipidemia	0.74	0.58-0.95	0.019		0.63	0.46-0.87	0.005		0.84	0.63-1.12	0.24	
Hypertension	1.05	0.75-1.47	0.79		0.82	0.55-1.23	0.33		1.33	0.87-2.03	0.19	
Diabetes	0.98	0.76-1.28	0.90		0.86	0.61-1.20	0.36		1.10	0.81-1.48	0.56	
Multivariable*												
Obesity	1.14	0.84-1.54	0.40	0.87	0.85	0.60-1.21	0.54	0.80	1.55	1.06-2.25	0.023	0.82
Hypertriglyceridemia	1.02	0.76-1.39	0.88	0.26	0.90	0.64-1.28	0.36	0.53	1.27	0.88-1.83	0.20	0.28
Dyslipidemia	0.99	0.73-1.33	0.94	0.38	0.84	0.59-1.18	0.31	0.72	1.21	0.84-1.74	0.31	0.29
Hypertension	0.94	0.63-1.40	0.74	0.18	0.80	0.52-1.25	0.33	0.31	1.17	0.71-1.95	0.54	0.30
Diabetes	1.10	0.81-1.51	0.54	0.91	0.91	0.63-1.30	0.59	0.87	1.39	0.95-2.03	0.089	0.93

*Adjusted for age, year, race, log transformed PSA, DRE, and log transformed TRUS.

Sensitivity Analysis

Upon reclassification of low-grade (GG 1-2) and high-grade (GG 3-5) PC, there were fewer high-grade PC cases and MS was not statistically associated with PC grade (p=0.07, Supplementary Table 3). We observed no other appreciable differences in overall trends with MS. MS remained associated with increased odds of high-grade PC, unrelated to low-grade PC and had no interactions with race (Supplementary Table 4 & 5).

Discussion

MS and PC are both common problems.[2] Despite a recent meta-analysis finding MS was associated with increased PC risk,[6] individual studies are mixed.[7–11] Importantly, the association between MS and PC risk in black men has not been well studied. Given black men are at increased risk of some MS components[18, 19] such as hypertension, obesity, diabetes, and aggressive PC,[20] understanding whether race modifies this association is of utmost importance. We tested the link between MS and PC risk in a black and non-black case-control study of men undergoing prostate biopsy. In the REDUCE study, where most of the participants were Caucasians, all men underwent mandated biopsies regardless of PSA levels, MS was associated with increased risk of high-grade PC but not with overall or low-grade PC,[21] therefore, we hypothesized that MS would not be linked with overall PC risk but would be linked with aggressive PC and results would be similar in both black and non-black men.

Consistent with our hypothesis, MS and individual components were not associated with overall PC risk regardless of race. While on the surface these results differ from the meta-analysis and several papers that found a positive association between MS and total PC risk,[6, 9, 11] it is noteworthy that in the present study the OR=1.17, identical to the OR=1.17 (95%CI 1.00-1.36) from the meta-analysis.[6] Thus, while our findings for PC risk were not significant, they are consistent with modest increased risk and in-line with prior studies. Given the modest link between MS and overall PC risk, this association is of unclear clinical significance.

Given practice trends away from trying to diagnose low-grade PC,[22] it is important to also focus on high-grade PC. On unadjusted analyses, there was no association between MS and high-grade PC. However, after adjusting for clinical characteristics, MS was significantly linked with nearly twofold increased odds of high-grade PC. Our results were nearly identical to the recent meta-analysis,[6] that found an OR=1.89 (95%CI 1.50-2.38, p<0.0001) for high-grade PC. Likewise, other large studies have also found a link between MS and high-grade PC.[9, 21] When we examined individual MS components separately, each component was modestly linked with increased PC risk, but none reached significance. Thus, there was no single MS component that drove the association with high-grade PC, but rather the greater number of components, the greater the risk. Collectively, our results and those of prior studies suggest that MS is a significant risk factor for high-grade PC.[9, 21]

A major gap in the literature, however, is that nearly all prior studies evaluating MS and PC risk focused on either white or Asian men.[10, 11] The association between MS and PC in black men is under-studied.[12] This is a major unmet need as black men are at increased risk for some MS components,[18, 19] and for aggressive PC.[20, 23] We found no evidence for an interaction between MS and race, suggesting results apply equally to black and non-black men, regardless of how we defined high-grade disease. One prior study examined interactions between race and MS for PC risk and found that MS was suggestively predictive of increased PC risk in black men, but not in white men.[12] However, this study only included 378 black men (vs. 613 in the current) and included controls that did not undergo biopsy. Moreover, no formal interaction testing was done in that study, and thus, whether the results truly differed by race is unknown. Clinically, our results are important as the known risk factors for PC are family history, age, and race. Our data support the hypothesis that regardless of race, MS should be considered a risk factor for high-grade PC. Ultimately, whether managing MS via drugs (statins, metformin, etc.) or lifestyle interventions can reduce the risk of high-grade PC warrants further study. [24, 25]

While the biological mechanisms why MS is differentially associated with high-grade PC are not clear, one possible mechanism is the MS-associated pro-inflammatory state.[26] Obesity-linked inflammation leads to altered metabolic signaling with activation of cytokines, imbalance between adipokines along with insulin growth factor-1 (IGF-1) axis expression.[27] This environment induces the production of reactive oxygen and free radicals with subsequent genomic alterations as DNA breaks promoting the transmembrane protease, serine 2, erythroblast transformation-specific-related gene (*TMPRSS2: ERG)* gene fusion[28] present in 50% of PCs.[29] Intriguingly, in tumors with *TMPRSS2: ERG* gene fusion, obesity is a particularly strong PC risk factor.[30] Unfortunately, as *TMPRSS2: ERG* gene fusion status is not known in this study, we are unable to verify this. While the *TMPRSS2: ERG* gene fusion is less common in black men[31] and we found no interaction by race, the strength of the association between MS and high-grade PC was slightly weaker in black men. Whether this association is indeed weaker in black men certainly requires further study, but if true, it is intriguing to speculate that this may, in part, relate to less *TMPRSS2: ERG* gene fusion positive tumors in black men.

Another MS component, dyslipidemia, appears to be related to PC,[32] with several mechanisms proposed, including accumulation of cholesterol in PC cells membranes allowing pro-carcinogenic cell signaling.[33] Consistent with MS being selectively linked with high-grade PC, we showed in the REDUCE study that high cholesterol was unrelated to overall PC risk, but was associated with high-grade PC.[32] Our study builds on prior studies supporting the need for PC prevention clinical trials to modify MS factors to reduce high-grade PC including both white and black men.

Our study has some limitations. First, our MS definition may differ from the rigorous NCP ATP III definition[3] but is consistent with classic MS definitions in prior studies.[6] Second, our observed null associations for overall PC risk may due to modest sample size and we cannot exclude a modest association between MS and overall PC risk. Third, our findings were based on Veterans in the VA system; whether results apply to men outside the VA system requires further study, though our results were consistent with the meta-analysis[6] which included nearly only men outside the VA system, suggesting that our results do apply outside the VA. Fourth, we lacked data on other key factors associated with MS such as glycemic control, distribution of diabetes type 1 vs type 2, diabetes duration, testosterone, inflammatory markers, physical activity, and diet, known confounders of MS[2] possibly attenuating the ORs in our results. In addition, the definition of PC aggressiveness was grade on biopsy. Though this correlates with long-term PC progression risk,[34] future studies with alternatives definitions (i.e., metastases, stage, and PC death) are recommended. Lastly, the study subjects were men referred for a biopsy due to elevated PSA, abnormal digital exam or both. Therefore, the prevalence of the exposure of MS in the “healthy” control may be different and this impact remains to be determined. Notwithstanding these limitations, our key strength was the use of a contemporary prospective collection of data from men all undergoing biopsy.

Conclusion

In our study of black and white men undergoing prostate biopsy, we found MS was not associated with overall PC risk but was linked to high-grade PC. Importantly, results were similar in black and non-black men. Given the strength of the data linking MS and high-grade PC, future studies should test whether interventions including lifestyle modifications can reduce the impact of MS on high-grade PC, and merits further investigation in large diverse multiethnic populations.

Declarations

Acknowledgments

LEADS Support; National Institute of General Medical Sciences, R25 GM116740 (LGR)

Funding

Research Scholar Grant, RSG-18-018-01 - CPHPS, from the American Cancer Society. (AV)

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Ethics Approval

The study was approved by Durham VA Medical CenterInstitutional Review Board, reference number #1141.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Disclosure of potential conflicts of interest

The authors have no financial or proprietary interests in any material discussed in this article.

There are no direct or indirect commercial financial incentive associated with publishing the article.

No funding agreement limits my ability to complete and publish this research/study.

Competing Interests

Dr Stephen J Freedland is Editor-in-Chief, Prostate Cancer and Prostatic Diseases

Data availability

Authors can confirm that all relevant data are included in the article and/or its supplementary information files.

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