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Larger men have larger prostates: Detection bias in epidemiologic studies of obesity and prostate cancer risk

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Abstract

BACKGROUND—Obesity is associated with risk of aggressive prostate cancer (PCa), but not with over-all PCa risk. However, obese men have larger prostates which may lower biopsy accuracy and cause a systematic bias towards the null in epidemiologic studies of over-all risk.

METHODS—Within a cohort of 6,692 men followed-up after a biopsy or transurethral resection of the prostate (TURP) with benign findings, a nested case-control study was conducted of 495 prostate cancer cases and controls matched on age, race, follow-up duration, biopsy versus TURP and procedure date. Data on body mass index and prostate volume at the time of the initial procedure were abstracted from medical records.

RESULTS—Prior to consideration of differences in prostate volume, overweight (OR = 1.41; 95% CI 1.01, 1.97) and obese status (OR = 1.59; 95% CI 1.09, 2.33) at the time of the original benign biopsy or TURP were associated with PCa incidence during follow-up. Prostate volume did not significantly moderate the association between body-size and PCa, however it did act as an inverse confounder; adjustment for prostate volume increased the effect size for overweight by 22% (adjusted OR = 1.52; 95% CI 1.08, 2.14) and for obese status by 23% (adjusted OR = 1.77; 95% CI 1.20, 2.62). Larger prostate volume at the time of the original benign biopsy or TURP was inversely associated with PCa incidence during follow-up (OR = 0.92 per 10 cc difference in volume; 95% CI 0.88, 0.97). In analyses that stratified case-control pairs by tumor aggressiveness of the case, prostate volume acted as an inverse confounder in analyses of non-aggressive PCa but not in analyses of aggressive PCa.

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CONCLUSIONS—In studies of obesity and PCa, differences in prostate volume cause a bias towards the null, particularly in analyses of non-aggressive PCa. A pervasive underestimation of the association between obesity and overall PCa risk may exist in the literature.

Introduction

In 2016, there are expected to be 180,890 new cases of prostate cancer (PCa), along with 26,120 deaths from the disease, making PCa the most commonly diagnosed non-skin cancer among men in the United States and the second leading cause of cancer death among men (1). Studies of obesity and PCa incidence have found positive, negative, and null associations (2–9). A meta-analysis found a modest increase in risk with increasing BMI, $RR=1.05$ (95% CI 1.01–1.08) per five unit increase in BMI (2). However, analyses by grade and stage suggest that obesity is more strongly associated with advanced PCa and unassociated with or perhaps even protective against localized or low-grade disease (2,5,10). However, obesity is associated with lower PSA, a thorough digital rectal exam may be more difficult to complete in obese men, and obesity is related to larger prostate size and potentially reduced sensitivity for biopsy based diagnoses (11–14). Therefore interpretation of the extant literature on obesity and PCa incidence is complex(13).

It has been argued that because prostate size is larger among overweight and obese men as compared to normal weight men the diagnostic accuracy of biopsies for detecting prostate cancer is lower in overweight and obese men. This in turn effects epidemiologic studies of obesity and PCa risk that may suffer from diagnostic bias with under-diagnosis of small non-aggressive tumors among obese men(13,15–17). Within a studied PCa case-series, the subgroup of men with larger prostates and higher BMI may include a higher percentage of men diagnosed with aggressive tumors whose tumors were missed at prior biopsies when the tumors were smaller and/or less aggressive(13). This phenomena would lead to an overestimate of the association between obesity and diagnosis of aggressive prostate tumors and an underestimate of the association between obesity and non-aggressive PCa. Furthermore, depending on the underlying distribution of aggressive and non-aggressive cancers in population the study draws cases from, this type of diagnostic bias could lead to a failure to observe a link between obesity and overall PCa risk.

Past research that has incorporated measures of prostate size into studies of obesity and PCa have derived cross-sectional case-control studies from series of men undergoing biopsy during a specified time period; men whose biopsy returns a finding of cancer are cases and men whose biopsy returns a benign finding are treated as controls(15–17). In these studies prostate size is measured at the time of biopsy when case-control status was ascertained(15–17). However, it is not clear that these biopsy series studies and data on prostate size at case-control ascertainment can be used to appropriately address potential bias caused by differences in prostate volume. With cross-sectional case-control studies derived from biopsy series the underlying at-risk cohort that produces the cases and controls is not defined and dynamic processes leading up to the enumeration period for the biopsy series, including prior biopsy history and changes in prostate size with aging, are not observed. Men in the underlying at-risk cohort with smaller prostates and growing tumors are more likely to be diagnosed at a biopsy occurring prior to the enumeration period used in any given biopsy

series study, than men with larger prostates and growing tumors. This “early detection” is an event that would have removed the man from consideration during the enumeration period of a given biopsy series study but would have been an observed event in a prospective cohort study. Further complicating matters, an enlarged prostate may itself be the factor that brings a man to medical attention and biopsy. Thus in a biopsy series derived case-control study, risk for biopsy, obesity, prostate size at diagnosis, diagnostic accuracy and case-control ascertainment are likely entangled. It is not clear that adjustment or stratification for prostate size at diagnosis in a biopsy series study fully addresses the potential for selection bias caused by differences in prostate volume.

Additionally, it is not clear how prostate size at diagnosis should be conceptualized in a data analysis of obesity and different levels of PCa risk. Prostate size at diagnosis has variously been conceptualized as a confounder or as an effect modifier of associations between obesity and PCa risk(15–17). Freedland et al, found that prostate size at case-control ascertainment was an inverse confounder that caused observed associations between obesity and PCa to be biased towards the null(16). However, Fowke et al., conceptualized prostate size at case-control ascertainment as an effect modifier and observed associations between obesity and aggressive PCa only among men with smaller prostates at diagnosis(15,17). Here using a prospective cohort design we measured prostate size at entry into the cohort and assessed its role as an effect modifier or confounder of the relationship between obesity and PCa risk.

Materials and Methods

This nested case-control study has been extensively described previously(8). A nested case-control of 574 case-control pairs was assembled from a historical cohort of 6,692 men who had a benign prostate specimen collected by needle core biopsy or TURP between January 1990 and December 2002 at Henry Ford Health System (HFHS) and who were followed up for PCa incidence to December 2007. ‘Date of cohort entry’ was defined as the date of the initial procedure (biopsy or TURP) that yielded a benign prostate specimen; ‘date of case diagnosis’ was the date of first cancer-positive tissue specimen or the date a clinician first reported a clinical diagnosis of PCa. Patients diagnosed with PCa less than one year from date of cohort entry were ineligible for the study. Incidence density sampling was used to select controls with replacement from all cohort members at risk at the time of case occurrence and controls were matched to cases on age at entry into cohort (± 2 years), date of entry into cohort (± 2 years), race (African American or White), and type of initial specimen (biopsy or TURP; 7% of cases had TURP).

Data

Data for this study were abstracted from the HFHS medical records. The presence of any notation in the medical record of a family history of PCa in the subject’s father or brothers was used to indicate a positive family history. Data on all PSA tests were abstracted and the PSA test value immediately prior to the initial benign procedure at the HFHS was used as the base-line PSA level. If a PSA test result immediately prior to the initial benign procedure was not available, the PSA level measured at the first PSA test subsequent to the procedure was used. Screening intensity was measured as the frequency of PSA tests and digital rectal

exams (DRE) during follow-up; for cases the period between cohort entry and diagnosis was examined and for controls the period between cohort entry and matching date (corresponding to the time interval between the initial procedure and diagnosis for the matched case) was examined. Medical record data on height and weight measured closest to the initial benign procedure was used to calculate body mass index (BMI) and overweight (BMI ≥ 25 and <30) and obese status (BMI ≥ 30) at the beginning of follow-up. Data on covariates and BMI were available from 495 case-control pairs.

Prostate size at biopsy was recorded in the pathology records in several ways, prostate volume, prostate dimensions in three axis or prostate weight; in some instances no data on prostate size was recorded. When prostate volume data was unavailable prostate volume was estimated from the reported prostate dimensions as (dimension 1 x dimension 2 x dimension 3) x (3.14/6). When volume and dimension data were not available, prostate weight was used to estimate volume; the density of the prostate is approximately 1 gram/cm³. For the 456 subjects where dimension and volume data were recorded the correlation between calculated prostate volume and recorded volume was 0.93 and for the 95 subjects where dimension and weight data were recorded the correlation between calculated prostate volume and volume estimated by weight was 0.97. Of the 495 case-control pairs with covariate and BMI data, 387 case-control pairs had prostate volume data or dimension or weight data from which prostate volume could be estimated.

Pathology data from the tumors were used to classify cases as having high (Gleason score ≥ 7 ; 4 primary, 3 secondary) or low grade tumors. Advanced stage disease was defined as pathologic or clinical stage T3a and higher. Aggressive PCa was defined as having either high-grade or advanced stage disease (18).

Statistical Analyses

Among those with complete data linear regression was used to assess whether body size was associated with prostate volume at initial biopsy adjusting for age, race and PSA at biopsy. For analyses of PCa incidence, missing prostate volume data were imputed using Fully Conditional Specification (FCS) regression multiple imputation methods (5 imputations) using data on body mass index, age, and race and yielded a sample size of 495 case control pairs. Conditional logistic regression models were used to estimate odds ratios for PCa incidence during follow-up for overweight and obese men compared to normal weight men and the analyses adjusted for baseline PSA and a family history PCa. To adjust for possible differences in screening intensity between obese, overweight and normal weight men, analyses also adjusted for the number of PSA tests and DRE during follow-up(8). As it is highly unlikely that a prostate biopsy is undertaken without a PSA test and/or DRE, adjustment for screening intensity during follow-up is expected to control for differences in surveillance, biopsy rates and overall contact with the medical system that might exist between men of different body sizes. This model is considered the baseline model and estimated the odds ratios for PCa incidence associated with overweight and obesity status at the initial biopsy without consideration of prostate volume. Prostate volume was initially considered as a possible effect modifier of the association between body size and PCa incidence (15,17). Prostate volume was classified in a binary fashion, with a large prostate

defined as being greater or equal to the study median prostate volume of 43.09 CC and interaction terms for overweight status and larger prostate size and obese status and larger prostate size were added to the baseline model. Prostate volume was then considered as a possible inverse confounder by removing the interaction term and adjusting for prostate volume in the baseline model(16). Additional analyses were performed among cases and their matched controls stratifying pairs on the disease aggressiveness status of cases. The conditional logistic regression analyses used the five multiple imputed data sets and pooled results are reported.

Results

The characteristics of the men included in the analyses are shown in Table 1. Those missing volume data were significantly older (1.86 years) and had lower PSA levels at biopsy (2.42 ng/ml); men for whom prostate volume data was and was not available did not differ for other variables included in the analyses.

After adjustment for age, race and PSA level at cohort entry, larger body size was significantly associated with larger prostate volume (see figure 1, $p=0.002$ for overweight verses normal weight, and $p<0.001$ for obese verses normal weight). Before consideration of prostate volume, obese and overweight status were significantly associated with PCa risk (OR = 1.59 for Obesity 95% CI 1.09, 2.33; OR = 1.41 for Overweight 95% CI 1.01, 1.97). In analyses stratified by prostate volume, overweight and obese status were both positively and significantly associated with PCa risk among men with smaller prostates, however the association with PCa risk was stronger for overweight than for obesity (see Table 2). Among men with larger prostates there was no association between PCa risk and overweight or obesity and the overweight x prostate volume and the obesity x prostate volume interaction terms were not statistically significant ($p=0.12$ and $p=0.59$ respectively).

In models that considered prostate volume as a confounder, volume was inversely associated with PCa risk (OR = 0.92 per 10 CC difference in volume, 95% CI 0.88, 0.97). As prostate volume was positively associated with body size and inversely associated with risk, it acted as an inverse confounder in unadjusted analyses of body size and PCa risk and adjustment for prostate volume increased the effect sizes for both obese and overweight status; a 23% increase in beta for obesity and a 22% increase in beta for overweight (table 3). Prior to adjustment for prostate volume at biopsy, overweight and obese status were non-significantly associated with aggressive and non-aggressive PCa (table 4). Adjustment for prostate volume increased the effect estimates for overweight (14%) and obesity (17%) for incidence of non-aggressive PCa but did not alter the effect estimates for aggressive PCa. Prostate volume was inversely associated with aggressive PCa but not with non-aggressive PCa (table 4).

Discussion

As observed in prior studies, in this cohort of men followed up after an initial benign biopsy, a larger body-size was associated with larger prostate volumes at initial biopsy(13,15,16). As prostate volume at benign biopsy was positively associated with body-size and inversely

associated with PCa risk during follow-up, prostate volume acted as an inverse confounder biasing unadjusted estimates of the association between body-size at initial benign biopsy and subsequent PCa risk towards the null. As we reported previously, being overweight or obese significantly increased risk for prostate cancer(8) and adjustment for prostate volume at initial benign biopsy further increased these risk estimates.

Prostate volume did not appear to act as a significant effect modifier of associations between body-size and PCa incidence. Similar to Fowke et al., (2007 and 2013), we observed associations between overweight and obesity and PCa risk in men with smaller prostate volumes but the body size by prostate volume interaction terms in the model were not statistically significant(15,17). Furthermore in the results presented here, the associations between PCa risk and overweight and obesity status among men with smaller prostates did not show a dose-response trend. Compared to the results presented here, Fowke et al. observed larger differences in the prostate volume stratified associations between body size and PCa risk. However, their case-control studies based on biopsy series were both analyzed as a cumulative incidence sampled case-control study in the context of a common outcome, a design that often exaggerates differences in strata specific associations and over estimates interaction effects(19–21).

Overall the analyses suggest that prostate volume primarily acted as an inverse confounder for the incidence of non-aggressive PCa; adjustment for prostate volume modestly increased the OR for obesity for non-aggressive tumors but did not alter the OR aggressive tumors. This finding is consistent with the idea that larger prostate volumes can obscure the detection of non-aggressive tumors and cause an underestimate of the association between obesity and this sub-set of PCa(13,15–17). Depending on the relative proportion of aggressive and non-aggressive tumors in any studied PCa case-series, bias induced by failing to adjust for prostate volume may cause a significant underestimate of the effect of obesity on overall PCa risk. Very few prior studies of PCa and body size also have data available on prostate volume and so this confounding effect is generally not accounted for (15–17). As such there may be a pervasive underestimation of the association between obesity and overall PCa risk in the literature.

The strengths of this study include its prospective design with prostate volume data available at cohort entry, adjustment for screening intensity during follow-up, and the availability of high quality medical records collected within a single integrated health system. The matching of controls to cases on date of cohort entry and duration of follow-up assures that cases and controls experienced the same temporal trends in medical practice, medical technology and case management, and have the same period of observation in which screening behaviors can occur. In addition, potential differences in PCa screening intensity by obesity status, that may otherwise have introduced bias into the study, were adjusted for using data on the number of PSA tests and DRE during follow-up. As it is highly unlikely that a prostate biopsy is undertaken without a closely preceding PSA test and/or DRE, adjustment for screening intensity during follow-up is expected to control for differences in surveillance, biopsy rates and men's engagement with the medical system that might exist between men of different body sizes. Thus the screening intensity adjusted analyses answer the question – conditional on having had the same number of PSA tests and DRE during

follow-up are obese men at higher risk of prostate cancer than normal weight men? A caveat for the study is that it was conducted in a high risk population who had already undergone a procedure for suspicion of PCa and thus the results may not be generalizable to the general male population. However, approximately 1 million prostate biopsies are performed annually in the US and two-thirds of these are negative(22). Thus the study is likely generalizable to a large population of men.

Conclusion

This is the first study to prospectively assess associations between prostate volume and PCa risk and to conduct analyses of body size and PCa incidence that account for confounding by prostate volume. The analyses suggest that failure to account for the inverse confounding effects of prostate volume causes an underestimation of the effects of obesity on PCa. Obesity status and prostate volume may be two factors to jointly consider when planning the intensity of clinical follow-up of men at increased risk for prostate cancer.

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Figure 1.

Mean prostate volume and 95% confidence intervals by body size category at cohort entry adjusting for age and PSA level at cohort entry and race.

Table 1

Characteristics of the study population

Age	Cases N=495 Mean, Median (inter-quartile range) of N(%)	Controls N=495 Mean, Median (inter-quartile range) of N(%)
PSA at Baseline	7.57, 5.90 (4.40–8.20)	5.72, 4.80 (1.900–6.80)
BMI at Baseline	28.03, 27.55 (25.25–30.56)	27.63, 27.19 (24.67–29.95)
Total PSA tests during follow-up	9.07, 8.00 (5.00–12.00)	7.15, 6.00 (4.00–9.00)
Total DRE during follow-up	5.55, 5.00 (2.00–8.00)	4.31, 3.00 (1.00–6.00)
Race		
Caucasian	303 (61.2%)	303 (61.2%)
Black	192 (38.8%)	192 (38.8%)
Family History of Prostate Cancer		
No	434 (87.7%)	457 (92.3%)
Yes	61 (12.3%)	38 (7.7%)
Body Size		
Normal weight (BMI<25)	110 (22.2%)	140 (28.3%)
Overweight (BMI>=25 – BMI<30)	241 (48.7%)	233 (47.0%)
Obese (BMI>=30)	144 (29.1%)	122 (24.7%)
Prostate volume (n=387 case-control pairs)	50.02, 44.30 (31.60–60.00)	50.46, 41.00 (30.09–61.60)

Table 2

Association between body size and prostate cancer risk stratified by prostate volume.

	Smaller Prostate Volume Odds Ratio (95% CI)	Larger Prostate Volume Odds Ratio (95% CI)
Normal Weight	1	1
Overweight	1.89 (1.18, 3.02)	1.08 (0.65, 1.81)
Obese	1.78 (1.04, 3.03)	1.45 (0.83, 2.52)

P for interaction between overweight status and larger prostate size = 0.12 and p for interaction between obese status and larger prostate size = 0.59. Analyses account for the matching factors and further adjust for family history of prostate cancer, PSA level at initial benign biopsy, and the number of PSA test and DRE during follow-up.

Table 3

Associations between body size and prostate cancer incidence before and after adjustment for prostate volume.

	Baseline model ^a Odds Ratio (95% CI)	Baseline model with further adjustment for prostate volume ^b Odds Ratio (95% CI)
Body Size		
Normal	1	1
Overweight	1.41 (1.01, 1.97)	1.52 (1.08, 2.14)
Obese	1.59 (1.09, 2.33)	1.77 (1.20, 2.62)
Prostate size (per 10 CC)	NA	0.92 (0.88, 0.97)

^aBaseline model accounts for matching and adjusts for family history, PSA level, and number of PSA tests and DRE during follow-up.

^bModel accounts for matching and adjusts for family history, PSA level, and number of PSA tests and DRE during follow-up and prostate volume.

Table 4

Association between body size and prostate cancer incidence for non-aggressive and aggressive tumors

	Non-Aggressive Tumors (n=338 pairs) Odds Ratio ^a (95% CI)	Aggressive Tumors (n=157 pairs) Odds Ratio ^a (95% CI)	Non-Aggressive Tumors (n=338 pairs) Odds Ratio ^b (95% CI)	Aggressive Tumors (n=157 pairs) Odds Ratio ^b (95% CI)
Body Size				
Normal	1	1	1	1
Overweight	1.47 (0.99, 2.16)	1.33 (0.69, 2.57)	1.55 (1.04, 2.31)	1.33 (0.67, 2.64)
Obese	1.54 (0.99, 2.41)	1.71 (0.80, 3.68)	1.66 (1.05, 2.63)	1.73 (0.78, 3.85)
Prostate size (per 10 CC)	NA	NA	0.96 (0.89, 1.02)	0.85 (0.76, 0.96)

^aModel accounts for matching and adjusts for family history, PSA level, and number of PSA tests and DRE during follow-up.^bModel accounts for matching and adjusts for family history, PSA level, and number of PSA tests and DRE during follow-up and prostate volume.