Prostate cancer incidence, clinical stage and survival in relation to obesity: a prospective cohort study in Denmark

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Category: Research Article

Keywords: Prostate cancer; obesity; survival; cohort study; Denmark

Novelty and Impact

The incidence of prostate cancer in obese men was similar to- or slightly lower than the incidence in non-obese men, but obese men were diagnosed with more advanced prostate cancer. Consequently, obese men with prostate cancer had higher prostate cancer specific mortality. In addition to the direct effect of stage, the data are suggestive of a stage-independent causal pathway where prostate cancer in obese men has higher fatality, even in early-stage disease.
Abstract

There is no clear link between obesity and prostate cancer incidence but an association has been reported between obesity and fatal prostate cancer. We report on two prospective cohort analyses on (1) the incidence of prostate cancer in relation to obesity in a cohort of men with no previous cancer, and on (2) the stage distribution and prostate cancer specific mortality in relation to obesity among men with prostate cancer. The ‘Diet, Cancer and Health’ prospective cohort study was established in Denmark in 1993-1997 and accrued 26,944 men aged 50-64 years. Data were extracted on height, weight, body mass index, waist circumference, and body fat percentage. Information on cancer incidence and deaths were obtained by record linkage with the Danish Cancer Register and the Danish Death Register. The incidence rate of prostate cancer was similar or slightly lower in obese men compared with non-obese men, but obese men tended to be diagnosed with more advanced prostate cancer. The proportion of stage 3-4 cancers was 37% in the lowest BMI quartile and 48% in the highest (p=0.006). Obese men with prostate cancer had higher prostate cancer specific mortality. The hazard ratio comparing the highest and the lowest quartiles of body mass index was 1.48 (95% confidence interval: 1.06-2.05; p-value for trend: 0.002). The association was attenuated but not eliminated by statistical adjustment for stage, and the data are suggestive of a stage-independent causal pathway where prostate cancer in obese men has higher fatality, even in early-stage disease.
Introduction

Many studies have explored the risk of prostate cancer, and its subsequent progression and prognosis in relation to obesity and related anthropometric measures, bioelectrical impedance measurements, and elements of the metabolic syndrome (1). Investigations have been carried out using different study designs and in populations with different ethnic composition, different attitudes to PSA testing and aggressiveness regarding therapy for prostate cancer.

In the USA, positive associations were observed between body mass index (BMI), waist circumference (WC), body fat mass (BFM) and fat-free mass (FFM) and Gleason 7+ prostate cancer (2). In the European EPIC cohort, abdominal adiposity was positively associated with risk of advanced prostate cancer (3). A prospective cohort study in Australia found that weight, BMI and adult weight gain were positively associated with the risk of aggressive prostate cancer, but not with overall risk of prostate cancer (4). A very large cohort study in Sweden found a strong association between BMI and fatal prostate cancer (5). Another cohort study in Sweden suggested an age-specificity in the effect of BMI. High BMI in early adulthood was negatively associated with risk of advanced prostate cancer, whereas BMI in middle aged and older men was positively associated with advanced prostate cancer risk (6). A systematic review and meta-analysis of prospective studies showed that high BMI was associated with a higher risk of advanced prostate cancer (7).

For men who underwent a radical prostatectomy, a positive association was found between BMI and biochemical recurrence (8).

Apart from overweight and obesity, several studies have investigated other components of the metabolic syndrome in relation to risk of prostate cancer. A case-control study in Italy found that components of the metabolic syndrome, especially hypercholesterolemia, were associated with prostate cancer risk (9). The risk was four-fold higher among those with four components of the metabolic syndrome (obesity, hypercholesterolemia, hypertension, diabetes) compared to those with none. Furthermore, a Mendelian randomisation study found that a single-nucleotide-polymorphism in the obesity-associated FTO gene was associated with the risk of high grade prostate cancer (10).

A pooled analysis of cohorts from Norway, Sweden and Austria found no higher risk of prostate cancer in men with the metabolic syndrome, but the risk of prostate cancer death was higher due to the underlying associations with BMI and high blood pressure (11).

The Danish population has had relatively low levels of PSA testing, and is a valid context for the study of occurrence of symptomatic (as opposed to PSA-detected or screen-detected) prostate cancer (12, 13). The national cancer registration system in Denmark is of high quality, and can provide information about the stage of disease at the time of diagnosis. The registration of deaths in the population is also of high quality, and information on deaths is routinely added to the national cancer registry.

The present paper describes two analyses in a prospective cohort. Firstly, we quantify the incidence of prostate cancer in relation to obesity in a cohort of men with no previous cancer. Secondly, we describe the stage distribution and quantify prostate cancer specific mortality in relation to obesity in the sub-cohort of men who developed prostate cancer.
Material and Methods

Study population and data selection

The present study uses the established ‘Diet, Cancer and Health’ prospective cohort study in Denmark (14-17). The data were collected in 1993-1997. The men were 50-64 years of age when included. The cohort has been described in detail elsewhere (14).

From the data collected in the prospective study, the following exposure variables describing body characteristics were extracted: height, weight, BMI, waist circumference (WC), and body fat percentage (BFP). All were measured by trained personnel at study baseline. Height was measured standing without shoes and rounded to the nearest half centimeter. Weight was measured on a digital scale in light clothing and rounded to the nearest 100 g. Waist circumference was measured at the narrowest part between the lower rib and the iliac crest and rounded to the nearest half centimeter. Body fat percentage was measured by bioelectrical impedance.

The cohort included 26,944 men. Sixty-seven men (0.2%) were excluded because data on body characteristics were missing, leaving 26,877 men for the present analysis.

Information on incident cancer cases, vital status and causes of death was obtained by record linkage with the Danish Cancer Register and the Danish Death Register. The end-of-study date was December 31st 2011.

Statistical analysis

In the follow-up analysis for prostate cancer occurrence, the incidence of prostate cancer overall and advanced prostate cancer were considered in relation to the separate and joint effects of the five body characteristics. BMI was analysed both as conventionally categorised and in quartiles of its distribution. For WC, BFP and height, we used quartiles. Statistical analysis was pursued with Cox proportional hazards regressions with age as the underlying time dimension. Occurrence of prostate cancer was considered from the age at entry into the cohort until the age at prostate cancer diagnosis, death or end of follow-up on 31 December 2011. For the analysis of advanced prostate cancer we considered a non-advanced prostate cancer as a censoring event.

Among the prostate cancer cases that occurred within the first cohort, we considered prostate cancer specific deaths in relation to the five exposure variables, as above. Occurrence of prostate cancer deaths were considered from the age at prostate cancer diagnosis until the age of prostate cancer death or end of follow-up. Death from another cause than prostate cancer was considered as a censoring event.

With longitudinal follow-up and censorings as described, the two time-to-event analyses are equivalent to cohort analyses based on enumeration of cancer occurrences and cancer deaths in the person-years’ experience of the cohorts, and subsequent analysis of the derived incidence and mortality rates.
Results

The details of the cohort are summarised in Table 1. The median age at cohort entry of the 26,877 male cohort members was 56 years and the median duration of follow-up was 15.5 years. During the course of follow-up 1,813 men developed prostate cancer. From the date of diagnosis these men were followed-up for a median of 3.6 years in which 290 died from prostate cancer. The men who died from prostate cancer had slightly higher BMI, WC, and BFP as measured at the time of entry into the cohort.

Table 2 shows the analysis of prostate cancer incidence in relation to body characteristics measured at the time of entry into the cohort. The incidence of prostate cancer was weakly inversely associated with measures of obesity. Obese men (body mass index ≥ 30 kg/m²) had a hazard ratio (HR) of 0.86 (95% confidence interval [CI]: 0.74-0.99). The p-value for trend over the three categories (-24.9; 25.0-29.9; 30.0+) was 0.03. When considering the quartile distributions of BMI and WC there was no statistically significant association with prostate cancer incidence. For BFP, there was a significant linear trend in prostate cancer incidence over the quartiles (p=0.018). The HR in the highest quartile vs. the lowest was 0.84 (95% CI: 0.74-0.96). Multivariate adjustment between the obesity-related measures did not lead to any material change in impression of the associations.

Height was positively associated with prostate cancer incidence (HR: 1.30 [95% CI: 1.14-1.48]) for the highest vs lowest quartile; trend p-value over quartiles: 0.0003. The association with height did not change after adjustment for any of the obesity measures, and the associations between the obesity measures and prostate cancer incidence did not change materially when height was included in the regression models.

Table 2 also shows the analysis for the risk of advanced (stage 3-4) prostate cancer (626 cases) in relation to the measured body characteristics. Measures related to obesity were positively associated with risk of advanced prostate cancer (HR for the highest vs. lowest quartiles of BMI, WC, and BFP: 1.20 [0.97-1.50], 1.23 [0.98-1.55] and 1.31 [1.04-1.64], respectively). The linear trends were not statistically significant. A positive association between height and advanced prostate cancer was also observed.

Table 3 shows the associations between the measured body characteristics and stage of prostate cancer. There were strong associations between the obesity measures (BMI; WC; BFP) and advanced stage of prostate cancer. The strongest of these associations was with BFP where 50% of prostate cancers were advanced in men in the highest quartile of BFP as opposed to 34% in men in the lowest quartile (chi-square for the trend over quartiles: 11.3; p=0.001). There was no association between height and prostate cancer stage.

Table 4 reports the results for the analysis of prostate cancer death in relation to the measured body characteristics in the 1,813 men with prostate cancer. Death from prostate cancer was positively associated with all analysed body characteristics. Obese men (BMI ≥30) with prostate cancer had a HR of 1.43 (95% CI; 1.01-2.01) compared to men with low or normal BMI. Men with prostate cancer who were in the highest quartiles of BMI, WC and BFP had HRs of 1.48 (95% CI; 1.06-2.05), 1.36 (0.98-1.88), and 1.61 (1.16-2.24), respectively, compared to men in the lowest quartiles. The linear trends over the quartiles were statistically significant (p=0.02, p=0.04, and p=0.007, respectively). Additional adjustment for stage attenuated the associations of death from prostate cancer with BMI, WC and BFP and excess death rates reduced by about half. The stage adjusted HRs for BMI (30+), and upper quartiles of BMI, WC and BFP were 1.27 (0.90-1.80), 1.21 (0.87-1.69), 1.15 (0.83-1.60), and 1.29
Stage was strongly associated with prostate cancer death, but there
no linear association between height and prostate cancer death.

Stage-stratified analyses of prostate cancer death in relation to the body characteristics are
shown in Table 5. Regardless of stage category (1-2; 3; 4; n/a), there was a positive
association between obesity related measures and prostate cancer death. In men with early
stage prostate cancer (stage 1-2) there were positive associations between the obesity
measures and prostate cancer death: HRs were 1.42 (0.57-3.53), 1.40 (0.59-3.36) and 1.78
(0.72-4.41) for the highest vs. lowest quartiles of BMI, WC and BFP.

Discussion

Principal findings

The principal findings of these analyses are: (a) The incidence of prostate cancer in obese
men was similar to- or slightly lower than the incidence in non-obese men, but (b) obese men
were diagnosed with more advanced prostate cancer. Consequently, (c) obese men with
prostate cancer had higher prostate cancer specific mortality. In addition to the direct effect of
stage, (d) the data are suggestive of a stage-independent causal pathway where prostate
cancer in obese men has higher fatality, even for men with early-stage disease.

The most interesting implication of these results concerns the relative importance of stage-
dependent and stage-independent mechanisms underlying the association between obesity
and the prognosis in prostate cancer. It is evident that all the used measures (obesity; high
BMI; high WC; high BFP) are associated with advanced stage distribution and increased
mortality in men with prostate cancer. The strengths of these associations were sensitive to
statistical adjustment for cancer stage which attenuated the associations. This suggests that
the increased mortality in obese men with prostate cancer may in part be due to the adverse
stage distribution. These data are also suggestive of a stage-independent mechanism of
action, but it is noted that stage is not recorded in all men with prostate cancer, and it is
inevitably collected with a degree of error. The grouping into stage categories entails a scope
for residual confounding and bias. We considered that in addition to the adjustment for stage
by means of multivariate analysis, it was useful also to explore the associations within strata
of stage. Despite the low fatality of stage 1-2 prostate cancer, there were sufficient numbers
of men with such early stage prostate cancer, and the results are suggestive of an adverse
effect of obesity on prognosis in men with early-stage prostate cancer. We note that the
stage-adjusted and the stage-stratified effects are not themselves statistically significant due
to the attenuation of the magnitudes of effect and to the loss of statistical power in these
analyses.

Possible biological mechanisms

The different measures of adiposity (BMI, WC, and BFP) are highly correlated, but describe
different aspects of obesity. BMI is a measure of general adiposity and high WC is
particularly indicative of abdominal adiposity. In large studies of overall mortality in the
general population, both BMI and WC are associated with mortality in a U-shaped fashion,
and conditionally on BMI, WC is separately and linearly associated with mortality (18). In
the present analyses of prostate cancer specific mortality, results were similar for BMI, WC
and BFP, and no particular association was seen in relation to BMI-adjusted WC. This is possibly because the associations with prostate cancer specific mortality are only moderately strong and the statistical power of the cohort analysis of prostate cancer patients is limited.

The adverse stage-distribution of prostate cancer in obese men may arise by different mechanisms. Clinically, it is more difficult to palpate the prostate in an obese man (1, 19) and obese men have lower PSA concentration in the blood, leading to a lower propensity for referral to biopsy (1, 20). Biological mechanisms have been suggested whereby obesity may lead to a higher growth rate of prostate tumours (21). For instance, pre-clinical evidence suggests that androgens stimulate prostate tumour growth via activation of pathways regulating lipogenic gene expression, which results in lipid accumulation (22) and crosstalk between androgen signaling and lipogenesis (23, 24). Castrate-resistant prostate cancer may synthesize androgens de novo from cholesterol and progesterone within the tumour, leading to androgen receptor activation independent of circulating androgens, and subsequent tumor growth (25, 26). Experimental evidence also suggests that fatty acid synthase (FAS) is involved in prostate tumorigenesis, with high expression in obese patients being associated with aggressive disease (27) and low survival (28). There is a growing body of literature on the link between prostate cancer risk and prognosis with obesity and other aspects of the metabolic syndrome (29, 30). Recently, it has been suggested that the effect of obesity on prostate cancer outcomes is especially manifest in those with the aggressive subtype of prostate cancer defined by TMPRSS2-ERG fusion (31).

**Height**

In addition to our findings for obesity in relation to risk and progression of prostate cancer, we found a positive association for height and risk of prostate cancer. However, we did not observe any association with stage or with disease prognosis. This pattern is in contrast with the findings for overweight and obesity. Results to date for the link between height and prostate cancer are inconsistent. A large study in Sweden found an association with height and incident prostate cancer, but no association with fatal prostate cancer (5). In contrast, the pooled EPIC cohort analysis (of which the present Danish cohort is a component) found no association between height and prostate cancer incidence (3).

**Changes in obesity over the life-course**

Unlike height, which does not change much over the course of the years in adulthood, measures of overweight and obesity may be subject to change. In the present study, measurements were taken at the time of entry into the cohort while aged 50-64 years and used to predict occurrence and fatality in the following 10-15 years. This approach is justified on the basis of the research question being about the typical constitutional body characteristic in middle-aged men and their association with disease risk thereafter. Other studies have in addition to the baseline measure of overweight and obesity also looked at changes in body weight during the life-course. Such studies reported a mixture of findings, e.g. opposite effects of obesity in early and late adulthood (6), weight gain being associated with increased prostate cancer mortality (4), and no association with either incidence or fatality (32).

**Strengths and limitations of the study, and implications for future research**

In the period of this study, the use of PSA testing in men without any symptoms was low, making these data less sensitive to diagnostic bias than in situations where PSA testing is
more frequent. In a sub-sample of the cohort it was estimated that 14% of the prostate cancer cases in the sample were diagnosed without any cancer-related symptoms and therefore most likely following a PSA test (13).

Data were not available about prostate cancer treatment administered over the cause of follow-up. We did not have access to data on tobacco smoking and other life-style factors over the course of follow-up.

There is a need for large studies including detailed information on both anthropometric and biological measures of obesity and metabolic syndrome. The UK Biobank cohort will present such opportunity in a few years’ time (33). Information on stage, grade and treatment should ideally be available in order to resolve the question of stage-dependent and stage-independent mechanisms and minimise the potential for error and bias. Valid information on prostate cancer grade may require central review of the histopathological material (34). New biological markers of prognosis can be obtained from diagnostic biopsy samples (35). In the present era of high or increasing rate of PSA testing, new studies should include the route to diagnosis.

The Gleason score was only available for half of the prostate cancers in the present dataset. We found that about 56% of the graded cancers were Gleason 7 or higher, but this proportion did not vary with the measures of overweight and obesity.

Conclusion

Obese men have a similar or slightly lower incidence rate of prostate cancer than other men, but with an adverse stage distribution which contributes to a higher case-fatality in obese men with prostate cancer. These results from a large cohort with complete follow-up and robust anthropological measures also suggest a worse prognosis for obese men independent of stage. Evidence is accumulating to support new studies with sufficient size, high data quality, and metabolomics and tumour information in order to resolve the roles of stage-dependent and stage-independent biological mechanisms. Such studies may lead to important information about modifiable risk factors for progression and death in men with prostate cancer.
Acknowledgement

This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.
References


33. [https://www.ukbiobank.ac.uk/](https://www.ukbiobank.ac.uk/)


Table 1. Overview of the cohort of 26,877 men and the sub-cohort of 1813 men who developed prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>Total cohort</th>
<th>Sub-cohort with prostate cancer</th>
<th>Prostate cancer deaths</th>
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<tr>
<td></td>
<td>26877</td>
<td>1813</td>
<td>290</td>
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<td>Age at entry (years)</td>
<td>Median; quartile range</td>
<td>56  52 - 60</td>
<td>57  54 - 61</td>
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<td>Duration from entry to death or censoring (years)</td>
<td>Median; quartile range</td>
<td>15.5  14.8 - 16.2</td>
<td>15.5  14.8 - 16.2</td>
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<tr>
<td>Duration from prostate cancer diagnosis to death or censoring (years)</td>
<td>Median; quartile range</td>
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<td>2.3  1.1 - 4.7</td>
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<td>Mean; SD</td>
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<td>26.4  3.3</td>
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<td>Mean; SD</td>
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Table 2. Analysis of prostate cancer occurrence in cohort of 26,877 men

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<th>Body characteristic</th>
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<th>#Risk</th>
<th>#Event</th>
<th>HR</th>
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<td>BMI: Low or Normal</td>
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**trend p-value**

| 0.0003 |
| 0.02 |
Table 3. Proportions of advanced prostate cancer in relation to body characteristics

Percent with advanced prostate cancer [1] in quartiles of the body characteristics [2]

<table>
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<tr>
<th>Body characteristic</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Trend p-value</th>
</tr>
</thead>
<tbody>
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<td>Body mass index</td>
<td>37</td>
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</tr>
<tr>
<td>Waist circumference, cm</td>
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<td>44</td>
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</tr>
<tr>
<td>Body fat percentage</td>
<td>34</td>
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<td>38</td>
<td>50</td>
<td>0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>40</td>
<td>43</td>
<td>43</td>
<td>41</td>
<td>0.90</td>
</tr>
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</table>

[1] TNM stage 3 or 4
[2] Cases with unknown stage (17%) were excluded from the denominator
Table 4. Analysis of prostate cancer specific deaths in sub-cohort of 1813 men with prostate cancer

<table>
<thead>
<tr>
<th>Body characteristic</th>
<th>Range</th>
<th>#risk</th>
<th>#event</th>
<th>HR</th>
<th>95% conf. interval</th>
<th>HR</th>
<th>95% conf. interval</th>
</tr>
</thead>
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<td>BMI: Low or Normal</td>
<td>15.4 - 24.9</td>
<td>649</td>
<td>92</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>BMI: Overweight</td>
<td>25.0 - 29.9</td>
<td>920</td>
<td>147</td>
<td>1.08</td>
<td>0.83 - 1.40</td>
<td>1.10</td>
<td>0.85 - 1.43</td>
</tr>
<tr>
<td>BMI: Obese</td>
<td>30.0 - 52.7</td>
<td>244</td>
<td>51</td>
<td>1.43</td>
<td>1.01 - 2.01</td>
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<td>0.90 - 1.80</td>
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<td><strong>0.19</strong></td>
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<tr>
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<td>15.4 - 24.1</td>
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<td>63</td>
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</tr>
<tr>
<td>(quartile)</td>
<td>24.2 - 26.1</td>
<td>446</td>
<td>71</td>
<td>1.16</td>
<td>0.82 - 1.62</td>
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<td>0.76 - 1.50</td>
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<tr>
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<td>1.16</td>
<td>0.82 - 1.63</td>
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<tr>
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<td>(quartile)</td>
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<td>0.72 - 1.43</td>
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<td>0.62 - 1.23</td>
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<td>0.77 - 1.53</td>
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<td>102.0 - 156.0</td>
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<tr>
<td>(quartile)</td>
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<td>0.93</td>
<td>0.66 - 1.33</td>
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Height, cm (quartile)

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TNM stage

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[1] Trend over the categories, excl. NA
Table 5. Analysis of prostate cancer specific deaths in sub-cohort of 1813 men with prostate cancer, stratified by stage

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<td>#event</td>
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<td>95% conf. interval</td>
<td>#risk</td>
<td>#event</td>
<td>HR</td>
<td>95% conf. interval</td>
<td>#risk</td>
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<td>0.57 - 2.17</td>
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<td>0.53 - 2.35</td>
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<td>1.00</td>
<td>0.53 - 2.35</td>
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<td>BMI: Overweight</td>
<td>25.0 - 29.9</td>
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<td>24</td>
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<td>0.57 - 2.17</td>
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<td>20</td>
<td>1.12</td>
<td>0.53 - 2.35</td>
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<td>BMI</td>
<td>15.4 - 24.1</td>
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<td>0.53 - 3.08</td>
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<td>0.60 - 3.75</td>
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<td>(quartile)</td>
<td>24.2 - 26.1</td>
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<td>0.53 - 3.15</td>
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