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# Childhood height increases the risk of prostate cancer mortality

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## Abstract

**Background—**Adult body size is positively associated with aggressive and fatal prostate cancers. It is unknown whether these associations originate in early life. Therefore, we investigated if childhood height, body mass index (BMI; kg/m$^2$) and growth are associated with prostate cancer-specific mortality and survival.

**Methods—**Subjects were 125,208 men from Copenhagen School Health Records Register, born 1930–1969 with height and weight measurements at ages 7–13 years. Linkage to the Danish Cancer Registry and the Register of Causes of Death enabled identification of incident and fatal prostate cancers. Cox proportional hazards regressions were performed.

**Results—**630 men had prostate cancer recorded as the underlying cause of death. Childhood height at age 13 years was positively associated with prostate cancer-specific mortality (hazard ratio [HR]=1.2, 95% confidence interval [CI]: 1.1–1.3. Associations were significant at all other childhood ages. Growth analyses showed that height at age 13 years had a stronger association with prostate cancer-specific mortality than height at age 7, suggesting the association at age 7 is largely mediated through later childhood height. The tallest boys at age 13 years had a significantly worse survival, but only when restricted to a diagnosis at <60 years of age ($HR_{z\text{-score }1}$=1.7, 95% CI: 1.3–2.4). These associations were significant at all other childhood ages. Childhood BMI was not associated with prostate cancer mortality or survival.

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**Conflict of interest statement**

None declared.

**Conclusion—**Childhood height was positively associated with the hard endpoint of prostate cancer-specific mortality, which strengthens prior epidemiologic observations of a positive association with prostate cancer incidence.

### Keywords

body height; body mass index; child; cohort studies; growth; mortality; prostate neoplasms

## Introduction

Worldwide, prostate cancer is the second most common form of cancer affecting men and the fifth leading cause of cancer-related death.(1, 2) Prostate cancer incidence increases steeply with age, and the majority of men at late ages will have developed the disease.(3) However, most prostate cancers are fairly indolent malignancies with low potential for progression—only a small proportion of prostate cancers cause death(3–5). Nonetheless, aggressive prostate cancer tumors diagnosed in younger men have a higher cause-specific mortality rate than in most older age-groups.(6)

Several studies have investigated associations between adult height and body mass index [BMI; kg/m$^2$] and the risk of incident and fatal prostate cancers. Adult height is positively associated with risk, especially for the aggressive forms(1, 7) as well as fatal prostate cancer(1, 8). Moreover, accumulating evidence suggests that greater adult BMI increases the risk of aggressive and fatal prostate cancers.(1, 9, 10) Previously we showed that childhood height is positively associated with incident prostate cancer(11), but we found little evidence supporting a link with childhood adiposity.(12)

The high cause-specific mortality rate of prostate cancer diagnosed in younger men has been interpreted as putative evidence for important biological differences in early-versus late-onset prostate cancer.(6) It is thus possible that the risk factor profile differs for such cancers and that childhood anthropometrics have different associations with prostate cancer mortality and survival. Therefore, we investigated if childhood height, BMI and growth are associated with prostate cancer-specific mortality and survival among men from a large population-based cohort and whether these associations differed by age at death and diagnosis.

## Methods

### Subjects

Subjects were from the Copenhagen School Health Records Register, which contains computerized information on 372,636 children born 1930–1989.(13) Children underwent mandatory health exams at private or public schools in Copenhagen annually through 1983 and thereafter only at school entrance and exit unless the child had special health requirements. School doctors or nurses measured their heights and weights.(13)

Height and BMI values were transformed into z-scores using the Lamda, Median, Sigma method.(14) Height z-scores were based upon internal sex-, age- and birth cohort-specific references due to secular increases in height. BMI z-scores were based on an internal age-

and sex-specific reference selected from a period with a low and stable obesity prevalence. (15) If a measurement was taken at the exact age this z-score was used, otherwise z-scores were interpolated or extrapolated within a ±12 month period.(15

All Danish residents alive or born after 2 April 1968 were assigned a unique identification (ID) number by the Danish Civil Registration System.(16) If a child was in school at this time or later, the ID number was recorded on their health card, and if a child left school prior to this time, the ID number was retrieved.

Using the ID number, vital status was obtained by linkage to the vital statistics register. (16) Incident prostate cancers were ascertained through linkage to the Danish Cancer Registry, which contains information on malignancies.(17) The completeness is high due to mandatory reporting of tumours, the majority of which are morphologically verified, ensuring high validity.(17, 18) Information on prostate cancer death was obtained by linkage to the Danish Register of Causes of Death.(19) Coverage is high as it is compulsory to state the underlying cause of death, defined as the disease or condition which started the process leading to death, on the death certificate. Incident prostate cancer was defined by the International Classification of Diseases (ICD) 10 code C61 and prostate cancer death was defined as ICD-8 185 until 1994 and ICD-10 C61 thereafter. Fatal cases were defined by having a diagnosis of prostate cancer in the Cancer Registry *and* having prostate cancer recorded as the underlying cause of death in the Register of Causes of Death.

## Study population

Men eligible for this study were those born 1930–1969, with an ID number and who were alive and living in Denmark at age 40 years. Among the 188,360 boys in the cohort, 153,441 were born 1930– 1969. Exclusions were made for not having an ID number (*N*=19,794), emigration (*N*=2,778), death (*N*=3,888) or loss to follow-up (*N*=105) prior to age 40 years. Additionally, men without a prostate cancer diagnosis date (*N*=1), missing height and/or weight measures at all childhood ages (*N*=1,663) and outlying height or BMI z-scores at all ages (z-score <-4.5 or >4.5) (*N*=4) were excluded. Twenty-five men were registered in the Register of Causes of Death with prostate cancer as the underlying cause of death without being recorded in the Cancer Registry and were not included as cases. Follow-up ended on the date of death (any or prostate cancer specific death), emigration, loss to follow-up or 31 December 2011, whichever came first.

The present study was approved by the Danish Data Protection Agency (*Datatilsynet*).

## Statistical methods

First we investigated associations between childhood height and prostate cancer-specific mortality using all eligible cohort subjects. Cox proportional hazards regression with age as underlying time axis was used to examine the association between height z-scores at each age from 7–13 years and the risk of prostate cancer death. All analyses were stratified by 5-year birth cohorts. Similarly, associations with BMI z-scores, with and without adjustment for height, were investigated. In the sub-sample of men with height measurements at ages 7 and 13 years, we conducted longitudinal growth analyses which were mutually adjusted for height at both ages. The growth parameter estimates were compared using the Wald test. The

linearity of the associations was assessed by linear splines and no deviations were detected (all P≥0.18). We investigated potential non-proportionality by testing if the associations differed by categories of age at prostate cancer death (40–59 and ≥60 years) using a likelihood ratio test. As the rate of prostate cancer-specific mortality is higher for individuals diagnosed at young ages, typically before age 60 years, this was chosen as the cut-off. No interactions between birth cohort and childhood body size on the risk of prostate cancer mortality were found (not shown).

Secondly we examined associations between childhood height and BMI at each age from 7–13 years and prostate cancer-specific survival by categories of age at prostate cancer diagnosis (40–59 and ≥60 years) among men with a prostate cancer diagnosis. We performed Cox proportional hazards regressions with time since diagnosis as the underlying time axis. All analyses were stratified by 5-year birth cohorts and age at diagnosis in 1-year categories. Longitudinal growth analyses with mutual adjustment for height at 7 and 13 years were also conducted. As non-linearity was detected in the associations between childhood body size and prostate cancer survival, childhood body size was modelled using linear splines with a knot at a z-score of 0. Point estimates are presented for z-scores of +1 and −1. We tested if the associations differed by categories of age at prostate cancer death using a likelihood ratio test. In the longitudinal growth analyses, height at age 7 years was modelled with linear splines with a knot at a z-score of 0 and height at age 13 was included as a continuous variable as non-linearity was not detected (P=0.66). No violations of the proportional hazards assumption or interactions between birth cohort and body size on prostate cancer survival were found (not shown).

## Results

The study included 125,208 boys, of whom 112,030 had measurements at both ages of 7 and 13 years. The median values of height and weight increased with age in childhood (Table 1). Although boys grew between 7 and 13 years, height z-scores only changed by a median of −0.01 (10, 90$^{th}$ percentiles: −0.55, 0.71) and BMI z-scores only changed by a median of 0.01 (10, 90$^{th}$ percentiles: −0.73, 0.89). During the 42-year period of this study and 2.7 million person-years of follow up, 3,355 men were diagnosed with prostate cancer and 630 men had it recorded as the underlying cause of death. The median age at prostate cancer death was 68 years (range: 47–82 years) and the median time from prostate cancer diagnosis to prostate cancer death was 2 years (range: 0–17 years).

In the analyses of prostate cancer-specific mortality, childhood height was positively associated with prostate cancer death and the associations were significant at all childhood ages (Table 2). There was a tendency for the association to be stronger among men dying from prostate cancer at younger ages (<60 years) compared with men who died from it at later ages (≥60 years), although this difference was not statistically significant (all P≥0.38, Supplementary Table 1). In the longitudinal growth analysis, height at age 7 years had no association whereas height at age 13 was strongly and significantly associated with prostate cancer-specific mortality. A comparison of the relative importance of height at both ages showed that height at age 13 years had a statistically stronger association with prostate cancer death than did height at age 7 (Table 3). In accordance with this, boys who were

consistently tall with height z-scores of +1 at both ages 7 and 13 years had a significantly higher risk of prostate cancer-specific mortality (hazard ratio [HR]=1.2, 95% confidence interval [CI]: 1.1–1.3) than boys who were consistently average in height with z-scores of 0 at both ages. We found indications that growth in height had a stronger association with dying from prostate cancer <60 versus ≥60 years. Height at 13 years had a borderline statistically significant stronger association with death from prostate cancer at <60 years than did height at age 7 (P=0.05). No differences were detected in the effects of height at 7 and 13 years among men who died from prostate cancer at ≥60 years (P=0.09) (Supplementary Table 2). We detected no associations between childhood BMI and prostate cancer-specific mortality at any age (Supplementary Table 3–4).

In the analyses of prostate cancer survival, the tallest boys had a worse survival if diagnosed with prostate cancer <60 years, whereas there was no association if diagnosed ≥60 years (Table 4). The associations between childhood height and the two categories of age at diagnosis were significantly or borderline significantly different at all childhood ages (Table 4). In the longitudinal growth analyses, no associations between height and prostate cancer survival were detected (Supplementary Table 5). Childhood BMI was not associated with prostate cancer survival (Supplementary Tables 6–7).

## Discussion

We found that childhood height is positively and significantly related to the later risk of prostate cancer-specific mortality as well as a poorer prostate cancer-specific survival if diagnosed <60 years. The associations between childhood height and prostate cancer-specific mortality were stronger in magnitude than those for incident prostate cancer.(11) Had the associations been identical in strength, this would imply that childhood height is unrelated to prostate cancer-specific survival. However, our results suggest that childhood height is associated with the severity and not just the occurrence of the neoplasm.

In longitudinal growth analyses, height at age 13 years had a stronger association with prostate cancer-specific mortality than did height at age 7. These results, suggest that associations with height at age 7 years and prostate cancer-specific death are, to a great extent, mediated through height at age 13. Further, boys who were generally tall during childhood had a significantly increased risk of dying from prostate cancer compared with boys who were of average height. The majority of these boys did not have large changes in their height z-scores from ages 7 to 13 years; boys who were tall at 7 years were also tall at 13 years. Thus, our findings imply that tallness poses a risk for prostate cancer mortality irrespective of whether a boy was tall only at age 13 or throughout childhood. These results are also analogous to our previous findings for incident prostate cancer.(11) In contrast, childhood growth in height was not associated with survival after a prostate cancer diagnosis. Childhood BMI was not associated with prostate cancer-specific mortality or survival, which is similar to results from our previous study on childhood BMI and incident and metastatic prostate cancers.(12)

Several studies have suggested that the age at onset of prostate cancer is a prognostic factor for the malignancy.(6, 20) Thus, men with early-onset prostate cancers have a higher cause-

specific mortality rate than men with late-onset prostate cancers, which is likely attributable to the severity of the disease.(6) Furthermore, early-onset prostate cancers often have a strong genetic component, possibly indicating etiologic heterogeneity by age.(6) There is no consensus on which age cut-point defines subsets with different risk profiles, but studies have generally stratified analyses at mid-life and we similarly choose a cut-point of 60 years. Potentially due to a limited number of early-onset prostate cancers, we only observed a weak indication for effect modification by age in the childhood height and prostate cancer-specific mortality analyses, as opposed to the statistically significant and borderline significant effect modification in the childhood height and prostate cancer-specific survival analyses. Our results suggest that prostate cancers diagnosed at early and later ages in men have different severities, and support that screening efforts need to balance potential harms and benefits to maximize their effectiveness. In the absence of biomarkers that have a high prognostic discriminant ability, a feasible approach to the problem of overdiagnosis may be to use a targeted screening approach based on an algorithm that could also include phenotypic indicators such as age and height.

Adult body size is associated with prostate cancer incidence and mortality.(1) Taller men have an increased risk of dying from prostate cancer.(8) Moreover a higher adult BMI is positively associated with prostate cancer-specific mortality and death among men with prostate cancer.(9) Our findings of an association between childhood height and prostate cancer-specific mortality are consistent with the findings for adult height. However, we did not find any associations with childhood BMI, which suggests that only adiposity accrued after childhood is a key risk factor for prostate cancer aggressiveness and death.

The positive association between childhood height and prostate cancer mortality suggests that early carcinogenic processes may affect the susceptibility of the cancer to being aggressive in nature. Potential mechanisms underlying this association, however, remain elusive. One suggestion is that tall men are at a higher risk of impaired venous drainage (varicocele) of the male reproductive system, resulting in extremely high prostatic testosterone levels thus promoting the development and progression of prostate malignancy.(21) Moreover, child and adult height are correlated(22), thus tracking of height may explain part of the association between childhood height and prostate cancer mortality. However, as we do not have information on adult height, we cannot assess and disentangle these effects.

The validity of the specified causes of death relies mainly upon physicians' recordings on death certificates. Although post-mortem examinations are not performed routinely on all deaths, we required men to have both a verified diagnosis of prostate cancer in the Danish Cancer Registry and a death certificate stating prostate cancer as the underlying cause of death, which likely increases the specificity of our outcome. Trends in prostate cancer incidence and mortality rates vary across European countries.(23) In Denmark, the age-standardized incidence rate of prostate cancer increased steeply after the introduction of prostate specific antigen testing whereas the age-standardized mortality rate remained largely constant(24) suggesting that the cause of death determination is likely unaffected by the intensity of diagnostic procedures. The major strengths of this population-based study include the mandatory health exams, with multiple measurements of heights and weights, among a large group of school children, who were followed for an extensive period.

In conclusion, our results suggest that childhood height is positively associated with a subsequently increased risk of prostate cancer-specific mortality as well as a worse survival if diagnosed with prostate cancer <60 years.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Abbreviations

| | |
|---|---|
| **BMI** | Body Mass Index |
| **CI** | Confidence Interval |
| **HR** | Hazard Ratio |
| **ID** | Identification |
| **ICD** | International Classification of Diseases |

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- Taller children have a higher risk of prostate cancer-specific mortality
- Taller children have a worse survival if diagnosed with prostate cancer ≤60 years
- Childhood BMI was not associated with later risk of dying from prostate cancer

**Table 1**

Median height and BMI values for 125,208 boys aged 7–13 years and born from 1930–1969 in the Copenhagen School Health Records Register according to case status (prostate cancer as the underlying cause of death)

| | Height (cm) | | | | BMI (kg/m$^2$) | |
|---|---|---|---|---|---|---|
| | N | | Non-case | Case | Non-case | Case |
| Age (years) | Non-case | Case | Median (5–95%) | Median (5–95%) | Median (5–95%) | Median (5–95%) |
| 7 | 117,509 | 574 | 122.1 (113.7–130.8) | 121.9 (113.2–130.8) | 15.3 (13.7–17.4) | 15.3 (13.9–17.3) |
| 8 | 119,785 | 590 | 127.4 (118.6–136.5) | 127.0 (117.8–136.3) | 15.6 (14.0–18.0) | 15.6 (14.2–17.8) |
| 9 | 119,588 | 591 | 132.8 (123.5–142.3) | 132.5 (122.5–142.4) | 16.0 (14.2–18.7) | 16.0 (14.3–18.4) |
| 10 | 119,482 | 589 | 137.8 (128.2–147.8) | 137.8 (127.2–147.8) | 16.3 (14.4–19.5) | 16.3 (14.6–19.0) |
| 11 | 119,496 | 589 | 142.6 (132.6–153.2) | 142.2 (132.1–153.0) | 16.7 (14.0–20.3) | 16.7 (14.9–19.9) |
| 12 | 118,977 | 581 | 147.4 (136.8–159.0) | 147.2 (136.7–158.7) | 17.2 (15.0–21.1) | 17.2 (15.2–20.4) |
| 13 | 117,828 | 565 | 153.0 (141.2–166.7) | 152,5 (140.8–165.6) | 17.7 (15.3–21.8) | 17.7 (15.6–21.2) |

BMI: Body Mass Index

**Table 2**

Hazard ratios and 95% confidence intervals for the risk of prostate cancer-specific mortality per unit increase in height z-score in childhood*

| Age (years) | N | Cases | Hazard Ratio | 95 % Confidence Interval |
|---|---|---|---|---|
| 7 | 118,083 | 574 | 1.15 | 1.06–1.25 |
| 8 | 120,375 | 590 | 1.15 | 1.06–1.25 |
| 9 | 120,179 | 591 | 1.17 | 1.08–1.27 |
| 10 | 120,071 | 589 | 1.17 | 1.08–1.27 |
| 11 | 120,085 | 589 | 1.18 | 1.09–1.28 |
| 12 | 119,558 | 581 | 1.20 | 1.11–1.31 |
| 13 | 118,393 | 565 | 1.21 | 1.11–1.31 |

*Stratified by 5-y birth cohorts

**Table 3**

Hazard ratios and 95% confidence intervals for the risk of prostate cancer-specific mortality per unit increase in height z-score in childhood in mutually adjusted longitudinal growth models *

| Age (years) | N | Cases | Hazard Ratio | 95 % Confidence Interval | P-value[a] |
|---|---|---|---|---|---|
| 7 | 112,030 | 519 | 0.90 | 0.75–1.07 | |
| 13 | 112,030 | 519 | 1.34 | 1.13–1.60 | 0.02 |

*Stratified by 5-y birth cohorts

[a]Likelihood ratio test of whether the estimates are alike

**Table 4**

Hazard ratios and 95% confidence intervals for the risk of prostate cancer-specific mortality, among those diagnosed with prostate cancer, per unit increase in height z-score in childhood and by age at diagnosis*

| | | | | Height z-scores | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | −1 | | 0 | 1 | | |
| Age (years) | Age at diagnosis (years) | N | Cases | Hazard Ratio | 95 % Confidence Interval | Hazard Ratio | Hazard Ratio | 95 % Confidence Interval | P-value[a] |
| 7 | 40–59 | 493 | 155 | 1.35 | 0.95–1.94 | 1.00 (ref.) | 1.75 | 1.25–2.45 | |
| | ≥ 60 | 2627 | 419 | 1.15 | 0.94–1.41 | 1.00 (ref.) | 1.07 | 0.90–1.28 | 0.05 |
| 8 | 40–59 | 503 | 157 | 1.29 | 0.88–1.89 | 1.00 (ref.) | 1.69 | 1.21–2.36 | |
| | ≥ 60 | 2671 | 433 | 1.14 | 0.93–1.40 | 1.00 (ref.) | 1.01 | 0.85–1.21 | 0.03 |
| 9 | 40–59 | 503 | 159 | 1.37 | 0.93–2.01 | 1.00 (ref.) | 1.75 | 1.28–2.39 | |
| | ≥ 60 | 2675 | 432 | 1.16 | 0.95–1.42 | 1.00 (ref.) | 1.06 | 0.89–1.26 | 0.03 |
| 10 | 40–59 | 503 | 159 | 1.42 | 0.97–2.09 | 1.00 (ref.) | 1.75 | 1.29–2.39 | |
| | ≥ 60 | 2664 | 430 | 1.18 | 0.96–1.44 | 1.00 (ref.) | 1.10 | 0.92–1.30 | 0.04 |
| 11 | 40–59 | 505 | 159 | 1.36 | 0.93–2.00 | 1.00 (ref.) | 1.71 | 1.25–2.35 | |
| | ≥ 60 | 2670 | 430 | 1.19 | 0.97–1-45 | 1.00 (ref.) | 1.12 | 0.95–1.33 | 0.07 |
| 12 | 40–59 | 505 | 159 | 1.44 | 0.96–2.15 | 1.00 (ref.) | 1.77 | 1.30–2.41 | |
| | ≥ 60 | 2634 | 422 | 1.15 | 0.94–1.42 | 1.00 (ref.) | 1.10 | 0.93–1.30 | 0.03 |
| 13 | 40–59 | 493 | 151 | 1.38 | 0.91–2.11 | 1.00 (ref.) | 1.74 | 1.28–2.38 | |
| | ≥ 60 | 2583 | 414 | 1.07 | 0.88–1.31 | 1.00 (ref.) | 1.08 | 0.90–1.29 | 0.03 |

*Stratified by 5-y birth cohorts and 1-year age at diagnosis categories

[a]Likelihood ratio test of whether the estimates are alike