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Title: Measures of Body Fatness and Height Across the Adult Lifecourse and Prostate Cancer Risk and Mortality in the Pooling Project of Prospective Studies of Diet and Cancer.

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KEY MESSAGE: Although studies have assessed obesity in mid to late adulthood and height with risk, few have examined the role of early adulthood BMI and changes in BMI in adulthood on advanced prostate cancer risk. We report positive associations of height, BMI and waist circumference in mid to late adulthood and BMI change with advanced prostate cancer risk, but no associations with BMI at early adulthood.

Abstract

Background: Advanced prostate cancer etiology is poorly understood. Few studies have examined the associations of anthropometric factors (e.g., early adulthood obesity) with advanced prostate cancer risk.

Patients and Methods: We performed a pooled analysis of 15 cohorts to examine associations between body fatness and height and prostate cancer risk. Among 830,772 men, 51,734 incident prostate cancer cases were identified, including 4,762 advanced (T4/N1/M1 or prostate cancer deaths) cases, 2,915 advanced restricted (same as advanced, but excluding localized cancers that resulted in death) cases, 9,489 high grade cases, and 3,027 prostate cancer deaths. Cox proportional hazards models were used to calculate study-specific hazard ratios (HR) and 95% confidence intervals (CI); results were pooled using random effects models.

Results: No statistically significant associations were observed for BMI in early adulthood and hip circumference at baseline for advanced, and high-grade prostate cancer and prostate cancer mortality. Positive associations were suggestive or significant for BMI at baseline with advanced prostate cancer (HR=1.30, 95% CI=0.95-1.78) and prostate cancer mortality (HR=1.52, 95% CI=1.12-2.07) comparing BMI$\geq$35kg/m^2 with 21-22.9kg/m^2. A 27% higher risk for prostate cancer mortality (95% CI:9-49%) was observed for men with BMI<25kg/m^2 in early adulthood and BMI$\geq$30kg/m^2 at baseline compared to a BMI<25kg/m^2 in early adulthood and BMI<30kg/m^2 at baseline. Waist circumference, comparing $\geq$110cm with <90cm, and waist-to-hip ratio, comparing $\geq$1.00 with <0.90, was associated with a 14-16% increase in high-grade prostate cancer risk and 20-39% increase in prostate cancer mortality risk. Height was associated with a 33-56% risk of advanced, advanced restricted prostate cancer and prostate cancer mortality, comparing $\geq$1.90m vs. <1.65m.

Conclusion: Our findings suggest that height and total and central adiposity in mid to later adulthood, but not early adulthood adiposity, are associated with advanced prostate cancer risk. Thus, maintenance of healthy weight may play a role in preventing advanced prostate cancer.

Introduction

Worldwide, prostate cancer is the second most common cancer in men[1]. Over the past two decades, there has been a shift to diagnosis of earlier stage, indolent disease[2], largely attributed to widespread testing with prostate specific antigen (PSA). Unlike early stage prostate cancer, advanced prostate cancer (defined here as distant prostate cancer) has a markedly different prognosis with a 29% five-year survival, making advanced prostate cancer the most clinically relevant outcome[3]. Earlier studies of advanced prostate cancer have generally had inadequate statistical power and used various definitions for advanced prostate cancer (*e.g.*, high-grade, advanced stage, fatal). Due to these factors and given that risk factors for high risk phenotypes may differ from those for low-risk tumors [4, 5], evidence of risks for advanced prostate cancer is inconsistent and limited.

In 2018, an expert panel for the World Cancer Research Fund (WCRF) [6], determined that the level of evidence was probable for a positive association between height and body fatness and risk of advanced/aggressive definitions of prostate cancer. In the WCRF meta-analysis, a 4% increase in risk of advanced prostate cancer and prostate cancer mortality was observed for a 5 cm increment in height and an 8-11% increase in risk of advanced prostate cancer and prostate cancer mortality was observed for a 5kg/m^2 increment in BMI[6]. In contrast, an International Agency for Research on Cancer (IARC) working group concluded in 2016 that the evidence for an association between body fatness and fatal prostate cancer was limited; other advanced / aggressive prostate cancer definitions were not evaluated[7]. Thus, questions remain concerning the role of body fatness on the risk of prostate cancer, particularly for different definitions of advanced/aggressive prostate cancer.

Few studies have examined the association of obesity earlier in life, changes in weight during adulthood, and central adiposity, typically measured in mid to late adulthood, with advanced prostate cancer risk. Of the five studies that examined BMI or weight at younger adult ages (18-21 years old) and advanced or aggressive prostate cancer[8-13], most[8-11] observed null associations. For studies

examining central adiposity (*e.g.*, waist circumference), most have reported non-significant associations with advanced prostate cancer[14-20]. However, a meta-analysis published in the WCRF of four studies noted a 12% (4-21%) increase in risk of advanced prostate cancer per 10 cm increment in waist circumference[6]; a similar 18% increase in risk for prostate cancer death for the same increment was noted in an recent updated analysis within the EPIC cohort[21]. Due to the relatively small number of advanced cases in these studies, and heterogeneity in outcome definitions, uncertainty remains about the strength and dose-response relationships of these anthropometric measures, as well as risk for certain subgroups (*e.g.*, younger onset, non-diabetics). Further, few studies of obesity have accounted for measures at both younger ages and mid to late adulthood in the same analysis[11, 12, 22], or have assessed if the associated with central adiposity, typically measured in mid to late adulthood, [15, 18, 21] is independent of BMI in mid to late adulthood.

To address these issues, we examined associations of obesity across the adult lifecourse and central adiposity in mid-to-late adulthood and adult height with risk of total, advanced, and aggressive prostate cancer and prostate cancer mortality using harmonized exposure, covariate and outcome definitions in one of the largest pooled analyses of individual level data.

Methods

Population

A pooled analysis of the primary data from 15 cohort studies[8, 9, 11, 12, 18, 21, 23-30] was conducted within The Pooling Project of Prospective Studies of Diet and Cancer (DCPP), an international consortium (**Table 1)**. The current analysis used cohort inclusion criteria that have been used for previous analyses of dietary factors in the DCPP[31]: (1) a minimum of 50 incident prostate cancer cases, (2) an assessment of usual diet, (3) validation of the dietary assessment tool or a closely related instrument and (4) publication of any diet and cancer association; these inclusions were employed to maximize the quality and comparability of the studies in the consortium[32]. The cohorts that met our

inclusion criteria and agreed to participate sent their primary data for analysis[8, 9, 11, 12, 18, 21, 23-30]. For one cohort (the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial)[30], only participants in the screened arm were included[33], whereas for the Prostate Cancer Prevention Trial (PCPT) both arms were included. The DCPP methods have been described in detail elsewhere[32].

Exposure Assessment

Self-reported current height and weight, typically at mid to late adulthood, were collected at baseline by 10 cohorts and five cohorts captured measured height and weight[18, 19, 21, 23, 24]. Self-reported weight during early adulthood (age 18 or 21 years) was collected by 11 cohorts. Seven cohorts collected waist and/or hip circumference, typically at mid to late adulthood, measured by study personnel [8, 18, 21] or by the participant themselves [11, 12, 26, 27]. At baseline, smoking habits were ascertained by all cohorts, physical activity was ascertained by 13 cohorts, and diabetes status was ascertained by 10 cohorts.

Outcome Assessment

Invasive prostate cancer, defined by ICD-9 code 185, was ascertained by self-report with subsequent medical record review [12, 24, 28], cancer registry linkage[9, 11, 25, 27, 29], or both methods[16, 23, 26, 30]. Some studies additionally obtained information from death registries [9, 11, 12, 16, 24-26, 28, 30]. For the Prostate Cancer Prevention Trial (PCPT)[18] only cases diagnosed through a biopsy performed because of an elevated PSA or abnormal digital-rectal examination suspicious for cancer were included as cases. Due to inconsistency in the literature regarding definitions for aggressive and advanced prostate cancer, and to better understand possible differences in the etiology of latent, advanced, aggressive and prostate cancer mortality, we classified advanced and aggressive prostate cancer cases as follows: (1) prostate cancer mortality cases, defined as prostate cancer that was the underlying cause of death on the death certificate, (2) advanced cases, defined as tumors with stage T4, N1, M1 or prostate cancer mortality cases, (3) advanced restricted cases, defined the same as for

advanced cases but excluding prostate cancer mortality cases that were initially diagnosed as localized or cases with missing stage information at diagnosis who died of prostate cancer during follow-up, and (4) high-grade cancers defined as having Gleason score ≥8 or being poorly differentiated / undifferentiated (see the Appendix in Wu et al.[31] for more detail). As a sensitivity analysis, we also examined a more restrictive definition of high-grade cancer that excluded poorly differentiated cases with Gleason score $\leq$7 or with missing Gleason score; this analysis was restricted to five cohorts [8, 21, 25, 26, 30] that had the necessary data (N=1348 out of 2,265 high-grade cases were included in this analysis). We also included results for total, localized prostate cancer cases (defined as cancer confined within the prostate) and low-grade prostate cancer cases (defined as having a Gleason score <8 or well/moderately differentiated) for comparison.

Exclusions

In addition to predefined study-specific exclusions, we excluded individuals with (1) $\log_e$-transformed self-reported energy intakes beyond three standard deviations from the $\log_e$-transformed mean energy intake of their respective cohort population (because we conducted these analyses in the study populations used in dietary analyses in the consortium) and (2) a history of cancer other than non-melanoma skin cancer at baseline. After these exclusions, we additionally excluded men (3) missing weight or height data (N=906 cases, N= 10,531 non-cases), or (4) a BMI $\leq$14kg/m^2 (*N*=23 cases, *N*=319 non-cases) or $\geq$50kg/m^2 (*N*=20 cases, *N*=527 non-cases). For analyses of sub-types of prostate cancer, studies were excluded if they had fewer than 50 cases of the outcome being evaluated.

Statistical Analysis

Anthropometric measures were modeled both continuously and categorically. For the categorical analysis, BMI at baseline and BMI in early adulthood were modeled using cutpoints proposed by the World Health Organization[34]. Absolute BMI change (BMI at baseline, typically measured at mid-to-late adulthood, minus BMI in early adulthood) was categorized as:<-2.0, -2.0-<2.0,

2.0-<5.0, 5.0-<10, ≥10kg/m^2. Waist circumference categories were defined using 10-cm increments, waist-to-hip ratio categories were defined using 0.05 increments, and height was modeled categorically using 5cm increments from <1.65 to ≥1.90cm.

For the prostate cancer incidence analyses, person-years of follow-up were calculated from the date of baseline questionnaire until the date of prostate cancer diagnosis, death from another cause, loss to follow-up or end of follow-up, whichever came first. For analyses for prostate cancer mortality, date of prostate cancer death was used instead of date of prostate cancer diagnosis. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated by fitting Cox proportional hazards regression models for each cohort. The models included stratification by age (years) at baseline and the calendar year at start of follow-up, and the time scale used was follow-up time (days). Multivariable-adjusted hazard ratios (MVHR) were adjusted for the following factors collected at baseline: race, education, marital status, alcohol intake, smoking habits, prostate cancer family history, personal history of diabetes, multivitamin use, and dietary calcium (from foods only), dietary lycopene (from foods only), and total energy intake. These variables were entered directly into the multivariable-adjusted model or, for studies with fewer than 200 cases, were modeled using propensity scores[35-37]. For models in which height was not the main exposure, height was included as a covariate in the model. For models in which height was the main exposure, we additionally adjusted for BMI at baseline. For models in which BMI in early adulthood, waist circumference, hip circumference and waist-to-hip ratio, typically measured at mid-to-late adulthood, was the main exposure, we conducted sensitivity analyses in which BMI at baseline, typically measured at mid-to-late adulthood, was included as a covariate in the model. For models in which absolute BMI change was the main exposure, we conducted sensitivity analyses in which we include BMI in early adulthood as a covariate in the model. Overall, results were similar between age-adjusted and multivariable-adjusted models; therefore, we only present multivariable-adjusted results.

Study-specific HRs were pooled using a random effects model[32]. Between-studies heterogeneity was evaluated using the Q statistic[38] and inconsistency was quantified by the I^2 statistic[39]. We also evaluated whether each anthropometric factor was linearly associated with prostate cancer risk using a non-parametric regression analysis in an aggregated data set. To test for non-linearity, we used a likelihood ratio test to compare the model fit including the linear plus any cubic spline terms selected by a stepwise regression procedure with the model fit with only the linear term [40-42]. To test for a linear trend in prostate cancer risk with each anthropometric factor, a continuous variable with values corresponding to the median value for each exposure category was included in the model; the statistical significance of the coefficient for that variable was evaluated using the Wald test.

We used a mixed effects meta-regression model to evaluate whether associations with anthropometric factors varied by geographic location (North America compared with Europe, Asia, and Australia), age at diagnosis (<60 vs. $\geq$60 years), smoking status (comparing never, former, and current smokers), physical activity (comparing low, medium, and high activity) and follow-up time (<5 vs. $\geq$5 years). We conducted sensitivity analyses excluding 1) individuals with a personal history of diabetes at baseline, and 2) studies with PSA screening (PLCO and PCPT) as part of their protocol. To examine differences by case definition, we employed a contrast test[43]. A *p-value* of 0.05 from a two-sided test was considered statistically significant. SAS software, version 9.3, was used.

RESULTS

During follow-up of 830,772 men, 51,734 men were diagnosed with incident prostate cancer (Table 1), including 4,762 advanced cases, 2,915 advanced restricted cases, and 9,489 high-grade cases. The median BMI in early adulthood, reported for ages 18 to 21 years, ranged from 21.4kg/m^2 in NIH-AARP to 22.9kg/m^2 in HPFS, while BMI at baseline, primarily measured in mid to late adulthood, ranged from 23.4kg/m^2 in JPHC1/2 to 27.7kg/m^2 in CARET (Table 2).

For BMI in early adulthood, comparing BMI $\geq$ 25kg/m^2 with 21.0-22.9kg/m^2, we observed null associations for all forms of advanced / aggressive prostate cancer risk (advanced, advanced restricted, high grade prostate cancer) and prostate cancer mortality and 6-9% lower risks for total, localized and low-grade prostate cancers (Table 3). Similar to the categorical results, the non-parametric regression analyses showed non-linear, inverse associations for BMI in early adulthood with total, localized and low-grade prostate cancer (*p-value*, test for non-linearity<0.001); non-significant linear associations were observed for the remaining outcomes. Results were similar when we additionally adjusted for BMI at baseline (Supplemental Table 1).

We observed statistically significant differences in risk associated with BMI at baseline, typically measured at mid-to-late adulthood, for advanced prostate cancer and prostate cancer mortality compared with localized tumors, and by grade (*p-value*, test for common effects $\leq$0.01; Table 3). High BMI ($\geq$ 35kg/m^2) compared with healthy BMI (21.0-22.9kg/m^2) at baseline was associated with 16-19% lower risk of localized and low-grade prostate cancers. In contrast, we observed positive, and significant, associations for advanced prostate cancer (HR=1.30, 95% CI=0.95-1.78; p-value, test for trend=0.01) and for prostate cancer mortality (HR=1.52, 95% CI=1.12-2.07; p-value, test for trend<0.01) for the same comparison. As suggested by the categorical analyses, the non-parametric regression analyses showed positive, linear associations (*p-value*, test for non-linearity >0.10) for advanced prostate cancer and prostate cancer mortality; when BMI at baseline was modeled as a continuous variable, statistically significant 7-10% increases in risk for both outcomes were observed for a 5kg/m^2 increment.

Total, localized and low-grade prostate cancer risk was 6-15% lower for those who were obese at baseline (BMI$\geq$30kg/m^2) regardless of whether or not they were overweight in early adulthood (BMI$\geq$25kg/m^2) compared with men reporting a BMI<25kg/m^2 in early adulthood and a BMI<30kg/m^2 at baseline (Table 3). A 27% higher risk for prostate cancer mortality (95% CI: 9-49%) was observed for

men who had a healthy BMI (<25kg/m^2) in early adulthood and were obese at baseline (BMI≥30kg/m^2), compared to men reporting a BMI<25kg/m^2 in early adulthood and a BMI<30kg/m^2 at baseline. A similar, but non-significant risk (HR=1.20, 95% CI=0.95-1.52), was observed for men with a BMI<25kg/m^2 in early adulthood and a BMI<30kg/m^2 at baseline. No statistically significant associations were noted for any of the BMI in early adulthood and BMI at baseline categories and risk of advanced, advanced restricted and high grade prostate cancer. No statistically significant differences in risk were noted across stage and grade. We observed a consistent interpretation to these findings when we examined the absolute difference of BMI at baseline, typically measured in mid-to-late adulthood, and BMI in early adulthood. Results were similar for absolute difference of BMI at baseline and BMI in early adulthood when we adjusted for BMI in early adulthood.

Waist circumference, typically measured in mid-to-late adulthood, was inversely associated with total (HR=0.95, 95% CI=0.90-1.00), localized (HR=0.93, 95% CI=0.88-0.99) and low-grade (HR=0.90, 95% CI=0.85-0.95) prostate cancer when comparing ≥ 110 with <90cm (Table 4). In contrast, we observed a positive association between waist circumference and prostate cancer mortality (comparing ≥ 110 with <90cm: HR=1.39, 95% CI=1.14-1.71) and high-grade prostate cancer (HR=1.16, 95% CI=1.03-1.31), and between waist-to-hip ratio and risk of high-grade prostate cancer (HR comparing ≥1.00 with <0.90=1.14, 95% CI=1.01-1.28). Overall, risk was similar when we adjusted for BMI at baseline (Supplemental table 1).

Height was associated with a higher risk of total, advanced, advanced restricted prostate cancer, and prostate cancer mortality (Table 5). A statistically significant difference in risk due to height was detected for prostate cancer mortality in comparison with localized prostate cancer (*p-value*, test for common effects<0.05). Results were similar when we removed BMI at baseline as a covariate (results not shown).

For advanced and advanced restricted prostate cancer, and prostate cancer mortality, results for most anthropometric factors were similar when we stratified by age at diagnosis and smoking habits (Supplemental table 2). Associations of waist circumference and BMI at baseline with risk of advanced prostate cancer and prostate cancer mortality appeared to differ among strata of physical activity, with positive associations suggested in the lowest and highest strata and null or inverse in the middle stratum of physical activity.

Results for anthropometric factors were similar when we excluded those with a personal history of diabetes (Supplemental table 2). As PSA testing has shifted the diagnosis to identification of mostly latent (or low-grade) disease[44-48] in places where the test has been in routine use, we examined results by geographic region. For all anthropometric factors, results were similar for studies conducted in North America, where widespread PSA testing began in 1992, compared with other regions where routine PSA testing, if adopted, was initiated later in time(data not shown). As all participants in the PLCO trial [49] and the PCPT [50] who were included in this study underwent PSA testing routinely as part of the trial protocol, we repeated our analyses excluding these two studies and results were essentially unchanged (data not shown). Further, in analyses for high-grade prostate cancer in which we excluded those that were poorly differentiated, the results were similar to the main findings (results not shown). To evaluate lag effects, models were stratified by follow-up time; results were similar for <5 years compared with $\geq$5 years of follow-up time (Supplemental table 2).

DISCUSSION

In this pooled analysis of prospective cohorts, we observed positive associations for BMI at baseline (primarily mid to late adulthood) with risk of advanced prostate cancer and prostate cancer mortality, and for waist circumference (primarily in mid to late adulthood) and risk of high-grade prostate cancer and prostate cancer mortality. In contrast, we observed inverse associations with total, localized and low grade cancers for these anthropometric factors. Risk of prostate cancer mortality was

also elevated for men with a healthy weight in early adulthood but were obese at baseline (primarily mid to late adulthood). We also observed suggestive or statistically significant positive associations for waist-to-hip ratio and height with more aggressive / advanced forms of prostate cancer and prostate cancer mortality. Null or nonsignificant associations were noted for BMI in early adulthood, and hip circumference and risk of more advanced / aggressive forms of prostate cancer and prostate cancer mortality, but inverse for localized and low grade prostate cancers.

Overall, our results were similar to the summary estimates published in the WCRF statement for BMI at baseline, BMI at younger ages, waist circumference, height and risk of advanced prostate cancer subtypes; 10 cohorts included in our pooled analysis were also included in the WCRF meta-analysis[6]. Unlike previous studies, we systematically examined the association between anthropometric factors with the various outcome definitions for advanced (e.g., advanced stage), aggressive (e.g., high-grade) prostate cancers and prostate cancer mortality across studies. Our results are among the first to demonstrate that measures of central adiposity, independent of BMI, are associated with advanced forms of prostate cancer. Visceral adiposity may increase risk of advanced forms of prostate cancer through changes in cytokines and growth factors, hormone regulation and metabolism [51-56].

Previous studies, that have examined risks for advanced forms of prostate cancer, have been limited in their ability to analyze population subgroups or to stratify by important risk factors for prostate cancer. In general, our results were consistent across stratas of age and smoking and in non-diabetics. However, we observed statistically significant multiplicative interactions by physical activity for BMI at baseline and waist circumference with risk of advanced forms of prostate cancer. Our results were similar to three previous studies (including one study that is included in our analysis)[57] that observed differences in associations between BMI and prostate cancer risk by physical activity[57-59]. It has been hypothesized that physical activity may modify the BMI-prostate cancer association due to modification of hormone and metabolic pathways. Or, this finding may be the result of heterogeneity in

measurement of physical activity across studies, heterogeneity in the fat and muscle mass distribution of men across different levels of physical activity, and/or reduced diagnostic effectiveness of PSA testing and digital-rectal examinations in obese men[57-61]. Given that we did not observe a discernable pattern, these results also could be due to chance.

A limited number of studies have examined associations between anthropometric factors and risk of aggressive and advanced subtypes of prostate cancer; most were generally limited by case numbers and statistical power. In addition, studies have applied different outcome definitions. As we pooled prospective data from 15 cohort studies, creating one of the largest pooled datasets to date, we had greater statistical power than any individual study to examine prostate cancer subtypes with regards to anthropometric measures. We harmonized the exposures, covariates and outcomes, along with the modeling approach, across individual studies, thereby reducing potential sources of heterogeneity across studies. In particular, our case definition included six subtypes of prostate cancer, defined uniformly across studies. Further, with adequate statistical power, we systematically examined whether these associations were modified by other prostate cancer risk factors.

For each cohort, anthropometric measures were collected prior to cancer diagnosis; thus, a cancer diagnosis was unlikely to influence the reporting of anthropometry as may occur in a case-control study. However, individuals who were diagnosed close in time to study enrollment may have already experienced changes in anthropometry due to prediagnostic disease; this would likely be limited to men who had very aggressive disease and likely would have had diagnosis at a distant metastatic stage. Reassuringly, results from analyses stratified by follow-up time were similar.

Although we cannot rule out uncontrolled confounding by unknown or unmeasured factors or residual confounding from measurement error in the included covariates, all studies collected information on established or suspected prostate cancer risk factors (*e.g.*, age, race, smoking history, physical activity) and the majority of studies collected diabetes history. Although height and weight

were self-reported in 10 cohorts, most studies have observed high correlations between self-reported and measured anthropometric factors[62, 63]; however, any misclassification of our exposures is likely to be non-differential which may result in our risk estimates being underestimated. In our analyses, we focused our exposures on baseline assessment, primarily assessed in mid to late adulthood and did not consider changes in anthropometric factors and covariates during follow-up time; thus, we may have some misclassification of our exposures and covariates over time. Our pooled analysis was unable to examine differences by race and ethnicity as most individuals in each cohort were non-Hispanic White. Further, we conducted multiple statistical tests and examined results in a number of subgroups and cannot rule out chance findings. On the other hand, the fact that our results were consistent across studies, and the cohorts in our analysis represent populations from different geographic regions with different age ranges and education levels and varied prevalence of PSA testing, adds to the robustness of our findings.

In summary, we observed positive associations of BMI, waist circumference and height, typically measured at mid to late adulthood, with risk of various definitions of advanced /aggressive forms of prostate cancer and prostate cancer mortality. However, measures of body fatness in early adulthood were not associated with risk of advanced prostate cancer and prostate cancer mortality. Thus, maintenance of healthy weight is important for prostate cancer risk as well as numerous other health conditions. Further, it is important to understand the underlying mechanism associated with measures of adiposity and height to reduce the morbidity and mortality associated with this and related diseases.

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Table 1. Baseline Characteristics of Studies included in the Pooled Analysis for Anthropometry and Risk of Prostate Cancer Incidence and Mortality

Cohort[1]	Country	Follow-up Time (Median)	Baseline cohort size[2,3]	Age Range (Median)	Prostate Cancer Cases (*N*)						
					Total	Localized [4]	Advanced[5]	Advanced (restricted)[6]	Protate Cancer Mortality [7]	Low grade[8]	High grade[9]
ATBC	Finland	1985-2002 (14)	26,963	49-70 (57)	1315	828	353	242	269	824	223
CARET	USA	1985-2005 (12)	10,402	44-75 (57)	730	439	68	** [10]	** [10]	551	79
CLUE II	USA	1989-2009 (19)	5,918	18-89 (51)	461	250	54	** [10]	** [10]	296	133
CPS II	USA	1992-2005 (12)	65,021	42-93 (64)	6863	5722	451	276	279	5375	1221
COSM	Sweden	1998-2008 (11)	43,010	45-79(59)	2834	1774	513	381	293	1670	343
EPIC	10 European countries	1991-2006 (9)	142,174	20-97 (52)	2727	1337	345	175	248	1325	298
HPFS	USA	1986-2008 (21)	46,648	32-79 (54)	5410	3798	651	313	518	4008	556
JPHC I	Japan	1990-2008 (15)	20,016	40-59 (50)	135	78	** [10]	** [10]	** [10]	90	** [10]
JPHC II	Japan	1993-2004 (12)	23,780	40-69 (54)	162	82	** [10]	** [10]	** [10]	90	** [10]
MCCS	Australia	1990-2006 (13)	14,811	27-72 (55)	910	737	76	** [10]	70	668	218
MEC	USA	1993-2004 (11)	83,591	45-78 (60)	5525	4549	508	365	280	3632	1553
NLCS	Netherlands	1986-2007 [2] (13)	58,279	54-70 (61)	2359	1231	733	544	450	1686	490
NIH-AARP	USA	1995-2007 (10)	244,857	50-71 (62)	18497	13654	870	532	542	13463	3878
PCPT	USA	1994-2003 (7)	15,462	55-86 (63)	846	786	** [10]	** [10]	** [10]	678	107
PLCO	USA	1993-2008 (9)	29,840	55-75 (62)	2960	2543	140	87	78	2552	390
Total			830772		51734	36291	4762	2915	3027	36908	9489

[1]ATBC= Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, CARET=Beta-Carotene and Retinol Efficacy Trial , CLUE II=CLUE II: Campaign Against Cancer and Heart Disease, CPS II=Cancer Prevention Study II Nutrition Cohort, COSM=Cohort of Swedish Men, EPIC= European Prospective Investigation into Cancer and Nutrition, HPFS=Health Professionals Follow-up Study, JPHC I=The Japan Public Health Center-Based Study Cohort I, JPHC II=The Japan Public Health Center-Based Study Cohort II, MCCS=Melbourne Collaborative Cohort Study, MEC=Multiethnic Cohort, NLCS =Netherland Cohort Study, NIH-AARP=The NIH-AARP Diet and Health Study, PCPT=Prostate Cancer Prevention Trial, PLCO=Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial

[2] Baseline cohort size and number of cases determined after applying exclusion criteria.

[3]NLCS is analyzed as a case-cohort study so the baseline cohort size does not reflect the exclusions, and we did not supply a median follow-up time for the cohort.

[4]"Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate;

[5]"Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal;

[6]"Advanced (restricted)": same as "advanced" but excluding prostate cancer mortality cases that were initially diagnosed as localized cases or cases with missing stage information at diagnosis;

[7]"Prostate Cancer Mortality": defined when prostate cancer was the underlying cause of death

[8]"Low grade": Gleason score <8 or well/moderately differentiated;

[9]"High grade": Gleason score ≥8 or poorly differentiated/undifferentiated

[10]Studies with less than 50 cases were excluded from the analysis of that prostate cancer outcome and is denoted by **

Table 2. Median and Interquartile Range of Anthropometric Factors by Study

	Median (Interquartile Range)[2]				
Study Acronym[1]	**BMI in Early Adulthood (kg/m^2)**	**BMI at baseline (kg/m^2)**	**Height (m)**	**Waist Circumference (cm)**	**Hip Circumference (cm)**
ATBC	**	26.0 (23.7-28.5)	1.74 (1.69-1.78)	**	**
CARET	**	27.7 (25.2-30.7)	1.75 (1.70-1.80)	**	**
CLUE II	22.7 (20.7-25.0)	25.9 (24.0-28.7)	1.78 (1.73-1.83)	**	**
CPS II	21.7 (19.8-23.7)	25.9 (24.0-28.4)	1.78 (1.75-1.83)	96.5 (91.4-104.1)	**
COSM	21.8 (20.4-23.3)	25.4 (23.6-27.7)	1.77 (1.73-1.82)	95.0 (90.0-102.0)	101.0 (97.0-106.0)
EPIC	22.6 (21.1-24.2)	26.1 (24.0-28.6)	1.75 (1.70-1.80)	94.2 (88.0-101.0)	101.0 (96.5-105.0)
HPFS	22.9 (21.1-24.4)	25.1 (23.5-27.1)	1.78 (1.73-1.83)	94.0 (88.9-100.3)	100.3 (96.5-104.8)
JPHC I	**	23.4 (21.6-25.3)	1.64 (1.60-1.68)	**	**
JPHC II	21.7 (20.3-23.3)	23.4 (21.5-25.3)	1.64 (1.60-1.68)	**	**
MCCS	22.4 (20.8-24.2)	26.8 (24.7-29.0)	1.73 (1.68-1.78)	92.5 (86.7-99.0)	100.5 (96.5-105.0)
MEC	21.8 (20.2-23.8)	25.9 (23.9-28.8)	1.73 (1.68-1.78)	**	**
NLCS	21.7 (20.3-23.2)	24.8 (23.4-26.5)	1.76 (1.72-1.81)	**	**
NIH-AARP	21.4 (19.6-23.5)	26.6 (24.4-29.3)	1.78 (1.73-1.83)	96.5 (90.2-104.1)	101.6 (96.5-108.0)
PCPT	**	27.2 (25.0-29.8)	1.78 (1.73-1.83)	102.0 (95.3-109.0)	104.0 (99.0-109.0)
PLCO	22.8 (20.9-24.4)	27.0 (24.8-29.7)	1.78 (1.73-1.83)	**	**
Total					

[1]ATBC= Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, CARET=Beta-Carotene and Retinol Efficacy Trial , CLUE II=CLUE II: Campaign Against Cancer and Heart Disease, CPS II=Cancer Prevention Study II Nutrition Cohort, COSM=Cohort of Swedish Men, EPIC= European Prospective Investigation into Cancer and Nutrition, HPFS=Health Professionals Follow-up Study, JPHC I=The Japan Public Health Center-Based Study Cohort I, JPHC II=The Japan Public Health Center-Based Study Cohort II, MCCS=Melbourne Collaborative Cohort Study, MEC=Multiethnic Cohort, NLCS =Netherland Cohort Study, NIH-AARP=The NIH-AARP Diet and Health Study, PCPT=Prostate Cancer Prevention Trial, PLCO=Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial

[2]Specific anthropometric factor was not assessed at baseline within

Table 3. Pooled Multivariable[1] Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Prostate Cancer According to Body Mass Index at Baseline and in Early Adulthood

Anthropometric Factor	HR (95% CI) by Categories of Anthropometric Factor							p-value, test for trend[2]	p-value, test for between-studies heterogeneity[3]	I^2 [4]	p-value, test for common effects[5]	Continuous HR (95% CI) for 5kg/m^2 increment	p-value, test for between-studies heterogeneity	I^2
BMI in Early Adulthood (kg/m^2)	**<18.5**	**18.5-20.9**	**21-22.9**	**23-24.9**	**≥25**									
All	0.97 (0.93-1.01)	1.00 (0.97-1.03)	1.00 (REF)	0.98 (0.95-1.01)	0.94 (0.90-0.98)			0.33	0.18	30%		**[11]		
By stage														
Localized[6]	0.97 (0.92-1.01)	1.01 (0.97-1.05)	1.00 (REF)	0.98 (0.95-1.01)	0.91 (0.88-0.95)			<0.01	0.42	2%		**[11]		
Advanced[7]	0.86 (0.69-1.09)	0.95 (0.87-1.04)	1.00 (REF)	0.92 (0.77-1.11)	0.97 (0.85-1.10)			0.58	0.30	16%	0.42	1.01 (0.89-1.15)	<0.01	72%
Restricted[8]	0.98 (0.76-1.26)	0.95 (0.85-1.07)	1.00 (REF)	0.89 (0.70-1.13)	0.93 (0.79-1.08)			0.82	0.50	0%	0.89	0.97 (0.85-1.12)	0.01	62%
Prostate Cancer Mortality[9]	0.90 (0.66-1.24)	0.93 (0.83-1.03)	1.00 (REF)	0.95 (0.80-1.13)	0.99 (0.86-1.14)			0.43	0.52	0%	0.28	1.03 (0.89-1.20)	<0.01	69%
By grade														
Low[9]	0.95 (0.91-1.00)	1.01 (0.97-1.04)	1.00 (REF)	0.97 (0.93-1.01)	0.93 (0.87-0.99)			0.15	0.05	48%		**[11]		
High[10]	0.98 (0.89-1.07)	0.94 (0.87-1.01)	1.00 (REF)	0.98 (0.89-1.09)	0.95 (0.88-1.03)			>0.99	0.56	0%	0.61	1.00 (0.96-1.05)	0.89	0%
BMI at baseline (kg/m^2)		**<21**	**21-22.9**	**23-24.9**	**25-29.9**	**30-34.9**	**≥35**							
All		0.96 (0.90-1.02)	1.00 (REF)	1.02 (0.99-1.06)	1.00 (0.96-1.05)	0.94 (0.89-1.00)	0.90 (0.81-1.00)	0.07	0.10	39%		**[11]		
By stage														
Localized[6]		0.97 (0.91-1.03)	1.00 (REF)	1.02 (0.97-1.07)	0.99 (0.95-1.04)	0.92 (0.88-0.96)	0.84 (0.76-0.93)	<0.01	0.25	23%		**[12]		
Advanced[7]		0.88 (0.74-1.04)	1.00 (REF)	0.97 (0.87-1.08)	1.01 (0.92-1.12)	1.05 (0.90-1.23)	1.30 (0.95-1.78)	0.01	0.11	37%	0.01	1.07 (1.02-1.12)	0.32	13%
Restricted[8]		0.74 (0.59-0.92)	1.00 (REF)	0.92 (0.81-1.04)	0.95 (0.83-1.09)	0.89 (0.75-1.05)	0.92 (0.68-1.25)	0.86	0.567	0%	0.60	1.01 (0.96-1.08)	0.34	11%
Prostate Cancer Mortality[9]		0.97 (0.79-1.19)	1.00 (REF)	0.96 (0.83-1.12)	1.02 (0.88-1.18)	1.13 (0.93-1.39)	1.52 (1.12-2.07)	<0.01	0.34	12%	<0.001	1.10 (1.05-1.16)	0.45	0%
By grade														
Low[10]		0.98 (0.92-1.05)	1.00 (REF)	1.01 (0.98-1.05)	0.99 (0.94-1.04)	0.91 (0.85-0.96)	0.81 (0.72-0.91)	<0.01	0.12	39%		**[12]		
High[11]		0.98 (0.86-1.11)	1.00 (REF)	1.06 (0.98-1.15)	1.03 (0.96-1.11)	1.03 (0.94-1.12)	1.15 (0.95-1.40)	0.18	0.23	27%	<0.01	1.03 (0.99-1.06)	0.30	18%
BMI change			**<25kg/m^2 in early adulthood, <30kg/m^2 at baseline**	**≥25kg/m^2 in early adulthood, <30kg/m^2 at baseline**	**<25kg/m^2 in early adulthood, ≥30kg/m^2 at baseline**	**≥25kg/m^2 in early adulthood, ≥30kg/m^2 at baseline**								
All			1.00 (REF)	0.96 (0.92-1.01)	0.94 (0.91-0.97)	0.90 (0.83-0.97)			0.05	49%				
By stage														
Localized[6]			1.00 (REF)	0.95 (0.91-0.99)	0.93 (0.88-0.99)	0.85 (0.77-0.93)			0.03	54%				
Advanced[7]			1.00 (REF)	1.00 (0.88-1.14)	1.09 (0.96-1.24)	1.13 (0.93-1.38)			0.25	22%	0.01			
Restricted[8]			1.00 (REF)	0.96 (0.81-1.14)	0.98 (0.83-1.17)	1.02 (0.81-1.28)			0.54	0%	0.15			
Prostate Cancer Mortality[9]			1.00 (REF)	1.05 (0.90-1.23)	1.27 (1.09-1.49)	1.20 (0.95-1.52)			0.32	14%	0.01			
By grade														
Low[10]			1.00 (REF)	0.96 (0.91-1.02)	0.91 (0.87-0.95)	0.87 (0.79-0.95)			0.03	54%				
High[11]			1.00 (REF)	1.00 (0.91-1.09)	1.04 (0.94-1.16)	0.97 (0.87-1.08)			0.92	0%	0.12			
Absolute BMI change (kg/m^2)		**Loss > 2**	**+/- 2**	**2-<5**	**5-<10**	**≥10**								
All		1.00 (0.90-1.11)	1.00 (REF)	1.03 (1.00-1.07)	0.99 (0.94-1.04)	0.95 (0.91-1.00)		0.22	0.93	0%				
By stage														
Localized[6]		0.94 (0.86-1.02)	1.00 (REF)	1.03 (0.99-1.08)	0.97 (0.91-1.03)	0.94 (0.89-0.99)		0.07	0.89	0%				
Advanced[7]		0.94 (0.74-1.18)	1.00 (REF)	0.97 (0.84-1.12)	1.02 (0.88-1.19)	1.20 (0.93-1.55)		0.36	0.04	50%	0.11			
Restricted[8]		0.96 (0.72-1.30)	1.00 (REF)	0.98 (0.84-1.15)	0.98 (0.85-1.12)	1.08 (0.77-1.52)		0.95	0.05	52%	0.46			
Prostate Cancer Mortality[9]		1.01 (0.77-1.34)	1.00 (REF)	0.93 (0.78-1.11)	1.01 (0.84-1.20)	1.31 (0.99-1.74)		0.38	0.10	42%	0.02			
By grade														
Low[10]		0.99 (0.87-1.14)	1.00 (REF)	1.04 (0.99-1.08)	0.97 (0.91-1.03)	0.92 (0.86-0.97)		0.04	0.99	0%				
High[11]		1.07 (0.91-1.25)	1.00 (REF)	1.01 (0.93-1.09)	1.03 (0.96-1.11)	1.04 (0.93-1.16)		0.37	0.41	4%	0.06			

Anthropometric Factor	HR (95% CI) by Categories of Anthropometric Factor	p-value, test for trend[2]	p-value, test for between-studies heterogeneity[3]	I^2 [4]	p-value, test for common effects[5]	Continuous HR (95% CI) for 5kg/m^2 increment	p-value, test for between-studies heterogeneity	I^2

[1]Multivariable relative risks (MVRR) were adjusted for race (Caucasian, African-American, Asian, Hispanic, other), education (<high school, high school, >high school), marital status (married, never married, widowed, divorced), alcohol (0,>0-<5, 5-<15, 15-<30 and ≥30g/day), smoking habits (never, past smoker and <15 pack years, past smoker and ≥15 pack years, current smoker and <40 pack years, and current smoker and ≥40 pack years), height (<1.70, 1.70–<1.75, 1.75–<1.80, 1.80–<1.85, ≥1.85m), , except for JPHC1 and JPHC2 in which the .05m category increments ranged from <1.60 to >1.75m, physical activity (low, medium, high), prostate cancer family history (no, yes), personal history of diabetes (no, yes), multiple vitamin use (no, yes), and dietary calcium (quintiles), dietary lycopene (quintiles), and total energy intake (kcal/d, continuous); for adjustment, these variables were entered directly into the multivariable model or, for studies with less than 200 cases, these variables were modeled using propensity scores.

[2]P-value, test for trend is evaluated using the wald test

[3]P-value, test for between-studies heterogeneity is based on the highest category

[4] I^2 value is based on the highest category

[5]P-value, test for common effects, is based on the highest category and compared the following: 1)advanced to localized, 2) advanced restricted to localized, 3) prostate cancer mortality to localized, and 4) high grade to low grade.

[6]"Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate;

[7]"Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal;

[8]"Advanced (restricted)": same as "advanced" but excluding prostate cancer mortality cases that were initially diagnosed as localized cases or cases with missing stage information at diagnosis

[9]"Prostate Cancer Mortality": defined when prostate cancer was the underlying cause of death

[10]"Low grade": Gleason score <8 or well/moderately differentiated

[11]"High grade": Gleason score ≥8 or poorly differentiated/undifferentiated

Table 4. Pooled Multivariable Hazard Ratios[1] and 95% Confidence Intervals(CI) of Prostate Cancer According to Waist and Hip Circumference

	HR (95% CI) by Categories of Anthropometric Factor				p-value, test for trend[2]	p-value, test for between-studies heterogeneity[3]	I^{2} [4]	p-value, test for common effects[5]	Continuous HR (95% CI)[6]	p-value, test for between-studies heterogeneity	I^{2}
Waist Circumference (cm)	**<90**	**90-<100**	**100-<110**	**≥110**							
All	1.00 (REF)	1.01 (0.96-1.06)	0.99 (0.95-1.04)	0.95 (0.90-1.00)	<0.01	0.79	0%		**[13]		
By stage											
Localized[7]	1.00 (REF)	1.01 (0.95-1.07)	0.98 (0.94-1.03)	0.93 (0.88-0.99)	<0.01	0.94	0%		**[13]		
Advanced[8]	1.00 (REF)	1.00 (0.89-1.13)	1.07 (0.94-1.22)	1.17 (0.95-1.44)	0.09	0.23	29%	0.04	1.05 (0.99-1.12)	0.12	44%
Restricted[9]	1.00 (REF)	0.94 (0.80-1.09)	1.03 (0.86-1.22)	0.92 (0.73-1.18)	0.98	0.65	0%	0.93	0.99 (0.93-1.05)	0.44	0%
Prostate Cancer Mortality[10]	1.00 (REF)	1.03 (0.89-1.19)	1.06 (0.90-1.25)	1.39 (1.14-1.71)	0.01	0.74	0%	<0.001	1.07 (1.01-1.13)	0.25	28%
By grade											
Low[11]	1.00 (REF)	1.00 (0.95-1.06)	0.97 (0.92-1.01)	0.90 (0.85-0.95)	<0.001	0.93	0%		**[13]		
High[12]	1.00 (REF)	1.06 (0.98-1.15)	1.11 (0.98-1.26)	1.16 (1.03-1.31)	0.02	0.40	5%	<0.001	1.05 (1.01-1.09)		
Hip Circumference (cm)	**<95**	**95-<100**	**100-<105**	**≥105**							
All	1.00 (REF)	0.99 (0.94-1.05)	1.02 (0.96-1.09)	0.93 (0.87-0.98)	<0.01	0.28	25%		**[13]		
By stage											
Localized[7]	1.00 (REF)	1.00 (0.95-1.06)	1.02 (0.96-1.08)	0.92 (0.87-0.97)	<0.01	0.54	0%		**[13]		
Advanced[8]	1.00 (REF)	1.05 (0.84-1.32)	1.10 (0.85-1.43)	1.06 (0.83-1.36)	0.76	0.11	49%	0.26	1.02 (0.97-1.07)	0.06	57%
Restricted[9]	1.00 (REF)	0.95 (0.72-1.27)	1.01 (0.74-1.38)	0.79 (0.63-0.98)	0.03	0.65	0%	0.18	0.98 (0.93-1.03)	0.55	0%
Prostate Cancer Mortality[10]	1.00 (REF)	1.03 (0.82-1.29)	1.20 (0.82-1.77)	1.26 (0.98-1.62)	0.03	0.24	29%	0.02	1.03 (0.98-1.07)	0.61	0%
By grade											
Low[11]	1.00 (REF)	1.00 (0.94-1.06)	1.00 (0.95-1.06)	0.88 (0.82-0.95)	<0.01	0.27	26%				
High[12]	1.00 (REF)	1.00 (0.89-1.12)	1.17 (0.93-1.48)	1.14 (0.92-1.41)	0.21	0.07	61%	0.03	1.01 (0.98-1.04)	0.30	25%
Waist to Hip Ratio	**<0.90**	**0.90-<0.95**	**0.95-<1.00**	**≥1.00**							
All	1.00 (REF)	1.02 (0.98-1.07)	1.02 (0.97-1.06)	1.04 (0.99-1.09)	0.21	0.88	0%		1.01 (1.00-1.02)	0.72	0%
By stage											
Localized[7]	1.00 (REF)	1.01 (0.95-1.08)	1.03 (0.97-1.08)	1.03 (0.97-1.09)	0.47	0.66	0%		1.01 (0.99-1.02)	0.77	0%
Advanced[8]	1.00 (REF)	1.04 (0.91-1.20)	1.04 (0.86-1.27)	1.17 (0.95-1.45)	0.06	0.21	34%	0.24	**[13]		
Restricted[9]	1.00 (REF)	1.03 (0.76-1.38)	0.96 (0.78-1.18)	1.07 (0.79-1.46)	0.85	0.14	45%	0.80	1.01 (0.95-1.08)	0.52	0%
Prostate Cancer Mortality[10]	1.00 (REF)	1.02 (0.85-1.23)	1.01 (0.77-1.33)	1.20 (0.99-1.46)	0.07	0.61	0%	0.14	**[13]		
By grade											
Low[11]	1.00 (REF)	1.01 (0.95-1.07)	1.01 (0.96-1.07)	1.02 (0.96-1.08)	0.48	0.46	0%		1.00 (0.99-1.02)	0.37	9%
High[12]	1.00 (REF)	1.09 (0.95-1.25)	1.09 (0.98-1.22)	1.14 (1.01-1.28)	0.02	0.54	0%	0.09	1.05 (1.01-1.08)	0.53	0%

[1]Multivariable relative risks (MVRR) were adjusted for race (Caucasian, African-American, Asian, Hispanic, other), education (<high school, high school, >high school), marital status (married, never married, widowed, divorced), alcohol (0 ,>0-<5, 5-<15, 15-<30 and ≥30g/day), smoking habits (never, past smoker and <15 pack years, past smoker and 15+ pack years, current smoker and <40 pack years, and current smoker and pack years ≥40), height (<1.70, 1.70–<1.75, 1.75–<1.80, 1.80–<1.85, ≥1.85m), except for JPHC1 and JPHC2 in which the .05m category increments ranged from <1.60 to >1.75m, (physical activity (low, medium, high), prostate cancer family history (no, yes), personal history of diabetes (no, yes) multiple vitamin use (no, yes), and dietary calcium (quintiles), dietary lycopene (quintiles), and total energy intake (kcal/d, continuous); for adjustment, these variables were entered directly into the multivariable model or, for studies with less than 200 cases, these variables were modeled using the propensity scores.

[2]P-value, test for trend is evaluated using the Wald test

[3]P-value, test for between-studies heterogeneity is based on the highest category

[4] I^{2} value is based on the highest category

[5]P-value, contrast test, is based on the highest category and compared the following: 1)advanced to localized, 2) advanced restricted to localized, 3) prostate cancer mortality to localized, and 4) high grade to low grade.

[6]Continuous estimate was based on an increment of 10cm for waist circumference, 5cm for hip circumference and 0.05 for waist to hip ratio.

[7]"Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate;

[8]"Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal;

[9]"Advanced (restricted)": same as "advanced" but excluding prostate cancer mortality cases that were initially diagnosed as localized cases or cases with missing stage information at

[10]"Prostate Cancer Mortality": defined when prostate cancer was the underlying cause of death

[11]"Low grade": Gleason score <8 or well/moderately differentiated

[12]"High grade": Gleason score >=8 or poorly differentiated/undifferentiated

[13]Continuous estimates were not calculated as the p-value, test for nonlinearity<0.05