Metabolic Syndrome and the Risk of Prostate Cancer in Finnish Men: A Population-Based Study

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Abstract

Objective: Individual components of metabolic syndrome have been linked to an increased risk for prostate cancers. We hypothesized that metabolic syndrome itself could confer an increased risk for incident prostate cancer. Methods: The participants were a population-based sample of 1,880 men from eastern Finland without history of cancer or diabetes mellitus at baseline. Results: The metabolic syndrome (WHO criteria) was present in 357 (19%) of subjects. During an average follow-up of 13 years, a total of 183 cancers occurred, of which 56 were due to prostate cancer. The metabolic syndrome at baseline was related to a 1.9-fold (95% confidence interval, 1.1-3.5) risk of prostate cancer after adjustment for age, alcohol consumption, physical fitness, and energy, fat, fiber, calcium, vitamin E, and n-3 polyunsaturated fatty acid intake. The association between metabolic syndrome and risk of prostate cancer was stronger among overweight and obese men with a body mass index ≥27 kg/m² (adjusted relative risk, 3.0; 95% confidence interval, 1.2-7.3) than in lighter men (relative risk, 1.8; 95% confidence interval, 0.7-4.7). Conclusions: Middle-aged men with the metabolic syndrome were more likely to develop prostate cancer in this prospective population-based study. This finding suggests that efforts to curb the epidemic of overweight and sedentary lifestyle and the accompanying metabolic syndrome may decrease the risk for prostate cancer.

Introduction

Some components of the metabolic syndrome have been associated with the risk of prostate cancer (1, 2). These components include obesity, an abdominal fat distribution, and hyperinsulinemia. The metabolic syndrome is becoming increasingly common worldwide and carries with it high morbidity and mortality (3-5). In Europe, the reported prevalence of the metabolic syndrome in middle-aged men ranges from 7% to 36% (3, 5). Although the pathogenesis of metabolic syndrome has multiple origins, overweight and sedentary lifestyle coupled with high-energy intake and unknown genetic factors interact to produce it (4, 6). Prostate cancer is also a common cause of morbidity and mortality in men. Incidence rates have been rapidly increasing largely due to the increasing number of prostate-specific antigen test (7). In Finland, the incidence is still increasing. Prostate cancer made up 32% of all cancer cases among Finnish men in 2001 (8).

Common potential denominators linking the metabolic syndrome and prostate cancer could be alterations in insulin and insulin-like growth factor-I (IGF-I), insulin-like growth factor binding proteins, and total and bioavailable plasma sex hormone levels, including testosterone and sex hormone binding globulin levels (9, 10). Population studies have suggested an association between the blood levels of IGF-I and the production of binding proteins and the risk of prostate cancer (11, 12).

Despite evidence suggesting that factors part of or related to the metabolic syndrome may predispose to prostate cancer, there are no prospective data on the role of the metabolic syndrome as a risk predictor for cancer. We therefore tested the hypothesis that the metabolic syndrome, as defined by the WHO, may predict incident prostate cancer during a 13-year follow-up of middle-aged men participating in a prospective population-based cohort study. The metabolic syndrome for men according to the WHO definition was modified in part for epidemiologic studies as proposed by the European Group for the Study of Insulin Resistance (5). This definition includes hyperinsulinemia or elevated fasting glucose and the presence of at least two of the following: abdominal obesity, mild dyslipidemia, or hypertension. We also shortly reported respective results to some other common cancer types in aim to give a broader view of cancer patterns among men with metabolic syndrome.

Materials and Methods

Study Population. The present study was carried out among participants of a prospective cohort, which was
initially designed to investigate risk factors for cardiovascular disease, atherosclerosis, and related outcomes in a population-based sample of middle-aged men from eastern Finland. Baseline examinations were conducted between March 1984 and December 1989. The study group is a representative sample of men living in the city of Kuopio and its surrounding rural communities, who were ages 42, 48, 54, or 60 years (mean, 52.6 years; range 42-61.2 years). Of 3,235 potentially eligible men, 2,682 (83%) volunteered to participate and 198 men were excluded because of death, serious disease, or migration away from area. Of those, men who had a history of a cancer (n = 46) at baseline or prevalent diabetes mellitus (n = 148) were excluded from the present study series, and complete data on the variables of metabolic syndrome were available for 1,880 men.

After the exclusion of men with cancer or diabetes, men with missing data on any component of metabolic syndrome were also excluded. Data were missing for serum insulin (n = 86), glucose (n = 38), high-density lipoprotein cholesterol (n = 47), triglycerides (n = 76), body mass index (BMI; n = 10), waist-to-hip ratio (n = 491), systolic blood pressure (n = 13), diastolic blood pressure (n = 15), and other variables (n = 26). The study was approved by the Research Ethics Committee of the University of Kuopio (Kuopio, Finland). Each participant gave written informed consent.

Metabolic Syndrome. The metabolic syndrome for men, according to the WHO definition (13) was modified in part for epidemiologic studies as proposed by the European Group for the Study of Insulin Resistance (5) and defined as hyperinsulinemia (fasting insulin levels in the upper 25% of the nondiabetic population, ≥12.8 mU/L or elevated fasting glucose and the presence of at least two of the following: abdominal obesity (waist-hip-ratio >0.90 or BMI 30 kg/m²), dyslipidemia (triglycerides ≥1.70 or high-density lipoprotein <0.90 mmol/L), or hypertension (blood pressure ≥140/90 mm Hg or the use of antihypertensive medications; ref. 3). This definition has been validated previously (3, 4).

Components of the Metabolic Syndrome. The subjects gave blood specimens between 8 and 10 a.m. on Tuesday, Wednesday, or Thursday. They were instructed to fast and to abstain from smoking for 12 hours and from drinking alcohol for 3 days (14). After the subjects had rested in the supine position for 30 minutes, blood was drawn with vacuum tubes (Terumo Venoject, Terumo, Tokyo, Japan). Serum insulin level was determined with a RIA kit (Novo Biobis, Novo Nordisk, Bagsvaerd, Denmark). The serum insulin samples were stored frozen at −80°C for 0.2 to 2.5 years. The between-batch coefficient of variation was 8.9% at 65 pmol/L and 17.5% at 222 pmol/L (n = 10). The assay has cross-reactivity with proinsulin and the values thus reflect immunoreactive insulin (14).

Blood glucose was measured by a glucose dehydrogenase method (Merck, Darmstadt, Germany) after precipitation of proteins by trichloroacetic acid. Elevated fasting glycemia was defined as fasting blood glucose ≥5.6 mmol/L. Diabetes was defined as fasting blood glucose ≥6.7 mmol/L or a clinical diagnosis of diabetes with either dietary, oral, or insulin treatment. Serum lipids and lipoproteins were measured as described elsewhere (15).

Resting blood pressure was measured between 8 and 10 a.m. by two trained nurses with a random-zero mercury sphygmomanometer (Hawksley, Lancing, United Kingdom). The measurement protocol included, after supine rest of 5 minutes, three measurements in supine, one in standing, and two in sitting position with 5-minute intervals. The mean of all six measurements was used as systolic and diastolic blood pressure.

Waist circumference was calculated as an average of one measurement taken after inspiration and one taken after expiration at the midpoint between the bottom of the rib cage and the top of the iliac crest. Waist-to-hip ratio was defined as waist girth/hip circumference measured at the trochanter major. BMI was computed as the ratio of weight (kilograms) to the square of height (meters).

Physical Fitness. A maximal symptom-limited exercise tolerance test was done using an electrically braked cycle ergometer. Physical fitness was measured by maximal oxygen uptake (VO2max), which was defined as the highest value for or the plateau in oxygen uptake.

Diet and Smoking. Dietary energy intake was assessed using 4-day food recording (16). Instructions were given and completed food records were checked by a nutritionist. Intake of nutrients was estimated using the Nutrica software. The data bank of Nutrica is compiled using mainly Finnish value nutrient compositions that take into account possible food preparation losses. The 4-day recordings are reasonable accurate as 4-day food records are used in all of our prospective studies as well as in other large population-based studies. These measurements are based on 4 consecutive days, starting from Sunday.

The lifelong exposure to smoking (cigarette pack-years) was estimated as the product of the number of smoking years and the number of tobacco products smoked daily at the time of examination (15).

Other Baseline Characteristics. Alcohol consumption was assessed with a structured quantity-frequency method on drinking behavior over the previous 12 months and from dietary record over 4 days (15, 16). Socioeconomic status (SES) was measured as a summary index that combined measures of income, education, occupation, occupational prestige, material standard of living, and housing conditions (17).

Outcome Events. Incident cancer cases were derived from the population-based Finnish Cancer Registry. Since 1953, every cancer in the health care system has been reported in a countrywide and population-based manner in Finland. Coverage of the national cancer registry is virtually complete (18). Our study cohort was record linked with the cancer registry data by using the personal identification code. Every resident of Finland has a unique personal identifier that is used in registers. Follow-up for cancer was done automatically using the personal identifiers. All prostate cancer diagnoses that occurred between the study entry (March 1984 to December 1989) and December 31, 2001 were included. The first occurrence of prostate cancer after Kuopio Ischemic Heart Disease baseline examination was registered and validated for 20 men in the Finnish Cancer Registry from 1984 to 1998 (19). No systematic
prostate-specific antigen screening programs in the Kuopio area occurred during the study period. Deaths were ascertained by linkage to the national causes of death register using the personal identifiers.

Due to the complete follow-up system of Finnish population, there are no losses to follow-up. The prevalent “death certificates only” cases at the Finnish Cancer Registry is <1% of all cancer sites. All prostate cancer cases were histologically verified (8).

**Statistical Analysis.** Descriptive data are presented as mean and SD for continuous data and percentages for categorical data. The relation between metabolic syndrome and risk factors for cancer was examined using Cox proportional hazards models. Prevalent metabolic syndrome at baseline was dichotomized. Three different sets of covariates were used: (1) age; (2) age, cigarette smoking, alcohol consumption, VO2max, and SES; and (3) age, alcohol consumption, VO2max, and fat, fiber, energy, dietary calcium, vitamin E, and -linolenic acid intake. Fat, fiber, calcium, vitamin E, and -linolenic acid intake were adjusted by energy intake (%). In addition, energy residual method was used for adjusting for total energy intake. Covariates were selected on the basis of their established role as a well-defined predictive factor on the basis of overall evidence and available data.

The fit of the proportional hazards models was examined by plotting the hazard functions in different categories of risk factors over time. Tests for statistical significance were two sided. Statistical analyses were done using the SPSS version 11.5 for Windows (SPSS, Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

**Results**

At baseline, 357 of 1,880 (19%) men had metabolic syndrome. Serum insulin and glucose levels, BMI, waist-to-hip ratio, and blood pressure were higher and VO2max was lower in men with metabolic syndrome, who also were more likely to be smokers and consumed more alcohol than men without metabolic syndrome (Table 1). Fasting serum insulin level correlated with BMI ($r = 0.43$; $P < 0.001$), fasting serum glucose ($r = 0.33$; $P < 0.001$), and serum triglycerides ($r = 0.27$; $P < 0.001$).

A total of 183 incident cancers occurred during the average 13.2 years (range, 0.2-16.7 years) of follow-up. There were 56 cases of prostate cancers. Other common cancer sites were cancers of lung ($n = 29$), urogenital tract or kidney ($n = 19$), upper gastrointestinal tract ($n = 14$), and colon ($n = 13$). There were 282 deaths, of which 62 deaths were due to cancer, during the follow-up period.

The cumulative incidence for prostate cancer incidence among men with metabolic syndrome at baseline exceeded 7% after a follow-up of ~15 years. Men with metabolic syndrome had a nearly 2-fold relative risk (RR) of prostate cancer after adjustment for age (model 1), some lifestyle factors (model 2), and dietary factors (model 3; Table 2). The adjusted risk of prostate cancer was 1.94-fold [95% confidence interval (95% CI), 1.07-3.53; $P = 0.030$] when energy intake correction was made using the residual methods for fiber, dietary calcium, vitamin E, and -linolenic acid intake. In overweight or obese men (BMI ≥27 kg/m², $n = 801$), the RR connected to the metabolic syndrome was higher (RR, 3.00; 95% CI, 1.22-7.34; $P = 0.016$) than among men with a BMI <27 kg/m² ($n = 1,079$; RR, 1.80; 95% CI, 0.70-4.65; $P = 0.226$) when adjusted for other risk predictors.

The multivariate adjusted RR of any cancer was 1.31 (95% CI, 0.94-1.85; $P = 0.115$) among men with metabolic syndrome. The metabolic syndrome was not related to the risk of any of the other types of cancer studied (colorectal, lung, or other genitourinary tract cancers). On the other hand, the association between metabolic syndrome and any death was strong (RR, 1.51; 95% CI, 1.16-1.96; $P = 0.002$), whereas the respective risk for cancer death was not statistically significant.

**Discussion**

This prospective population-based study shows for the first time that middle-aged men with the metabolic syndrome were nearly 2-fold more likely to develop prostate cancer than those without. The association of the metabolic syndrome with prostate cancer was not attenuated by potential confounding lifestyle or nutritional factors such as alcohol, smoking, physical fitness, and dietary energy, fat, fiber, calcium, vitamin E, and -linolenic acid intake. These results may imply that factors closely related to metabolic syndrome are likely to play a role in the development of prostate cancer.

The most obvious mechanisms by which the metabolic syndrome may predispose to prostate cancer include not only its core components, including obesity and

**Table 1. Baseline characteristics of the study population [mean (SD)]**

<table>
<thead>
<tr>
<th></th>
<th>Men without metabolic syndrome ($n = 1,079$)</th>
<th>Men with metabolic syndrome ($n = 357$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>52.4 (5.7)</td>
<td>53.4 (5.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 (3.0)</td>
<td>29.7 (3.9)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.94 (0.06)</td>
<td>0.99 (0.06)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>32.7 (9.2)</td>
<td>38.7 (8.7)</td>
</tr>
<tr>
<td>Cigarette smoking (pack-years)</td>
<td>7.81 (16.1)</td>
<td>7.37 (15.4)</td>
</tr>
<tr>
<td>Alcohol consumption (g/wk)</td>
<td>73.0 (133.7)</td>
<td>88.1 (144.1)</td>
</tr>
<tr>
<td>Fasting serum glucose (mmol/L)</td>
<td>4.51 (0.44)</td>
<td>4.89 (0.62)</td>
</tr>
<tr>
<td>Fasting serum insulin (mU/L)</td>
<td>9.2 (3.6)</td>
<td>19.8 (9.9)</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/L)</td>
<td>5.82 (1.05)</td>
<td>5.93 (0.99)</td>
</tr>
<tr>
<td>Serum low-density lipoprotein cholesterol (mmol/L)</td>
<td>3.99 (1.00)</td>
<td>3.94 (0.92)</td>
</tr>
<tr>
<td>Serum high-density lipoprotein cholesterol (mmol/L)</td>
<td>1.33 (0.31)</td>
<td>1.14 (0.25)</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/L)</td>
<td>1.16 (0.60)</td>
<td>1.97 (1.11)</td>
</tr>
<tr>
<td>Plasma fibrinogen (g/L)</td>
<td>2.98 (0.56)</td>
<td>3.11 (0.58)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130.6 (15.2)</td>
<td>141.3 (18.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>86.1 (10.3)</td>
<td>93.2 (11.2)</td>
</tr>
<tr>
<td>Dietary energy intake (kJ/d)</td>
<td>10,141 (2,626)</td>
<td>9,410 (2,700)</td>
</tr>
<tr>
<td>Dietary fiber intake (g/d)</td>
<td>25.7 (9.2)</td>
<td>23.6 (8.1)</td>
</tr>
<tr>
<td>Dietary fat intake (g/d)</td>
<td>101.7 (33.9)</td>
<td>95.3 (35.3)</td>
</tr>
<tr>
<td>VO2max (mL/kg/min)</td>
<td>10.8 (4.8)</td>
<td>11.2 (4.8)</td>
</tr>
<tr>
<td>Family history of any cancer (%)</td>
<td>24.0</td>
<td>27.2</td>
</tr>
<tr>
<td>SES*</td>
<td>10.8 (4.8)</td>
<td>11.2 (4.8)</td>
</tr>
</tbody>
</table>

*SES was a summary index that combined measures of income, education, occupation, occupational prestige, material standard of living, and housing conditions (17). A high value on the SES index indicated a low socioeconomic state."
abdominal fat distribution, hyperinsulinemia, and insulin resistance, but also other factors related to it. These include disturbances in the metabolisms of IGF-I, sex hormones, and sex hormone binding globulin (9, 20). Some studies have found an association between BMI and incident prostate cancer (21, 22), whereas no independent association was found in other cohort studies (23-25). Men who were both insulin resistant and abdominally obese have been reported to be at an increased risk to develop prostate cancer (26). Consistent with studies showing that insulin resistance may be an indicator for prostate cancer risk among obese subjects (25, 26), we found that especially overweight men with the metabolic syndrome were at a particularly high risk of developing prostate cancer.

Some prospective studies have suggested that men with elevated plasma levels of IGF-I may have an increased risk of prostate cancer (27, 28). IGF-I concentrations are elevated in obesity and insulin resistance. IGF-I is a mitogen for prostate epithelial cells and it also may inhibit apoptosis (28). Insulin and insulin-like growth factor binding proteins can modulate the biological activity of IGF-I. According to a meta-analysis published in 2000 (29), men with IGF-I levels in the upper quartile of the population distribution had an ~2-fold higher risk for developing prostate cancer than in men with lowest quartile, and in the later reports (25, 28, 30), the risk has varied from 1.7 to 4.3 among those with highest levels of IGF-I. Because these associations were seen also among middle-aged men, circulating IGF-I may be involved in the initiation of prostate cancer (27).

Some nutrients may be associated with prostate cancer, including high intakes of α-linolenic acid, calcium, and total fat and low intakes of dietary lycopene and α-tocopherol (30). Many of these dietary factors such as the high intakes of energy and fat may be also related to obesity and the metabolic syndrome. In our study, the association of the metabolic syndrome with incident prostate cancer remained unaltered after adjustment for these nutritional factors. All nutrients were adjusted for dietary intake using the total calorie intake and the residual method. Energy adjustment is based on notion that a larger, more physically active person requires a higher absolute intake of nutrients. Furthermore, it is possible that there was seasonal variation in dietary intake such as vitamins intake, although the seasonal variation in dietary intake is random among subjects. In this study, it is reported previously that plasma vitamins may have seasonal variation and the average intake decreases during winter in eastern Finland (31).

Our findings raise the possibility that treatment or prevention of the metabolic syndrome may be a way to decrease the risk of prostate cancer. The recent evidence suggests that relatively modest lifestyle interventions can have a major impact in decreasing the risk for diabetes in glucose-intolerant individuals, most of whom have the metabolic syndrome (32, 33). We have also shown that men who engage in higher levels of moderate and vigorous physical activity are less likely to develop the metabolic syndrome during follow-up (34). A low fat diet and regular exercise results in changes in serum hormones and growth factors that can reduce growth and induce apoptosis of prostate tumor cells (35). The effects of physical activity and diet together on insulin action may help to block initiators of cancer if exercise is done regularly. Furthermore, regular exercise could exert a suppressive effect on the initiation on prostate cancer by modulating the production of sex hormone binding globulin and circulating sex hormones (36) and their bioavailability with aging (37).

The strengths of this study include its prospective population-based design, reliable assessment of incidence of prostate cancer, and detailed assessment of metabolic factors. Secondly, the participation rate was high and there were no losses during follow-up. We also used an accepted and validated definition of the metabolic syndrome. We excluded diabetes, because the importance of the metabolic syndrome from a public health standpoint is greatest in its earlier stages, before development of diabetes (3, 4). Moreover, diabetes could mask the association between metabolic syndrome and prostate cancer due to high selected morbidity and mortality. This study represents a sample of middle-aged male population from eastern Finland, an area known for its high prevalence and incidence of atherosclerotic vascular diseases (38). The metabolic syndrome is related to an increased risk of cardiovascular mortality in this study population (3), indicating that impact on overall mortality was mediated by cardiovascular diseases. Prostate cancer is an important disease among men with metabolic syndrome, although the risk of other cancers and cancer death was not increased. The proportion of men who die due to prostate cancer remains apparently low and the risk of cancer death may not be markedly increased.

In conclusion, our results suggest that the metabolic syndrome increases the risk of prostate cancer. Because the metabolic syndrome is common and increasing at an epidemic rate, the metabolic syndrome may pose a substantial public health problem for prostate cancer. Therefore, preventive strategies to curb the epidemic of overweight, sedentary lifestyle and the accompanying metabolic syndrome may also reduce the risk of prostate cancer.

Table 2. Risk ratios of prostate cancer (56 cases) according to metabolic syndrome in men with no prior cancer or diabetes mellitus (reference: no metabolic syndrome at baseline)

<table>
<thead>
<tr>
<th>Risk ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Model 1*a</td>
<td>1.79</td>
<td>1.01-3.17</td>
</tr>
<tr>
<td>Model 2*b</td>
<td>1.97</td>
<td>1.08-3.57</td>
</tr>
<tr>
<td>Model 3*c</td>
<td>1.94</td>
<td>1.06-3.53</td>
</tr>
</tbody>
</table>

*aAdjusted for age.
*bAdjusted for age, cigarette smoking, alcohol consumption, VO2max, and SES.
*cAdjusted for age, alcohol consumption, VO2max, and fat, fiber, energy, dietary calcium, vitamin E, and α-linolenic acid intake. Age, alcohol consumption, and VO2max are included due to P < 0.2 in model 2.

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References


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