Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2009 March 25.

Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2008 September ; 17(9): 2325–2336. doi: 10.1158/1055-9965.EPI-08-0342.

Height and Prostate Cancer Risk:

A Large Nested Case-Control Study (ProtecT) and Meta-analysis

Luisa Zuccolo[1], **Ross Harris**[1], **David Gunnell**[1], **Steven Oliver**[2], **Jane Athene Lane**[1], **Michael Davis**[1], **Jenny Donovan**[1], **David Neal**[3], **Freddie Hamdy**[4], **Rebecca Beynon**[1], **Jelena Savovic**[1], and **Richard Michael Martin**[1]

[1]Department of Social Medicine, University of Bristol, Bristol, United Kingdom

[2]Department of Health Sciences, University of York and the Hull York Medical School, Heslington, York, United Kingdom

[3]Surgical Oncology (Uro-Oncology S4), Departments of Oncology and Surgery, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom

[4]Academic Urology Unit, University of Sheffield, Royal Hallamshire Hospital, Sheffield, United Kingdom

Abstract

Background—Height, a marker of childhood environmental exposures, is positively associated with prostate cancer risk, perhaps through the insulin-like growth factor system. We investigated the relationship of prostate cancer with height and its components (leg and trunk length) in a nested case-control study and with height in a dose-response meta-analysis.

Methods—We nested a case-control study within a population-based randomized controlled trial evaluating treatments for localized prostate cancer in British men ages 50 to 69 years, including 1,357 cases detected through prostate-specific antigen testing and 7,990 controls (matched on age, general practice, assessment date). Nine bibliographic databases were searched systematically for studies on the height-prostate cancer association that were pooled in a meta-analysis.

Results—Based on the nested case-control, the odds ratio (OR) of prostate-specific antigen-detected prostate cancer per 10 cm increase in height was 1.06 [95% confidence interval (95% CI): 0.97-1.16; p_{trend} = 0.2]. There was stronger evidence of an association of height with high-grade prostate cancer (OR: 1.23; 95% CI: 1.06-1.43), mainly due to the leg component, but not with low-grade disease (OR: 0.99; 95% CI: 0.90-1.10). In general, associations with leg or trunk length were similar. A meta-analysis of 58 studies found evidence that height is positively associated

Requests for reprints: Luisa Zuccolo, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, BS8 2PR, Bristol, United Kingdom. Phone: 44-117-928-7296; Fax: 44-117-928-7236. E-mail: l.zuccolo@bristol.ac.uk.

Contributions: The hypothesis was developed by D. Gunnell, R.M. Martin, and S. Oliver. L. Zuccolo and R. Harris conducted the statistical analyses. L. Zuccolo and R.M. Martin cowrote the first draft and L. Zuccolo coordinated completion of the article. R.M. Martin and L. Zuccolo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. R. Beynon, J. Savovic, and L. Zuccolo conducted the systematic review, deciding on inclusion/exclusion of manuscripts and extracting data for the meta-analysis. M. Davis and J.A. Lane managed the data collection and the study database. J. Donovan, D. Neal, and F. Hamdy designed the study and obtained funding for data collection. All authors critically commented on and edited earlier drafts and approved the final version of the article.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Department of Health disclaimer: The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Department of Health.

Europe PMC Funders Author Manuscripts

with prostate cancer (random-effects OR per 10 cm: 1.06; 95% CI: 1.03-1.09), with a stronger effect for prospective studies of more advanced/aggressive cancers (random-effects OR: 1.12; 95% CI: 1.05-1.19).

Conclusion—These data indicate a limited role for childhood environmental exposures—as indexed by adult height—on prostate cancer incidence, while suggesting a greater role for progression, through mechanisms requiring further investigation.

Introduction

A growing body of evidence indicates that greater height—a marker of diet and health throughout the growing years (1)—is positively associated with prostate cancer risk. Many cohort and case-control studies published thus far show an increase in risk of up to 20% to 40% for the top compared with the bottom height quantiles, suggesting the possibility of a long-term influence of childhood nutrition on carcinogenesis (2). Many studies are based on very small numbers, overall findings are inconsistent, and few studies assess the components of height (leg and trunk length) in relation to prostate cancer. Examining the relationship of cancer with leg and trunk length may indicate sensitive periods during childhood growth when risk factors or biological mechanisms underlying height-cancer associations operate (3). It has been shown that prepubertal growth is due more to an increase in leg length rather than trunk length (4), and leg length is sensitive to maternal smoking in pregnancy (5), socioeconomic conditions, nutrition (in particular milk intake; ref. 6), and energy intake in prepubertal children (7). Trunk length reflects factors influencing pubertal growth (7, 8) and is affected by “shrinkage” in late adult life due to compression of the spine (9).

The most plausible biological mechanism for the association of height with prostate cancer is that involving insulin-like growth factor-I (IGF-I) levels in childhood, of which height is a marker (10). In turn, IGF-I levels in adulthood are positively associated with prostate cancer (11).

We investigated the relationship of height and its components to prostate cancer in a case-control study nested within the intensive population-based prostate-specific antigen (PSA) testing phase of the Prostate Testing for Cancer and Treatment (ProtecT) study (12).

In addition, we placed our results in the context of the available evidence by systematically reviewing the published literature on the association between height and prostate cancer and meta-analyzing dose-response estimates derived from retrieved studies. Two previous reviews have been published on this topic (3, 13), but only one included a meta-analysis and was not specifically focused on height as it was part of a broader study on body size and composition (13). Compared with previous studies, our analysis explored in greater detail sources of heterogeneity, including publication bias and the influence of PSA testing on effect estimates (14, 15). We performed additional analysis in the ProtecT study and the meta-analysis by distinguishing between clinical subgroups (defined by grade and/or stage), where possible, to explore whether height could have differing effects on prostate cancer initiation versus progression.

Subjects and Methods

Nested Case-Control Study

Prostate Cancer Detection—ProtecT is an ongoing randomized controlled trial, evaluating the effectiveness of treatment for clinically localized prostate cancer (12). Men aged 50 to 69 years registered with 400 general practices located around nine U.K. cities are invited to a prostate check clinic where PSA testing is carried out. Men with an increased

Europe PMC Funders Author Manuscripts

PSA (≥3 ng/mL) are invited for digital rectal examination, repeat PSA test, and transrectal ultrasound-guided biopsy (10 cores).

Men with a normal biopsy are offered repeat biopsy if the PSA is persistently increased or if there is a high index of clinical suspicion (chiefly evidence of high-grade prostatic intraepithelial neoplasia or suspicious features on initial biopsy). Histologic material obtained at biopsy is reviewed by specialized pathologists and given a Gleason score; tumors with a Gleason score ≥7 were considered high grade. Clinical staging used the tumor-node-metastasis staging system (16). Cases with stages T1-T2 and NXM0 were classified as localized cancers; those with T3-T4 were classified as advanced prostate cancers.

Case-Control Selection—This study is nested within the ProtecT PSA-tested cohort. Cases were men aged 50 to 69 years with histologically confirmed prostate cancer, detected among the 59,217 men who attended for PSA testing and had their PSA result recorded between November 2001 and November 2006. Prostate cancers diagnosed over 2 years after the initial PSA test were excluded from this analysis to distinguish “PSA-detected” from possible “incident” cancers. During this period, 6,329 men (11%) had increased PSA levels; of these, 2,022 (32%) had histologically confirmed prostate cancer.

All participants in the ProtecT cohort who had no evidence of prostate cancer were eligible for selection as controls. These included all men with a PSA below 3.0 ng/mL and any men with a PSA above this threshold who were biopsy negative. Cases were frequency matched to up to six controls by age of attendance at the check clinic (5-year age bands) and the general practice from which they were recruited. As the clinics were held and completed in each general practice in turn, matching for general practice automatically matched for the calendar date of recruitment.

All study participants gave fully informed consent for the use of their data for research purposes. The study received ethical approval from Trent MREC.

Exposure Assessment—All participants were asked to complete a health and lifestyle questionnaire after the check clinic but before their PSA result was available. The questionnaire included the following questions on height and leg length: “How tall are you?” (feet and inches) and “What is your inside leg measurement? (If you do not know, please examine a pair of your trousers)” (inches). All measures were converted to centimeters, and trunk length was calculated as total height minus leg length (estimated from inside leg measurement). Self-reported data on current weight, lifestyle, diet, comorbidities, occupation, ethnicity, and early-life factors (including birth weight and number of siblings) were also obtained from the questionnaires.

Overall 1,419 (70% of the total) men with histologically confirmed prostate cancer [1,230 (87%) localized cancers] and 8,343 controls returned the questionnaire and completed the sections on height and leg length. Sixty-two cases and 353 controls were excluded because of implausible values; thus, the analysis was based on 1,357 (67% of the total) cases (1,180 localized) and 7,990 controls.

Statistical Analysis of the ProtecT Nested Case-Control Study

Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association of height, leg, and trunk length with PSA-detected prostate cancer. As the men were stratum-matched in broad 5-year age bands (5 years), and the risk of prostate cancer increases steeply with age, age as a continuous variable was also entered in all models. ORs were compared across quartiles of height measures, using cutoffs

derived from the distribution of controls and the lowest quartile as the reference group. Estimates of dose-response effects were then derived, per 10 cm increase in height and 5 cm increase in leg or trunk length, and per SD increase for all exposures, by fitting models with the exposures as continuous variables. Wald tests were used to test for linear trend across the height distribution. Additional models for leg length were adjusted for trunk length and vice versa, to account for total height and investigate whether the biologically relevant measurement is disproportion or absolute length of the leg or trunk (17). Genetic susceptibility, as indexed by family history of prostate cancer, and early life factors correlated with adult height were adjusted for in multivariable models. These factors included self-reported birth weight, number of siblings, and occupational socioeconomic class (dichotomized as manual and nonmanual, according to their main occupation throughout life). Number of siblings and socioeconomic class may index some of the putative risk factors for prostate cancer that height is a marker for, rather than confound the height-cancer association, so the fully adjusted multivariable models were interpreted with caution.

To investigate whether associations of height with prostate cancer differed for sporadic compared with familial tumors, age, or ethnic groups—which have very different baseline rates of incident and fatal disease—we tested for interactions using likelihood ratio tests.

Associations of cancer risk with height measures were assessed separately by stage, using multinomial logistic regression adjusted for the matching factors, with the outcome variable grouped into three categories: controls, localized cases (stage T1 or T2; NXM0), and advanced cases (stage T3 or T4). Similarly, low-grade (Gleason sum <7) and high-grade (Gleason sum ≥7) cases were compared with controls in multinomial regression models. Heterogeneity in associations of height with localized compared with advanced stage or low-grade compared with high-grade cancers were tested using Wald tests.

A different probability of detecting prostate cancer in taller men compared with shorter men could bias the estimates of height-prostate cancer association. To evaluate the likelihood of this particular detection bias, the mean percentage variation of PSA levels across quartiles of height among controls was estimated by fitting linear regression models to logged PSA values, adjusting for age, center, and date of PSA testing.

Stata 10.1 was used for all statistical analyses (Stata Corp.).

Systematic Review

This review was undertaken as part of a systematic review on the associations of food, nutrition, and physical activity with prostate cancer, funded by the World Cancer Research Fund (18). The review protocol is publicly available (19) and details on searches, inclusion criteria, data extraction procedures, and statistical analysis are available in the Supplementary Methods.

We fitted to the data both fixed-effect and random-effects models; we gave preference to the random-effects meta-analysis, which accounts for between-study heterogeneity.

Sensitivity Analysis

Study Quality—No set of quality criteria on the design and analysis of observational studies is available. It is generally agreed that cohort studies provide higher quality/more robust evidence than case-control studies. Therefore, results from prospective studies (including cohort, case-cohort and nested case-control, and hereafter referred to as “cohort”) were analyzed separately from case-control studies, and further subgroup analyses were done on cohort results only. For the initial (main) pooled analysis, case-control studies were

classified based on the selection of controls as stated by the authors. We indicated as "same population" case-control studies those in which the sampled controls were such that they would have become cases (according to the study's definition of case) had they developed the disease, and all the others as "non-same population," which we considered to be of lower quality. Differences across study design were formally tested by fitting meta-regression models.

Publication Bias—Most prospective studies collect baseline data on anthropometry. Out of 31 publications from cohort studies included in this meta-analysis, 19 reported on height or anthropometry as (one of) their primary exposure(s) in the abstract: 18 from the systematic review and the ProtecT nested case-control study. However, 12 articles, not mentioning height in the title or abstract, included results on the height-prostate cancer association in the full text and we classified these as "incidental" findings. To assess whether positive results on the height-prostate cancer association were more likely to be published and included in the abstract, we further distinguished between primary versus incidental reporting and tested for the difference in the pooled effect estimates by fitting a linear meta-regression model.

Detection Bias—The advent of widespread use of PSA screening started in the early 1990s and changed the nature of the cases being identified from more advanced to early/small lesions. Choosing 1990 as the temporal cutoff, we did a further subgroup analysis, stratifying on whether the follow-up period was mostly pre-PSA (>50% of follow-up occurring <1990) or during the PSA era. The contribution of the proportion of pre-PSA follow-up time to explaining heterogeneity was explored in a meta-regression analysis.

Biological Significance—Because it is not known whether the mechanisms underlying the association with height act on progression rather than initiation, increasing the risk of poorly rather than well-differentiated lesions, we did subgroup analyses after restricting to data on advanced or aggressive cancers (available from 13 cohort studies). We referred to "advanced or aggressive" cases if the article specified any of the following in their case definition: (*a*) T stage 3 to 4 on the American Joint Committee on Cancer 1992 classification, (*b*) advanced cancer, (*c*) advanced or metastatic cancer, (*d*) metastatic cancer, (*e*) stage C or D on the Whitmore/Jewett scale, (*f*) fatal cancer, (*g*) "high-stage" or "high-grade," or (*h*) Gleason score ≥7.

Due to the poor reporting of ethnicity, no stratified analysis was attempted. Results on subgroups of black men available from three cohort (20, 21) and two same population case-control studies (22, 23) from the United States were presented in narrative form.

Results

ProtecT Nested Case-Control Study

Of the 1,357 PSA-detected cases of prostate cancer included in the analysis, 173 had advanced-stage disease (missing for 4 cases) and 402 had Gleason score ≥7 (missing for 19 cases; ≥8 for 59 cases). The distribution of demographic, anthropometric, and socioeconomic characteristics of the 1,357 cases and 7,990 controls are presented in Table 1.

There was a 6% (95% CI, −3;-16%) increased risk of PSA-detected prostate cancer per 10 cm increase in height but the statistical evidence supporting this association was weak (p_{trend} = 0.2). There was no evidence that associations were stronger comparing leg length versus trunk length (Table 2). Comparable results were found for localized and advanced-stage prostate cancer end points, for all height measures (all *p* for differences in effect estimates

by stage ≥0.74; Table 2). Models including simultaneously leg and trunk length yielded very similar effect estimates to the ones from this main analysis (data not shown).

There was no evidence of an increased risk of low-grade tumors with increasing height, leg length, or trunk length. However, for high-grade tumors, we found strong evidence of a 23% increase in risk per 10 cm increase in height ($p_{trend} < 0.01$), with a p value of 0.02 for the difference in height associations for low-grade compared with high-grade cancers (Table 2). This seemed to be mainly due to the leg component and in particular to long-for-total-height legs, as in a model including both height components there remained some evidence for an effect of leg length (OR per 5 cm increase, 1.13; 95% CI, 1.01-1.27; $p_{trend} = 0.04$), but less so for trunk length (OR per 5 cm increase, 1.09; 95% CI, 0.98-1.21; $p_{trend} = 0.12$). As a sensitivity analysis, we reclassified as high grade only those cases with Gleason ≥8 and obtained similar point estimates with wider confidence intervals due to the limited number of cases ($n = 59$). Results were very similar when ORs were estimated per SD increase in height (SD 6.7 cm), leg length (SD 4.3 cm), and trunk length (SD 4.7 cm; data not shown). Further adjustments for family history of prostate cancer, socioeconomic position, birth weight, or number of siblings did not change the estimates and are thus not reported. There was no evidence of effect modification by family history of prostate cancer, age, or self-reported ethnic origin.

An analysis adjusted for age, center, and date of PSA testing showed evidence that PSA values were on average 9% lower (95% CI, 4-14%, $p = 0.001$) for controls in the tallest quartile compared with those in the shortest quartile. For both leg and trunk length, the corresponding average PSA difference was 6% (95% CI, 1-10%, $p = 0.02$).

Systematic Review

The search strategy for the broad World Cancer Research Fund review yielded 19,448 hits, of which 1,070 were retrieved for full-text screening. From these, results on 30 cohort (20, 21, 24-48) and 27 case-control studies (22, 23, 49-73) could be included in the current meta-analysis (Fig. 1). Table 3 presents the characteristics of studies identified through the systematic searches and included in the meta-analysis. We included 20 of the 21 cohorts and all 18 case-control studies that were in the meta-analysis of MacInnis et al. (13), although the article by Giovannucci et al. (74) was excluded as we included a more recent report from the same study (43). Additionally, we included three more cohorts (36, 42, 75) and five case-control studies (57, 60, 64, 65, 70) published in the period covered by MacInnis' searches (up to October 31, 2004), and six (26, 35, 38, 39, 46, 47) and four (61, 66, 67, 69) new studies published between November 1, 2004, and July 31, 2007.

Overall, the meta-analysis pooling adjusted results from all 58 studies found evidence of a modest increase in risk of prostate cancer per 10 cm increase in height (random-effects OR, 1.06; 95% CI, 1.03-1.09; Fig. 2).

Results from the Egger test showed no evidence of small study effects for case-control studies, but some for prospective studies (cohorts, $p = 0.013$), which was not confirmed by Begg's test (cohorts: $p = 0.424$). There was no clear indication of asymmetry from the funnel plot, for any of the study designs (Supplementary Fig. S1).

Sensitivity Analysis

Study Quality—There was evidence of heterogeneity across study design ($p_{heterogeneity} = 0.001$; Fig. 2). Evidence for, and the magnitude of, the effect of height on prostate cancer were strongest for cohorts (OR, 1.09; 95% CI, 1.06-1.12, $n = 31$) and heterogeneity was lower ($I^2 = 23\%$) compared with all case-control studies. Only weak evidence of an

association of height with prostate cancer was found pooling same-population case-control studies (OR, 1.03; 95% CI, 0.97-1.10, I^2 = 36%, n = 15), and there was no evidence of a height-prostate cancer association for non-same population studies (OR, 0.98; 95% CI, 0.86-1.10; I^2 = 49%, n = 12; Fig. 2).

Publication Bias—There was evidence that pooled estimates differed according to whether the study reported on height as (one of) the primary exposure(s) or only incidentally ($p_{heterogeneity}$ = 0.002; Table 4). Based on data from the 19 publications focused on height-cancer associations, there was evidence of an 11% increase in prostate cancer risk per 10 cm increase in height (95% CI, 9-13%; I^2 = 7%). In contrast, the 12 studies reporting results as incidental findings yielded an OR of 1.01 (95% CI, 0.95-1.07; I^2 = 0%; Table 4).

Detection Bias—When stratifying on whether the follow-up period was mostly in the pre-PSA era (>50% of follow-up occurring <1990) or during the PSA era, we found similar effects ($p_{heterogeneity}$ = 0.12), with the former studies carrying more heterogeneity (I^2 = 29% versus 4%; Table 4).

Stage and Grade—Results based on advanced or aggressive cancer outcomes, including fatal disease, were available from 13 cohorts (12 from the review and the current ProtecT data) and showed marked between-study heterogeneity (I^2 = 47%; Table 4). The pooled estimate was higher than for the all-prostate cancer analysis based on prospective studies (OR, 1.12; 95% CI, 1.05-1.19).

Ethnicity—None of the five studies (all from the United States) presenting ethnicity-specific results found evidence of a height-prostate cancer association among high-risk ethnic groups. Habel et al. (20) reported a hazard ratio of 0.75 (95% CI, 0.42-1.31) comparing the top versus bottom quintile of height among black men in a cohort study. Results on black men were included in a publication with results from rounds I and II of the Cancer Prevention Study: the hazard ratio for prostate cancer comparing black men ≥70 versus ≤66 inches were 0.63 (95% CI, 0.32-1.25) and 0.89 (95% CI, 0.66-1.21), respectively (21). One case-control study did not find any difference in mean height comparing black cases and controls (23). Another presented an OR of 0.9 (95% CI, 0.6-1.5) comparing black men who were tall in childhood versus those who were short (22).

Discussion

Based on a meta-analysis of 58 studies, including new results from a nested case-control of PSA-detected prostate cancer (ProtecT), we found evidence that greater stature is associated with an increased prostate cancer risk. The overall magnitude of the effect was modest and varied with study design, yet results from cohort studies were compatible with a 6% to 12% increase in risk per 10 cm increase in height, and a 5% to 19% increase in risk for more advanced and/or aggressive cancers. Between-study heterogeneity was higher for case-control studies and for those cohorts including higher proportions of clinically detected, more advanced, or aggressive cancers. Results from the ProtecT nested case-control study were in line with the meta-analysis, with a stronger association for high-grade cancers.

This article benefits both from the strengths offered by analyzing original data and from the power of a meta-analysis based on inclusive systematic searches. The ProtecT case-control series is a population-based study that allowed us to investigate the separate effects of different height components on cancer risk, split by both stage and grade (76). These data are unlikely to be affected by detection bias for two reasons. First, all men had been invited to PSA testing and therefore the likelihood of cancer detection should be unrelated to confounding factors associated with access to or take up of PSA testing. Second, we showed

that PSA levels among controls were not positively associated with height, ruling out PSA-mediated access to biopsy as a potential explanation for our findings. Others also found a lower probability of detecting prostate cancer following PSA testing in taller men (77-79). Histologic confirmation of all cancers guarantees high specificity, and the 10-core biopsy protocol standardized the diagnosis of prostate cancer.

Strengths of the meta-analysis include its large power, derived from pooling results on 68,133 cases overall (54,152 from cohorts and 13,981 from case-control studies) and using dose-response models to assess trend effects per 10 cm increase in height. The extensive effort of the searches allowed us to minimize the effect of search and publication bias and to explore the pattern of reporting of the height-prostate cancer associations in prospective studies, as well as other potential sources of between-study heterogeneity that we had specified a priori. One of these was detection bias, potentially introduced by opportunistic use of PSA testing starting from the 1990s and leading to over-diagnosis of microscopic lesions that could have otherwise remained asymptomatic (80, 81). The effect of height could be artifactually overestimated, if taller people, often more educated and better off (82), were also more likely to undergo screening (81, 83). In the absence of data on national PSA screening practices and coverage over time for the countries included in the meta-analysis, we compared studies whose case ascertainment occurred mainly before 1990 (including predominantly clinically presenting cases) with those conducted subsequently (including increasing proportions of asymptomatic cases) and found a modestly increased effect of height for the former, against the suggestion of detection bias.

The dose-dependent nature of the observed height-cancer association adds strength to the evidence of an effect. However, whether this is causal should be assessed in light of the limitations of the studies included in this meta-analysis. Marked differences were observed across study designs, which could be explained by different biases affecting them, mainly selection bias from choice of control population or differential participation in case-control studies. More detailed investigation of heterogeneity across cohort studies suggested that positive results were more likely to be highlighted in the title or abstract of a publication, whereas those null findings that were published were usually only found in the body of any article. However, we found no evidence of a small-study effect, suggesting that such positive results may not be spurious.

None of the well-established risk factors are likely to explain the association with height. Age, which was adjusted for in all prospective studies but one, is expected to be inversely associated with height, if anything (because of marked cohort effects on height). Adjustment for family history of prostate cancer, carried out by some studies including this one, did not appreciably alter the effect estimates. Ethnicity did not seem to play a role in height-cancer associations, its relationship with stature not being obvious and ethnic-specific results for height-prostate cancer generally being similar to those from multiethnic populations. There are reports of an increased risk of more advanced/fatal prostate cancer associated with obesity (84); however, adjustment for body mass index did not change the observed effect estimates in our nested case-control study.

The present nested case-control and most of the studies included in the meta-analysis used self-reported data on height (and leg length), which are subject to measurement error. However, a validation carried out on data from the pilot phase of the study based on 4,708 men found a correlation of 0.96 for measured versus self-reported height, and no systematic misreporting (85), in line with the literature (86, 87). Data on measured and self-reported (inside leg) leg length were available for 3,673 men and showed that inside leg is a shorter measure of leg length (by around 6 cm). However, the difference was consistent across the range of leg lengths (85); thus, it would not result in a biased estimate of the leg length-

prostate cancer association. Moreover, any error is likely to be nondifferential, because both exposures were reported before knowledge of prostate cancer diagnosis. Such error would attenuate rather than explain the observed associations. The same is true for trunk length, derived from total height and leg length, which is likely to have produced a large measurement error. The ProtecT and other studies included in the meta-analysis recorded height of subjects late in life. However, shrinkage in middle-aged men could produce a dilution of the effect (especially for the trunk component) but should not affect cancer incidence or mortality (88).

The case definition in the ProtecT nested case-control only included men with screen-detected cancers. Although the association of height with prostate cancer is unlikely to be seen only in PSA-diagnosed men, this was done to ensure homogeneity in case definition. In any case, only two men in total were excluded who developed “incident” prostate cancer and the results are not altered by their inclusion in our analyses. It is possible that among our group of men with localized, low-grade prostate cancers, some would have been recently initiated and, despite aggressive potential in some, might not have had time to become more advanced. This heterogeneity in the localized, low-grade group may have attenuated any differences in associations between height and localized versus advanced cancers in the ProtecT study.

Between-study heterogeneity was investigated among the prospective studies. If height, as a marker of early environmental factors, had a different effect on various clinical subtypes of prostate cancer, then heterogeneity of findings could be due to differing proportions (or definitions) of the clinical subtypes. This was suggested by our ProtecT results for low-grade versus high-grade cancers and by the pooled estimate from cohorts reporting on advanced/aggressive cancers, consistently showing stronger effects compared with localized or well-differentiated cancers. It was also supported by the modest difference between estimates from pre-PSA and PSA era studies, the latter likely to include a higher proportion of smaller asymptomatic tumors. Therefore, factors associated with height could be risk factors for progression to fatal prostate cancer, rather than for the initiation of a well-differentiated tumor (76).

A plausible mechanism to explain the association of height with breast and prostate cancer risk involves dietary programming of the IGF-I system (89, 90). IGF-I plays an important role in the regulation of postnatal growth, and there is evidence that its levels in adulthood can be influenced (“programmed”) by dietary manipulation in early childhood (91). IGF-I levels are also associated with prepubertal growth in height (10), although no stronger association was found for leg versus trunk length in the current study and in three published cohort studies (24, 32, 92). In line with our height findings, there is some evidence that associations of IGF-I with prostate cancer are stronger for advanced versus local disease (11). It is therefore possible that variations in the IGF-I system may underlie associations of height with prostate cancers that are more likely to progress (11).

We conclude that there is evidence that height is positively associated with prostate cancer risk, but the magnitude of the effect is modest and the literature is influenced by publication bias. Overall, these data indicate only a small role for childhood environmental exposures—as indexed by adult height—on prostate cancer incidence. However, the positive association with high-grade cancers in ProtecT was consistent with the evidence on advanced or aggressive cancers from the meta-analysis, suggesting that early life environmental factors may play some role in the development and/or progression of neoplasia with a worse prognosis. Mechanisms that could underlie a height effect on the more aggressive forms of the disease now need to be elucidated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the tremendous contribution of all members of the ProtecT study research group and especially the following who were involved in this research: Prasad Bollina, Sue Bonnington, Debbie Cooper, Andrew Doble, Alan Doherty, Emma Elliott, David Gillatt, Pippa Herbert, Peter Holding, Joanne Howson, Mandy Jones, Roger Kockelbergh, Howard Kynaston, Teresa Lennon, Norma Lyons, Hilary Moody, Philip Powell, Stephen Prescott, Liz Salter, and Pauline Thompson. We thank Prof. Jonathan Sterne, Dr. Trudy Bekkering, Margaret Burke, and Dr. Anne-Marie Mayer for their help and assistance at different stages of the systematic review.

Grant support: The ProtecT trial is funded by the National Health Service Health Technology Assessment Program (projects 96/20/06, 96/20/99). The database and analytical support for epidemiological studies was supported by a project grant from the National Cancer Research Institute (administered by the Medical Research Council), which provided funding through ProMPT (Prostate Mechanisms of Progression and Treatment), and grants from Cancer Research UK (project grant C18281/A7062) and the World Cancer Research Fund (grants 2006/15 and 2007/07). The systematic review was funded by the World Cancer Research Fund. L. Zuccolo was partially funded by a fellowship from the Cancer Epidemiology Unit, CeRMS and CPO Piemonte, University of Turin, Turin (Italy), and partly by a Medical Research Council Special Training Fellowship. The sponsors had no role in the analysis, the interpretation of the results, the preparation of the manuscript, or the decision to submit the manuscript for publication.

References

1. Tanner, JM. Foetus into man: physical growth from conception to maturity. Ware (United Kingdom): Castlemead Publications; 1989.
2. Gunnell D. Can adult anthropometry be used as a ‘biomarker’ for prenatal and childhood exposures? Int J Epidemiol. 2002; 31:390–4. [PubMed: 11980801]
3. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JMP. Height, leg length, and cancer risk: a systematic review. Epidemiol Rev. 2001; 23:313–42. [PubMed: 12192740]
4. Leitch I. Growth and health. Br J Nutr. 1951; 5:142–51. [PubMed: 14886531]
5. Leary S, Smith GD, Ness A. Smoking during pregnancy and components of stature in offspring. Am J Hum Biol. 2006; 18:502–12. [PubMed: 16788904]
6. Rogers I, Emmett P, Gunnell D, Dunger D, Holly J. Milk as a food for growth? The insulin-like growth factors link. Public Health Nutr. 2006; 9:359–68. [PubMed: 16684388]
7. Gunnell DJ, Smith GD, Frankel SJ, Kemp M, Peters TJ. Socio-economic and dietary influences on leg length and trunk length in childhood: a reanalysis of the Carnegie (Boyd Orr) survey of diet and health in prewar Britain (1937-39). Paediatr Perinat Epidemiol. 1998; 12(Suppl 1):96–113. [PubMed: 9690276]
8. Wadsworth ME, Hardy RJ, Paul AA, Marshall SF, Cole TJ. Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. Int J Epidemiol. 2002; 31:383–90. [PubMed: 11980800]
9. Chandler PJ, Bock RD. Age changes in adult stature: trend estimation from mixed longitudinal data. Ann Hum Biol. 1991; 18:433–40. [PubMed: 1952801]
10. Rogers I, Metcalfe C, Gunnell D, Emmett P, Dunger D, Holly J. Insulin-like growth factor-I and growth in height, leg length, and trunk length between ages 5 and 10 years. J Clin Endocrinol Metabol. 2006; 91:2514–9. [PubMed: 16670160]
11. Renehan AG, Zwahlen M, Minder C, O’Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004; 363:1346–53. [PubMed: 15110491]
12. Donovan J, Mills N, Smith M, et al. Quality improvement report: improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. BMJ. 2002; 325:766–70. [PubMed: 12364308]
13. MacInnis R, English D. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer Causes Control. 2006; 17:989–1003. [PubMed: 16933050]

14. Hankey BF, Feuer EJ, Clegg LX, et al. Cancer surveillance series: interpreting trends in prostate cancer-part I: evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. J Natl Cancer Inst. 1999; 91:1017–24. [PubMed: 10379964]
15. Kvale R, Auvinen A, Adami HO, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. J Natl Cancer Inst. 2007; 99:1881–7. [PubMed: 18073376]
16. Ohori M, Wheeler TM, Scardino PT. The new American Joint Committee on Cancer and International Union Against Cancer TNM classification of prostate cancer. Cancer. 1994; 73:104–14. [PubMed: 7516262]
17. Gunnell D. Can adult anthropometry be used as a biomarker for prenatal and childhood exposures? Int J Epidemiol. 2002; 31:390–4. [PubMed: 11980801]
18. American Institute for Cancer Research and World Cancer Research Fund. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC: AICR; 2007.
19. WCRF. Systematic literature review protocol. Accessed 2008 Jan 23WCRF Web site 2008 January 23. Available from http://www.wcrf.org/research/research_pdfs/prostate_protocol.pdf
20. Habel LA, Van Den Eeden SK, Friedman GD. Body size, age at shaving initiation, and prostate cancer in a large, multiracial cohort. Prostate. 2000; 43:136–43. [PubMed: 10754529]
21. Rodriguez C, Patel AV, Calle EE, Jacobs EJ, Chao A, Thun MJ. Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States. Cancer Epidemiol Biomarkers Prev. 2001; 10:345–53. [PubMed: 11319175]
22. Hayes RB, Ziegler RG, Gridley G, et al. Dietary factors and risks for prostate cancer among blacks and whites in the United States. Cancer Epidemiol Biomarkers Prev. 1999; 8:25–34. [PubMed: 9950236]
23. Whittemore AS, Kolonel LN, Wu AH, et al. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. J. 1995; 87:652–61. [see comment]. [PubMed: 7752270]
24. Albanes D, Jones DY, Schatzkin A, Micozzi MS, Taylor PR. Adult stature and risk of cancer. Cancer Res. 1988; 48:1658–62. [PubMed: 3345534]
25. Andersson SO, Wolk A, Bergstrom R, et al. Body size and prostate cancer: a 20-year follow-up study among 135006 Swedish construction workers. J. 1997; 89:385–9. [PubMed: 9060961]
26. Batty GD, Shipley MJ, Langenberg C, Marmot MG, Davey Smith G. Adult height in relation to mortality from 14 cancer sites in men in London (UK): evidence from the original Whitehall study. Ann Oncol. 2006; 17:157–66. [PubMed: 16249213]
27. Cerhan JR, Torner JC, Lynch CF, et al. Association of smoking, body mass, and physical activity with risk of prostate cancer in the Iowa 65+ Rural Health Study (United States). Cancer Causes Control. 1997; 8:229–38. [PubMed: 9134247]
28. Davey-Smith G, Hart C, Upton M, et al. Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. J Epidemiol Community Health. 2000; 54:97–103. [PubMed: 10715741]
29. Engeland A, Tretli S, Bjorge T. Height, body mass index, and prostate cancer: a follow-up of 950000 Norwegian men. Br J Cancer. 2003; 89:1237–42. [PubMed: 14520453]
30. Freeman VL, Liao Y, Durazo-Arvizu R, Cooper RS. Height and risk of fatal prostate cancer: findings from the National Health Interview Survey (1986 to 1994). Ann Epidemiol. 2001; 11:22–7. [PubMed: 11164116]
31. Greenwald P, Damon A, Kirmss V, Polan AK. Physical and demographic features of men before developing cancer of the prostate. J. 1974; 53:341–6. [PubMed: 4843267]
32. Gunnell D, May M, Ben-Shlomo Y, Yarnell J, Smith GD. Height, leg length, and cancer: the Caerphilly Study. Nutr Cancer. 2003; 47:34–9. [PubMed: 14769535]
33. Hebert PR, Ajani U, Cook NR, Lee IM, Chan KS, Hennekens CH. Adult height and incidence of cancer in male physicians (United States). Cancer Causes Control. 1997; 8:591–7. [PubMed: 9242474]
34. Jonsson F, Wolk A, Pedersen NL, et al. Obesity and hormone-dependent tumors: cohort and co-twin control studies based on the Swedish Twin Registry. Int J Cancer. 2003; 106:594–9. [PubMed: 12845658]

35. Kurahashi N, Iwasaki M, Sasazuki S, Otani T, Inoue M, Tsugane S. Association of body mass index and height with risk of prostate cancer among middle-aged Japanese men. Br J Cancer. 2006; 94:740–2. [PubMed: 16465189]
36. Lamharzi N, Johnson MM, Goodman G, et al. Polymorphic markers in the 5A-reductase type II gene and the incidence of prostate cancer. Int J Cancer. 2003; 105:480–3. [PubMed: 12712437]
37. Le Marchand L, Kolonel LN, Wilkens LR, Myers BC, Hirohata T. Animal fat consumption and prostate cancer: a prospective study in Hawaii. Epidemiology. 1994; 5:276–82. [see comment]. [PubMed: 8038241]
38. Littman AJ, White E, Kristal AR. Anthropometrics and prostate cancer risk. Am J Epidemiol. 2007; 165:1271–9. [PubMed: 17395597]
39. Lund HL, Wisloff TF, Holme I, Nafstad P. Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. Am J Epidemiol. 2006; 164:769–74. [PubMed: 16952929]
40. MacInnis RJ, English DR, Gertig DM, Hopper JL, Giles GG. Body Size and composition and prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2003; 12:1417–21. [PubMed: 14693731]
41. Nilsen TI, Vatten LJ. Anthropometry and prostate cancer risk: a prospective study of 22,248 Norwegian men. Cancer Causes Control. 1999; 10:269–75. [PubMed: 10482485]
42. Platz EA, De Marzo AM, Erlinger TP, et al. No association between pre-diagnostic plasma C-reactive protein concentration and subsequent prostate cancer. Prostate. 2004; 59:393–400. [PubMed: 15065087]
43. Platz EA, Leitzmann MF, Hollis BW, Willett WC, Giovannucci E. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. Cancer Causes Control. 2004; 15:255–65. [PubMed: 15090720]
44. Putnam SD, Cerhan JR, Parker AS, et al. Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. Ann Epidemiol. 2000; 10:361–9. [PubMed: 10964002]
45. Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA. Anthropometry in relation to prostate cancer risk in the Netherlands Cohort Study. Am J Epidemiol. 2000; 151:541–9. [see comment]. [PubMed: 10733035]
46. Sequoia JSP, Wright ME, McCarron P, et al. A Prospective Investigation of Height and Prostate Cancer Risk. Cancer Epidemiol Biomarkers Prev. 2006; 15:2174–8. [PubMed: 17119043]
47. Stattin P, Bylund A, Biessy C, Kaaks R, Hallmans G, Adlercreutz H. Prospective study of plasma enterolactone and prostate cancer risk (Sweden). Cancer Causes Control. 2004; 15:1095–102. [PubMed: 15801493]
48. Tulinius H, Sigfusson N, Sigvaldason H, Bjarnadottir K, Tryggvadottir L. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. Cancer Epidemiol Biomarkers Prev. 1997; 6:863–73. [PubMed: 9367058]
49. Andersson SO, Baron J, Wolk A, Lindgren C, Bergstrom R, Adami HO. Early life risk factors for prostate cancer: a population-based case-control study in Sweden. Cancer Epidemiol Biomarkers Prev. 1995; 4:187–92. [PubMed: 7606192]
50. Dal ML, Zucchetto A, la VC, et al. Prostate cancer and body size at different ages: an Italian multicentre case-control study. Br J Cancer. 2004; 90:2176–80. [PubMed: 15150581]
51. Demark-Wahnefried W, Conaway MR, Robertson CN, Mathias BJ, Anderson EE, Paulson DF. Anthropometric risk factors for prostate cancer. Nutr Cancer. 1997; 28:302–7. [PubMed: 9343840]
52. Fincham SM, Hill GB, Hanson J, Wijayasinghe C. Epidemiology of prostatic cancer: a case-control study. Prostate. 1990; 17:189–206. [PubMed: 2235728]
53. Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG. Case-control study of anthropometric measures and prostate cancer risk. Int J Cancer. 2004; 110:278–83. [PubMed: 15069694]
54. Furuya Y, Akimoto S, Akakura K, Ito H. Smoking and obesity in relation to the etiology and disease progression of prostate cancer in Japan. Int J Urol. 1998; 5:134–7. [PubMed: 9559838]
55. Giles GG, Severi G, English DR, et al. Early growth, adult body size and prostate cancer risk. Int J Cancer. 2003; 103:241–5. [PubMed: 12455039]

56. Hayes RB, de Jong FH, Raatgever J, et al. Physical characteristics and factors related to sexual development and behaviour and the risk for prostatic cancer. Eur J Cancer Prev. 1992; 1:239–45. [PubMed: 1467769]
57. Hill P, Wynder EL, Garbaczewski L, Walker AR. Effect of diet on plasma and urinary hormones in South African black men with prostatic cancer. Cancer Res. 1982; 42:3864–9. [PubMed: 6179613]
58. Hsieh CC, Thanos A, Mitropoulos D, Deliveliotis C, Mantzoros CS, Trichopoulos D. Risk factors for prostate cancer: a case-control study in Greece. Int J Cancer. 1999; 80:699–703. [PubMed: 10048970]
59. Hsing AW, Deng J, Sesterhenn IA, et al. Body size and prostate cancer: a population-based case-control study in China. Cancer Epidemiol Biomarkers Prev. 2000; 9:1335–41. [PubMed: 11142419]
60. Huang SP, Chou YH, Chang WS, et al. Androgen receptor gene polymorphism and prostate cancer in Taiwan. J Formos Med Assoc. 2003; 102:680–6. [PubMed: 14691592]
61. John EM, Schwartz GG, Koo J, Van Den BD, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. Cancer Res. 2005; 65:5470–9. [PubMed: 15958597]
62. Key TJ, Silcocks PB, Davey GK, Appleby PN, Bishop DT. A case-control study of diet and prostate cancer. Br J Cancer. 1997; 76:678–87. [PubMed: 9303371]
63. Kolonel LN, Yoshizawa CN, Hankin JH. Diet and prostatic cancer: a case-control study in Hawaii. Am J Epidemiol. 1988; 127:999–1012. [PubMed: 3358418]
64. Koppel M, Meranze DR, Shimkin MB. Characteristics of patients with prostatic carcinoma: a control case study on 83 autopsy pairs. J Urol. 1967; 98:229–33. [PubMed: 6047000]
65. La Vecchia C, Negri E, Parazzini F, et al. Height and cancer risk in a network of case-control studies from Northern Italy. Int J Cancer. 1990; 45:275–9. [PubMed: 2303293]
66. Lightfoot N, Conlon M, Kreiger N, Sass-Kortsak A, Purdham J, Darlington G. Medical history, sexual, and maturational factors and prostate cancer risk. Ann Epidemiol. 2004; 14:655–62. [PubMed: 15380796]
67. Liu X, Rybicki BA, Casey G, Witte JS. Relationship between body size and prostate cancer in a sibling based case-control study. J Urol. 2005; 174:2169–73. [PubMed: 16280757]
68. Norrish AE, McRae CU, Holdaway IM, Jackson RT. Height-related risk factors for prostate cancer. Br J Cancer. 2000; 82:241–5. [PubMed: 10638996]
69. Porter MP, Stanford JL. Obesity and the risk of prostate cancer. Prostate. 2005; 62:316–21. [PubMed: 15389806]
70. Rao AV, Fleshner N, Garwal S. Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: a case-control study. Nutr Cancer. 1999; 33:159–64. [PubMed: 10368811]
71. Villeneuve PJ, Johnson KC, Kreiger N, Mao Y, The Canadian Cancer Registries Epidemiology Research Group. Risk factors for prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System. Cancer Causes Control. 1999; 10:355–67. [PubMed: 10530605]
72. Walker AR, Walker BF, Tsotetsi NG, Sebitso C, Siwedi D, Walker AJ. Case-control study of prostate cancer in black patients in Soweto, South Africa. Br J Cancer. 1992; 65:438–41. [PubMed: 1558801]
73. Wynder EL, Mabuchi K, Whitmore WF Jr. Epidemiology of cancer of the prostate. Cancer. 1971; 28:344–60. [PubMed: 5109447]
74. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Height, body weight, and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 1997; 6:557–63. [PubMed: 9264267]
75. Thune I, Lund E. Physical activity and the risk of prostate and testicular cancer: a cohort study of 53,000 Norwegian men. Cancer Causes Control. 1994; 5:549–56. [PubMed: 7827242]
76. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J Cancer. 2007; 121:1571–8. [PubMed: 17450530]
77. Fowke JH, Signorello LB, Chang SS, et al. Effects of obesity and height on prostate-specific antigen (PSA) and percentage of free PSA levels among African-American and Caucasian men. Cancer. 2006; 107:2361–7. [PubMed: 17031814]

78. Werny DM, Thompson T, Saraiya M, et al. Obesity is negatively associated with prostate-specific antigen in U.S. men, 2001-2004. Cancer Epidemiol Biomarkers Prev. 2007; 16:70–6. [PubMed: 17179487]
79. Fowke JH, Motley SS, Cookson MS, et al. The association between body size, prostate volume and prostate-specific antigen. Prostate Cancer Prostatic Dis. 2006; 10:137–42. [PubMed: 17179979]
80. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 2003; 95:868–78. [PubMed: 12813170]
81. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst. 2002; 94:981–90. [PubMed: 12096083]
82. Batty GD, Leon DA. Socio-economic position and coronary heart disease risk factors in children and young people: evidence from UK epidemiological studies. Eur J Public Health. 2002; 12:263–72. [PubMed: 12506501]
83. Spencer BA, Babey SH, Etzioni DA, et al. A population-based survey of prostate-specific antigen testing among California men at higher risk for prostate carcinoma. Cancer. 2006; 106:765–74. [PubMed: 16419068]
84. Freedland SJ, Platz EA. Obesity and prostate cancer: making sense out of apparently conflicting data. Epidemiol Rev. 2007; 29:88–97. [PubMed: 17478439]
85. Oliver, SE. PhD Thesis. Department of Social Medicine, University of Bristol; 2002.
86. Gunnell D, Berney L, Holland P, et al. How accurately are height, weight and leg length reported by the elderly, and how closely are they related to measurements recorded in childhood? Int J Epidemiol. 2000; 29:456–64. [PubMed: 10869317]
87. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr. 2002; 5:561–5. [PubMed: 12186665]
88. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Height loss in older men: associations with total mortality and incidence of cardiovascular disease. Arch Intern Med. 2006; 166:2546–52. [PubMed: 17159023]
89. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor I and prostate cancer risk: A prospective study. Science. 1998; 279:563–6. [PubMed: 9438850]
90. Vatten LJ, Kvinnsland S. Body height and risk of breast cancer. A prospective study of 23,831 Norwegian women. Br J Cancer. 1990; 61:881–5. [PubMed: 2372490]
91. Ben-Shlomo Y, Holly J, McCarthy A, Savage P, Davies D, Davey Smith G. Pre and post natal milk supplementation and adult insulin-like growth factor I: long term follow-up of a randomised controlled trial. Cancer Epidemiol Biomarkers Prev. 2005; 14:1336–9. [PubMed: 15894699]
92. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of weight, body mass index and other anthropometric measurements in relation to site-specific cancers. Int J Cancer. 1994; 57:313–7. [PubMed: 8168989]
93. Veierod MB, Laake P, Thelle DS. Dietary fat intake and risk of prostate cancer: a prospective study of 25,708 Norwegian men. Int J Cancer. 1997; 73:634–8. [PubMed: 9398038]

Europe PMC Funders Author Manuscripts

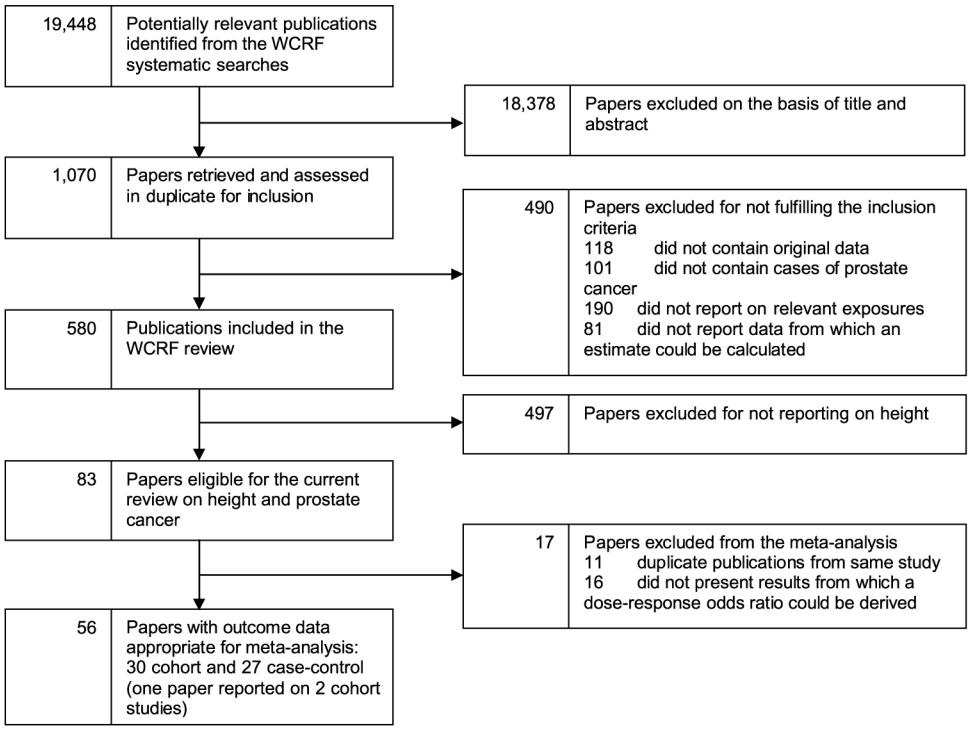

Figure 1.
Flow diagram of study selection.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

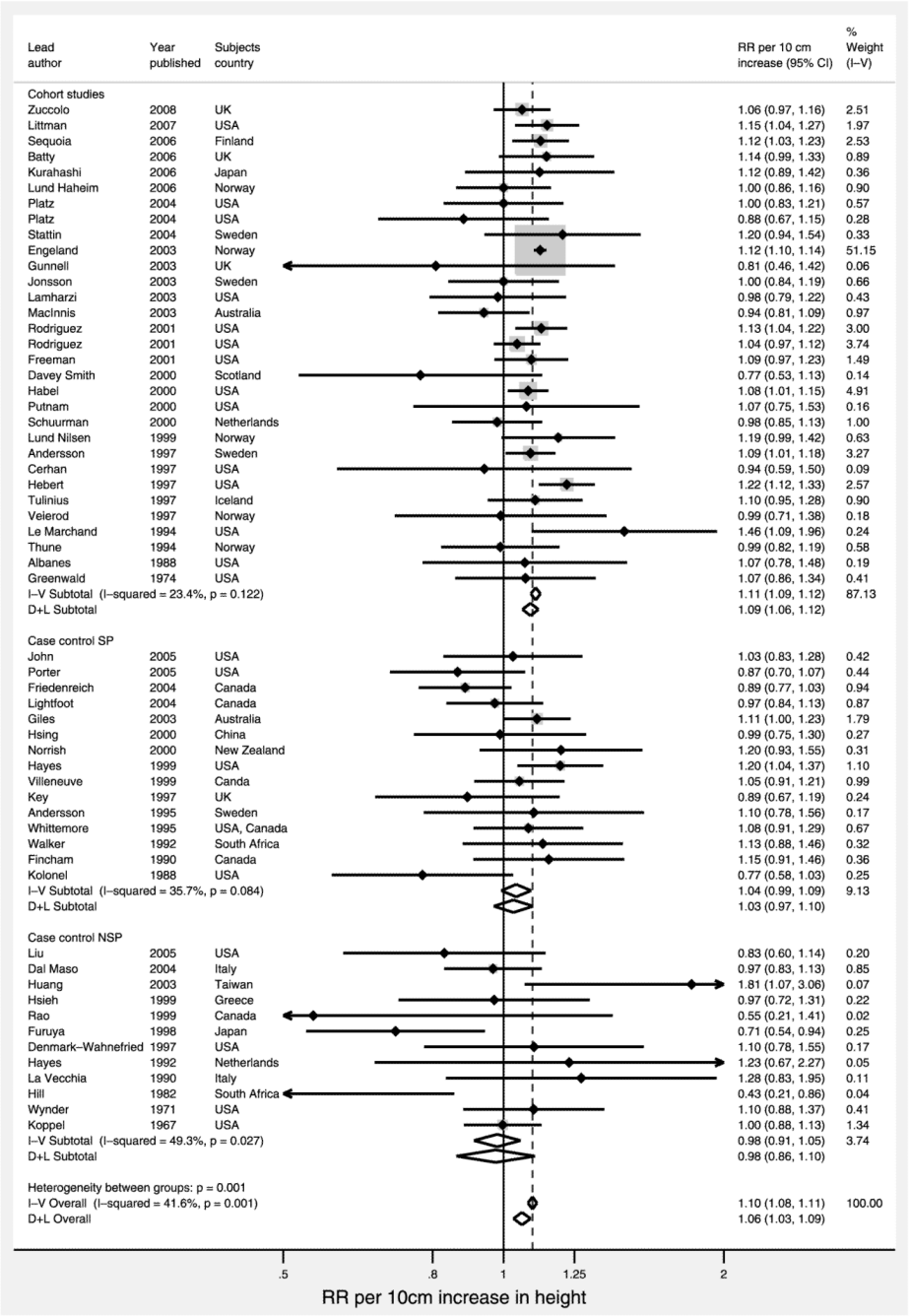

Figure 2.

Association of height and prostate cancer—random-effects meta-analysis of adjusted risk ratio (*RR*) per 10 cm increase in height, plotted on the log scale, stratified by study design [cohort, same-population (*SP*) and non-same population (*NSP*) case-control studies]. *I-V*, inverse-probability weighting model (fixed-effect); *D+L*, DerSimonian and Laird model (random effects).

Europe PMC Funders Author Manuscripts

Table 1

Characteristics of participants included in the analysis—1,357 cases and 7,990 controls, frequency-matched on 5-y age band and general practice

	Controls		Cases	
	n *	Mean (SD) or %	*n* *	Mean (SD) or %
Age (y)	7,990	61.8 (5.0)	1,357	62.2 (4.9)
Height (cm)	7,990	176.0 (6.7)	1,357	176.2 (6.8)
Leg length (cm)	7,990	76.6 (4.3)	1,357	76.7 (4.4)
Trunk length (cm)	7,990	99.3 (4.7)	1,357	99.5 (4.7)
BMI (kg/m^2)	7,893	27.1 (3.8)	1,341	26.7 (3.5)
Birth weight (kg)	4,305	3.47 (0.72)	684	3.46 (0.71)
Family history of prostate cancer	7,990	5.2%	1,357	7.4%
White ethnic origin	7,912	99.0%	1,330	98.7%
3+ siblings (vs <3)	7,750	33.8%	1,300	31.0%
Nonmanual occupation (vs manual) †	5,519	45.8%	975	45.7%

Abbreviation: BMI, body mass index.

*Number with complete data.

†Nonmanual occupation includes codes for professional, managerial, nonmanual, and skilled nonmanual occupations. Manual occupation includes codes for manual and skilled manual, semiskilled, and unskilled manual occupations.

Europe PMC Funders Author Manuscripts

Table 2

Associations of height and height components with PSA-detected prostate cancer, in 1,357 cases and 7,990 controls, frequency-matched on 5-y age band and general practice

	Quartiles*				Dose-response†	p_{trend}	p‡
	Q_1	Q_2	Q_3	Q_4			
Total prostate cancer§ (n = 1,357)							
Height	1.00	1.06 (0.88-1.29)	1.05 (0.90-1.22)	1.11 (0.93-1.33)	1.06 (0.97-1.16)	0.20	-
Leg length	1.00	1.05 (0.87-1.27)	1.01 (0.87-1.17)	1.08 (0.92-1.27)	1.03 (0.96-1.10)	0.47	-
Trunk length	1.00	1.07 (0.89-1.28)	1.01 (0.84-1.22)	1.11 (0.94-1.32)	1.04 (0.98-1.10)	0.24	-
Localized prostate cancer‖ (n = 1,180)							
Height	1.00	1.06 (0.85-1.28)	1.07 (0.91-1.26)	1.09 (0.90-1.32)	1.06 (0.96-1.16)	0.20	-
Leg length	1.00	1.04 (0.85-1.27)	1.01 (0.86-1.19)	1.09 (0.92-1.29)	1.02 (0.95-1.10)	0.49	-
Trunk length	1.00	1.08 (0.89-1.31)	1.01 (0.82-1.23)	1.13 (0.94-1.35)	1.04 (0.97-1.11)	0.23	-
Advanced prostate cancer‖ (n = 173)							
Height	1.00	1.00 (0.63-1.61)	0.82 (0.56-1.21)	1.07 (0.69-1.67)	1.02 (0.81-1.28)	0.86	0.74
Leg length	1.00	1.02 (0.64-1.64)	0.88 (0.59-1.31)	0.99 (0.65-1.49)	1.00 (0.84-1.19)	0.99	0.78
Trunk length	1.00	0.89 (0.54-1.40)	0.89 (0.49-1.30)	0.97 (0.64-1.55)	1.02 (0.87-1.19)	0.80	0.83
Low-grade prostate cancer‖ (n = 936)							
Height	1.00	0.97 (0.78-1.21)	0.98 (0.82-1.17)	1.01 (0.82-1.24)	0.99 (0.90-1.10)	0.87	-
Leg length	1.00	0.96 (0.77-1.19)	0.96 (0.81-1.14)	0.94 (0.78-1.14)	0.97 (0.90-1.05)	0.49	-
Trunk length	1.00	1.01 (0.82-1.25)	1.04 (0.84-1.28)	1.08 (0.88-1.32)	1.02 (0.94-1.09)	0.69	-
High-grade prostate cancer‖ (n = 402)							
Height	1.00	1.31 (0.95-1.82)	1.21 (0.92-1.58)	1.39 (1.02-1.89)	1.23 (1.06-1.43)	<0.01	0.02
Leg length	1.00	1.19 (0.87-1.65)	1.13 (0.87-1.47)	1.41 (1.08-1.84)	1.14 (1.02-1.28)	0.02	0.02
Trunk length	1.00	1.17 (0.86-1.59)	0.89 (0.64-1.23)	1.21 (0.90-1.63)	1.10 (0.99-1.23)	0.07	0.20

*Cutoffs based on distribution of controls only. Quartile cutoffs are as follows: height 172.5, 175, 181 cm; leg length 74, 77, 80 cm; trunk length 96, 99, 101.6 cm.

†Height: per 10 cm increase. Leg length and trunk length: per 5 cm increase.

‡Test for difference in the effect estimates for localized versus advanced and low-grade versus high-grade prostate cancer.

§OR and 95% CI values from conditional logistic regression models, additionally adjusted for age as a continuous variable.

// Relative risk ratios and 95% CIs from logistic regression, adjusted for matching factors. For definitions of localized/advanced stage and low/high grade, see Subjects and Methods.

Europe PMC Funders Author Manuscripts

Table 3

Characteristics of studies (from the systematic review) included in the dose-response meta-analysis for height and prostate cancer

A. Prospective studies

First author (year)	Location	Ethnicity	Reporting (incidental or primary)	Age at baseline (y)*	Dates of recruitment and follow-up	% Follow-up <1990	Exposure assessment	Outcome	No. cases
Greenwald (1974; ref. 31)	Harvard (USA)	White	Incidental	NS	1880-1916 to 1967	100	Mixed	Mortality	268
Albanes (1988; ref. 24)	USA	Multiethnic	Primary	(52)	1971-1975 to 1982-84	100	Measured	Incidence	95
Le Marchand (1994; ref. 37)	Hawaii (USA)	Multiethnic	Incidental	45-90	1975-1980 to 1989	100	Self-report	Incidence	198
Thune (1994; ref. 35)	Norway	NS	Incidental	35-54	1972-1978 to 1991	94	Measured	Incidence	220
Tulinius (1997; ref. 48)	Iceland	NS	Primary	23-60	1967-1995 to 1995	64	Measured	Incidence	524
Hebert (1997; ref. 33)	USA	NS	Primary	40-84	1982 to 1995	62	Self-report	Incidence	1,047
Andersson (1997; ref. 25)	Sweden	NS	Primary	40+	1971-1975 to 1991	94	Measured	Incidence	2,368
								Mortality	708
Cerhan (1997; ref. 27)	Iowa (USA)	NS	Incidental	65-101	1982 to 1993	73	Self-report	Incidence	71
Veierod (1997; ref. 93)	Norway	NS	Incidental	16-56	1977-1983 to 1992	83	Measured	Incidence	72
Nilsen (1999; ref. 41)	Norway	NS	Primary	(59)	1984-1986 to 1997	42	Measured	I+M	642
Davey-Smith (2000; ref. 28)	Scotland (UK)	NS	Primary	45-64	1972-1976 to 1996	73	Measured	Mortality	59
Habel (2000; ref. 30)	USA	Multiethnic	Primary	18-84	1964-1973 to 1996	78	Measured	Incidence	2,079
Putnam (2000; ref. 44)	Iowa (USA)	White	Primary	40-86	1986-1989 to 1995	33	Self-report	Incidence	101
Schuurman (2000; ref. 45)	The Netherlands	NS	Primary	55-69	1986 to 1992	67	Self-report	Incidence	681
Rodriguez (2001; ref. 21)	USA (CPS I)	Multiethnic	Primary	(52)	1959 to 1972	100	Self-report	Mortality	1,590
Rodriguez (2001; ref. 21)	USA (CPS II)	Multiethnic	Primary	(57)	1982 to 1996	57	Self-report	Mortality	3,622
Freeman (2001; ref. 30)	USA	Multiethnic	Primary	50+	1986 to 1994	50	Self-report	Mortality	633
Jonsson (2003; ref. 34)	Sweden	NS	Incidental	44-83	1961-1967 to 1997	79	Self-report	I+M	631
Engeland (2003; ref. 29)	Norway	NS	Primary	20-74	1963 to 2001	71	Measured	I+M	33,314
MacInnis (2003; ref. 40)	Australia	NS	Incidental	27-75	1990-1994 to 2002	0	Measured	Incidence	477
Gunnell (2003; ref. 32)	South Wales (UK)	NS	Primary	45-59	1979-1983 to 2003	41	Measured	Incidence	33
Lamharzi (2003; ref. 36)	USA	Multiethnic	Incidental	45-69	1985-1994 to 1998	6	Measured	Incidence	300
Platz (2004; ref. 43)	USA	White	Incidental	40-75	1993-1995 to 1998	0	Self-report	I+M	460
Platz (2004; ref. 42)	Maryland (USA)	White	Incidental	(65)	1989 to 2002	8	Self-report	Incidence	264
Stattin (2004; ref. 47)	Sweden	NS	Incidental	40+	1985-1994 to 2001	4	Measured	Incidence	265
Batty (2006; ref. 26)	London (UK)	NS	Primary	40-64	1967-1970 to 2002	64	Measured	Mortality	434

Europe PMC Funders Author Manuscripts

A. Prospective studies

First author (year)	Location	Ethnicity	Reporting (incidental or primary)	Age at baseline (y)*	Dates of recruitment and follow-up	% Follow-up <1990	Exposure assessment	Outcome	No. cases
Lund Haheim (2006; ref. 39)	Norway	NS	Incidental	40-49	1972-1973 to 1998	70	Measured	Incidence	507
Kurahashi (2006; ref. 35)	Japan	NS	Primary	40-69	1990-1993 to 2003	0	Self-report	Incidence	311
Sequoia (2006; ref. 46)	Finland	White	Primary	50-69	1985-1988 to 1993	54	Measured	Incidence	1,346
Littman (2007; ref. 38)	Washington State (USA)	Multiethnic	Primary	50-76	2000-2002 to 2004	0	Self-report	Incidence	832

B. Case-control studies

First author (year)	Location	Ethnicity	Mean age (cases, controls)	Exposure assessment	Outcome	No. cases/controls
Same-Population case-control studies						
Kolonel (1988; ref. 63)	Hawaii (USA)	Multiethnic	NS	NS	I+P	452/899
Fincham (1990; ref. 52)	Canada	NS	NS	Self-report	Incidence	382/NS
Walker (1992; ref. 72)	South Africa	Black	(69.2, 69.6)	Measured	PP	166/166
Whittemore (1995; ref. 23)	USA	Multiethnic	(70.8, 70.2)	Mixed	Prevalence	1,655/1,645
Andersson (1995; ref. 49)	Sweden	NS	(70.0, 69.8)	Measured	Incidence	256/252
Key (1997; ref. 62)	UK	White	(68.1, 68.1)	NS	Incidence	328/267
Villeneuve (1999; ref. 71)	Canada	Multiethnic	NS	Self-report	I+P	1,623/1,623
Hayes (1999; ref. 22)	USA	Multiethnic	40-79†	Mixed	Incidence	934/1,201
Norrish (2000; ref. 58)	New Zealand	NS	40-80†	Self-report	Incidence	317/480
Hsing (2000; ref. 59)	Shangai (China)	NS	(72.7, 73.1)	Mixed	Incidence	238/471
Giles (2003; ref. 54)	Australia	NS	(60.3, 60.6)	Self-report	Incidence	1,476/1,409
Lightfoot (2004; ref. 66)	Canada	White	(68.0, 67.8)	Self-report	PP	760/1,632
Friedenreich (2004; ref. 53)	Canada	NS	NS	Mixed	Incidence	988/1,063
John (2005; ref. 61)	San Francisco (USA)	Non-Hispanic white	(64.0, 65.0)	Measured	Incidence	450/455
Porter (2005; ref. 69)	Washington State (USA)	Multiethnic	(58.0, 58.0)	Self-report	Incidence	753/703
Non-same-population case-control studies						
Koppel (1967; ref. 64)	Philadelphia (USA)	Multiethnic	(72.2, 71.5)	Measured	PP	83/83
Wynder (1971; ref. 73)	NYC (USA)	Multiethnic	(65.2, 64.4)	NS	PP	300/400
Hill (1982; ref. 57)	South Africa	Black	(70.0, 66.0)	Measured	PP	21/6
La Vecchia (1990; ref. 65)	Milan (Italy)	NS	(65.0, 55.0)	Self-report	PP	80/1971
Hayes (1992; ref. 56)	The Netherlands	NS	(63.1, 60.7)	Self-report	PP	100/113

Europe PMC Funders Author Manuscripts

B. Case-control studies

First author (year)	Location	Ethnicity	Mean age (cases, controls)	Exposure assessment	Outcome	No. cases/controls
Denmark-Wahnefried (1997; ref. 51)	USA	Multiethnic	NS	Measured	Incidence	159/156
Furuya (1998; ref. 54)	Chiba (Japan)	NS	(72.8, 69.5)	NS	Incidence	329/190
Rao (1999; ref. 70)	Toronto (Canada)	NS	(62.0, 65.1)	NS	PP	12/12
Hsieh (1999; ref. 58)	Athens (Greece)	NS	(71.2, 70.4)	Self-report	Incidence	320/246
Huang (2003; ref. 60)	Taiwan	NS	(71.5, 71.7)	NS	Incidence	66/104
Dal Maso (2004; ref. 50)	Italy	NS	(66.0, 63.0)	Self-report	Incidence	1,294/1,451
Liu (2005; ref. 67)	USA	Multiethnic	(61.0, 63.0)	Self-report	Prevalence	439/479

Abbreviations: NS, not stated; I+M, incidence and mortality; I+P, incidence and prevalence; PP, presumed prevalence.

*Range or mean (if in brackets).

†Age range of both cases and controls.

Europe PMC Funders Author Manuscripts

Table 4

Pooled-effect estimates for the associations of height and prostate cancer from prospective studies only, by selected study characteristics

	No. studies	Pooled dose-response*	Heterogeneity (I^2), %	p †
All cohorts	31	1.09 (1.06-1.12)	23.4	
Advanced/aggressive/fatal prostate cancers only	13	1.12 (1.05-1.19)	47.3	
Incidental reporting of height findings	12	1.01 (0.95-1.07)	0.0	<0.01
Primary reporting of height findings	19	1.11 (1.09-1.13)	6.6	
Pre-PSA era (>50% of follow-up occurring <1990)	19	1.10 (1.06-1.13)	28.7	0.12
PSA era (≤50% of follow-up occurring <1990)	12	1.07 (1.02-1.12)	4.3	

*Pooled-effect estimates per 10 cm increase in height, and 95% CI, from random-effects models using adjusted results.

†*P* value for heterogeneity between strata, from linear meta-regression models.