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Research Article

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The Metabolic Syndrome and the Risk of Prostate Cancer under Competing Risks of Death from Other Causes

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Abstract

Background: Associations between metabolic syndrome (MetS) components and prostate cancer development have not been studied comprehensively; results have been divergent. Using the National Cholesterol Education Program Adult Treatment panel III (NCEP) and International Diabetes Federation (IDF) definitions of the MetS, we investigated such associations taking competing risks of death into consideration.

Methods: In the prospective Uppsala Longitudinal Study of Adult Men of 2,322 Caucasian men with 34 years of follow-up baseline, MetS measurements at age 50 years were used. Cumulative incidence of prostate cancer and death with/without the MetS were calculated. Competing risk of dying was taken into account by calculating the conditional probability of prostate cancer with/without the MetS.

Results: Two hundred and thirty-seven prostate cancers were identified. Prostate cancer probability by age 80 years with baseline MetS compared with without MetS was nonsignificantly higher [5.2 percent units (confidence interval (CI), −0.8% to 11.3%; NCEP); 2.7 percent units (CI, −2.7% to 8.0%; IDF)]; cumulative incidence proportions of death was significantly higher [19.3 percent units (CI, 13.4-25.3%; NCEP); 15.3 percent units (CI, 9.5-21.1%; IDF)]; and conditional probability of prostate cancer considering death from other causes was significantly higher [7.3 percent-units (CI, 0.2-14.5%); odds ratio of 1.64 (CI, 1.03-2.23; NCEP)] and nonsignificantly higher [5.0 percent-units (CI, −1.6% to 11.6%); odds ratio of 1.43 (CI, 0.89-1.90; IDF].

Conclusions: The MetS by the NCEP definition is associated with prostate cancer, taking the competing risk of early death from other causes into account.

Impact: The results further highlight the public health effect of the increasing prevalence of MetS and the importance of considering competing risks when studying risk factors for cancer. *Cancer Epidemiol Biomarkers Prev; 19(8); 2088–96. ©2010 AACR.*

Introduction

Previous studies of an association between the metabolic syndrome (MetS) and prostate cancer have shown divergent results. The studies differ in size, baseline characteristics of those included, methods used in analyses, and length of follow-up (1). Few studies have considered the full MetS. Among those that have, some have found a positive association in Scandianvians (2, 3) and in African-Americans (4, 5), whereas others found an inverse association in a mixed population (6) or no relationship in Scandinavians (7) or whites in the United States (6).

Most studies have analyzed the association between prostate cancer and selected components of the MetS rather than the full syndrome (8-11). Some studies found more pronounced associations between components of the MetS and aggressive prostate cancer, examples being insulin resistance (12) and adiposity or high body mass index (BMI; refs. 8, 13-16), whereas others showed an association between components of the MetS and prognosis or mortality in prostate cancer. Such associations have been shown for obesity and high plasma C-peptide concentration (17), high BMI (18, 19), hyperinsulinemia, and insulin resistance (20).

The Uppsala Longitudinal Study of Adult Men (ULSAM; ref. 21) has characterized a cohort of men in detail with regard to the MetS and cardiovascular risk prediction (22, 23). In the ULSAM cohort with more than three decades of follow-up, we investigated whether the MetS following two accepted definitions or components of the MetS and life-style factors at baseline at the age of 50 years influence the risk of developing clinically relevant prostate cancer. As the MetS is a risk factor for premature death and may be associated with smoking, we

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included the competing risks of early death and smoking in our analysis.

Materials and Methods

The source population used in the present study is the ULSAM. In 1970 to 1974, all male resident in Uppsala county born in 1920 to 1924 ($n = 2,841$) were invited to take part in a prospective health survey to identify risk factors for diabetes and cardiovascular disease (CVD). Eighty two percent ($n = 2,322$) of the invited men participated at baseline, for all men at age 50 years, forming the ULSAM cohort (21). The study was approved by the Ethics Committee of the Faculty of Medicine at Uppsala University, and individual informed consent was obtained.

For all analyses, we used the two clinically oriented definitions of the MetS recommended by the National Cholesterol Education Program Adult Treatment panel III (NCEP; ref. 24) and the International Diabetes Federation (IDF; ref. 25), definitions that were both previously applied in relation to CVD in ULSAM (23).

The NCEP defines the MetS as established if three or more of the following components are present: elevated fasting plasma glucose level (≥6.1 mmol/L), elevated blood pressure (≥130/85 mm/Hg) or pharmacologic treatment for hypertension, elevated triglyceride level (≥1.7 mmol/L), lowered high density lipoprotein (HDL) cholesterol level (<1.03 mmol/L for males), and large waist circumference (>102 cm for males).

The IDF defines the MetS as established if the absolute criterion abdominal obesity (waist circumference of ≥94 cm in Caucasian males) is present and at least two of the following: elevated fasting plasma glucose level (≥5.6 mmol/L) or pharmacologic treatment for type 2 diabetes, hypertension (≥130/85 mmHg) or pharmacologic treatment for hypertension, elevated triglyceride level (≥1.7 mmol/L) or pharmacologic treatment thereof, lower than normal levels of HDL cholesterol (<1.0 mmol/L for males), or pharmacologic treatment thereof. As waist circumference was only measured in a subsample of the men, the definitions were modified using a BMI cut point. Waist circumferences of 102 cm (NCEP) and 94 cm (IDF) correspond to BMIs of 29.4 and 27.4, respectively, in a linear regression analysis. This is similar to BMI cut points used in previous modified definitions of the MetS (23, 26). The men for whom results of blood sample analyses and body measurements for the determination of the MetS (NCEP and/or IDF) were available constitute our study base.

The men were characterized as smokers or nonsmokers/ex-smokers as per interview at age 50 years. At the ULSAM baseline examination at age 50 years, enzyme assays to measure fasting plasma glucose, HDL cholesterol, and triglyceride concentrations of serum were used, and waist and BMI measurements were done as has been described before (23), including coding of smoking using baseline interview reports.

Follow-up started at the baseline examination in 1970 to 1974 at 50 years of age of the participants, and the censoring date for the present study was December 31, 2003, with a median of 30.3 years of observation for the cohort of 2,184 men (NCEP) and with 1,071 men then still alive. Total number of years of follow-up was 56,600. The age of the men still alive at the end of follow-up was thus between 79 and 83 years. Follow-up to identify prostate cancer and cause of death was achieved by linking the unique personal registration numbers to nationwide registers in Sweden: the Population Register, the Cancer Register, the Hospital Discharge Register, and the Causes of Death Register.

Diagnosis of invasive prostate cancer (ICD-10, C61) was considered an event. Both the Cancer Register and the Causes of Death Register started in 1958, whereas the Hospital Discharge Register is available for all somatic inpatient health care since 1987. Reporting to these registries is compulsory, and the coverage of prostate cancer in the Cancer Register is >95% (27). Mortality data from the Causes of Death Register and the Hospital Discharge Register are an efficient validated alternative to revised hospital discharge notes and death certificates (28, 29). Confirmation of prostate cancer events identified using national registries was made through systematically reviewing the medical records for men reported with prostate cancer. Clinical tumor characteristics of the confirmed prostate cancer cases were then obtained from their respective medical records. In nine cases in which the medical records could not be retrieved, the diagnosis was verified by cross-checking with data in the National Prostate Cancer Registry, a nationwide clinical database started in 1997 and detailing stage of disease and treatment (30). Men without prostate cancer were censored at the time of death from a cause other than prostate cancer or if alive at end of follow-up. Recommendations for prostate-specific antigen (PSA) testing were restrictive—and thus practice limited—during the period of follow-up, both nationally and in the region of the University Hospital of Uppsala. General screening is currently still not recommended and not common in men who are over the age of 70 years.

Statistical analysis

Absolute risks of prostate cancer and of death without a diagnosis of prostate cancer were calculated by means of cumulative incidence proportions (31), in which the events of prostate cancer and of death, whichever came first, was considered as competing events, censoring for end of follow-up.

The probability of being diagnosed with prostate cancer was calculated as one minus the Kaplan Meier estimate of prostate cancer–free survival, censoring for both death and end of follow-up.

The conditional probability of prostate cancer given that death did not occur was calculated as the fraction of the cumulative incidence of prostate cancer divided by one minus the cumulative incidence of death without

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prostate cancer, and confidence intervals (CI) were calculated according to Pepe (32), using R-code (33, 34). Relative risks (RR) in the conditional probability setting were calculated as odds ratios (OR) with 95% bootstrap CIs.

To our knowledge, this is the first study using the methods according to Pepe when analyzing the longitudinal relationship between the MetS and prostate cancer as the outcome taking competing risk of mortality into account.

RRs of prostate cancer and death was calculated by means of Cox proportional hazard models (35). In the analysis of death, we censored for occurrence of prostate cancer. Similarly, in the analysis of prostate cancer, we censored for death.

Results

In the ULSAM cohort, 2,183 men had measurements allowing a classification according to NCEP and 2,287 allowing a classification according to IDF. In the cohort, 237 prostate cancers were identified, for 226 of which we had data to determine status according to the NCEP definition and for 234 according to the IDF definition.

Table 1 presents the distribution of the components of the MetS and smoking at baseline, age 50 years. Data for the men in the study base unclassifiable by NCEP (n = 137) and IDF (n = 34) criteria are also presented. Presence of the MetS as defined by NCEP, IDF, and their components did not significantly influence the RR of prostate cancer, not considering competing risks. Smoking did not influence the risk of prostate cancer. The presence of MetS, all of its components, and smoking conferred a statistically significant higher risk of death without prostate cancer compared with the nonpresence of these factors. The most common cause of death in ULSAM is CVD (22).

Table 2 shows the clinical characteristics of the men with prostate cancer by presence or absence of the MetS (NCEP/IDF) at age 50 years. The median age at prostate cancer diagnosis was 73 years. The majority (76% of all 237) of the men had their cancer detected after lower urinary tract symptoms or other symptoms (e.g., skeletal pain), signaling a clinically relevant or advanced disease. The majority of men were diagnosed with advanced stages of disease: the percentage of men diagnosed with tumor stage T2 and above was 64.1%, with another 9.7% unclassified as regards stage. There was no clear association between the presence of the MetS and tumor-node-metastasis status at diagnosis, mode of detection, or Gleason score. None of the men presented with a combination of a PSA value of <10, a Gleason sum of <7, and a T stage of less or equal to T2, which would be typical for screening-detected cancers.

Figure 1A to D illustrates the probability of prostate cancer censoring for end of follow-up without events, and considering occurrence of prostate cancer and death as competing events. Men fulfilling the NCEP MetS criteria (Fig. 1A) and, slightly less so, men fulfilling the IDF MetS criteria (Fig. 1B) have a modestly higher risk of developing prostate cancer than men not fulfilling any of these criteria at baseline. However, when men reach age 80 years, the difference is not statistically significant: 4.4 percent units (CI, −1.7% to 10.5%; NCEP), 1.7 percent units (CI, −3.5% to 6.9%; IDF). We show two examples of components of the MetS: men with abdominal obesity (NCEP) at age 50 years (Fig. 1C) also seemed to have a higher probability of developing clinically relevant prostate cancer (not significant at age 80 y), whereas high fasting plasma glucose levels (IDF; Fig. 1D) did not affect the probability of being diagnosed with prostate cancer.

Figure 2A to D shows the cumulative incidence proportion of death from all causes censored for a diagnosis of prostate cancer, which was at age 80 years, 19.2 percent units (CI, 13.3-25.3%) higher in the men diagnosed with the MetS-NCEP (Fig. 2A) and 15.8 percent units (CI, 10.5-21.7%) higher in men diagnosed with MetS-IDF (Fig. 2B). In men with abdominal obesity (NCEP; Fig. 2C) and in men with high fasting plasma glucose (IDF; Fig. 2D) cumulative incidence proportion of death was also significantly higher. Presence of any components of the MetS (high blood pressure (NCEP, IDF) high triglycerides (NCEP, IDF) and low HDL cholesterol (NCEP, IDF), or being a smoker was associated with a significantly higher cumulative incidence proportion of death from all causes than nonpresence of the factors (data not shown).

As presence of the MetS at age 50 years in our cohort is associated with a higher RR of death without prostate cancer, we assessed the risk of prostate cancer in men with the MetS independently of the early risk of death by estimating the risk of prostate cancer conditioned on survival at a given time (Fig. 3A-D).

In Fig. 3A, the conditional probability of being diagnosed with prostate cancer at age 80 years is statistically significantly higher in the men with the MetS-NCEP at age 50 years with a 7.3-percent-unit (CI, 0.2-14.5%) higher absolute risk in the MetS (NCEP) group translating into an OR of 1.64 (CI, 1.03-2.23). The same tendency is seen in Fig. 3B for men with the MetS-IDF at age 50 years who, at age 80 years, had a 5.0-percent-unit (CI, −1.6% to 11.6%) higher conditional probability of being diagnosed with prostate cancer than men without the MetS (OR, 1.43; CI, 0.89-1.90). Abdominal obesity (NCEP; Fig. 3C) is likewise associated with a nonsignificantly higher conditional probability of 8.1 percent units (CI, −1.3 to 17.5; OR, 1.71; CI, 0.95-2.78), whereas high fasting plasma glucose (IDF) did not influence the conditional probability of being diagnosed with prostate cancer in men up to 80 years of age (Fig. 3D), the difference being 1.5 percent units (CI, −4.6% to 7.6%), giving an OR of 1.12 (CI, 0.69-1.68). High triglycerides (NCEP, IDF) increased the risk of prostate cancer nonsignificantly by 3.0 percent units (CI, −0.8% to 6.8%; OR, 1.26; CI, 0.94-1.55; not shown in figure), whereas high blood pressure (NCEP, IDF) and low HDL cholesterol (NCEP, IDF) were only marginally associated with a higher risk of prostate cancer

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Table 1. Number of men without and with prostate cancer, RRs for prostate cancer, and RR for death without prostate cancer in men with or without the MetS according to the NCEP and IDF definitions and their respective components and smoking at age 50 over 34 y of follow-up

	No prostate cancer	Prostate cancer	PC RR (95% CI)	Death without PC RR (95% CI)
MetS (NCEP*), *n* (%)				
No MetS	1,673 (80.3)	195 (82.3)	Reference	Reference
MetS	284 (13.26)	32 (13.5)	1.29 (0.89-1.88)	1.86 (1.59-2.19)
Missing data	127 (6.1)	10 (4.2)		
MetS (IDF†), *n* (%)				
No MetS	1,755 (84.2)	202 (85.2)	Reference	Reference
MetS	298 (14.3)	32 (13.5)	1.18 (0.81-1.71)	1.7 (1.46-2.00)
Missing data	31 (1.5)	3 (1.3)		
Abdominal obesity, >102 cm (NCEP), *n* (%)				
Not abdominal obesity	1,913 (91.8)	217 (91.6)	Reference	Reference
Abdominal obesity	171 (8.2)	20 (8.4)	1.31 (0.83-2.08)	1.79 (1.48-2.17)
Missing data	0 (0.0)	0 (0.0)		
Abdominal obesity >94 cm (IDF), *n* (%)				
No abdominal obesity	1,648 (79.1)	190 (80.2)	Reference	Reference
Abdominal obesity	436 (20.9)	47 (19.8)	1.11 (0.8-1.52)	1.5 (1.31-1.73)
Missing data	0 (0.0)	0 (0.0)		
Elevated fasting plasma glucose level, ≥6.1 mmol/L (NCEP), *n* (%)				
No elevated level	1,966 (94.3)	223 (94.1)	Reference	Reference
Elevated level	112 (5.4)	12 (5.1)	1.18 (0.66-2.11)	1.57 (1.23-2.00)
Missing data	6 (0.3)	2 (0.8)		
Elevated fasting plasma glucose level, ≥5.6 mmol/L (IDF), *n* (%)				
No elevated level and not DM	1,812 (86.9)	206 (86.9)	Reference	Reference
Elevated level or DM	266 (12.8)	29 (12.2)	1.04 (0.71-1.54)	1.23 (1.04-1.47)
Missing data	6 (0.3)	2 (0.8)		
Hypertension, ≥130/80 mmHg (NCEP, IDF), *n* (%)				
No Hypertension	724 (34.7)	88 (37.1)	Reference	Reference
Hypertension	1,359 (65.2)	149 (62.9)	1.03 (0.79-1.35)	1.41 (1.23-1.61)
Missing data	1 (0.0)	0 (0.0)		
High triglycerides, ≥1.7 mmol/L (NCEP, IDF), *n* (%)				
Not high triglycerides	1,073 (51.5)	122 (51.5)	Reference	Reference
High triglycerides	1,011 (48.5)	115 (48.5)	1.15 (0.89-1.48)	1.47 (1.3-1.66)
Missing data	0 (0.0)	0 (0.0)		
Low HDL‡ cholesterol, <1.03 mmol/L (NCEP, IDF), *n* (%)				
Not Low HDL cholesterol	1,357 (65.1)	152 (64.1)	Reference	Reference
Low HDL cholesterol	344 (16.5)	31 (13.1)	0.95 (0.65-1.4)	1.44 (1.23-1.69)
Missing data	383 (18.4)	54 (22.8)		
Smoking, *n* (%)				
Nonsmoker or ex-smoker	999 (47.9)	138 (58.2)	Reference	Reference
Current smoker	1,085 (52.1)	99 (41.8)	0.84 (0.65-1.08)	1.88 (1.65-2.13)

Abbreviation: PC, prostate cancer; DM, diabetes mellitus.
*As defined in the NCEP panel III definition of the metabolic syndrome.
†As defined in the IDF definition of the metabolic syndrome.
‡High-density lipoprotein.

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Table 2. Clinical characteristics of the prostate cancer disease in men without or with the MetS as per NCEP and IDF definitions

	No MetS NCEP definition	MetS NCEP definition	No MetS IDF definition	MetS IDF definition	All PC
Age, median (range)	73 (51-83)	74 (60-81)	73 (51-83)	72 (60-81)	73 (51-83)
Method of diagnosis, *n* (%)					
Histology	159 (81.5)	25 (80.6)	162 (80.2)	26 (81.2)	190 (80.2)
Cytology	27 (13.8)	4 (12.9)	30 (14.9)	3 (9.4)	34 (14.3)
Clinical	2 (1.0)	0 (0.0)	4 (2.0)	0 (0.0)	4 (1.7)
Missing	7 (3.6)	2 (6.5)	6 (3.0)	3 (9.4)	9 (3.8)
Method of detection, *n* (%)					
PSA screening	3 (1.5)	0 (0.0)	3 (1.5)	0 (0.0)	3 (1.3)
Incidentally discovered*	12 (6.2)	3 (9.7)	15 (7.4)	1 (3.1)	16 (6.8)
Other urological/skeletal symptoms	7 (3.6)	1 (3.2)	7 (3.5)	1 (3.1)	8 (3.4)
LUTS†	119 (61.0)	16 (51.6)	120 (59.4)	21 (65.6)	143 (60.3)
Other symptoms	29 (14.9)	6 (19.4)	31 (15.3)	5 (15.6)	37 (15.6)
Missing	25 (12.8)	5 (16.1)	26 (12.9)	4 (12.5)	30 (12.7)
PSA level, *n* (%)					
≤4	7 (3.6)	1 (3.2)	7 (3.5)	1 (3.1)	8 (3.4)
4.01-10.0	27 (13.8)	2 (6.5)	28 (13.9)	2 (6.2)	31 (13.1)
10.01-20.0	28 (14.4)	5 (16.1)	33 (16.3)	1 (3.1)	34 (14.3)
20.01-100.0	37 (19.0)	5 (16.1)	38 (18.8)	8 (25.0)	47 (19.8)
>100	18 (9.2)	6 (19.4)	20 (9.9)	5 (15.6)	25 (10.5)
Missing	78 (40.0)	12 (38.7)	76 (37.6)	15 (46.9)	92 (38.8)
Tumor stage‡, *n* (%)					
T0/T1ab	25 (12.8)	7 (22.6)	27 (13.4)	6 (18.8)	34 (14.3)
T1c	24 (12.3)	2 (6.5)	25 (12.4)	3 (9.4)	28 (11.8)
T2	74 (37.9)	15 (48.4)	79 (39.1)	15 (46.9)	96 (40.5)
T3-4	51 (26.2)	5 (16.1)	51 (25.2)	5 (15.6)	56 (23.6)
TX/missing	21 (10.8)	2 (6.5)	20 (9.9)	3 (9.4)	23 (9.7)
N stage‡, *n* (%)					
N0	29 (14.9)	5 (16.1)	31 (15.3)	4 (12.5)	35 (14.8)
N1	12 (6.2)	0 (0.0)	10 (5.0)	1 (3.1)	12 (5.1)
NX	132 (67.7)	25 (80.6)	140 (69.3)	24 (75.0)	166 (70.0)
Missing	22 (11.3)	1 (3.2)	21 (10.4)	3 (9.4)	24 (10.1)
M stage‡, *n* (%)					
M0	81 (41.5)	13 (41.9)	80 (39.6)	18 (56.2)	99 (41.8)
MX, PSA ≤20	10 (5.1)	1 (3.2)	11 (5.4)	1 (3.1)	12 (5.1)
MX, 20<PSA≤100	27 (13.8)	5 (16.1)	31 (15.3)	2 (6.2)	34 (14.3)
M1/PSA>100	44 (22.6)	8 (25.8)	46 (22.8)	6 (18.8)	53 (22.4)
Missing	33 (16.9)	4 (12.9)	34 (16.8)	5 (15.6)	39 (16.5)
Gleason score§, *n* (%)					
2-6	76 (39.0)	10 (32.3)	77 (38.1)	12 (37.5)	90 (38.0)
7	48 (24.6)	8 (25.8)	50 (24.8)	8 (25.0)	59 (24.9)
8-10	51 (26.2)	11 (35.5)	55 (27.2)	8 (25.0)	64 (27.0)
Missing	20 (10.3)	2 (6.5)	20 (9.9)	4 (12.5)	24 (10.1)

*Incidentally discovered under investigation for symptoms not related to the urinary tract.
†Lower urinary tract symptoms.
‡As classified by the International Union Against Cancer.
§WHO grade translated into Gleason score G1 (2-6), G2 (7), G3 (8-10).

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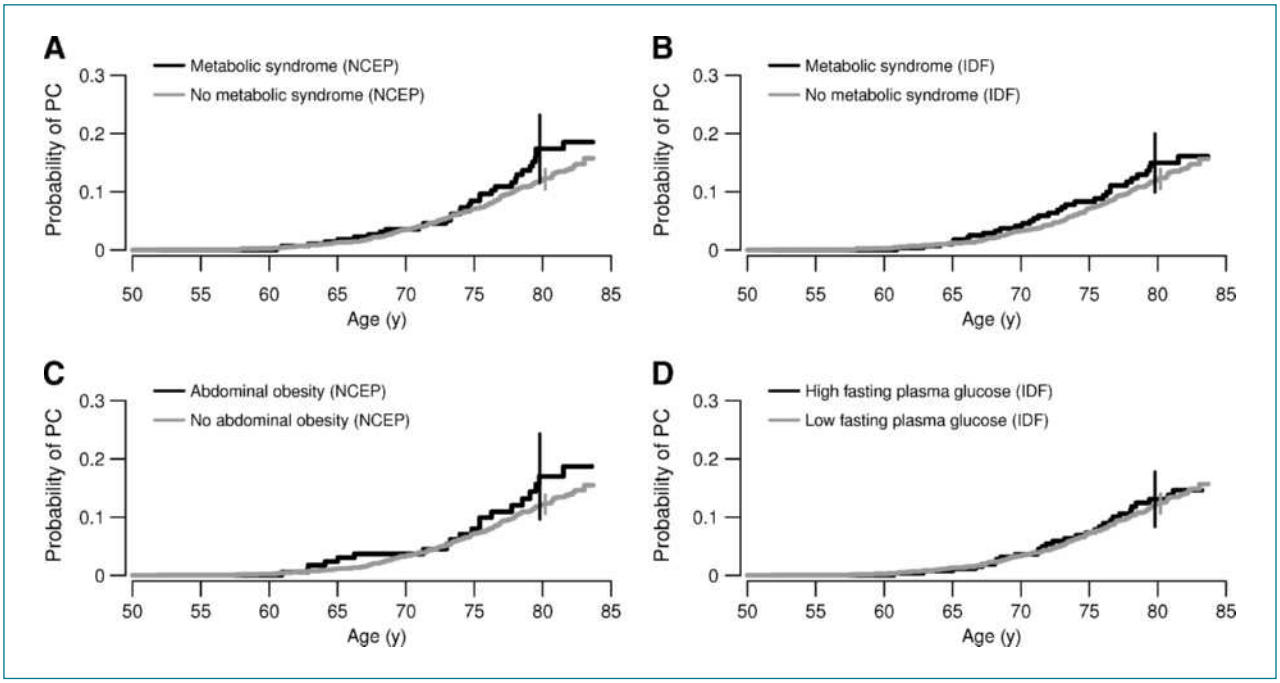

Figure 1. Probability of prostate cancer (PC), censored for death, from baseline at age 50 y in men with or without the MetS by the NCEP definition (A) and the IDF definition (B), in men or without with abdominal obesity as defined by the NCEP (waist, ≥102 cm; C), and in men with or without high fasting plasma glucose by the IDF definition (≥5.6 mmol/L; D). 95% CIs for curves in A to D at age 80 y are also presented.

(not shown in figures). Smoking nonsignificantly increased the conditional probability of later prostate cancer.

Discussion

We show that the presence of the full MetS according to the NCEP definition at age 50 years is a risk factor for clinically relevant or advanced stages of prostate cancer over 34 years of follow-up. Results for the MetS according to the IDF definition were of similar magnitude; however, they were not statistically significant. Few of the men in the study presented with clinically nonadvanced or nonaggressive prostate cancer. The components of the MetS predominately responsible for the finding seem to be abdominal obesity and a high serum triglyceride level. The findings become more evident when accounting for the competing risk of early death due to the MetS. High fasting blood glucose, high blood pressure, and a low HDL cholesterol level are only marginally associated with the conditional probability of prostate cancer whereas smoking is not.

The ULSAM cohort used in this study is population based, homogeneous about ethnic background, and standardized for age of the participants at baseline. The participants have been thoroughly characterized about the components of the MetS, smoking status, and occurrence of prostate cancer. The participation rate is high, and the data on individual follow-up of up to 34 years is almost complete through linkage to personal hospital records and nationwide registers with high coverage. In addition, <2% of the prostate cancer cases are screening detected, and our results thus mainly pertain to clinically relevant prostate cancer with a high risk of progressive disease.

Although the ULSAM cohort is relatively small and modest, or weak associations may go undetected, its annotation is unprecedented in details and precision. It is indeed similar in size to other studies published on the relationship between a fully characterized MetS and prostate cancer, and the follow-up is considerably longer. The measurements for diagnosing the full MetS used for the present study were made at only one point in time, on average 25 years before diagnosis, a design feature shared with most studies in the field. However, several of the components of the MetS reflect long-term life-style habits, which will not likely vary significantly over time, once established in middle-aged men. Any misclassifications of men who after the age of 50 years have established the MetS would most probably lead to an underestimation of the risks observed rather than overestimate them.

There may be several reasons why previous cohort studies have come to divergent conclusions about the MetS and prostate cancer risk. This may be attributed to several factors; among these, the different definitions of the MetS used and the effects of competing factors are probably the most important. The four generally accepted definitions used to define the MetS have been put forth by the WHO, NCEP, the European Group for the Study of Insulin Resistance, and IDF. None of these can

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yet be considered the gold standard because they emphasize different aspects of the MetS. This may in part explain differences in the results in the various studies. Furthermore, several investigators used modified versions of these definitions (2, 5, 7) or only selected parts of these definitions (4). We feel that a more important reason for equivocal results is the lack of consideration given to the effect of competing risks; many men with the MetS will not live to an age when prostate cancer risk is highest but will die early from other causes, leaving an excess risk of prostate cancer undetected.

The commonly used statistical analyses assume that censored individuals have the same risk of the event under study as those observed until the end point (35). When an exposure is associated both with risk of early death and the disease under study, especially when the outcome is increasing in frequency with age, this criterion is not fulfilled (35). We used a conditional probability method described by Pepe (32) to try to circumvent such a possible violation of the assumptions underlying the standard techniques and revealed that the full MetS and key elements of the MetS are linked to prostate cancer risk.

Further reasons for diverging results in previous studies may be differences in age at baseline measurement and length of follow-up, e.g., measurements vary from those done early in life (7) to those in the elderly close to or at the time of diagnosis of prostate cancer (4). Some of the published studies on prostate cancer detected outside PSA screening end their follow-up before the mean age of diagnosis for nonscreening-detected prostate cancer (2, 3, 7), thereby studying only a younger part of the prostate cancer spectrum.

Our findings are in line with those of Laukkanen et al. (3) who in their younger cohort found that men with a modified WHO definition of the MetS had a 1.9-fold higher RR (CI, 1.1-3.5) of developing clinically relevant prostate cancer later in life. They considered the effects on the estimates due to high morbidity and mortality in men with diabetes and excluded these men. Lund-Håheim et al. (2) studied modified components of the MetS according to NCEP in a large cohort and found a weak positive relation to prostate cancer with an increased RR of 1.56 (CI, 1.21-2.00). The weak associations may be due to this cohort being young. The median age at the end of follow-up was 73 years, which is below the mean age of diagnosis for clinically detected prostate cancer in our cohort. Tande et al. (6) observed in a cohort study on comparatively young and overweight American men a lower RR of developing prostate cancer of 0.77 (CI, 0.60-0.98) in men with the MetS (NCEP). The study had a 50% participation rate. The cases were identified by a combination of questionnaire and registry findings, and the prostate cancers were to an unknown extent screening detected.

Martin et al. (7) used a revised NCEP definition of the MetS and found little evidence of a relationship between

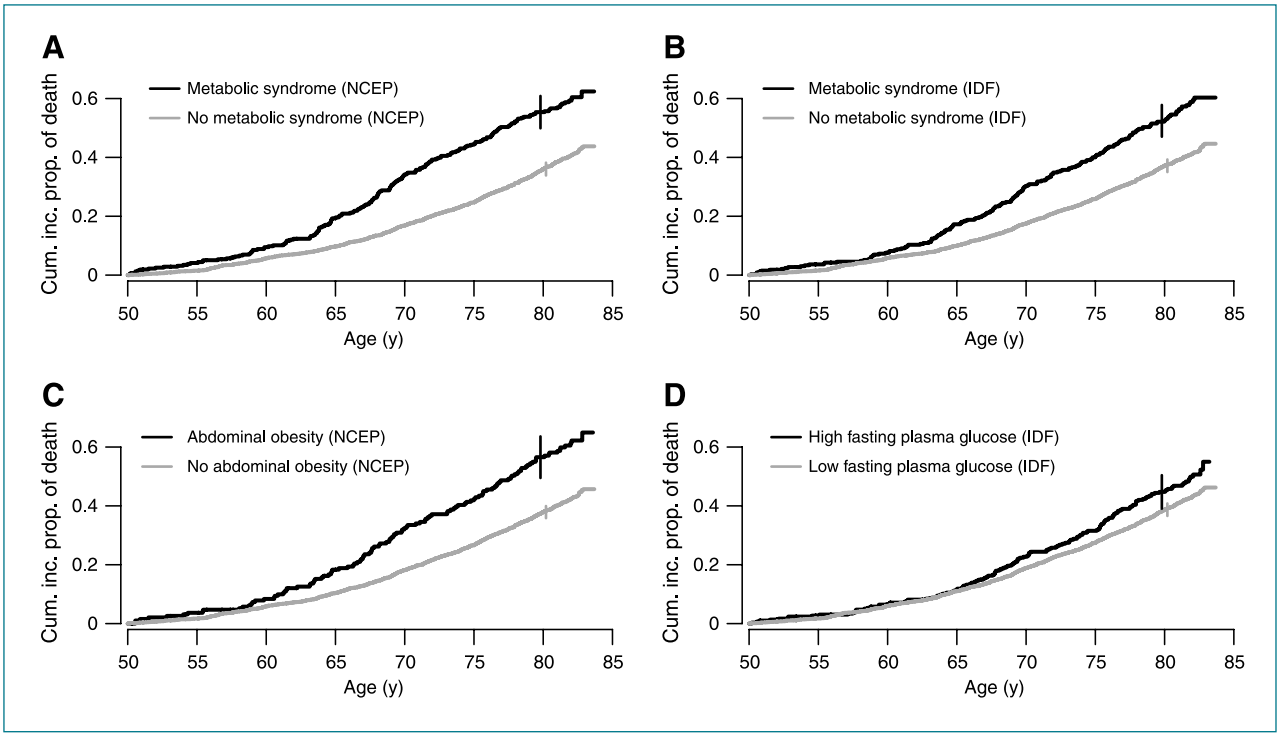

Figure 2. Cumulative incidence proportion of death (cum. inc. prop of death) in men with or without the MetS by the NCEP definition (A) and the IDF definition (B), in men or without with abdominal obesity as defined by the NCEP (waist ≥102 cm; C), and in men with or without high fasting plasma glucose by the IDF definition (≥5.6 mmol/L; D). 95% CIs for curves in A to D at age 80 y are also presented.

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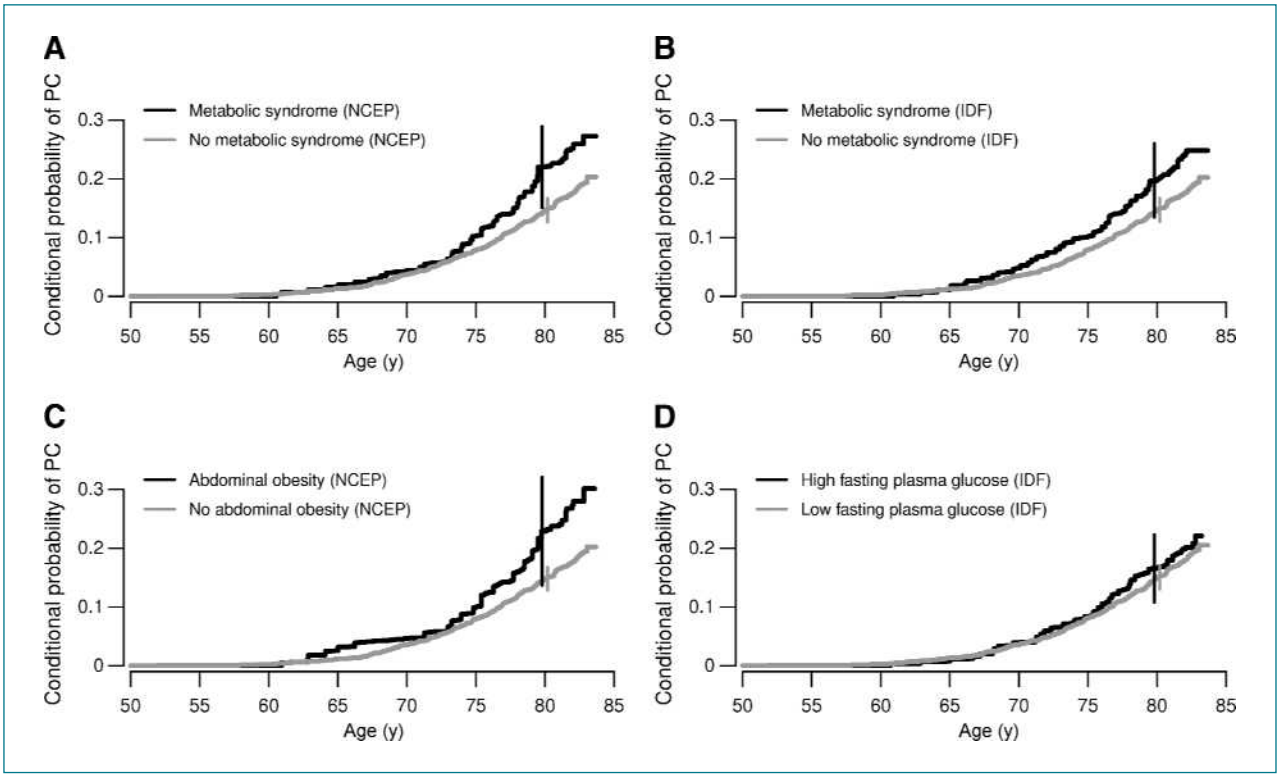

Figure 3. Conditional probability of prostate cancer (PC; the condition being that death from other causes has not occurred) in men with or without the MetS by the NCEP definition (A) and the IDF definition (B), in men or without with abdominal obesity as defined by the NCEP (waist ≥102 cm; C), and in men with or without high fasting plasma glucose by the IDF definition (≥5.6 mmol/L; D). 95% CIs for curves in A to D at age 80 y are also presented.

the MetS or most of the components thereof and later clinically relevant prostate cancer (RR, 0.91; CI, 0.77-1.09). Their study included 29,364 men with an average age of 50 years followed for a mean of 9.3 years, that is, mainly men of ages with low prostate cancer risk. Competing risks were not considered. The only significant finding was a positive relationship between elevated blood pressure and prostate cancer. Prostate cancer in the young may in 30% to 40% of cases be associated with dominantly inherited genetic traits with high penetrance (36) and less influenced by metabolic factors. In two previous studies on the relationship between type 2 diabetes mellitus and prostate cancer risk, although they did not take competing risk of mortality into consideration, an increased risk of prostate cancer was observed in men with lower BMI in one study (37) but not in the other one (38). These studies did not take competing risk of death into account when analyzing the relationship to prostate cancer, which is a cancer typically diagnosed at higher ages, and further, that type 2 diabetes is a condition with an expected shorter life span due to an increased risk of cardiovascular death mediated by elevated blood glucose.

Our results indicate that life-style factors giving rise to the MetS according to either the NCEP or the IDF definition, in particular abdominal obesity, increase the risk of clinically relevant prostate cancer once the competing risk of dying from other outcomes of the MetS has been taken into account. If this is substantiated in further studies, it will not only be an important public health message, but will also prompt research to further understand the underlying mechanisms and to find out whether a reversal of the MetS components, e.g., obesity, will attenuate the risk. The findings also call for a methodologic development to better analyze competing risks for risk factors with complex effects, e.g., our findings indicate that smoking is indeed a risk factor for prostate cancer, which is still unclear (39, 40), plausibly owing to its being a relatively weak risk factor in a disease that mainly occurs late in life while also leading to a high risk of premature death from other causes such as CVD and lung cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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