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The effects of metabolic conditions on prostate cancer incidence over 15 years of follow-up: results from the Olmsted County Study

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Abstract

- To determine if combinations of obesity, hypertension and diabetes influence the development of prostate cancer over 15 years of follow-up.
- In 1990, a randomly selected cohort of Caucasian men from Olmsted County, MN, USA, aged 40–79 years, was recruited; 2445 completed a questionnaire that included physician-diagnosed diabetes and hypertension.
- Anthropometric measures were collected during clinical examination. Biopsy-confirmed prostate cancer was identified from medical records.
- Proportional hazards regression was used to estimate the effects of these metabolic conditions, both individually and in combination, on the incidence rate of prostate cancer.
- Men with hypertension alone or in combination with diabetes were more likely to develop prostate cancer than were men without any of the metabolic conditions.
- The metabolic syndrome – the presence of all three conditions compared with men with no metabolic components – was only minimally and inversely associated with prostate cancer [hazard ratio (HR): 0.81; 95% confidence interval (CI): 0.20, 3.3] and no monotonic association between the number of metabolic components and prostate cancer was observed.
- Our results suggest that it may not be sufficient to treat metabolic conditions as one variable when investigating the aetiology of prostate cancer in Caucasian men.
- Further research should focus on the separate and combined effects of these metabolic conditions in large samples.

MeSHprostate cancer; obesity; diabetes; hypertension; metabolic syndrome

INTRODUCTION

Prostate cancer is the most common non-cutaneous cancer among American men and the second leading cause of cancer death among men in the United States [1]. The incidence of this disease is estimated to exceed 192 000 cases among American men in 2009 [2].

Metabolic syndrome, a cluster of conditions including type 2 diabetes, hyperlipidemia, hypertension and obesity, is also a highly prevalent condition in the ageing US population with overall prevalence in US adults estimated to be 25% [3]. The main components of metabolic syndrome, type 2 diabetes, hypertension and obesity, are arguably reaching epidemic proportions in the United States, resulting in substantial morbidity and millions of men requiring medical attention each year. Currently, 34% of US adults, aged >20 years, are described as obese [4]; 31% suffer from high blood pressure [5]; and 18 million adults are currently reported to have type 2 diabetes [6,7].

Recently, several groups of investigators have suggested that features of the metabolic syndrome may be predictive of prostate cancer risk. Specifically, men with more than three components of the metabolic syndrome in a prospective study of 16 209 men were 1.5 times more likely to be diagnosed with prostate cancer in the 27 years of follow-up than were men with no metabolic syndrome components [8]. Hammarsten *et al.* found that men with disseminated (T3) prostate cancer were more likely than men with localized (T2) disease to have multiple components of the metabolic syndrome [9]. Furthermore, a prospective study of Finnish men found that men with the metabolic syndrome had a twofold increased risk of prostate cancer, and that the risk was greater in men with a body mass index (BMI) ≥ 27 kg/m² compared with the risk in men with a BMI <27 kg/m² [10]. These results are in conflict with a recent prospective study that found little to no evidence that metabolic syndrome or its components were associated with prostate cancer in 29 364 Norwegian men followed for an average of 9.3 years [11].

Each of the primary components of the syndrome, diabetes, obesity and hypertension, have been found to be associated with prostate cancer. While large population-based studies have shown that BMI is positively associated with the incidence of prostate cancer [12–15], more recent studies have found either no association or an inverse association between obesity and prostate cancer incidence [16–18]. It is unclear whether these findings reflect the effect of obesity on the risk of prostate cancer, the prognostic effect of obesity on prostate cancer progression or the effect of obesity on detection of the disease.

Evidence of the association between type 2 diabetes and prostate cancer yields conflicting findings; results may reflect the changing action of insulin over the course of diabetes progression. A recent meta-analysis found that most of the evidence to date supports that there was a reduction in prostate cancer risk associated with type 2 diabetes [19]. Previous work assessing the association between hypertension and prostate cancer is sparse; however, the presence of hypertension may increase the risk of prostate cancer [11,20].

It is unclear whether combining these conditions into one syndrome is an appropriate approach when investigating the aetiology of prostate cancer. Specifically, combining multiple components of the syndrome into a single variable may confound or obscure the separate effects and interactions of these metabolic components on prostate cancer risk.

Therefore, the goal of the present study was to determine whether obesity, hypertension and diabetes alone, and in combination, influence the incidence of prostate cancer over 15 years of follow-up.

MATERIALS AND METHODS

SUBJECT SELECTION

The Olmsted County Study (OCS) of Urinary Symptoms and Health Status among Men is a longitudinal, population-based investigation of Caucasian men, residing in Olmsted County, MN, USA [21,22]. In 1990, a random sample of men aged 40–79 years, as enumerated by the Rochester Epidemiology Project, was screened for inclusion [23]. Exclusion criteria included men with a history of prostate or bladder surgery, urethral surgery or stricture or medical or neurological conditions that affect normal urinary function. Eligible men ($n = 3874$) were invited to take part in the study, and 2115 (55%) agreed to participate. Participants completed a previously validated baseline questionnaire that ascertained information on urinary symptoms, medical histories and various demographic and behavioural characteristics. A 25% random subset of the total cohort was invited to participate in a detailed urological clinical examination. Of the 537 randomly selected men, 475 (88%) agreed to participate in the clinical portion of the study.

Since 1990, the cohort has been followed biennially using a similar questionnaire to that used at baseline. During the second and third rounds of visits, men who did not participate in the follow-up were replaced by randomly selected eligible men from the community ($n = 332$ total cohort; $n = 159$ clinic cohort). After the third round, the study has been maintained as a fixed cohort.

MEASUREMENTS

Biopsy-confirmed cases of prostate cancer were identified through detailed review of medical records, yielding a total of 206 cases.

Information on self-reported physician-diagnosed type 2 diabetes and high blood pressure was collected at baseline. Men who reported using antihypertensive medication before baseline or who reported a physician diagnosis of hypertension at baseline were considered hypertensive for this analysis. Men that reported diabetes at baseline were considered diabetic. A trained research assistant measured height and weight, and BMI was calculated by dividing the weight in kilograms by the height in meters squared. Men with a BMI ≥ 30 kg/m² were considered obese, based on the definition established by the World Health Organization (WHO) [4].

Metabolic syndrome was defined using a modified version of the WHO definition [24] and focused on the presence of all three of the following components measured at baseline: self-reported type 2 diabetes, self-reported diagnosis of hypertension and/or use of antihypertensive medication before baseline and measured obesity at baseline.

Potential confounders and effect modifiers included in these analyses were a family history of prostate cancer based on self-reported first degree relative with physician-diagnosed prostate cancer, non-steroidal anti-inflammatory drug (NSAID), 5-alpha reductase inhibitor (5-ARI) or statin use before baseline, household income, years of education and age at baseline.

STATISTICAL ANALYSIS

Incidence rates of prostate cancer were estimated for the total cohort and by category of selected demographic, medical history and metabolic component status by dividing the number of incident prostate cancer cases by the amount of person-time at risk. Participants' person-time contribution began on the date they completed their baseline questionnaires and ended at the diagnosis of prostate cancer or the last date of passive surveillance chart review, whichever came first. The associations of sociodemographic characteristics and baseline metabolic conditions with prostate cancer were described using crude incidence rates. Age-adjusted hazard (incidence rate) ratios and 95% CI measuring the associations between the metabolic characteristics and prostate cancer incidence were estimated using Cox proportional hazards regression (SAS procedure proc phreg). The proportional hazards assumption was assessed using Schoenfeld residuals as well as an interaction term with time and not found to be violated for the three metabolic components. The effects of the various combinations of the metabolic conditions, as well as their interactions, on prostate cancer risk were assessed using multivariable Cox models adjusted for age, family history of prostate cancer and baseline statin use. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC, USA).

RESULTS

Among this cohort of Caucasian men, 206 cases of prostate cancer were detected, and the estimated incidence rate was 6.88 per 1000 per year. Prostate cancer was positively associated with age (Table 1; P for trend <0.001). The incidence rate of prostate cancer was greater in men with a family history of prostate cancer than in men without a family history of prostate cancer ($P < 0.001$). Also, men who were more educated and earned more income had lower incidence rates of prostate cancer when compared with men with less education (P for trend = 0.005) and income (P for trend = 0.008) (Table 1).

Table 2 displays the crude and age-adjusted HR for each metabolic variable, unadjusted for the others. Men with a history of diabetes did not have an elevated rate of prostate cancer (Table 2). Hypertensive men were 1.5 times more likely to develop prostate cancer than were non-hypertensive men (HR: 1.5; 95% CI: 1.1, 2.0), although this association was attenuated when adjusted for age (HR: 1.1; 95% CI: 0.79, 1.4). An increasing number of metabolic components were not consistently associated with prostate cancer incidence, adjusting for age (Table 2). Those with one component had a slightly increased rate, whereas those with two or three components had a slightly decreased rate of prostate cancer. Adjustment for age, family history of prostate cancer and baseline statin use did not change these results, nor did adjustment for age, family history of prostate cancer, baseline statin use, education and income (data not shown).

Despite the small number of cases, the combined categories of the three conditions were also examined. Figure 1 displays the unadjusted HR and age-adjusted HR of prostate cancer for all eight combinations of the three components of metabolic syndrome. Compared with men with no components of the syndrome, men with all three did not have an elevated rate of prostate cancer, adjusting for age (HR: 0.81; 95% CI: 0.20, 3.3); however, this estimate is imprecise because there were only two cases diagnosed in the group with all three conditions. The presence of diabetes alone was inversely associated with prostate cancer (age-adjusted HR: 0.62; 95% CI: 0.15, 2.5), but men who were hypertensive, diabetic and not obese were more likely to develop prostate cancer compared with men who did not have any of the three conditions (age-adjusted HR: 1.3; 95% CI: 0.53, 3.2). Obesity and hypertension alone were associated with an increased risk of prostate cancer; however, the combination of the two was associated with a decreased risk of prostate cancer compared with men with none of the conditions (age-adjusted HR: 0.50; 95% CI: 0.23, 1.1) (Fig. 1).

After further examination of the interaction between obesity and hypertension, the only notable departure from multiplicative effects in the proportional hazards model was the interaction between obesity and hypertension ($P = 0.013$) (Table 3). The estimated hazard ratio, comparing men with both conditions to men with neither condition, was 0.69 (95% CI: 0.35, 1.4). By contrast, the estimated hazard ratio for men with only hypertension was 1.8 (95% CI: 1.3, 2.5).

DISCUSSION

In this prospective study of 2445 Caucasian men age 40–79 years, the metabolic syndrome, defined as the presence of all three metabolic components (obesity, hypertension and type 2 diabetes), was minimally and inversely associated with the development of prostate cancer over 15 years of follow-up. However, the components of the metabolic syndrome alone were differentially associated with the rate of prostate cancer. After adjustment for age, the presence of only hypertension was associated with an increased rate of prostate cancer. The combinations of components were also found to influence the rate of prostate cancer differently, as men who were hypertensive and obese were less likely to develop prostate cancer and men who were diabetic and hypertensive were more likely to develop prostate cancer, adjusting for age. Obesity modified the association between hypertension and prostate cancer, as men who were obese and hypertensive were less likely to develop prostate cancer, whereas men who were hypertensive alone were more likely to develop prostate cancer compared with men who did not have either condition.

The association between diabetes and prostate cancer risk has been studied in several epidemiologic studies. In their recent meta-analysis, Kasper and Giovannucci found that most of the evidence supports that there was a reduction in prostate cancer risk associated with type 2 diabetes [19]. A weak inverse association between diabetes and prostate cancer was also observed in the present study, but it may have been a chance finding. Alternatively, our findings may obscure the changing association between insulin level and prostate cancer risk over the course of diabetes progression. Insulin levels are initially high in type 2 diabetes but fall over time because of the damage to the pancreatic β cells. Therefore, the relation between diabetes and prostate cancer may change from positive to inverse as diabetes progresses. This explanation is supported by research suggesting that men with early-stage diabetes have an increased risk of prostate cancer whereas men with later stage disease have a decreased risk [25,26]. Unfortunately, we did not have information on insulin levels or the duration of diabetes in our database, and we observed only nine cases of prostate cancer among diabetics.

Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was minimally and inversely associated with prostate cancer in this cohort when compared with a $\text{BMI} < 30 \text{ kg/m}^2$. Our results are consistent with previous studies, suggesting either no association or an inverse association between obesity and prostate cancer incidence [16–18]. In addition, obesity has been differentially associated with aggressive vs. non-aggressive prostate cancers; a reduced risk of low-grade disease and an increased risk of high-grade disease have been observed for obese men [27–29]. Our results, however, did not change when stratified by grade and stage of prostate cancer (data not shown).

While other large, population-based studies have found obesity to be associated with an increased risk of prostate cancer, the current literature as a whole has yielded inconsistent results [12–15]. Several recent studies have suggested that detection bias associated with obesity may partly explain the inverse association between obesity and prostate cancer incidence [30]. Obese men have lower prostate-specific antigen (PSA) levels than do non-obese men [31,32], possibly as a result of decreased testosterone concentrations or a

haemodilution effect as a result of increased prostate volumes [33]. As a result, obese men are less likely to be recommended for a biopsy based on their PSA levels. Furthermore, the difficulty of detecting cancer upon biopsy is increased because of the larger prostate volumes [31,32], thereby lowering the number of cancers detected in this group. While it is plausible that obesity can influence the growth of prostate cancer through the action of adipocytes, it is unclear if the associations seen in the present study and in previous work are biased owing to detection issues that occur among obese men.

Research investigating the role hypertension plays in prostate cancer aetiology is very sparse. Hypertension was positively associated with the rate of prostate cancer in this study, which is similar to results found in the Flint Men's Health Study, a population-based study of African-American men that was modelled after the OCS [20]. Also, a prospective cohort study of 29 364 Norwegian men it was found that every 12 mm increase in blood pressure resulted in an 8% increase in the incidence of prostate cancer [11]. It is plausible that hypertension could increase the risk of prostate cancer through sympathetic nervous system activity that can result in androgen-mediated stimulation of prostate cancer growth [34]. In the present study, men with both hypertension and obesity had a lower rate of prostate cancer compared with men with neither condition, and men with hypertension who were not obese were at an increased risk. This apparent heterogeneity of effects may be influenced by the likelihood of these men receiving biopsies. Specifically, it is possible that men with both comorbidities are less likely to be biopsied, as a result of physician perception that these comorbidities are more life threatening than prostate cancer.

In the present study, little association was seen between the presence of all three components of metabolic syndrome and prostate cancer. While we did observe an association between the presence of one component and an increase in the rate of prostate cancer adjusting for age, an increasing number of components was not found to be positively and consistently associated with prostate cancer. These results seem to conflict with previous population-based studies that found more than three components of the metabolic syndrome were associated with an increased risk of prostate cancer [8–10]. The discrepancy in results may in part be because of the varying definitions of metabolic syndrome used in the current and previous investigations (i.e. three vs. more than three components of the metabolic syndrome) or to the small number of cases detected among men with all three components. Additionally, the definitions of metabolic syndrome recommended by the WHO and Adult Treatment Panel III were used in previous investigations, but the present study focused on the combination of the components rather than the syndrome alone. It is also possible that the differing results are as a result of the unaccounted influence of dyslipidaemia on prostate cancer risk in the OCS.

Our results are consistent with previous findings, which found men with at least three out of the five metabolic syndrome components were approximately 25% less likely to develop prostate cancer [35]. Men who had two or three components had a slightly decreased risk of prostate cancer compared with those who had no components of metabolic syndrome. It is possible that metabolic syndrome reduces the risk of prostate cancer through the action of sex hormones. The cross-talk between androgens, sex hormone-binding globulin and insulin is thought to influence prostate cancer [36], and men with metabolic syndrome exhibit decreased testosterone levels [37], thus potentially decreasing their risk of prostate cancer. It is also possible that these results are explained in part by a detection bias that results in a lower rate of prostate cancer among obese men.

The present study utilized a large, ongoing cohort of Caucasian men, which included 15 years of follow-up to date. However, there are several limitations that must be considered. First, the baseline measures of diabetes and hypertension do not account for changes in these

conditions over time. Furthermore, ages at diagnosis of diabetes and hypertension are not available in this cohort and thus limit our ability to make inferences about the progression of these conditions. Also, while we are limited in our reliance on self-report of several metabolic conditions, diabetes diagnosis was validated among self-reported cases in a larger cohort study of diabetes in Olmsted County from 1950 to 2000 [38]. Finally, the small number of prostate cancer cases when stratifying by the metabolic components limited our statistical power such that we may not be able to detect true associations that exist between these metabolic conditions and prostate cancer risk.

Although the long follow-up period lends itself to problems associated with attrition, previous work in this cohort found that participant dropout was not associated with diabetes, hypertension or PSA level after adjustment for age, thus suggesting the potential impact of this bias may be limited [39]. Also, because this is a Caucasian sample of men, generalizing these findings to other racial groups may not be appropriate. The incidence rate of prostate cancer as well as the prevalence of the components of metabolic syndrome are thought to differ by race [40,41]; therefore, our effect estimates in Caucasians may not be applicable to other racial groups with different incidences of these conditions. However, the methods used in the present study to estimate the effects of metabolic conditions on the incidence of prostate cancer can be applied to other populations from diverse settings. Finally, it is possible that our results were influenced by the detection bias that is thought to exist in obese men.

In summary, we assessed whether different combinations of metabolic conditions confer different risks of prostate cancer. Men who were hypertensive and obese had a lower incidence rate of prostate cancer than did men without either condition, although this association was imprecisely estimated and may have been influenced by detection bias, as noted earlier. However, men with hypertension alone were at an increased risk of disease, suggesting that the different combinations of these metabolic conditions may affect prostate cancer incidence differently. Explanations as to why these conditions may differentially influence prostate cancer risk remain unclear. Previous work dealing with the influence of the overall metabolic syndrome on prostate cancer aetiology may have obscured the separate and combined effects of the conditions it includes. Future studies therefore should examine the individual components of the metabolic syndrome in addition to combining them into a single variable; however, large samples will be needed to achieve sufficient precision and power.

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Abbreviations

HR	hazard ratio
CI	confidence interval
BMI	body mass index
OCS	Olmsted County Study
NSAID	non-steroidal anti-inflammatory drug
5-ARI	5-alpha reductase inhibitor
PSA	prostate-specific antigen

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FIG. 1.

Comparison of prostate cancer incidence among all eight combined categories of three metabolic syndrome components, shown as a Venn diagram. Diabetes is defined as self-reported physician-diagnosed diabetes at baseline. Obesity was calculated using the measured height and weight from the clinic examination, with those $\geq 30 \text{ kg/m}^2$ classified as obese. Hypertension was defined as those with high blood pressure at baseline or who reported using anti-hypertensive medication prior to baseline. Note: 46 patients are missing from the above Venn diagram because of missing data on metabolic components.

TABLE 1
Crude incidence rate (IR), hazard ratio (HR) and age-adjusted HR, by category of selected baseline demographic variables

Variable category	Prostate cancer cases	Person-years	Crude IR (per 1000/ year)	P-value (association/trend)	Crude HR (95% CI)	Age-adjusted HR (95% CI)
Age at baseline (years)				<0.01/<0.01		
40–49	33	13 743	2.40		1	–
50–59	63	8 076	7.80		3.2 (2.1, 4.9)	–
60–69	71	5 511	12.88		5.4 (3.6, 8.1)	–
70+	39	2 633	14.81		6.3 (4.0, 10.1)	–
Family history of prostate cancer				<0.01		
No	169	27 224	6.21		1	1
Yes	37	2 739	13.51		2.2 (1.5, 3.1)	2.0 (1.4, 2.9)
5-ARI use				0.58		
No	205	29 882	6.86		1	1
Yes	1	81	12.38		1.8 (0.26, 13.1)	1.5 (0.21, 10.8)
NSAID use				0.55		
No	158	23 505	6.72		1	1
Yes	48	6 458	7.43		1.1 (0.80, 1.5)	0.79 (0.57, 1.1)
Statin use				0.82		
No	199	28 756	6.92		1	1
Yes	7	1 206	5.80		0.83 (0.39, 1.8)	0.67 (0.32, 1.4)
Education				<0.01/<0.01		
Less than high school graduate	36	2 604	13.83		1	1
Finished high school/some			6.57		0.47 (0.32, 0.69)	0.78 (0.52, 1.2)
College	101	15 364				
College degree and beyond	68	11 698	5.81		0.42 (0.28, 0.62)	0.84 (0.55, 1.3)
Marital status				0.90		
Single, divorced, widowed, separated	23	3 038	7.57		1	1
Married/living together	183	26 833	6.82		0.89 (0.58, 1.4)	0.79 (0.51, 1.2)
Salary				<0.01/<0.01		
<\$25 000	58	5 148	11.27		1	1
\$25 000–\$44 999	62	8 786	7.06		0.62 (0.43, 0.88)	0.82 (0.57, 1.2)

Variable category	Prostate cancer cases	Person-years	Crude IR (per 1000/ year)	P-value (association/trend)	Crude HR (95% CI)	Age-adjusted HR (95% CI)
\$45 000–\$64 999	31	7 573	4.09		0.36 (0.23, 0.55)	0.65 (0.41, 1.0)
\$65 000+	47	7 226	6.51		0.57 (0.39, 0.84)	1.1 (0.74, 1.7)

Crude incidence rate (IR), hazard ratio (HR) and age-adjusted HR, by category of selected baseline metabolic characteristics

TABLE 2

Characteristic category	Prostate cancer cases	Person-years	Crude IR (per 1000/year)	Crude HR (95% CI)	Age-adjusted HR (95% CI)
Diabetes diagnosis at baseline					
No	197	28 764	6.85	1	1
Yes	9	1 198	7.51	1.1 (0.57, 2.2)	0.77 (0.39, 1.5)
Hypertensive at baseline					
No	140	22 832	6.13	1	1
Yes	66	7 130	9.26	1.5 (1.1, 2.0)	1.1 (0.79, 1.4)
Obesity					
Not obese (<30 kg/m ²)	169	23 316	7.25	1	1
Obese (≥ 30 kg/m ²)	36	6 228	5.78	0.80 (0.56, 1.1)	0.88 (0.61, 1.3)
Number of metabolic syndrome components					
0	111	18 348	6.05	1	1
1	81	8 974	9.03	1.5 (1.1, 2.0)	1.3 (0.96, 1.7)
2 or 3	14	2 641	5.30	0.88 (0.50, 1.5)	0.65 (0.37, 1.1)

TABLE 3

Estimated crude hazard ratios (HR) for combined categories of hypertension and obesity

	<u>Hypertension</u>	<u>No hypertension</u>	
	HR (95% CI)	HR (95% CI)	<i>P</i> value[*]
Obese	0.69 (0.35, 1.4)	1.1 (0.70, 1.6)	0.013
Not obese	1.8 (1.3, 2.5)	1	

* Corresponds to a two-sided test of the null hypothesis that the effects of hypertension and obesity are multiplicative on the rate scale.