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Prostate Cancer, Prostate Cancer Death, and Death from Other Causes, Among Men with Metabolic Aberrations

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Background: Few previous studies of metabolic aberrations and prostate cancer risk have taken into account the fact that men with metabolic aberrations have an increased risk of death from causes other than prostate cancer. The aim of this study was to calculate, in a real-life scenario, the risk of prostate cancer diagnosis, prostate cancer death, and death from other causes.

Methods: In the Metabolic Syndrome and Cancer Project, prospective data on body mass index, blood pressure, glucose, cholesterol, and triglycerides were collected from 285,040 men. Risks of prostate cancer diagnosis, prostate cancer death, and death from other causes were calculated by use of competing risk analysis for men with normal (bottom 84%) and high (top 16%) levels of each factor, and a composite score.

Results: During a mean follow-up period of 12 years, 5,893 men were diagnosed with prostate cancer, 1,013 died of prostate cancer, and 26,328 died of other causes. After 1996, when prostate-specific antigen

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testing was introduced, men up to age 80 years with normal metabolic levels had 13% risk of prostate cancer, 2% risk of prostate cancer death, and 30% risk of death from other causes, whereas men with metabolic aberrations had corresponding risks of 11%, 2%, and 44%.

Conclusions: In contrast to recent studies using conventional survival analysis, in a real-world scenario taking risk of competing events into account, men with metabolic aberrations had lower risk of prostate cancer diagnosis, similar risk of prostate cancer death, and substantially higher risk of death from other causes compared with men who had normal metabolic levels.

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Prostate cancer incidence is up to 20-fold higher in industrialized countries compared with developing countries,¹ and nutrition and other lifestyle factors have been suggested as a cause for this difference.² To date, many studies have investigated the putative etiological association between metabolic aberrations and prostate cancer risk, with inconsistent results.^{3–8} We have previously investigated this within the Metabolic Syndrome and Cancer Project by use of Cox regression analysis, and we found no associations between metabolic aberrations and prostate cancer risk.⁹ In contrast, high levels of BMI, blood pressure, and a composite score of all metabolic factors were associated with increased risk of prostate cancer death.

However, men with metabolic aberrations have a higher risk of death from cardiovascular disease and other diseases,¹⁰ and such events are censored in studies of etiologic risk using conventional methods similar to the Cox model, despite the fact that they are considered competing events in analysis of prostate cancer. Few studies to date have taken risk of competing events into account when assessing a person's risk of prostate cancer in a real-world scenario. This risk—previously denoted as actual risk,¹¹ cumulative absolute risk,¹² real-world probabilities,¹³ and crude probabilities¹⁴—can be calculated by cumulative incidence functions.

The aim of this study was to assess the risk of prostate cancer diagnosis, prostate cancer death, and death from other causes for men with normal metabolic levels and metabolic aberrations in a real-world scenario by use of data in a large prospective pooled European cohort.

METHODS

Study Population

This study was conducted within the Metabolic Syndrome and Cancer Project, which has previously been described in detail.¹⁵ In brief, the project consists of 7 sub-cohorts from Norway, Sweden, and Austria, with prospectively collected data on body mass index (BMI), systolic and diastolic blood pressure, and circulating levels of glucose, total cholesterol, and triglycerides from 578,700 men and women from 1972 to 2005.

The study was approved by The Research Review Board of Umeå, Sweden, the Regional Committee for Medical and Health Research Ethics, Southeast Norway and the Ethikomission of the Land Vorarlberg, Austria. Participants from Sweden and Austria provided written informed consent to participate in this study. In Norway, the participants were invited to come to the health survey and a questionnaire was sent together with the invitation. An attendance to the health examination where the participants delivered their filled in questionnaire, has been accepted by the Data Inspectorate as an informed consent, but not a written consent. Written consent was obtained from 1994 onwards.

Endpoints

Prostate cancer cases were identified through linkage to each National Cancer Register, by use of code 177 in the International Statistical Classification of Diseases, revision 7 (ICD-7). All men diagnosed with prostate cancer were selected. Of these, approximately 5% were secondary or later cancer diagnoses for men previously diagnosed with cancer at another site. We excluded 78 men with prostate cancer diagnosed at the date of death. Causes of death were obtained by linkage to each National Cause of Death Register, with data available until the last date of follow up (31 December 2003 in Austria, and until 31 December 2004 in Norway and Sweden), and coded according to Eurostat European shortlist for causes of death.¹⁶ We used data only from the first health examination, and we excluded men with first health examination after last date of follow up (1,742 men) or without a recorded cause of death cause (3,084 men). Data were also linked to The Register of Total Population and Population Changes for migration status in Norway and Sweden.

Statistical Analysis

Follow-up started 1 year after the first health examination and continued until the first date of either the main event or the competing event, or until date of censoring due to emigration or end of follow-up. Incident prostate cancer and prostate cancer death were the main events in separate analyses, and death from all causes and death from causes other than prostate cancer were the competing events, respectively.

To investigate whether the risk of prostate cancer was related to diagnostic intensity—with a larger proportion of low-risk cancers after the introduction of prostate-specific

antigen (PSA) testing—we performed sub-group analysis for 2 periods of follow up. The cut-point of 31 December 1996 was chosen because that time marked the beginning of an increase in the incidence of prostate cancer due to the introduction of PSA testing in Sweden,¹⁷ Norway,¹⁸ and Austria.¹⁹ We denoted the earlier period ending at 31 December 1996, as “pre-PSA era,” and the later period, beginning 1 January 1997, as “PSA era.” No sub-group analyses were performed for prostate cancer death.

Metabolic factors were transformed to a standardized score (z-score), with zero as mean and 1 as standard deviation in all analyses.⁹ BMI and blood pressure were transformed into z-scores separately for each sub-cohort, whereas glucose, cholesterol, and triglycerides were transformed into z-scores separately by sub-cohort and also according to fasting time (less than 1h, 1–2h, 2–4h, 4–8h, more than 8h). As the distributions of glucose and triglycerides were skewed, natural logarithm was applied before z-score transformation. Mid blood pressure was defined as (systolic + diastolic blood pressure)/2, and a composite score was defined as the sum of all single z-scores. The z-scores were dichotomized at $z = 1$, resulting in a nonexposed group comprising 84% of the participants who had measured levels of each metabolic factor and the composite score below this cut-point and the exposed group consisted of the remaining 16% with levels above this cut-point. We denoted men in the lower 84% of the composite score as “men with normal metabolic levels” and men in the top 16% of the composite score as “men with metabolic aberrations.”

For the main and competing event in each analysis, we calculated cumulative incidence functions,²⁰ for men with normal and high levels of metabolic factors. Attained age was used as the time scale. All analyses also included smoking status (never, former, or current), 5 categories of birth year (before 1927, 1927–1929, 1930–1932, 1933–1938, 1939, and later), age at health examination, and sub-cohort. The cumulative incidence functions were calculated based on Cox regression models in which smoking and age at health examination were allowed to have different effects on the main event and competing events, in addition to each metabolic factor. The assumption of proportional hazards in the Cox regression model was tested with Schoenfeld residuals and was found to be valid.

Calculations were performed with STATA MP/2 version 11.2 (StataCorp LP, College Station, TX).

RESULTS

Mean baseline age among the 285,040 men in the study was 44 years ($SD = 11$), 44% of the men were overweight ($BMI = 25$ – 29.9 kg/m^2) and 10% were obese ($BMI \geq 30 \text{ kg/m}^2$) (Table).

A total of 5,893 men were diagnosed with prostate cancer, and 1,013 men died of prostate cancer during follow up, which was on average 12 years ($SD = 8$) (Figure 1). Of these men, 1,366 men had been diagnosed with prostate cancer in the pre-PSA era with end of follow up at December 31, 1996,

TABLE. Baseline Characteristics^a of Men in the Metabolic Syndrome and Cancer Project (n = 285,040)

Sub-cohort			
Norway			
Oslo study I	16,311	(6)	
Norwegian Counties Study	25,511	(9)	
Cohort of Norway	51,660	(18)	
Age 40-programme	60,549	(21)	
Austria			
Vorarlberg Health Monitoring and Prevention Programme	72,961	(26)	
Sweden			
Västerbotten Intervention Project	36,675	(13)	
Malmö Preventive Project	21,373	(7)	
Age at health examination (years)			
<40	82,390	(29)	
40–49	142,266	(50)	
50–59	32,596	(11)	
60 +	27,788	(10)	
BMI (kg/m ²) ^b			
Normal weight	129,108	(45)	
Overweight	125,757	(44)	
Obese	30,175	(11)	
Blood pressure ^c			
Normotension	176,791	(62)	
Hypertension	108,249	(38)	
Smoking status			
Never	111,62	(39)	
Former	85,047	(30)	
Current	87,546	(31)	
Metabolic factors; mean (SD)			
BMI (kg/m ²)	26	(3)	
Mid blood pressure (mmHg)	107	(13)	
Glucose (mmol/L) ^d	5.1	(1.3)	
Total cholesterol (mmol/L) ^d	5.6	(1.2)	
Triglycerides (mmol/L) ^d	1.6	(1.2)	

^aNo. (%), unless otherwise specified.^bOverweight defined as BMI 25 to 29.9 kg/m², obesity BMI \geq 30 kg/m².^cHypertension defined as systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg.^dFor men with more than 8 hours of fasting before health examination.

and 4,527 men were diagnosed in the PSA era. The earliest prostate cancer case was diagnosed in 1974.

The risk of prostate cancer diagnosis was lower for men with metabolic aberrations than for men with normal metabolic levels, in both the pre-PSA and PSA eras. In the pre-PSA era, the risk of prostate cancer for men up to age 80 years was 6% for men with normal metabolic levels and 5% for men with metabolic aberrations (Figure 2A). In the PSA era, the corresponding risk of prostate cancer diagnosis was 13% for men with normal levels and 11% for men with metabolic aberrations, and the risk of death from any cause was 37% and 47%, respectively (Figures 2B and 3). Risk for men with

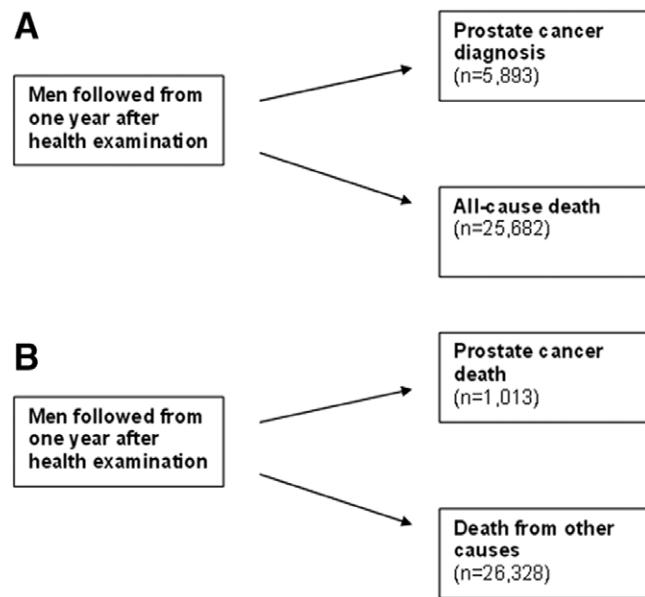


FIGURE 1. Main and competing events in analysis of risk of (A) prostate cancer diagnosis and (B) prostate cancer death in the Metabolic Syndrome and Cancer Project of 285,040 men. Men were followed until the first point in time of main or competing event, or until censoring due to migration or end of follow-up. The number of deaths from all causes in analysis (A) is smaller than the number of deaths from other causes in analysis (B) because many of men followed from date of prostate cancer diagnosis in (A) have died either from prostate cancer or other causes in (B).

normal and high levels of BMI, blood pressure, glucose, total cholesterol, and triglycerides were similar to the results for men with normal metabolic levels and metabolic aberrations. (See eFigure 1, <http://links.lww.com/EDE/A831> which illustrates the risk of prostate cancer for separate metabolic factors in the PSA era.)

All men in the study up to age 80 had approximately 2% risk of prostate cancer death regardless of metabolic status. Men with normal metabolic levels had 30% risk of death from other causes and men with metabolic aberrations had 44% risk (Figure 4). Risk for men with normal and high levels of BMI, blood pressure, glucose, total cholesterol, and triglycerides was also around 2%. (See eFigure 2, <http://links.lww.com/EDE/A831> which illustrates the risk of prostate cancer death for separate metabolic factors.)

DISCUSSION

Etiologic studies with data in the PSA era have found no increased risk of prostate cancer for men with metabolic aberrations using conventional survival analysis.^{9,21,22} In our study of a real-world scenario with competing events taken into account, men with metabolic aberrations had a lower risk of prostate cancer diagnosis, similar risk of prostate cancer death, and substantially higher risk of death from other causes, compared with men who had normal metabolic levels.

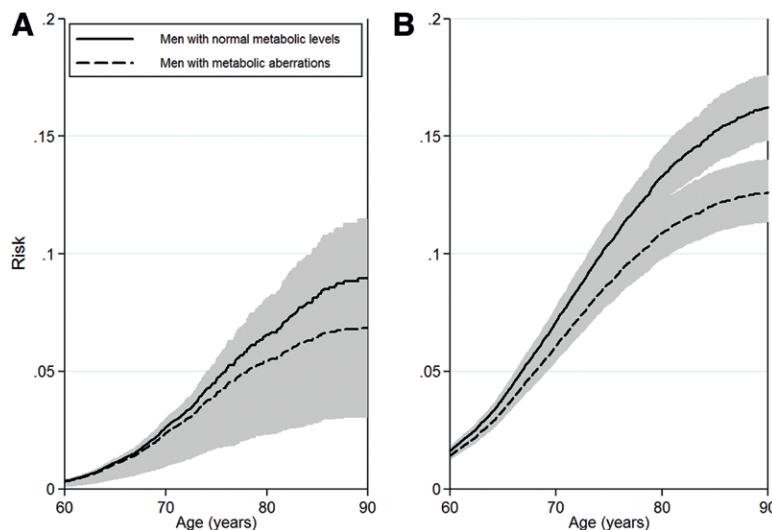


FIGURE 2. Risk of prostate cancer in (A) the pre-PSA era and (B) the PSA era in the Metabolic Syndrome and Cancer Project. Shaded areas are 95% confidence intervals. Smoking status, 5 categories of birth year, age at health examination, and sub-cohort were included in the analyses.

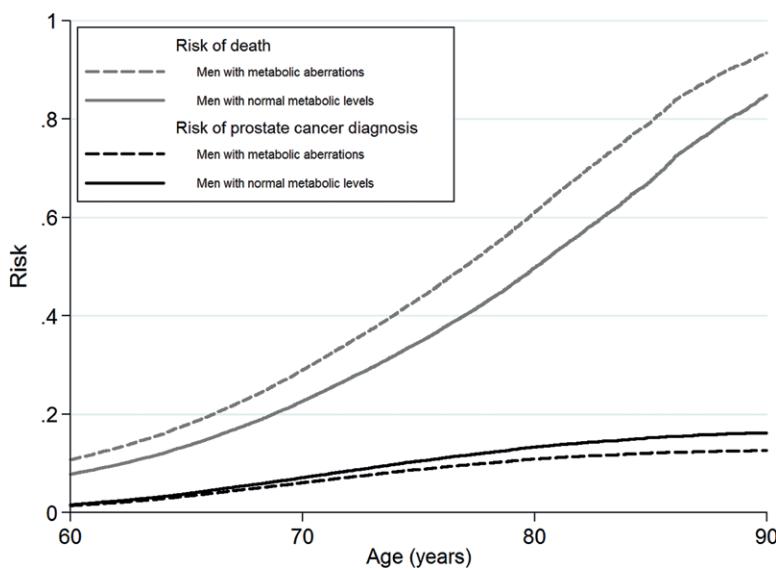


FIGURE 3. Risk of prostate cancer diagnosis and of the competing event, death, in the PSA era in the Metabolic Syndrome and Cancer Project. The curves are stacked for each level of exposure, and the remaining area above the curves corresponds to the risk of no event. Smoking status, 5 categories of birth year, age at health examination, and sub-cohort were included in the analyses.

Strengths of our study include the large sample size from 7 European sub-cohorts and almost complete follow-up of cancer diagnoses.^{23–25} The main limitation was the lack of information on tumor characteristics and on covariates that affect the risk of a prostate cancer diagnosis, such as family history of prostate cancer²⁶ and socioeconomic status.²⁷

We previously found no association of these metabolic factors with prostate cancer diagnosis, but we did find an association of high BMI, blood pressure and the composite score with increased risk of prostate cancer death,⁹ in accordance with several other large studies.^{7,28,29} In the current study we considered whether men with metabolic aberrations have a different risk of prostate cancer diagnosis and prostate cancer death, compared with men with normal metabolic levels, when competing events are taken into account. There are 2 reasons why the present results differ from those in our earlier analyses. First, prostate cancer tends to be diagnosed at older ages,

when many other men have already died (mean age at prostate cancer diagnosis in Scandinavia is 70–75 years);³⁰ therefore, conventional survival analysis may overestimate the absolute risk.³¹ Second, high levels of metabolic factors are related to increased risk of death from all causes,¹⁰ which may affect calculations of relative risk,¹¹ since men with high levels of metabolic factors have a shorter life expectancy, and are therefore more likely to be censored in conventional survival analysis. In other words, among men who are censored due to death from other causes there is a larger proportion of men with high levels of metabolic factors, than among men censored because of migration or end of follow-up. This difference is similar to reports on smoking as risk factor for Alzheimer disease³² and melanoma,³³ in which a decreased risk of the disease was found among smokers. This is most likely a spurious association due to selection bias, since smokers have a shorter life expectancy compared with nonsmokers and therefore have

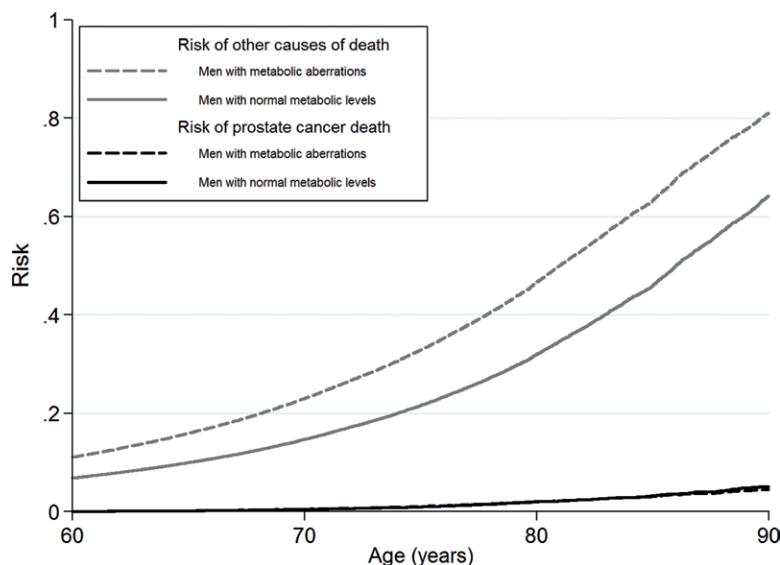


FIGURE 4. Risk of prostate cancer death and of the competing event, other causes of death, Metabolic Syndrome and Cancer Project. The curves are stacked for each level of exposure and the remaining area above the curves corresponds to the risk of no event. Smoking status, 5 categories of birth year, age at health examination, and sub-cohort were included in the analyses.

lower risks of diseases occurring later in life. Accordingly, we hypothesize that a similar selection bias occurs in studies of metabolic factors and prostate cancer, since men with high levels of metabolic factors have a shorter life expectancy than men with normal levels.

Only a few studies on metabolic factors and prostate cancer have used methods of competing risk analysis, and results have been inconsistent.^{28,29,34} In our study, men with metabolic aberrations had lower risk of prostate cancer, in accordance with results from Fine and Gray regression analysis of a Swedish cohort study of almost 37,000 men, in which men with high levels of BMI at age 60 years had a lower risk of localized prostate cancer, slightly higher risk of advanced cancer, and an higher risk of prostate cancer death.²⁹ However, our findings are in contrast with 2 studies^{28,34} based on conditional probability of prostate cancer—a method that yields results that are difficult to interpret.³⁵ The first of these studies used data from 200,000 men with 5,000 prostate cancer cases and found an increased risk of prostate cancer for high levels of triglycerides and glucose at age 75.²⁸ The second study of 2,322 men found that men with the metabolic syndrome had an increased risk of prostate cancer at age 80.³⁴

A high proportion of men with high socioeconomic status undergo PSA testing,³⁶ and therefore have an increased risk of prostate cancer, in particular of low-risk cancer.²⁷ In contrast, men with high socioeconomic status have a lower prevalence of the metabolic syndrome,³⁷ obesity,³⁸ and diabetes mellitus type 2.³⁹ Consistent with these associations, the metabolic syndrome, obesity, diabetes, and other metabolic aberrations have been linked to lower risk of prostate cancer diagnosis during the PSA era.^{9,21,22}

Taking competing events into account, the risk of the event of interest will depend on the all-cause mortality. Our calculated risks of prostate cancer are in accordance with prostate cancer incidence in the Nordic countries during the same

calendar period,³⁰ and our results can be generalized to populations with similar all-cause mortality, e.g. Western countries.

In conclusion, conventional studies by use of Cox regression analysis from the PSA era have found a similar risk of prostate cancer for men with or without metabolic aberrations. In this study, taking risk of competing events into account in a real world scenario, men with metabolic aberrations had a lower risk of prostate cancer diagnosis, similar risk of prostate cancer death, and a higher risk of death from other causes, compared with men who had normal metabolic levels.

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