Original Contribution

Metabolic Syndrome Predicts Prostate Cancer in a Cohort of Middle-aged Norwegian Men Followed for 27 Years

L. Lund Håheim1, T. F. Wisløff1,2, I. Holme3, and P. Nafstad2,4

1 Norwegian Knowledge Centre for Health Services, Oslo, Norway.
2 Norwegian Institute of Public Health, Oslo, Norway.
3 Ulleval University Hospital, Oslo, Norway.
4 University of Oslo, Oslo, Norway.

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The aim of the study was to establish whether metabolic syndrome predicts the incidence of prostate cancer. The hypothesis was tested using the 27-year follow-up of the prospective cohort of 16,209 men aged 40–49 years who participated in the Oslo Study in 1972–1973. Men with established diabetes and men with cancer diagnosed before screening were excluded, leaving 15,933 for analyses. Metabolic syndrome is here composed of body mass index, nonfasting glucose, triglycerides, and blood pressure or drug-treated hypertension. Two analytical approaches were compared, namely, predefined (adjusted from National Cholesterol Education Program) and quartile values of risk factors. Age, body mass index, and sedentary versus intermediate physical activity at work were significant predictors in univariate proportional hazards regression analyses. Combinations of any two (relative risk = 1.23; \( p = 0.04 \)) or any three (relative risk = 1.56; \( p = 0.00 \)) factors of the metabolic syndrome using quartile values of risk factors were predictive of prostate cancer. The number of cases for four factors was too small for analyses. Predefined values of the risk factors were not found to be predictive. In conclusion, metabolic syndrome was found to predict prostate cancer during 27 years of follow-up, indicating an association between insulin resistance and the incidence of prostate cancer.

incidence; insulin resistance; metabolic syndrome X; prospective studies; prostatic neoplasms

Abbreviations: CI, confidence interval; IGF-1, insulin-like growth factor-1; IGFBP, insulin-like growth factor binding protein; NCEP, National Cholesterol Education Program; RR, relative risk.

No major cause of prostate cancer has been established, although genes, dietary factors, and lifestyle-related factors are believed to contribute to the development of prostate cancer (1–3). Prostate cancer occurs mainly after the age of 50 years, and the incidence increases sharply with advancing age. This is the most common cancer in men in Norway and the incidence is increasing (4). In the period from 1988 to 1997, the age-adjusted incidence rate increased from 44.6 to 67.2 per 100,000. The incidence rate has to some extent been influenced by an increase in screening by prostate-specific antigen testing, but the high rates call for further etiologic study.

Norwegian men aged 40–42 years are reported to have increased their mean weight by 9.1 kg (from 76.9 to 86.0 kg) during the period of 1963–1999 (5). The mean height also increased. The weight increase observed during this period coincides with the present increase in the incidence of prostate cancer. Metabolic syndrome, of which body mass index constitutes an important factor, is established as being associated with increased risk of cardiovascular disease (6).

Correspondence to Dr. Lise Lund Håheim, Norwegian Knowledge Centre for Health Services, P.O. Box 7004, St. Olavs Plass, N-0130 Oslo, Norway (e-mail: lise.lund.haheim@nokc.no).
More uncertainty exists with regard to prostate cancer (7, 8). Insulin resistance and compensatory hyperinsulinemia are thought to be an underlying pathway by stimulating production of insulin-like growth factor-1 (IGF-1) and related factors (9–11). Metabolic syndrome has been posited as a cause of several forms of cancer, such as prostate cancer (9–12) and cancers of the breast (13, 14), pancreas (15), and colon (16, 17). The predictiveness of metabolic syndrome for cancer of the prostate is studied in this prospective cohort of Norwegian men initially aged 40–49 years who were followed for 27 years.

MATERIALS AND METHODS

The Oslo Study cohort of men was screened in 1972–1973 (18). The main objective was to study the prevention and epidemiology of cardiovascular diseases. The participants were aged 20–49 years in 1972. This presentation concerns the men aged 40–49 years (n = 25,915) at the time of the screening, of whom 16,209 men attended the screening. In short, the men had to answer a questionnaire on their history of cardiovascular symptoms or diseases, diabetes, medication for hypertension, smoking, mental stress, and physical activity at work and at leisure. Physical activity was coded as sedentary, intermediate, moderate, and high. A blood sample was taken while the participant was in a nonfasting state to estimate the serum total cholesterol level, triglycerides, and glucose levels. Height and weight were measured. Blood pressure was measured with a mercury sphygmomanometer.

Information on level of education achieved, cancer incidence, and cause-specific mortality was added to the screening data. The level of education achieved was coded to nine levels as follows: no education or per-school education, primary, three levels of secondary, postsecondary nontertiary, and three levels of graduate education. Information on the level of education achieved and cause of death was given by Statistics Norway (Oslo, Norway). Incident cases of any cancer diagnosis were provided by the Cancer Registry of Norway (Oslo, Norway). The last day of follow-up was December 31, 1998.

All examinations were done according to the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm), and the necessary permits were granted by the Norwegian Data Directorate and the Norwegian Board of Health (Statens Helsetilsyn, Oslo, Norway).

Men with a history of cancer (n = 123) or diabetes (n = 153) at the time of screening were excluded from the analyses, leaving 15,933 eligible for analysis. The incidence rate is the number of cases per 1,000 person-years. Descriptive values of risk factors are presented as the mean or percentage and standard deviation. Statistical significance is indicated by p < 0.05 (two sided). The main statistical analysis of an association between risk factors and prostate cancer was proportional hazards regression (Cox regression).

The identification of cases was through obligatory reporting to the Cancer Registry of Norway of all newly diagnosed cancers since 1954. The diagnoses are validated by questionnaire information, pathology reports, or other diagnostic tests. The register is believed to include close to 100 percent of all cancer cases. The 11-digit personal identification number of all Norwegians allows for a complete follow-up on cancer and mortality. Men who were diagnosed with other cancer or died from any cause during follow-up were censored in the Cox regression analyses.

The metabolic syndrome was composed of the risk factors body mass index, diastolic blood pressure, nonfasting glucose, and triglycerides based on the factors used by the National Cholesterol Education Program (NCEP) (19). Cutpoints for risk factors of the metabolic syndrome were tested by use of either the upper quartile values or the predefined values of NCEP. Their standard code includes five factors of which a person must have a risk level in three of these five factors to have the metabolic syndrome. As this data set did not include exactly the same factors, adjustments were made. Body mass index was used instead of waist measurement for overweight. High density lipoprotein cholesterol was not measured. The predefined values used were blood pressure (systolic/diastolic blood pressure of 130/85 mmHg or above) or drug-treated hypertension, nonfasting glucose of 11.0 mmol/liter or above, triglycerides of 2.0 mmol/liter or above, and body mass index of 30 kg/m² or above. The upper quartile values were as follows: systolic/diastolic blood pressure = 144/92 mmHg, nonfasting glucose = 6.10 mmol/liter, triglycerides = 3.01 mmol/liter, and body mass index = 26.31 kg/m². The analyses were adjusted for time since the last meal in the Cox analyses to compensate for the serum samples taken in the nonfasting state. Interaction analyses were performed for any two risk factors of the metabolic syndrome.

A sequential analysis of metabolic syndrome was made by four multivariate proportional hazards regression models including any one of the four factors, then any of two, then any of three, and finally all four factors. The quartile values used are those of the fourth quartile compared with those of quartiles 0, 1, and 3 together. Every comparison is with those that did not have that many risk factors; that is, “any three factors” are those with three factors compared with all others. In addition, these models were compared by calculating the proportion attributable risk, which is defined as the proportion of the incidence in these models that is due to the additional factor (compared with the models with one less factor): proportion attributable risk = (relative risk – 1)/relative risk. The proportional hazard models were tested for proportionality by use of Schoenfeld residuals. Analyses were done mainly with SPSS, version 12.0, software (SPSS, Inc., Chicago, Illinois), but splines and the test for proportionality were done in S-PLUS, version 6.1, software (Insightful Corporation, Seattle, Washington).

RESULTS

The incidence of prostate cancer in this cohort was 1.45 per 1,000 person-years. In all, 507 cases were identified among the 15,933 men at risk. Comparing cases with noncases, we found that risk factor levels by mean values were not significantly different except for physical activity at work on a scale from 1 to 4 (highest) (cases = 1.69, standard deviation: 0.87; noncases = 1.76, standard deviation: 0.87) (table 1).
Results of age-adjusted univariate proportional hazards regression analyses for risk factors predicting prostate cancer showed significantly increasing risk by age per year (relative risk (RR) = 1.12; 95 percent confidence interval (CI): 1.08, 1.15) and body mass index (weight (kg)/height (m)²) (RR = 1.03; 95 percent CI: 1.001, 1.06) (table 2). Trend analyses of physical activity at leisure and at work were inversely related. Intermediate versus sedentary activity at work was significantly different (RR = 0.77; 95 percent CI: 0.63, 0.96). Former analyses on this data set found nitrogen oxide (NOx) to be a risk factor for lung cancer (20), but these analyses did not find air pollution to be associated with prostate cancer. Age was not found to fulfill the criteria of proportionality. However, analysis with splines did not give ideas for alternative parameterizations.

The predictiveness of metabolic syndrome was analyzed by using one of two strategies: 1) the upper quartile as risk factor or 2) the predefined risk factor levels (table 3). The number of persons at risk in the quartile or predefined categorizations of metabolic syndrome varied for each model. In all, 317 cancer cases had one of the metabolic risk factors at the upper quartile value, 133 had two, 72 had three, and 10 had all four risk factors. The equivalent number of cases for the predefined values was 430 cases for one risk factor, 127 cases for two, 17 for three, and none for four factors. Any one of the four factors by upper quartile value was not predictive, but any two (RR = 1.23; 95 percent CI: 1.08, 1.47) or three (RR = 1.23; 95 percent CI: 1.08, 1.47) of the factors were predictive. The model of all four factors of the metabolic syndrome was not significant because of low power, as only 10 cases had this risk factor profile. The attributable risk estimates for any two quartile criteria were 10 percent and for any three quartile criteria were 17 percent. None of the four models with predefined values was predictive. There were no interactions between any two of the risk factors of the metabolic syndrome using quartile values (data not shown).

DISCUSSION

The knowledge of the increase in incidence of prostate cancer, the increase in mean weight of middle-aged men...
in Norway, and the research information on the association of IGF-1 and related factors to prostate cancer is the background for this paper’s focus on metabolic syndrome as a predictor of prostate cancer. The incidence of prostate cancer is, however, influenced by opportunistic screening. To what extent this has influenced the Norwegian rate of incidence of prostate cancer is uncertain. Simulation modeling (21) of Dutch screening data gives an estimated mean lead time of 12.3 years for a single screening at age 55 years. Overweight is a major factor of metabolic syndrome and is also found to be a predictor in these analyses. Insulin resistance and the compensatory hyperinsulinemia are the underlying factors of the metabolic syndrome (9–11). Hyperinsulinemia stimulates the production of IGF-1 and suppresses the production of sex-hormone binding globulin and insulin-like growth factor binding protein (IGFBP)-1 and -2. Through these modulations the insulin resistance is believed to affect hormone-related cancers, such as prostate cancer. Circulating levels of IGF-1 and IGFBP-3 have been found to be predictive in the univariate analyses of the proportional hazards analyses. The well-known age gradient was confirmed and, in addition, body mass index, low physical activity at work, and a subsidiary question on recorded mental stress were identified. Of these factors, only body mass index is one of the factors constituting metabolic syndrome. As noticeable are the factors that are not predictive. Although there was a protective trend with increasing physical activity at leisure, physical activity was not significant at any level compared with the sedentary level of activity. Two Norwegian prospective studies have not found any association between anthropometry (24) or dietary fat intake and risk of prostate cancer (25). However, a more recent prospective study found height but not body mass index to predict prostate cancer (26). The effect of overweight on prostate cancer has been studied

TABLE 3. Multivariate proportional hazards regression analyses (Cox analyses) of risk factors of metabolic syndrome for prostate cancer in four models, Norway, 1972–1998*

<table>
<thead>
<tr>
<th>Definition of analytical models†</th>
<th>Population</th>
<th>Proportional hazards regression analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of persons with metabolic syndrome</td>
<td>No. of prostate cancer cases</td>
</tr>
<tr>
<td>Model 1 (any one factor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile</td>
<td>9,979</td>
<td>317</td>
</tr>
<tr>
<td>Predefined</td>
<td>13,234</td>
<td>430</td>
</tr>
<tr>
<td>Model 2 (any two factors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile</td>
<td>3,766</td>
<td>133</td>
</tr>
<tr>
<td>Predefined</td>
<td>4,501</td>
<td>127</td>
</tr>
<tr>
<td>Model 3 (any three factors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile</td>
<td>1,702</td>
<td>72</td>
</tr>
<tr>
<td>Predefined</td>
<td>573</td>
<td>17</td>
</tr>
<tr>
<td>Model 4 (all four factors)</td>
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<td></td>
</tr>
<tr>
<td>Quartile</td>
<td>357</td>
<td>10</td>
</tr>
<tr>
<td>Predefined</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

* The risk level was set to the upper quartile value versus the lower values.
† All the analyses were adjusted for age and time since the last meal.
‡ NA, not available.
prospectively, but risk has been found to be an independent risk factor (27), has not been confirmed (28–30), or has been related to age and familial risk (30). A prospective Finnish study, however, found metabolic syndrome at baseline to be associated with a 1.9 times increased risk for prostate cancer (12). The study was on a population-based sample of 1,880 men, of whom 56 men got prostate cancer. It strengthens the hypothesis of metabolic syndrome’s possible association with prostate cancer.

The predefined values used for the analyses of the metabolic syndrome were modeled after those in the NCEP. NCEP uses systolic/diastolic blood pressure of 130/85 mmHg or above or blood pressure medication, waist measured to 102 cm or above for men, fasting glucose of 6.1 mmol/liter or more, high density lipoprotein cholesterol to be less than 1.0 mmol/liter for men, and triglycerides greater than 1.7 mmol/liter. However, this database did not have all the factors measured, such as high density lipoprotein cholesterol and waist measurement, nor were the serum samples taken in the fasting state. This is a limitation and reduces comparability with other studies. For this reason, upper quartile values were used in comparative analyses. The last approach of using upper quartile values gave, however, the significant findings of increasing risk estimates with two or alternatively with three factors added in the analytical model except for the full model of four factors. It seems as if there is a trend toward higher impact of the metabolic syndrome with more factors included in its definition. For four risk factors, however, the data set seems too small. Lakka et al. (6) used the same approach as did NCEP and the World Health Organization standard criteria and upper quartile values in studying metabolic syndrome and predicting cardiovascular disease and total mortality. The NCEP codes gave less consistent results than did the upper quartile values. The analyses are sensitive to the number of cases in the analyses, which explains why having all four factors present was not predictive in our study. One should also note the different numbers of persons falling into the risk categories in the four models. This reflects a possible discrepancy between a Norwegian cohort and cohorts of other countries. These results indicate that a cautious approach should be held when extrapolating data from international data.

Information on familial risk was not obtained at the screening. This would have given an indication of genetic susceptibility for prostate cancer. It has been found that polymorphism of the insulin gene is associated with increased prostate cancer risk, indicating a possible linkage between metabolic syndrome and cancer development (31). The interplay of androgens on IGF-1, insulin, and leptin has been studied in a nested case-control study, indicating a complex association among these factors (32). However, in a nested case-control study, no causal association between IGF-1 and prostate cancer was found (33).

This prospective cohort study gives evidence for an association between metabolic syndrome (consisting of the risk factors body mass index, blood pressure, triglycerides, and glucose) and prostate cancer over a 27-year period. The results of this study indicate that metabolic syndrome may be associated with the increasing Norwegian national incidence rate of prostate cancer.

ACKNOWLEDGMENTS
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REFERENCES
tection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Pro-