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Childhood height increases the risk of prostate cancer mortality

J. Aarestrup [a], M. Gamborg [a], M.B. Cook [b], J.L. Baker [a,c,*]

[a] *Institute of Preventive Medicine, Bispebjerg and Frederiksberg Hospitals, The Capital Region, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark*
[b] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, 9609 Medical Center Drive, MSC 9774, Bethesda, MD 20892-9774, USA*
[c] *Novo Nordisk Foundation Center for Basic Metabolic Research, Section on Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 1, 1. Floor, 2100 Copenhagen Ø, Denmark*

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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 the 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 $[HR]_{per\ z\text{-}score} = 1.2$, 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 ($HR_{z\text{-}score\ of\ 1} = 1.7$, 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.

Abbreviations: BMI; body mass index; CI; confidence interval; HR; hazard ratio; ID; identification; ICD; International Classification of Diseases

* *Corresponding author at:* Tel.: +45 38 16 30 58.
E-mail addresses: Julie.Aarestrup@regionh.dk (J. Aarestrup), Michael.Orland.Gamborg@regionh.dk (M. Gamborg), cookmich@mail.nih.gov (M.B. Cook), Jennifer.Lyn.Baker@regionh.dk (J.L. Baker).

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

1. 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 tumours 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.

2. Methods

2.1. Subjects

Subjects were from the Copenhagen School Health Records Register, which contains computerised 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 $\pm$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.

2.2. 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