META-ANALYSIS: RACIAL DISPARITIES IN PROSTATE CANCER SURVIVAL

AND CASE-CONTROL STUDY: ASSOCIATION BETWEEN FAMILY HISTORY

OF CANCERS, OBESITY AND PROSTATE CANCER

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Epidemiology at Virginia Commonwealth University.

by

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CASE-CONTROL STUDY: ASSOCIATION BETWEEN OBESITY AND PROSTATE CANCER

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I. Meta-Analysis: Racial Disparities in Prostate Cancer Survival

Prostate cancer is the second leading cause of cancer-related mortality in men. Previous studies have drawn inconsistent conclusions on racial differences in prostate cancer survival. This meta-analysis was conducted to investigate the relationship between race and survival from prostate cancer. A systematic review of published articles from 1968 to 2007 assessing survival from prostate cancer among African American and White men was conducted. The search yielded 20 eligible published manuscripts. Analysis of unadjusted studies showed African American men have an increased risk of all-cause mortality (Hazard ratio (HR) = 1.47, 95% confidence interval (CI): 1.31, 1.65, $P < 0.001$). However, examination of adjusted studies showed no difference (HR = 1.07, 95% CI: 0.94, 1.22, $P = 0.308$). No statistically significant difference was observed in prostate cancer-specific survival in both analyses using unadjusted (HR = 1.11, 95% CI: 0.94, 1.31, $P = 0.209$) and adjusted studies (HR = 1.15, 95% CI: 0.95, 1.41, $P = 0.157$). There was evidence of heterogeneity that was unexplained by factors analyzed in overall survival but explained by stage in prostate cancer-specific survival. This meta-analysis concludes that there are no racial differences in the overall and prostate cancer-specific survival between African American and White men.

II. Case-Control study: Association between Family History of Cancers and Prostate Cancer

Family history of prostate cancer is an established risk factor for prostate cancer. However, the relationship between family history of cancers other than prostate cancer and prostate cancer risk is inconclusive. This study sought to examine the association between family history of cancers and prostate cancer. A case-control study was conducted in which cases and controls were randomly selected from a large urology clinic in Central Virginia. Cases were 600 histologically confirmed prostate cancer patients who were diagnosed between January 2000 and December 2005, and controls were 686 patients who visited the clinic during the same period and diagnosed with urological illnesses other than cancers and prostate-related problems. Data on family history of cancers, lifestyle and demographic factors were collected. Unconditional logistic regression analysis was used to estimate the odds ratios and the corresponding 95% confidence intervals after adjustment for potential confounding factors. Multiple comparisons adjustments were made using Bonferroni adjustment. Men with family history of any cancer in first-degree relatives including parents (OR=2.42, 95% CI: 1.53, 3.84) and parents only (OR=1.90, 95% CI: 1.23, 2.94) were at increased risk of developing prostate cancer compared to men with no such family history of cancer. Significant increased risk was also observed with family history of prostate cancer in first-degree relatives (OR=2.68, 95% CI: 1.53, 4.69) and parents only (OR=3.26, 95% CI: 1.71, 6.24) compared to men with no family history of prostate cancer. Even after adjustments for multiple comparisons, the significance persisted both in first-degree relatives (OR=2.68, 95% CI: 1.16, 6.21) and parents alone (OR=3.26, 95% CI:

1.24, 8.63). No association was found with family history of other cancers including breast, colon, lung, skin, digestive tract, stomach, liver, pancreas, female cancers, urogenital, urinary bladder, brain, blood and lymph node and other cancers and risk of prostate cancer. This study demonstrated an increased prostate cancer risk for men with a family history of any cancer or prostate cancer in first-degree relatives including parents and parents alone. Health care providers need to be aware of the potential risk of family history of cancers on prostate cancer.

III. Case-Control study: Association between Obesity and Prostate Cancer

Obesity is a major public health problem in the United States. Several studies have investigated the association between obesity and prostate cancer risk. However the impact of early-adult obesity on prostate cancer is not well studied. This study proposes to investigate the relationship between prostate cancer and early-onset obesity and current obesity. A case-control study was conducted to investigate the relationship between obesity and prostate cancer in a large urology clinic population in Central Virginia. Cases included histologically confirmed prostate cancer patients of all stages and grades diagnosed from January 2000 to December 2005. Controls were patients who were diagnosed with urological illness other than cancers and prostate-related problems. Self-reported data was collected on anthropometric, lifestyle and demographic factors through a mail survey. Unconditional logistic regression analysis was conducted to investigate the association between prostate cancer and early-onset obesity (BMI at age 18) and current obesity. Odds ratios and corresponding 95% confidence intervals were calculated after accounting for significant interaction terms and adjusting for potential confounding variables. This study showed statistically significant association between BMI at age 18 and prostate cancer risk in the multivariate analysis when BMI was evaluated as a continuous variable. There was a 7% decrease in the odds of prostate cancer risk for every 1 kg/m^2 increment in BMI at age 18 (OR=0.93, 95% CI: 0.87, 0.98). Analysis of BMI at age 18 as a categorical variable also showed reduced risk though statistically non-significant. Obese men (OR=0.62, 95% CI: 0.12, 3.08) and overweight men (OR=0.60, 95% CI: 0.35, 1.05) had a non-significant decreased risk of developing prostate cancer

compared to normal weight men at age 18. Examination of current BMI showed a non-statistically significant decreased risk of prostate cancer when examined as a continuous variable. However, there was significant interaction between current BMI treated categorically and age. This study concludes that there is decreased prostate cancer risk associated with increasing BMI at age 18. Future large prospective studies are needed to better understand the association between early-onset obesity and risk of prostate cancer and explore the biological factors associated especially in the early ages. This document was created in Microsoft Word 2003.

META-ANALYSIS: RACIAL DISPARITIES IN PROSTATE CANCER SURVIVAL

INTRODUCTION

Prostate cancer is the most common cancer in men excluding basal and squamous cell skin cancer. In 2008, approximately 186,320 new cases are estimated to be diagnosed with prostate cancer in the United States.[1] This estimate accounts for 25% of all the cancers diagnosed in men.[1] African American men have the highest incidence rates of prostate cancer. The risk of prostate cancer in African Americans is 60% higher than White men.[2] Prostate cancer is the second leading cause of cancer-related mortality in men. In the United States, approximately 28,660 men will die from prostate cancer in 2008 alone; accounting for approximately 10% of all the cancers deaths in men.[1] The mortality rate from prostate cancer is 2.4 times higher in African Americans compared to White men.[3]

More than 90% of prostate cancers are diagnosed in the local and regional stages and the 5-year relative survival for these cancers is 100%.[1] However, the 5-year relative survival for distant prostate cancer is significantly lower (31.9%).[1] Although overall survival rates are high, rates differ by race; the 5-year survival rates are approximately 7% higher for Whites than African Americans at all stages. The 5-year survival rate for localized cancer is approximately 93% for Whites and 86% for African Americans.[4]

Disparity in survival rate is also documented for regional (83% vs. 68%) and metastatic cancers (29% vs. 22%).[4]

Although descriptive studies show that African Americans are disproportionately affected by this disease compared to Whites, it is not clear if the increased mortality is due to race or factors affecting this population such as access to care, quality of care, socio-economic status, stage and grade of tumor, treatment and comorbidity. Several researchers have attempted to clarify this disparity by controlling for some of the above mentioned confounding factors; however, these studies have produced inconsistent findings.[4-19] Several studies have shown that there is an association between race and survival from prostate cancer[4, 15-19] whereas other studies have not found such an association.[5-14]

Although several observational studies have had conflicting findings, to our knowledge there are only two meta-analyses conducted examining the impact of race on survival from prostate cancer. Overall survival is defined as death due to any cause and prostate cancer-specific survival is death from prostate cancer as the underlying cause. The first meta-analysis, by Bach et al. in 2002, included 17 studies that examined racial differences in prostate cancer survival between Whites and African Americans who received the same treatment for similar stages of cancer.[20] The study showed that African Americans had a statistically significant increased risk of mortality due to all causes. But this statistical significance disappeared after adjusting for other causes of death derived indirectly from population mortality rates from the National Center for Health Statistics 1997 decennial life tables to account only for cancer-specific mortality. This manuscript examined similar cohorts of men receiving same treatment and similar stages of disease

and also used indirect adjustment for other causes of death to account for prostate cancer-specific mortality. These results are not generalizable to men with all stages of the disease who are receiving different treatments and this problem was addressed in the recent meta-analysis by Evans et al.[21] They derived the estimates for prostate cancer-specific mortality directly instead of applying indirect population adjustments.

Evans et al. evaluated 28 studies exploring all-cause and prostate cancer-specific mortality as potential outcomes.[21] The study showed increased statistically significant risk for overall survival (Hazard ratio (HR) = 1.35, 95% confidence interval (CI): 1.23, 1.48, $P < 0.001$) and prostate cancer-specific survival (HR = 1.29, 95% CI: 1.13, 1.47, $P < 0.001$) among African Americans compared to Whites when using the studies that did not adjust for any confounders or adjusted only for age. When studies that adjusted for age, clinical and other socioeconomic factors were used this statistical significance disappeared for the overall survival (HR = 1.01, 95% CI: 0.88, 1.16, $P = 0.93$); however, prostate cancer-specific survival still showed a marginal increased risk of mortality for African Americans compared to Whites (HR = 1.13, 95% CI: 1.00, 1.27, $P = 0.052$).

Although this meta-analysis included all the key articles, there was a major methodological drawback. The authors have included more than one article from the same SEER cancer registry data, which represented overlapping time periods and included the same SEER location (San Francisco Bay region) for prostate cancer-specific mortality.[10, 11, 16, 22] When the meta-analysis was repeated after removing the two SEER articles namely Du et al[10] and Polednak et al,[11] the increased risk was not statistically significant (HR = 1.14, 95% CI: 0.95, 1.36, $P = 0.15$) (confidence interval and P value obtained through communication with the author). However the article did not discuss

this crucial information and reported increased risk among African American men for prostate cancer-specific mortality.

We conducted a meta-analysis of studies that exclusively address the impact of race, not just as a primary exposure variable, but also as one of the potential independent variables, on survival in men for localized and advanced prostate cancer. This meta-analysis mitigates the limitations in the previous meta-analyses.[20, 21] Recognizing the varied nature of the studies in terms of standard errors, sample sizes and adjustments for potential confounding variables, this study utilized two distinct methodologies to examine the association.

MATERIALS AND METHODS

Study selection

A Medline/PubMed search of published articles in English from 1968 to 2007 was performed. We used keywords and MESH terms including terms as “prostate cancer”, “survival”, “mortality” and “race”. We used three levels of screening to select relevant publications for this analysis. First, two independent reviewers examined all the identified abstracts to find relevant publications using the criteria that included race as the primary exposure variable, or at least one of the covariates, and survival either overall or prostate cancer-specific survival as the outcome. Second, each relevant publication was examined thoroughly to determine that the inclusion criteria were fulfilled. Additionally, the reference section of the selected relevant publications was examined for additional publications that were missed in the initial search. Third, the selected publications were reviewed and abstracted. At this stage, publications from the same data sources, place and

overlapping time periods were identified and made sure that only one publication was selected.

Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis included original research manuscripts that: a) were published between 1968 and 2007, b) had race, specifically Whites and African Americans, as the main exposure variable or covariate, c) had overall survival or prostate cancer-specific survival as one of the outcome variables, d) provided estimates from which log hazard ratios and standard errors can be calculated directly or indirectly. We included articles published in English. Review articles or letters were not included in this analysis. Manuscripts that either compared blacks to non-blacks or non-whites to whites were also excluded from the analysis.

When there were several publications from the same data source, such as the SEER cancer registry data, with overlapping time frames and locations, only one publication was selected to be included in the analysis. Factors such as the most recent year of publication, larger sample size, number and types of confounders examined, longer follow-up period, and inclusion of relevant effect sizes were considered to select publications. Although the initial search yielded 505 publications, only 20 articles met the inclusion criteria for this analysis (Figure 1). Detailed descriptions of the selected studies are available in supplementary data.

Out of the 20 publications, 17 studies provided estimates for overall survival.[5-10, 23- 33] Thirteen manuscripts had estimates available to calculate the crude overall survival hazard ratios and 95% confidence intervals directly (2 studies)[23, 24] or indirectly from Kaplan-Meier survival curves (11 studies).[5-7, 8, 10, 28-33] Eight manuscripts had estimates

available to calculate the adjusted overall survival hazard ratios and 95% confidence intervals directly.[7, 9, 10, 23-27] Prostate cancer-specific survival was reported in nine manuscripts.[10, 12, 23, 25-27, 31, 34, 35] Six manuscripts had estimates available to calculate the crude hazard ratios and 95% confidence intervals for prostate cancer-specific survival directly (2 studies)[23, 34] or indirectly from Kaplan-Meier survival curves (4 studies).[10, 12, 31, 35] Seven manuscripts had estimates available to calculate the adjusted hazard ratios and 95% confidence intervals for prostate cancer-specific survival directly.[10, 12, 23, 25-27, 34] Some studies provided both unadjusted and adjusted estimates, while others reported only the unadjusted or adjusted effect sizes.

Data abstraction

Data abstraction form was developed and two independent reviewers abstracted relevant information from the selected publications. Information including bibliographic information (authors, title, journal of publication and date, whether peer reviewed or not), study setting (study location, type, name and data source), study population characteristics (age, race, stage and grade of cancer), study design details (sample size, year of prostate cancer diagnosis, length of follow-up), model characteristics (exposure variable, outcome variable, other covariates assessed and controlled for confounders) and study results (hazard ratios and 95% confidence intervals or p values from Cox proportional hazard regression, Kaplan-Meier survival curves) were abstracted.

Statistical analysis

The selected publications reported different estimates for the association between race and survival, including hazard ratios and 95% confidence intervals or *P* values from Cox proportional hazard regression or Kaplan-Meier survival curves. We used log hazard

ratios and standard errors to determine the summary hazard ratios and 95% confidence intervals. The method described by Parmar et al was used to derive the log hazard ratios and standard errors directly for the manuscripts providing hazard ratios and 95% confidence intervals or *P* values.[36] The log hazard ratios and standard errors were determined indirectly for the crude analysis using Parmar et al.[36] and Microsoft Excel spreadsheets provided by Tierney et al.[37] from Kaplan-Meier survival curves.

Depending on the results of the tests for heterogeneity including Q statistic and I^2 statistic a decision was made whether to use fixed effects or Dersimonian-Laird random effects model. As the tests for heterogeneity was significant in all the analysis, random effects model results are reported.

To account for the differences among the studies in terms of standard errors, sample size and adjustment for confounders, weighted analysis was considered. Weighting the studies with respect to standard errors is straight forward. In addition to this, weighting the studies according to their other characteristics that are considered important in public health studies was also considered. We believe studies that adjust for these variables provide valid information about the racial differences than those that do not and therefore, the studies with adjusted analysis received a higher weight. For this purpose an objective quality scoring method was utilized to assign scores to each study.

Previous publications have provided mixed opinions on whether quality scoring should be used as a weighting variable. Some manuscripts comment that quality scoring adds subjective bias, may lack validity and results may not represent quality. [38-41] Other studies claim that quality scoring can be done, but recommend not using the scores as weights but rather use the summary score as a covariate to conduct subgroup and

sensitivity analysis. [40, 42, 43] As suggested in the literature, this study utilized standard error as weighting variable and investigated if the analysis using summary score as weighting variable also holds true with this analysis. These two distinct methods were considered to maximize the validity of this meta-analysis.

In order to preserve objectivity of the scoring, only the factors that are important predictors of prostate cancer and those that do not pose any scoring ambiguity, such as age of the patient, stage of the disease, grade of the tumor, treatment, comorbidity, socioeconomic status, pre biopsy PSA levels and sample size of the study were considered. Moreover, two independent researchers scored these studies so that reliability could be established. Based on the quality scores, weights proportional to the scores were calculated. That is, a study with higher score received a higher weight. Then the analysis was performed in two ways: first, with weights obtained from standard errors alone, then by using summary weights that are averages of the weights based on the standard errors and the weights based on the quality scores.

Funnel plots were used to examine publication bias. Sensitivity analysis was performed to determine robustness of the meta-analysis. To examine the effects of small and outlier studies we removed one study at a time and repeated the analysis with the remaining studies. Further subgroup and meta-regression analysis were done on selected covariates to identify potential explanations for heterogeneity among studies. All analysis was done using STATA Statistical software version 10.1 (StataCorp, College Station, TX). All p-values were two-sided and values less than 0.05 were considered significant.

RESULTS

(A) Overall survival

Unadjusted and adjusted summary estimates using standard error as weights. Pooled estimate from the 13 studies with unadjusted estimates showed a statistically significant increased risk of mortality among African American men compared to White men (HR = 1.47, 95% CI: 1.31, 1.65, $P < 0.001$). However, no statistically significant difference was observed in the analysis using the adjusted hazard ratios from the eight studies that adjusted for age, clinical and other demographic variables (HR = 1.07, 95% CI: 0.94, 1.22, $P = 0.308$). Figure 2 shows that there was evidence of heterogeneity among the studies in the adjusted analysis (Q = 36.45, df 7, $P < 0.001$).

Adjusted summary estimates using summary score as weights. Utilizing summary score as weights evenly distributed the weights among the studies compared to using standard error as weights. Conversely, the summary estimates from the eight adjusted studies remained the same (HR = 1.06, 95% CI: 0.90, 1.25, $P = 0.463$) compared to the pooled estimates obtained using standard error as weights.

Table 1 compares the summary estimates derived from the standard error and summary score methods for the unadjusted, adjusted and overall analysis. The findings from the two methods were fairly similar and comparable.

Publication bias. Figure 3 shows equal dispersion of studies. Both the unadjusted and adjusted models showed no evidence of publication bias in the funnel plots.

Sensitivity analysis. Small studies and potential outliers were identified using standard errors and funnel plots. These studies were removed one at a time and the summary estimates were evaluated each time. In the unadjusted analysis, removal of the

following small studies and outliers provided the following estimates: Zagars et al (HR = 1.44, 95% CI: 1.29, 1.61, $P < 0.001$)[29], Powell et al (HR = 1.52, 95% CI: 1.35, 1.71, $P < 0.001$)[6] , and Hussain et al (HR = 1.38, 95% CI: 1.27, 1.49, $P < 0.001$).[33] Eliminating all three manuscripts at the same time yielded similar results as the overall unadjusted analysis (HR = 1.35, 95% CI: 1.29, 1.41, $P < 0.001$).

In the adjusted analysis, removing the following studies resulted in the following estimates: Halabi et al (HR = 1.12, 95% CI: 0.99, 1.28, $P = 0.069$)[25] , Freeman et al (HR = 1.02, 95% CI: 0.91, 1.14, $P = 0.745$)[27] , and Optenberg et al (HR = 1.10, 95% CI: 0.97, 1.25, $P = 0.155$).[7] Excluding all the three manuscripts at the same time produced similar results as the overall adjusted analysis (HR = 1.08, 95% CI: 1.00, 1.17, $P = 0.065$).

Subgroup and Meta-regression analysis. Subgroup and meta-regression analysis were conducted across several covariates to explain the heterogeneity among the studies (Table 2 and 3). The analysis showed that the heterogeneity observed among the studies examining overall survival cannot be explained by any of the covariates including stage, recruitment year or study type.

(B) Prostate cancer-specific survival

Unadjusted and adjusted summary estimates using standard error as weights. Evaluation of the six studies with unadjusted estimates showed no statistically significant excess risk of prostate cancer-specific mortality among African American men compared to White men (HR = 1.11, 95% CI: 0.94, 1.31, $P = 0.209$). Similarly, analysis of the seven studies with the adjusted estimates also showed no increased risk among African American men compared to White men (HR = 1.15, 95% CI: 0.95, 1.41, $P = 0.157$).

Further examination of these studies showed evidence of heterogeneity among the studies in the adjusted analysis (Q = 22.46, df 6, $P = 0.001$) (Figure 4).

Adjusted summary estimates using calculated summary score as weights. A modest difference in weights occurred when quality scores were added to the weights obtained from standard errors, compared to the weights from standard error alone. The pooled estimates from the seven adjusted studies did not change (HR = 1.17, 95% CI: 0.96, 1.43, $P = 0.113$) compared to the estimates obtained using standard error as weights. Summary estimates derived from the standard error and summary score methods yielded consistent findings for the unadjusted, adjusted and overall analysis (Table 4).

Publication bias. Funnel plots showed equal dispersion of studies and no evidence of publication bias in both unadjusted and adjusted models (Figure 5).

Sensitivity analysis. Exclusion of Fowler et al (HR = 1.17, 95% CI: 1.02, 1.33, $P = 0.022$)[12] , Kim et al (HR = 1.05, 95% CI: 0.90, 1.23, $P = 0.520$)[31] , Roach et al (HR = 1.07, 95% CI: 0.91, 1.26, $P = 0.435$)[23] and all manuscripts at the same time (HR = 1.05, 95% CI: 0.97, 1.15, $P = 0.229$) yielded similar findings as the overall unadjusted analysis.

In the adjusted analysis, removing studies including Halabi et al (HR = 1.22, 95% CI: 1.09, 1.35, $P < 0.001$)[25], Freeman et al (HR = 1.08, 95% CI: 0.90, 1.31, $P = 0.395$)[27] , and both manuscripts at the same time (HR = 1.18, 95% CI: 1.06, 1.32, $P = 0.003$) resulted in statistically significant estimates compared to the summary estimates obtained in the pooled adjusted analysis.

Subgroup and Meta-regression analysis. The heterogeneity among the studies examining the association between race and prostate cancer-specific survival can be

explained by stage of the disease including local/regional (HR = 1.17, 95% CI: 1.04, 1.32, *P* = 0.009), metastatic (HR = 0.76, 95% CI: 0.63, 0.92, p=0.005), recruitment period in 1987 or earlier (HR = 1.19, 95% CI: 1.02, 1.38, *P* = 0.026) and retrospective cohort study types (HR = 1.22, 95% CI: 1.07, 1.39, *P* = 0.004) in the subgroup analysis and by metastatic stage in the meta-regression analysis (Table 5 and 6).

DISCUSSION

This study found no statistically significant increased risk of mortality due to all causes and prostate cancer-specific causes in African American men compared to White men. These results were consistent with the observations made by Bach et al who showed no increased risk in African Americans compared to Whites for prostate cancer-specific survival.[20] While the overall survival results of this study was consistent to the findings observed by Evans et al., inconsistency between the two studies was observed in the prostate cancer-specific mortality.[21] Evans et al. showed increased risk in prostate cancer-specific survival whereas this study observed no increased risk.[21]

The major reason for this discrepancy in the prostate cancer-specific survival analysis between these studies may be due to the differences in manuscript selection. This meta-analysis only included one manuscript from the SEER cohort that spanned across all 11 SEER sites, that is most recent, had a large sample size and was comprehensive.[10] However, Evans et al[21] utilized four studies from the SEER cohorts that not only had overlapping time periods but also included the San Francisco Bay region (Table 7).[10, 11, 16, 22] When Evans et al. conducted sensitivity analysis and excluded Du et al[10] and Polednak et al[11] from the prostate cancer-specific survival analysis, they also observed no increased risk (HR = 1.14, 95% CI: 0.95, 1.36, *P* = 0.15) consistent with our analysis.

This manuscript excluded some studies due to the inclusion/exclusion criteria for reasons including estimates not available.[44-46] Additionally, this study included only one publication from University of Texas MD Anderson Cancer Center[47] and SEER cohorts.[11, 16, 18, 22]

Unlike other studies, this meta-analysis has several strengths. It addresses and accounts for serious methodological flaws observed in other studies. The study excluded more than one manuscript from the SEER registry data with overlapping time periods and only included one publication from the SEER registry data. Additionally, this study evaluated all published manuscripts from 1968 to 2007 and excluded manuscripts not meeting the inclusion criteria compared to the earlier meta-analyses.

The limitations of this study include that it only includes published manuscripts from 1968 to 2007. This excludes unpublished studies and usually unpublished studies are more likely to show negative results. Therefore this study may be overestimating the summary hazard ratios due to exclusion of those manuscripts. However, the tests showed no evidence of publication bias. In the adjusted analysis there was evidence for heterogeneity that was accounted for by performing random effects modeling, subgroup analysis and meta-regression analysis. However, the potential still exists for a lack of homogeneity among all the studies used to produce the summary hazard ratios.

In conclusion, there are no differences between African American and Whites in survival from prostate cancer. Future studies are needed to study the racial disparity in prostate cancer survival.

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Table 1. Summary Estimates Comparing Standard Error and Summary Score Methods for Overall Survival

	Standard error	Summary score
Unadjusted	1.47 (1.31, 1.65), *P* <0.001	1.52 (1.31, 1.78), *P* <0.001
Adjusted	1.07 (0.94, 1.22), *P* = 0.308	1.06 (0.90, 1.25), *P* = 0.463
Overall	1.29 (1.13, 1.47), *P* <0.001	1.30 (1.12, 1.52), *P* = 0.001

*All *P* values are two-sided

Table 2. Subgroup Analysis for Overall Survival

Subgroups		Summary hazard ratios	95% confidence intervals	*P* value	No. of studies
Stage					
	Local/regional	1.02	0.98, 1.06	0.424	3
	Metastatic	0.88	0.60, 1.30	0.511	3
	All stages	1.39	0.90, 2.13	0.135	2
Recruitment period in PSA era or earlier					
	Yes	1.06	0.91, 1.22	0.470	4
	No	1.11	0.88, 1.40	0.370	4
Study type					
	Randomized control trial	1.03	0.77, 1.40	0.830	3
	Retrospective cohort study	1.09	0.93, 1.29	0.285	5

*All *P* values are two-sided

Table 3. Meta-regression Analysis for Overall Survival

Subgroups		Summary hazard ratios	95% confidence intervals	*P* value
Stage				
	Local/regional	1.00	-	-
	Metastatic	0.69	0.43, 1.12	0.131
	All stages	1.37	0.87, 2.16	0.172
Recruitment period in PSA era or earlier				
	Yes	0.83	0.57, 1.20	0.317
	No	1.00	-	-
Study type				
	Randomized control trial	1.27	0.81, 1.98	0.305
	Retrospective cohort study	1.00	-	-

*All *P* values are two-sided

Table 4. Summary Estimates Comparing Standard Error and Summary Score Methods for Prostate Cancer-Specific Survival

	Standard error	Summary score
Unadjusted	1.11 (0.94, 1.31), *P* = 0.209	1.14 (0.91, 1.44), *P* = 0.262
Adjusted	1.15 (0.95, 1.41), *P* = 0.157	1.17 (0.96, 1.43), *P* = 0.113
Overall	1.12 (0.97, 1.30), *P* = 0.128	1.16 (0.98, 1.38), *P* = 0.092

*All *P* values are two-sided

Table 5. Subgroup Analysis for Prostate Cancer-Specific Survival

Subgroups		Summary hazard ratios	95% confidence intervals	*P* value	No. of studies
Stage					
	Local/regional	1.17	1.04, 1.32	0.009	4
	Metastatic	0.76	0.63, 0.92	0.005	1
	All stages	1.47	0.99, 2.17	0.055	2
Recruitment period in PSA era or earlier					
	Yes	1.19	1.02, 1.38	0.026	4
	No	1.14	0.75, 1.72	0.540	3
Study type					
	Randomized control trial	0.97	0.59, 1.59	0.899	2
	Retrospective cohort study	1.22	1.07, 1.39	0.004	5

*All *P* values are two-sided

Table 6. Meta-regression Analysis for Prostate Cancer-Specific Survival

Subgroups		Summary hazard ratios	95% confidence intervals	*P* value
Stage				
	Local/regional	1.00	-	-
	Metastatic	0.53	0.35, 0.81	0.003
	All stages	1.28	0.96, 1.71	0.098
Recruitment period in PSA era or earlier				
	Yes	0.89	0.69, 1.13	0.330
	No	1.00	-	-
Study type				
	Randomized control trial	1.18	0.84, 1.67	0.342
	Retrospective cohort study	1.00	-	-

*All *P* values are two-sided

Table 7. Listing of Studies using the SEER Registry Data

No.	Author and year	Recruitment period	Source	Population characteristics
1	Robbins et al (2000)[16]	1973-1993	SEER - San Francisco Bay region	All prostate cancer cases
2	Polednak et al (2003)[11]	1988-1997	9 SEER sites including Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco/Oakland, Seattle-Puget Sound and Utah	Advanced prostate cancer cases
3	Oakley-Girvan et al (2003)[22]	1987-1991	SEER – Hawaii, Los Angeles, San Francisco and Vancouver	All prostate cancer cases
4	Du et al (2006)[10]	1992-1999	11 SEER sites including San Francisco/Oakland, Detroit, Atlanta, Seattle, Los Angeles county, San Jose-Monterey area, Connecticut, Iowa, New Mexico, Utah and Hawaii	Local/regional stage prostate cancer cases

Figure 1. Flowchart of study selection criteria

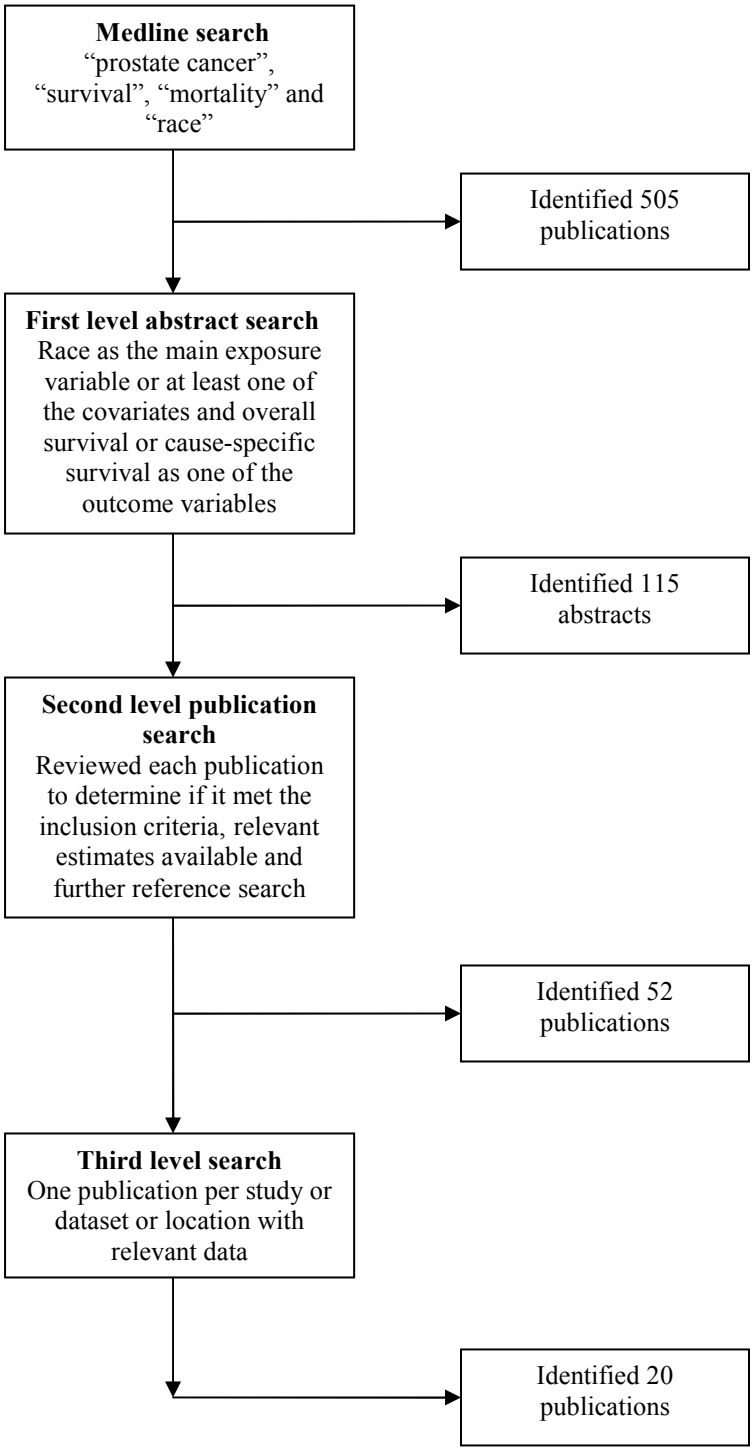


Figure 2. Forest plot of studies with adjusted estimates for overall survival

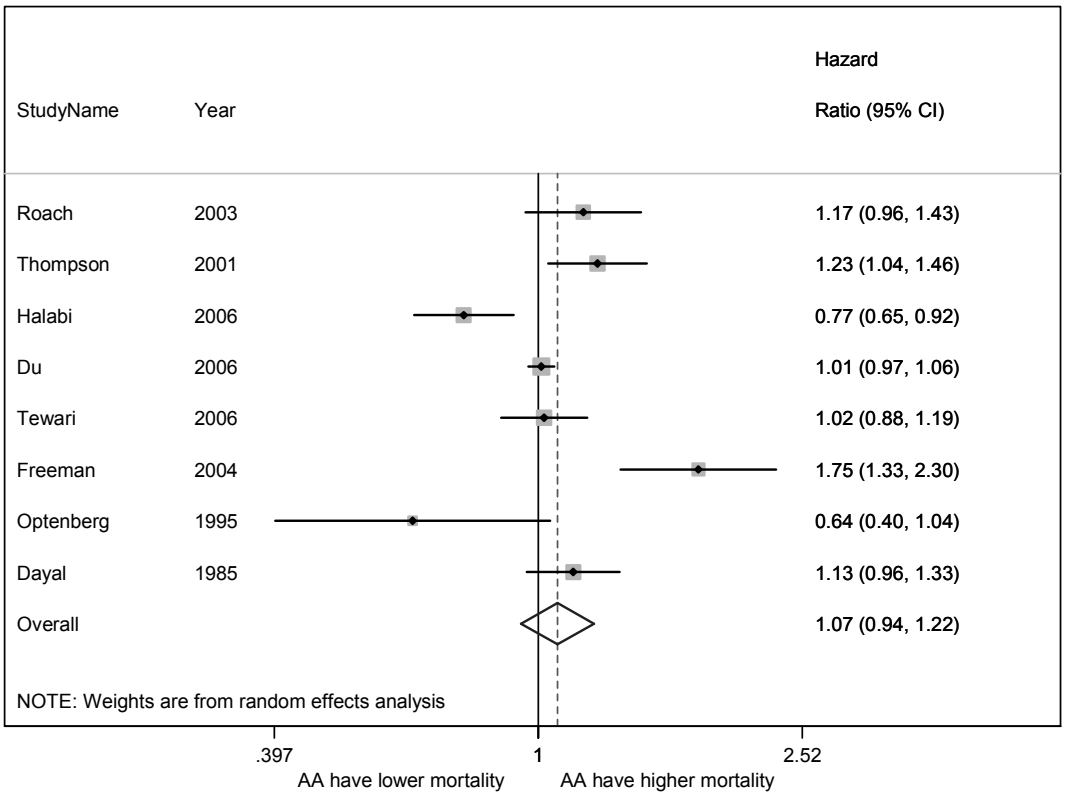
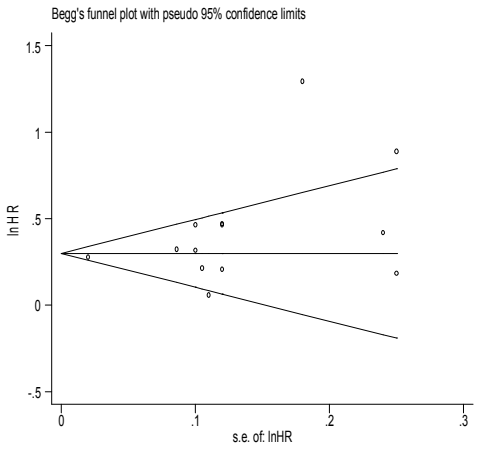
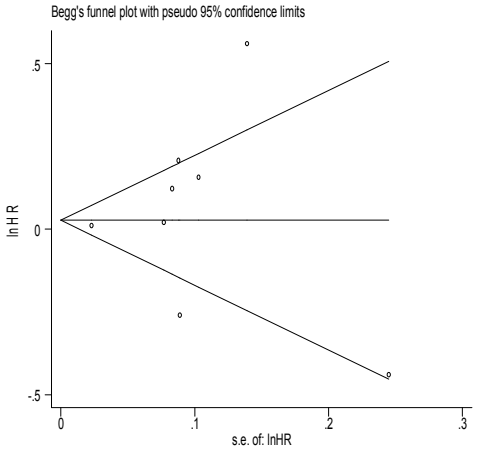


Figure 3. Funnel plots of studies with unadjusted and adjusted estimates for overall survival



Unadjusted analysis



Adjusted analysis

Figure 4. Forest plot of studies with adjusted estimates for prostate cancer-specific survival

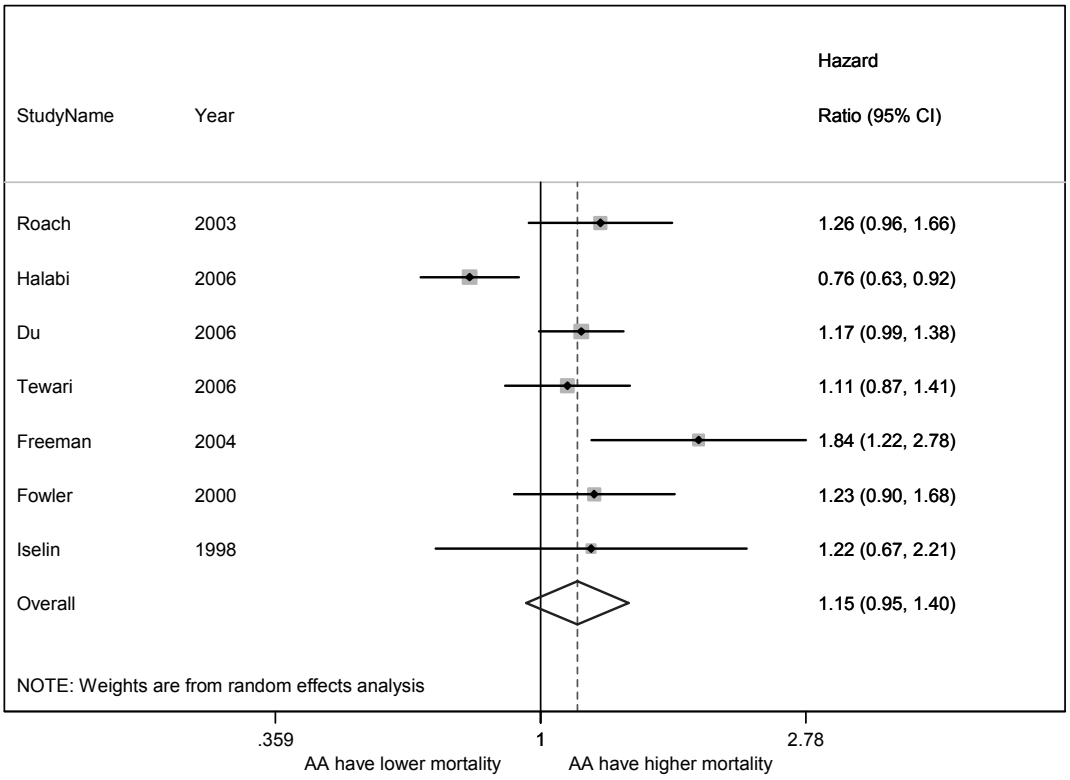
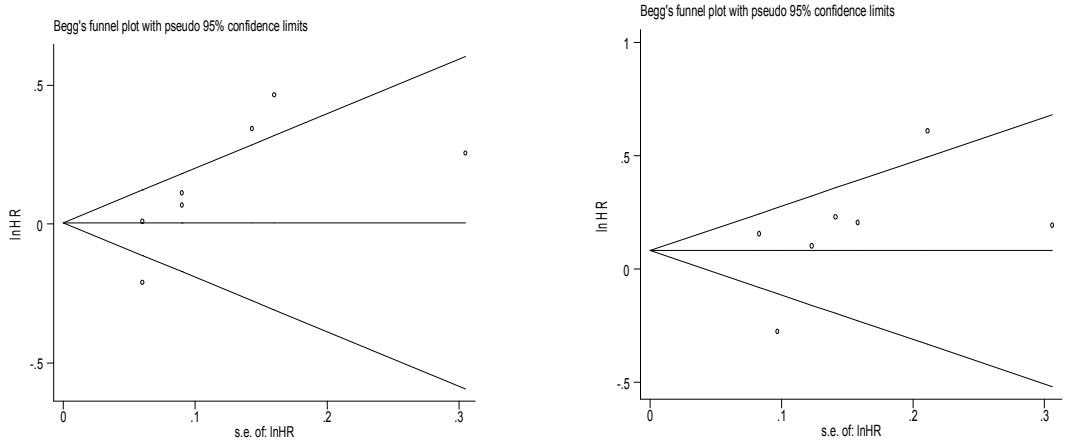


Figure 5. Funnel plots of studies with unadjusted and adjusted estimates for prostate cancer-specific survival



Unadjusted analysis

Adjusted analysis

CASE-CONTROL STUDY: ASSOCIATION BETWEEN FAMILY HISTORY OF CANCERS AND PROSTATE CANCER

INTRODUCTION

Prostate cancer is the most common cancer among men in the United States. It accounts for about 25% of all the cancers diagnosed in men.[1] Family history of prostate cancer is a well established risk factor for prostate cancer risk in men. Several prospective [2, 3, 4, 5] and retrospective[6, 7, 8, 9, 10, 11, 12, 13] studies have reported a two to four-fold increased risk of prostate cancer in men with a positive family history of prostate cancer especially in a first-degree relative.

To date, three meta-analyses have confirmed the association between family history of prostate cancer and risk of prostate cancer in men. They consistently concluded that there was an increased risk of prostate cancer in men with affected first-degree family members; and the risk was greater for men with affected brother than affected father, increases with decreasing age of the patient and family members and increasing number of affected individuals in the family.[14, 15, 16]

However there are only limited studies exploring the association between family history of other forms of cancers other than prostate cancer and risk of developing prostate cancer. Some studies have implicated family history of breast cancer as a risk factor for prostate cancer [6, 17, 18, 19, 20, 21, 22, 23, 24, 25] whereas others have not.[2, 26, 27, 28, 29, 30]

Similarly, a few studies have shown an association between family history of colorectal cancer, [4, 22] ovarian cancer,[31] kidney cancer,[25, 31, 32, 33] stomach cancer,[25, 34] esophageal cancer,[28, 31], bladder cancer,[31], brain cancer,[35], leukemia,[35], central nervous system,[36] and prostate cancer risk in men. However, a number of studies have not found such an association with certain cancers.[2, 6, 20, 26, 27, 28, 31, 35, 37]

The major problem with existing corpus of literature was the inability of investigators to control for potential confounders. It was evident that some of these studies were only able to control for the effect of age and other studies were not able control for any of the potential confounding factors due to inadequate sample size. Small sample size and neglecting the impact of other demographic and lifestyle factors have had potential impact on the association. It is also important to note that some of these studies utilized cancer registry data to calculate the observed and expected incidence rates and examined the association between family history of different cancers and prostate cancer risk, which may not be accurate. The data in the cancer registries is obtained from hospital and medical records and only limited to information and accuracy available in those datasets. Additionally, it is important to note that most of the studies exploring family history of cancers and prostate cancer were conducted in countries other than the US. The few studies conducted in the US predominantly focused on Caucasian population.

In conclusion, the methodological limitations of the current body of literature are evident and require further investigation. This study proposes to investigate the association between family history of cancers and risk of prostate cancer in a heterogeneous population in Central Virginia.

MATERIALS AND METHODS

Study design

The study sample included 3,710 patients from a large, multi-site private urology practice located in Central Virginia. Cases were a random sample of 1,237 patients with histologically confirmed diagnosis of prostate cancer. This included prostate cancers of all stages and grades diagnosed from January 2000 to December 2005. Controls were a random sample of 2,473 patients who visited the clinic during the same time as the cases and were diagnosed with urological illnesses other than cancers and prostate-related problems including prostatitis and chronic prostate hypertrophy. Patients with prostate-related problems or any urological cancer were excluded to reduce misclassification bias. Furthermore, chronic prostatitis and benign prostate hypertrophy were not included because of the potential link with excess risk of prostate cancer.[38, 39, 40] Additionally, this study excluded patients diagnosed before January 2000 and after December 2005, who were non-English speaking and unable to complete the questionnaire due to mental or cognitive problems.

Data collection

A mail survey was conducted to collect data on family history of cancers, life style behaviors and demographic information. Data included family history of cancers, age, race, education, employment, income, marital history, height, weight, behavioral risk factors such as diet history, sunlight exposure, smoking habits, alcohol use, physical activity, STD history and history of vasectomy. The survey included validated questions from the BRFSS,[41, 42, 43] NHIS,[44] NHANES,[45] Family history survey, [46] and Nurses' health study[47] surveys. Information on family history of cancers was obtained using the

family history table from Quillin et al.[46] The question asked to complete a family history table and indicate if there were family members diagnosed with cancers, their relationship with the patient, the type of cancer, age at diagnosis, the side of the family (maternal or paternal) and if they died from the cancer.

The survey was conducted after the questionnaire was pre-tested and approved by the institutional review board. The mail survey utilized the method suggested by Dillman.[48] First, a brief pre-notice postcard was mailed in first class mail to the selected 3,510 participants. Four weeks after the pre-notice postcard, the questionnaire was mailed to 3,490 participants after excluding those who did not want to be contacted (n=4) and deceased (n=16). Five days after the questionnaire was mailed, a thank-you letter was sent to 3,271 participants after removing those who did not want to be contacted (n=2), deceased (n=2) and wrong addresses without forwarding addresses (n=215). Two weeks after the thank-you letter, a replacement questionnaire was mailed to 2,219 non-responders as a reminder to complete the survey after excluding deceased (n=57), those who did not want to participate (n=37), valid surveys returned (n=862), wrong addresses (n=68) and other reasons (n=28). This mailing methodology yielded an overall 37% response rate; a total sample size of 1,286 participants (600 cases and 686 controls).

Definitions of variables

Patient status, having prostate cancer (case) and no prostate cancer (control) served as the outcome variable. The main exposure variable family history of cancers was defined as self-reported history of cancers including prostate, breast, colon, lung, skin, digestive tract, stomach, liver, pancreas, female cancers, urogenital, urinary bladder, brain, blood and lymph node and other cancers among first-degree relatives including

parents, siblings or offspring and also parents and siblings separately. Other covariates including BMI (<25 kg/m^2, 25-29.99 kg/m^2, ≥30 kg/m^2), physical activity (0 days per week, 1-2 days per week, ≥3 days per week), alcohol consumption (0 drinks per day, 1-2 drinks per day, ≥3 drinks per day), smoking (non-smoker, former smoker, current smoker), diet including fruits and vegetables intake (<2 servings per day, 2-4 servings per day, >4 servings per day), milk consumption (never, at least once per week, ≥1 time per day), vitamin intake (yes, no), history of vasectomy (yes, no) and STD (yes, no), age (≤60, 61-70, >70), race (White, African American, Hispanic, Other), marital status (married, divorced, never married), education (less than grade 12, grade 12 or GED, some college, college graduate) and income (less than $25,000, $25,000 to less than $50,000, $50,000 to less than $75,000, $75,000 to less than $100,000, $100,000 or more) were collected.

Statistical analysis

A descriptive analysis was done to examine the distribution of the study participants and assess the comparability of cases and controls. Chi square test and p-values were calculated to examine the association between categorical variables.

Univariate analysis was conducted using the main exposure variable and other covariates. The association between family history of any cancer and cancer at each location including prostate, breast, colon, lung, skin, digestive tract, stomach, liver, pancreas, female cancers, urogenital, urinary bladder, brain, blood and lymph node and other cancers in first-degree relatives, parents and siblings alone and risk of developing prostate cancer in men were estimated using unconditional logistic regression. First-degree relatives were defined as parents, siblings or off-springs. Odds ratios and

corresponding 95% confidence intervals were determined in the multivariate analysis after accounting for the potential confounding variables. Multiple comparisons adjustments were made using Bonferroni adjustment. All the analysis was conducted in SAS version 9.1 and all the tests were two-sided. Comparison between responders and non-responders would be appropriate; however, information on non-responders was not available.

RESULTS

The study sample included 600 cases (47%) and 686 controls (53%). Cases were more likely to be older than controls but less likely to be college educated and have high income (Table 1). Cases and controls were similar in marital status and race distribution. About 52.4% of the cases were over 70 years old compared to 12.4% in the controls. Cases had about 45% college educated and 22% with some college education compared to 46% and 26% in controls respectively. More cases had less than high school education (14% compared to 6% in controls). One-fourth of the cases made over $100,000 per years compared to 35% among controls. Over 40% of the cases made less than $50,000 per year compared to 25% of the controls. Both cases and controls had over 80% Whites, about 10% African Americans, over 80% married and about 15% divorced.

In the crude analysis, compared to men with no family history of cancers, those who have family history of any cancer in first-degree relatives were 1.8 times more likely to develop prostate cancer (Table 2). An increased risk was also observed with history of cancers in siblings. Compared to men with no family history of cancers, those who have family history of any cancer in siblings were 2.6 times respectively more likely to develop prostate cancer. Significant increased risk was also shown with family history of

prostate cancer in first-degree relatives, only parents and siblings compared to men with no family history of prostate cancer. Compared to men with no family history of lung cancer, men with a family history of lung cancer in siblings were at increased prostate cancer risk (OR=4.56, 95% CI: 1.95, 10.68). There was a significant protective effect observed with family history of skin cancer in first-degree relatives (OR=0.55, 95% CI: 0.32, 0.94) and just parents (OR=0.47, 95% CI: 0.25, 0.91) compared to men with no family history of skin cancer.

Adjusted analysis confirmed that men with family history of any cancer in first-degree relatives were 2.42 times more likely to develop prostate cancer (OR=2.42, 95% CI: 1.53, 3.84) compared to men with no family history of cancers (Table 2). Men with family history of any cancer in parents alone were 1.90 times more likely to develop prostate cancer (OR=1.90, 95% CI: 1.23, 2.94) compared to men with no family history of cancers. Significant increased risk was observed with family history of prostate cancer in first-degree relatives (OR=2.68, 95% CI: 1.53, 4.69) and only parents (OR=3.26, 95% CI: 1.71, 6.24) compared to men with no family history of prostate cancer. Even after adjustments for multiple comparisons, there was a statistically significant increased risk among men with family history of prostate cancer in first-degree relatives (OR=2.68, 95% CI: 1.16, 6.21) and parents alone (OR=3.26, 95% CI: 1.24, 8.63) compared to men with no family history of prostate cancer. Men who have a family history of brain cancer in first-degree relatives were 9.09 times more likely to develop prostate cancer (OR=9.09, 95% CI: 1.48, 55.96) compared to men with no family history of brain cancer. This association lost its statistical significance when adjustments were made for multiple comparisons (OR=9.09, 95% CI: 0.60, 138.64) (Table 2).

DISCUSSION

This study showed that there was increased prostate cancer risk associated with family history of any cancer in first-degree relatives. Specifically men with family history of any cancer only in parents were two times more likely to develop prostate cancer. This is similar to the observation in the population-based case-control study conducted at Shanghai, China where a 1.79 times increased prostate cancer risk was reported with any type of cancer in first-degree relatives (OR=1.79, 95% CI: 1.21, 2.63) and 2.21 times increased risk was observed with any type of cancer in only parents compared to no family history of any cancer (OR=2.21, 95% CI: 1.31, 3.73).[28] Negri et al. also reported that family history of cancer at all sites (OR=1.5, 95% CI: 1.3, 1.8) and family history of cancer at all sites excluding prostate cancer (OR=1.3, 95% CI: 1.1, 1.6) in first-degree relatives was associated with an increased risk of prostate cancer.[31] On the other hand, a case-control study conducted in Italy showed 1.6 times increased risk with family history of cancer in all sites in first-degree relatives (OR=1.6, 95% CI: 1.2, 2.3) but reported no statistically significant risk with family history of cancer in all sites excluding prostate cancer in first-degree relatives (OR=1.2, 95% CI: 0.8, 1.7).[35]

Consistent with the past literature [2, 6, 17, 19, 20, 26, 27, 29, 30, 31, 35] this study showed a two fold increased risk of prostate cancer among men with family history of prostate cancer in first-degree relatives and three fold increased risk for those with family history of prostate cancer in only parents. This significance persisted even after adjusting for multiple comparisons.

This study concluded that men who have a family history of brain cancer in first-degree relatives were 9.09 times more likely to develop prostate cancer. This finding is

similar to the conclusions made by the case-control study conducted in Italy in 2007 among men 60 years or less.[35] They found that men with family history of brain cancer in first-degree relatives were 3.7 times more likely to develop prostate cancer (OR=3.7, 95% CI: 1.2, 11.7). The current study found a stronger association and this could be explained by the fact that Gallus et al. study had 8 cases and 6 controls with family history of brain cancer compared to 13 cases and 5 controls with family history of brain cancer in the present study. This result has to be interpreted with caution due to small cell sizes, wide confidence intervals and multiple comparisons. Small changes in the cell sizes can drastically change the estimates. It is important to note that the statistical significance was lost after adjustment for multiple comparisons. So the association that we observed may be due to chance. But studies have shown that Li-fraumeni syndrome occurring in young patients with an aggregation of cancers including brain tumor, leukemia, adrenocortical carcinoma, breast cancer and sarcoma could occasionally be accompanied by prostate cancer and this is attributed to germline mutation in p53.[20] Future large prospective studies with larger cell sizes and adequate control for potential confounders are needed to confirm is this association is due to chance or if there is a genetic component and co-clustering with other cancers.

There was a non-statistically significant decreased risk associated with skin cancer in the unadjusted analysis both among first-degree relatives (OR=0.55, 95% CI: 0.32, 0.94) and just parents (OR=0.47, 95% CI: 0.25, 0.91) that disappeared after adjusting for potential confounders. This finding has never been shown or explored in any other studies before. Many studies exclude skin cancers which may be due to the reason that skin cancer is underreported as reporting is not mandatory except for

melanoma and skin cancer is the most common and curable cancer. This result could be due to chance but should be explored further in future studies or could be due to shared genetic factors.

The current study found non-significant increased risk with family history of cancers including breast, colon, lung, digestive tract, pancreas, female cancers, urogenital, bladder and blood and lymph node. Linkage studies have shown co-clustering between prostate cancer, breast, ovarian and colon cancer due to BRCA 1 and 2 genes in the chromosome 17q.[49, 50] But our study did not find an association between family history of breast, ovarian and colon cancer and prostate cancer. This could be due to extensive control for potential confounders.

This study found non-significant decreased risk with stomach and liver cancers both in first-degree relatives and parents alone. In contrast, past studies have shown non-significant increased risk associated with stomach and liver cancer both in first-degree relatives and parents alone.[28, 31] This difference noted may be due to extensive control for confounders in the present study but there are no apparent biological explanations available for this finding.

Knowledge of family history of cancers is very important. It helps distinguish between the hereditary and sporadic cancers that have some key differences. A review article by Bratt et al. in 2002 examined the differences in clinical characteristics between hereditary and sporadic prostate cancer.[55] They found that one major difference between the hereditary and sporadic cancer is that hereditary prostate cancer is diagnosed at least 6 or 7 years earlier than sporadic cancer.[55] But hereditary and sporadic prostate cancers do not have any differences in tumor grade or pathological stage at diagnosis.[56, 57, 58, 59]

Studies have shown mixed findings with differences in outcomes between hereditary and sporadic cancers [57, 59, 60, 61] As a result of early diagnosis, more men with hereditary prostate cancer tend to die due to the disease.[55] This difference calls for early screening in men with family history of cancer specifically prostate cancer and other cancers. A recent US randomized control trial, Prostate, Lung, Colorectal and Ovarian cancer screening study [62] reported that routine PSA screening has no effect in reducing the rate of death from prostate cancer. However, a European randomized study on prostate cancer screening [63] concluded that there was a decrease in death rate due to prostate cancer by 20% but there was an increased risk of overdiagnosis. Therefore PSA screening may not be mandatory and necessary in sporadic prostate cancers. However, in the case of hereditary prostate cancer, early PSA screening may be necessary so that the cancer can be diagnosed and treated at early stages and grades. But it is necessary to conduct randomized control trials to confirm that early diagnosis and treatment of hereditary prostate cancers improves survival and quality of life. To determine if a patient has a hereditary or sporadic prostate cancer, knowledge of family history of cancers is very crucial.

Potential strengths of this study include good response rate to mail surveys, extensive collection of data and control of known and potential confounders, thorough exploration of family history of several cancers on prostate cancer risk and adjusting for multiple comparisons in the analysis. This study collected and controlled for extensive list of known and potential confounders and controlled for them in the data analysis. Past studies had controlled either only for age or had a partial control for confounders. This

could have partly played a role in past studies showing more statistically significant results. [2, 19, 20, 28, 31, 35, 37]

Limitations include that there may have been a problem of misclassification of the family history as it is based on self-reported data. No additional validation of the self-reported information was conducted. However, past studies have shown that self-reported family history data can be accurate. Two studies from Sweden and US have shown that self-reported family history of prostate cancer in prostate cancer cases have an accuracy of 92% and 86% respectively. King et al. also found accuracy of self-reported family history with other cancers- 95% for breast cancer, 92% for colon cancer, 100% for bladder and kidney cancer and 82% for all sites.[51, 52, 53, 54] Considering the design of this study, it is possible that the cases over reported and the controls under reported the exposure resulting in overestimation of the association. The crude estimate was calculated using the proportions of family history of prostate cancer in cases and controls from a meta-analysis by Bruner et al. This yielded estimate similar to the estimate obtained in the current study.[15]

Another inherent problem with case-control study is recall bias as cases may recall family history of cancers different than the controls. This could overestimate our results. This study used clinic controls and they may be different from the general population controls. It is possible that the cases and controls may share common risk factors and this may underestimate the association. Since the cases were selected from this clinic, it is a preferred population to select the controls from the same clinic to be comparable. But patients with any urological cancer and prostate-related problem were

excluded and controls were selected from a variety of diagnosis to reduce misclassification of controls.

This study was done in a private urology clinic and majority of the cases may more have been referred to this clinic. This makes the cases different from the control population and may overestimate the association. However, differential referral patterns between cases and controls were not expected since the study participants were urology patients. The mail survey obtained an overall 37% response but a 53% response rate among cases and 29% among controls. If the non-responders are systematically different from the responders, this can overestimate or underestimate the association. It is possible that cases or those with family history of cancers may be more willing to respond than the controls or those without the risk factor; resulting in underestimation of the association. However, information on non-responders was not available in this study to assess comparability of non-responders with responders.

The current study showed that there is an increased risk of prostate cancer for men with a family history of any cancer and prostate cancer in first-degree relatives and parents alone. But the association between family history of other cancers and prostate cancer risk was not statistically significant. Future studies should be conducted to explore the association between family history of other cancers and prostate cancer risk in a large prospective follow-up study accounting for known and potential confounders. Additionally, future studies should examine the genetic and shared environmental influences associated with prostate cancer risk. This is important as the hereditary and sporadic cancers behave differently in terms of mortality. Knowledge of family history of cancers is very important to differentiate hereditary and sporadic cancers. Health care

practitioners need to be educated about the importance of family history of cancers so that this information can be routinely collected.

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Table 1: Distribution of the study characteristics

	Cases (%)	Controls (%)
Age (Years)		
≤60	70 (13.2)	375 (59.7)
61-70	183 (34.4)	175 (27.9)
>70	279 (52.4)	78 (12.4)
Race		
White	474 (81.0)	563 (83.0)
African American	63 (10.8)	63 (9.3)
Hispanic	40 (6.8)	33 (4.9)
Other	8 (1.4)	19 (2.8)
Marital status		
Married	498 (83.7)	557 (82.0)
Divorced	90 (15.1)	95 (14.0)
Never Married	7 (1.2)	27 (4.0)
Education		
<Grade 12	80 (13.8)	41 (6.2)
Grade 12 or GED	113 (19.5)	147 (22.2)
Some college	126 (21.8)	172 (26.0)
College graduate	260 (44.9)	301 (45.5)
Household income		
< $25,000	69 (14.0)	55 (9.0)
$25,000 to < $50,000	132 (26.8)	107 (17.5)
$50,000 to < $75,000	95 (19.3)	134 (21.9)
$75,000 to < $100,000	74 (15.0)	100 (16.4)
≥ $100,000	123 (25.0)	215 (35.2)
BMI		
≤24.99	178 (30.5)	145 (21.6)
25-29.99	281 (48.2)	302 (44.9)
≥30	124 (21.3)	226 (33.6)
Moderate activity (in days per week)		
0	82 (15.1)	106 (16.6)
1-2	86 (15.8)	124 (19.4)
≥3	377 (69.2)	408 (64.0)
Alcohol (drinks per day)		
0	203 (39.1)	174 (28.8)
1-2	285 (54.9)	391 (64.6)
≥3	31 (6.0)	40 (6.6)
Smoking		
Current smoker	43 (7.2)	87 (12.7)
Former smoker	62 (10.3)	46 (6.7)
Non-smoker	495 (82.5)	553 (80.6)
Fruits and Vegetables (servings per day)		
<2	145 (25.3)	208 (31.1)
2-4	264 (46.1)	305 (45.6)
>4	164 (28.6)	156 (23.3)

	Cases (%)	Controls (%)
Milk (servings)		
Never	52 (9.0)	60 (9.2)
At least 1 time per week	328 (57.0)	397 (61.2)
≥1 time per day	195 (33.9)	192 (29.6)
Vitamin intake		
Yes	390 (66.0)	418 (61.8)
No	201 (34.0)	258 (38.2)
Vasectomy		
Yes	155 (27.4)	193 (29.0)
No	411 (72.6)	473 (71.0)
STD		
Yes	50 (8.6)	84 (12.4)
No	530 (91.4)	592 (87.6)

Table 2: Association of family history of cancers and risk of developing prostate cancer

Family history of cancers		First-degree relatives		Parents		Siblings	
		Crude OR	Adjusted OR*	Crude OR	Adjusted OR*	Crude OR	Adjusted OR*
Any cancer							
	Yes	1.83 (1.40, 2.38)	2.42 (1.53, 3.84)	1.09 (0.85, 1.40)	1.90 (1.23, 2.94)	2.64 (1.95, 3.58)	1.55 (0.94, 2.56)
	No	1.00	1.00	1.00	1.00	1.00	1.00
Prostate							
	Yes	2.77 (1.99, 3.86)	2.68 (1.53, 4.69)**	1.88 (1.28, 2.75)	3.26 (1.71, 6.24)****	4.85 (2.74, 8.60)	2.13 (0.88, 5.19)
	No	1.00	1.00	1.00	1.00	1.00	1.00
Breast							
	Yes	1.11 (0.77, 1.58)	1.09 (0.58, 2.05)	0.84 (0.55, 1.27)	1.00 (0.48, 2.07)	1.85 (0.98, 3.48)	1.10 (0.35, 3.48)
	No	1.00	1.00	1.00	1.00	1.00	1.00
Colon							
	Yes	1.34 (0.88, 2.04)	1.12 (0.55, 2.28)	1.22 (0.74, 2.00)	1.17 (0.52, 2.63)	1.96 (0.98, 3.89)	1.84 (0.53, 6.36)
	No	1.00	1.00	1.00	1.00	1.00	1.00
Lung							
	Yes	1.25 (0.87, 1.81)	1.41 (0.79, 2.53)	0.83 (0.55, 1.25)	1.22 (0.64, 2.30)	4.56 (1.95, 10.68)	1.91 (0.48, 7.60)
	No	1.00	1.00	1.00	1.00	1.00	1.00
Skin							
	Yes	0.55 (0.32, 0.94)	0.86 (0.37, 1.98)	0.47 (0.25, 0.91)	0.73 (0.27, 1.96)	0.63 (0.24, 1.70)	1.19 (0.28, 5.04)
	No	1.00	1.00	1.00	1.00	1.00	1.00
Digestive tract							
	Yes	0.63 (0.30, 1.31)	1.18 (0.41, 3.42)	0.42 (0.15, 1.16)	0.55 (0.10, 3.06)	1.28 (0.45, 3.67)	2.65 (0.59, 11.87)
	No	1.00	1.00	1.00	1.00	1.00	1.00
Stomach							
	Yes	1.15 (0.46, 2.86)	0.44 (0.09, 2.11)	1.28 (0.41, 3.99)	0.64 (0.09, 4.48)	0.96 (0.21, 4.29)	0.24 (0.02, 3.51)
	No	1.00	1.00	1.00	1.00	1.00	1.00
Liver							
	Yes	1.06 (0.53, 2.14)	0.70 (0.24, 1.99)	0.67 (0.28, 1.60)	0.45 (0.13, 1.54)	3.01 (0.77, 11.69)	3.92 (0.25, 62.62)
	No	1.00	1.00	1.00	1.00	1.00	1.00

Family history of cancers	First-degree relatives		Parents		Siblings	
	Crude OR	Adjusted OR*	Crude OR	Adjusted OR*	Crude OR	Adjusted OR*
Pancreas						
Yes	1.28 (0.59, 2.80)	1.81 (0.47, 7.00)	1.14 (0.44, 2.97)	1.13 (0.23, 5.49)	1.60 (0.43, 5.99)	4.74 (0.36, 62.92)
No	1.00	1.00	1.00	1.00	1.00	1.00
Female cancers (uterus, ovary, cervix, vagina)						
Yes	1.37 (0.68, 2.74)	1.10 (0.37, 3.25)	1.02 (0.40, 2.61)	1.17 (0.25, 5.49)	1.71 (0.59, 4.97)	1.03 (0.23, 4.67)
No	1.00	1.00	1.00	1.00	1.00	1.00
Urogenital (kidney, rectum, ureter, testis)						
Yes	1.28 (0.57, 2.88)	1.14 (0.31, 4.24)	1.54 (0.47, 5.07)	2.59 (0.38, 17.44)	0.73 (0.21, 2.50)	0.21 (0.02, 2.67)
No	1.00	1.00	1.00	1.00	1.00	1.00
Urinary bladder						
Yes	2.06 (0.99, 4.30)	2.07 (0.56, 7.65)	1.68 (0.73, 3.86)	2.00 (0.41, 9.90)	4.52 (0.93, 21.85)	2.14 (0.22, 21.05)
No	1.00	1.00	1.00	1.00	1.00	1.00
Brain						
Yes	3.38 (1.20, 9.56)	9.09 (1.48, 55.96)***	1.80 (0.57, 5.70)	6.79 (0.92, 50.10)		
No	1.00	1.00	1.00	1.00		
Blood and lymph node						
Yes	1.41 (0.79, 2.52)	1.80 (0.68, 4.72)	1.11 (0.52, 2.35)	2.68 (0.82, 8.71)	2.22 (0.87, 5.68)	0.86 (0.19, 3.84)
No	1.00	1.00	1.00	1.00	1.00	1.00
Other						
Yes	0.54 (0.28, 1.05)	0.60 (0.22, 1.63)	0.28 (0.11, 0.75)	0.42 (0.10, 1.78)	1.12 (0.40, 3.11)	0.65 (0.15, 2.86)
No	1.00	1.00	1.00	1.00	1.00	1.00

*Adjusted for BMI, alcohol intake, physical activity, smoking, diet, history of vasectomy and STD, age, race, marital history, education and income
** Bonferroni corrected estimate 2.68 (1.16, 6.21)
*** Bonferroni corrected estimate 9.09 (0.60, 138.64)
**** Bonferroni corrected estimate 3.26 (1.24, 8.63)

CASE-CONTROL STUDY: ASSOCIATION BETWEEN OBESITY AND PROSTATE CANCER

INTRODUCTION

Obesity is a major public health problem in the United States and affects over 30% of the adult population. The prevalence of obesity in adults has continued to increase over the past several decades. The recent 2003-04 data published by the National Health and Nutrition Examination Survey (NHANES), which measured height and weight from 4,431 adults, showed that 32.2% of the adult population in the US was obese.[1]

Disease conditions including diabetes, hypertension, high cholesterol, asthma, arthritis and poor health status are associated with obesity.[2] Furthermore, prospective studies have shown that there is increased risk of death due to cardiovascular disease and several cancers including prostate cancer in men who are obese.[3, 4, 5] Prostate cancer is the most common malignant neoplasm in men. In 2008 alone, approximately 186,320 new cases were estimated to be diagnosed in the United States.[6] Several studies have explored the association between obesity and risk of developing prostate cancer in men. These studies have shown mixed findings between higher BMI and prostate cancer risk.

The most recent prospective study using over 280,000 men who participated in the NIH-AARP diet and health study showed significant decreased risk with localized

prostate cancer for men with BMI ≥40 kg/m^2 compared to men in lower BMI category <25 kg/m^2 (RR=0.67, 95% CI: 0.50, 0.89) and extraprostatic disease with BMI 35-39.9 kg/m^2 compared to men in lower BMI category <25 kg/m^2 (RR=0.68, 95% CI: 0.49, 0.94).[7] Similarly, the prospective study using the cohort of 50,000 men from the Health Professionals follow-up study found that men with high BMI of ≥ 30kg/m^2 compared to men in normal BMI category 23-24.9 kg/m^2 had lower risk of developing prostate cancer among those who were less than 60 years old (RR=0.52, 95% CI: 0.33, 0.83) or had a family history of prostate cancer (RR=0.74, 95% CI: 0.45, 1.19).[8]

A meta-analysis looking at 31 cohort studies and 25 case-control studies from 1966 to 2004 found that obesity was weakly associated with prostate cancer (RR=1.05 per 5 kg/m^2 increment, 95% CI: 1.01, 1.08). There was increased risk observed with advanced disease (RR=1.12 per 5 kg/m^2 increment, 95% CI: 1.01, 1.23) and decreased risk with localized disease (RR=0.96 per 5 kg/m^2 increment, 95% CI: 0.89, 1.03).[9] A large Swedish retrospective cohort study conducted on 135,000 construction workers with an average of 18 years follow-up also showed a non-significant positive association between prostate cancer risk and weight, height, BMI >26.2 kg/m^2 (RR=1.13, 95% CI: 0.99, 1.29) compared to BMI <22.1 kg/m^2 and lean body mass. The association was stronger for prostate cancer mortality than prostate cancer incidence.[10] Several other studies have shown that obesity increases the risk of developing prostate cancer.[11, 12, 13, 14, 15]

In contrast, numerous studies have shown that there is no association between obesity and risk of prostate cancer.[16, 17, 18, 19, 20, 21, 22, 23, 24, 25] Furthermore, a report from the Baltimore longitudinal study of aging revealed that greater waist to hip ratio was

associated with an increased but not statistically significant risk for prostate cancer both in age-adjusted and multivariate analysis adjusted for age, smoking and fasting insulin.[26] The Netherlands cohort study that followed over 58,000 men for 6.3 years also found no association between BMI and development of prostate cancer.[27] The Health Professionals study in the US also assessed the relationship between anthropometric measurements and prostate cancer risk on 47,781 men. The study showed that adult BMI, and hip and waist circumferences were not associated with risk of total or advanced prostate cancer.[28]

Recent studies have show that higher BMI is associated with increased risk of advanced prostate cancer and has a protective effect on localized early prostate cancer. A prospective study from the Cancer Prevention Study II cohort found that BMI $\geq 35 kg/m^2$ was inversely associated with risk of non-metastatic low-grade prostate cancer (RR=0.84, 95% CI: 0.66, 1.06) compared to BMI $<25 kg/m^2$. It further found that BMI 30-$<35 kg/m^2$ compared to BMI $<25 kg/m^2$ was positively associated with risk of non-metastatic high-grade prostate cancer (RR=1.22, 95% CI: 0.96, 1.55) and metastatic and fatal prostate cancer (RR=1.54, 95% CI: 1.06, 2.23).[29] Another study from the Prostate cancer prevention trial found that obese men with BMI $\geq 30 kg/m^2$ compared to BMI $<25 kg/m^2$ had an 18% decreased risk of low grade prostate cancer (RR=0.82, 95% CI: 0.69, 0.98) and 29% increased risk of high grade prostate cancer (RR=1.29, 95% CI: 1.01, 1.67).[30]

Majority of these studies have looked at obesity in late adult life either before cancer diagnosis or study onset. It is important to examine the effects of obesity in early childhood and adulthood on prostate cancer risk to determine the true association before the cancer process has begun. Studying obesity in late adult life during study onset or before cancer diagnosis may not be a true indicator as the cancerous conversion may have

already started. To our knowledge, there is only one recent systematic review and meta-analysis that studied the association between early-adult obesity and prostate cancer risk. Robinson et al. analyzed nine cohort and seven case-control studies that explored the association between early-adult BMI and prostate cancer risk. They showed that there was non-significant increased prostate cancer risk associated with five-unit increase in early-adult BMI (RR=1.06, 95% CI: 0.99, 1.14). Additionally, this study showed limited evidence of protective effect between early-adult obesity and advanced prostate cancer but not with localized cancer.[31]

Compared to the wealth of literature examining obesity before cancer diagnosis or at the time of study entry and prostate cancer risk, the studies addressing early-onset obesity and prostate cancer risk are limited. Only a few studies as addressed in the meta-analysis by Robinson et al. have looked at early-onset obesity and prostate cancer risk.[31] Some of these studies looking at early-onset obesity showed increased risk of prostate cancer [13, 16, 18, 22, 23, 27, 32, 33] whereas others showed decreased risk.[7, 28, 34, 35] The scant literature in this area has also presented several methodological problems. Most of these studies have examined BMI only as a categorical variable with inconsistent definitions and cut-off points. The inconsistency in the definition of obesity has made comparability of these studies very difficult. Although most studies have used BMI to determine obesity, studies have categorized obesity into different ranges disregarding the standard and internationally accepted World Health Organization (WHO) categories. Another limitation of these studies is also the poor and inconsistent control of confounders with some studies only controlling for age. There is no adequate control for individual level demographic, behavioral and clinical factors. Therefore the current study investigated the

relationship between early-onset obesity, current obesity and prostate cancer risk controlling for known and postulated confounding factors, utilizing the widely accepted WHO definitions for categorizing BMI. This study also evaluated BMI both as categorical and continuous variable.

MATERIALS AND METHODS

Study design

This study used data from a case-control study conducted in Central Virginia between September and October 2008. The study was designed to examine the influence of obesity, lifestyle behaviors and demographic factors on prostate cancer.

Study setting and population

Potential study participants (N=3,710) were recruited from a private urology practice that consists of nine clinics serving Central Virginia. Cases (N=1,237) were randomly selected from histologically confirmed prostate cancer patients of all stages and grades diagnosed from January 2000 to December 2005. Controls included a random sample of 2,473 urologic patients other than cancers and prostate-related problems who were diagnosed during the same time period. This study excluded patients diagnosed before January 2000 and after December 2005, non-English speaking and those with mental and cognitive problems who cannot complete the questionnaire.

Data collection

Before the beginning of the study, data collection instrument was pre-tested and necessary adjustments were made. To enhance the response rate, this study used the Dillman mail survey methodology.[36] The survey procedure included a series of mailings including a pre-notice postcard, questionnaire, thank-you letter and a replacement

questionnaire. Initially a pre-notice postcard was mailed to 3,510 potential study participants informing them the intent of the study. The questionnaire accompanied by a cover letter and a return envelope was mailed following the pre-notice postcard. A thank-you letter was then sent to 3,271 participants after removing the deceased, wrong addresses and those who did not want to be contacted. Two weeks after the thank-you letter, 2,219 participants were sent with a final reminder and replacement questionnaire. Overall a 37% response rate was obtained and 1,286 (600 cases and 686 controls) valid questionnaires were collected. Adequate information was not available on the non-responders and therefore comparison between responders and non-responders was not done.

Measurement of covariates

Validated questions from the BRFSS,[37, 38, 39] NHIS,[40] NHANES,[41] Family history survey,[42] and Nurses' health study[43] surveys were adopted. Data on current height, weight and weight at age 18 were collected. Lifestyle factors such as diet history, sunlight exposure, smoking habits, alcohol use, physical activity, STD history and history of vasectomy and demographic information including age, race, education, employment, income, marital status were also collected. Relevant questions to collect all the necessary information on lifestyle and demographic factors were not available in one standardized questionnaire. Therefore appropriate questions were selected from several validated questionnaires, combined and used in the mail survey.

The main outcome variable for this study was patient status (cases and controls). Cases were prostate cancer patients regardless of the stage and severity of the disease. Controls were patients who visited the clinic for urological problems other than cancers

and prostate problems. The main exposure variable obesity was depicted by BMI, defined as weight (in kilograms) divided by square of the height (in meters). BMI was categorized in accordance to the World Health Organization classification as, normal (BMI less than 25kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obese (BMI >=30 kg/m^2).[44] Covariates such as, physical activity (0 days per week, 1-2 days per week, ≥3 days per week), alcohol consumption (0 drinks per day, 1-2 drinks per day, ≥3 drinks per day), smoking (non-smoker, former smoker, current smoker), diet including fruits and vegetables intake (<2 servings per day, 2-4 servings per day, >4 servings per day), milk consumption (never, at least once per week, ≥1 time per day), vitamin intake (yes, no), history of vasectomy (yes, no) and STD (yes, no), age (≤60, 61-70, >70), race (White, African American, Hispanic, Other), marital status (married, divorced, never married), education (less than grade 12, grade 12 or GED, some college, college graduate) and income (less than $25,000, $25,000 to less than $50,000, $50,000 to less than $75,000, $75,000 to less than $100,000, $100,000 or more) were examined.

Statistical analysis

The association between BMI and risk of developing prostate cancer were estimated using unconditional logistic regression. Univariate analysis was done using the main exposure variable and other covariates. Four unconditional multiple logistic regression models were built to examine the associations between prostate cancer and BMI. BMI at age 18 and current BMI was examined both as categorical and continuous variable. Interaction effects were assessed using the likelihood ratio test and then potential confounders were assessed using the 10% change in estimate rule. Odds ratios and corresponding 95% confidence intervals were determined after accounting for

potential interactions and adjusting for the potential confounding variables. Data analysis was performed in SAS version 9.1 and all the statistical tests were two-sided.

RESULTS

Distribution of the study characteristics

The demographic and characteristics of the population are described in Table 1. Majority of the men were white (82.1%), married (82.8%), college graduate (45.2%) or have completed some college (24.0%). About half the participants earn $75,000 or more per year (46.4%). About 81% of the men were normal weight at age 18 whereas 46% of them were overweight and 28% obese at present. Cases were more likely to be older than controls but less likely to college educated and have high income. They are both similar in race and marital status distributions.

BMI at age 18

The crude analysis showed that being overweight at age 18 had a significant protective effect on prostate cancer risk. Overweight men at age 18 had a 39% decreased risk of prostate cancer (OR=0.61, 95% CI: 0.44, 0.84) compared to normal weight men. On the other hand, obese men had a 43% decreased risk compared to normal weight men; however, this association was not statistically significant (OR=0.57, 95% CI: 0.24, 1.35). Test for trend showed a statistically significant trend associated with increasing BMI and decreasing prostate cancer risk ($P = 0.002$).

A statistically significant decreased risk of prostate cancer was also observed when BMI was analyzed as a continuous variable. Per unit increase in BMI, there was 6% reduced odds of prostate cancer risk (OR=0.94, 95% CI: 0.91, 0.97). Additionally, a statistically significant association was observed between family history of prostate

cancer and risk of developing prostate cancer in men (OR=2.76, 95% CI: 2.05, 3.72) compared to men with no family history of prostate cancer. Increasing age had a significant increased prostate cancer risk (Table 2).

When the effect of potential confounders was controlled, BMI at age 18 remained significant. There was a 7% decrease in the odds of developing prostate cancer for every unit increase in BMI (OR=0.93, 95% CI: 0.87, 0.98) (Table 2). However, the association lost its statistical significance when BMI at age 18 was analyzed as a categorical variable. Although not statistically significant the direction of association remained the same; showing that overweight men at age 18 (OR=0.60, 95% CI: 0.35, 1.05) and obese men at age 18 (OR=0.62, 95% CI: 0.12, 3.08) had a non-significant decreased risk of developing prostate cancer compared to normal weight men.

Family history of prostate cancer remained statistically significant in the adjusted analysis both when BMI at age 18 was treated as categorical and continuous variable. Compared to men with no family history, men with a family history of prostate cancer were 2.85 times more likely to develop prostate cancer (OR=2.85, 95% CI: 1.77, 4.58). Similarly, when BMI at age 18 was analyzed as continuous variable, there was increased prostate cancer risk associated with family history of prostate cancer compared to no history of prostate cancer (OR=2.99, 95% CI: 1.91, 4.69). There was a statistically significant association between age and risk of developing prostate cancer. Men who were between 61-70 years old were 8.52 times more likely to develop prostate cancer (OR=8.52, 95% CI: 5.23, 13.88) compared to men 60 years old or younger. Similarly, men 70 years and over had an increased risk of prostate cancer (OR=23.82, 95% CI: 13.67, 41.51) compared to men 60 years or younger (Table 2).

Current BMI

There was a statistically significant association between currently obese men and prostate cancer in the unadjusted analysis. Currently obese men were 0.45 times less likely to develop prostate cancer compared to normal weight men (OR=0.45, 95% CI: 0.33, 0.61) whereas currently overweight men were 0.76 times less likely to develop prostate cancer though not statistically significant (OR=0.76, 95% CI: 0.58, 1.00) compared to normal weight men. There was an evident trend of decreasing risk of prostate cancer with increasing BMI ($P<.0001$). There was statistically significant decreased risk in prostate cancer for a unit increase in BMI when evaluated as a continuous variable (OR=0.94, 95% CI: 0.92, 0.96) (Table 2).

Adjusted analysis showed that there was a non-significant decreased prostate cancer risk for a unit increase in BMI (OR=0.97, 95% CI: 0.92, 1.02) when BMI was analyzed as a continuous variable (Table 2). When BMI was examined as a categorical variable, there was a significant interaction between current BMI and age. Among men aged 60 years or less, overweight men had an increased risk of developing prostate cancer compared to normal weight men (OR=1.01, 95% CI: 0.59, 1.74) and obese men had a decreased risk (OR=0.73, 95% CI: 0.38, 1.40) compared to normal weight men, though not statistically significant. In the 61-70 years old age category, both overweight men (OR=0.73, 95% CI: 0.34, 1.57) and obese men (OR=0.44, 95% CI: 0.18, 1.10) were less likely to develop prostate cancer compared to normal weight men. This association was also not statistically significant. Similar relationship was observed in men over 70 years with overweight (OR=0.71, 95% CI: 0.27, 1.87) and obese men (OR=0.74, 95% CI:

0.22, 2.56) having decreased prostate cancer risk compared to normal weight men (Table 3 and Figure 1).

Increased prostate cancer risk was evident with having a family history of prostate cancer compared to no family history and increasing age both when BMI was evaluated and categorical and continuous variable. Additionally, there was a two fold increased risk of prostate cancer in African American men compared to White men when BMI was analyzed as a continuous variable (OR=2.39, 95% CI: 1.15, 4.94) (Table 2).

DISCUSSION

This study showed that there was statistically significant decreased prostate cancer risk associated with increasing BMI at age 18 when evaluated as a continuous variable. To our knowledge, there were only two other studies examining BMI as a continuous variable to define early-onset obesity and risk of prostate cancer. Andersson et al. in 1995 conducted a case-control study among men under 80 years born in Sweden and found that there was no association between unit increase in BMI at age 20 and prostate cancer risk (OR=1.0 per 5 kg/m^2 increment, 95% CI: 0.6, 1.5). But this analysis only adjusted for age, grade of urbanization and adult farming.[45] The Netherlands cohort study examined association between BMI at age 20 and risk of developing prostate cancer. They found that there was a increase in the odds of prostate cancer risk by 1.08 for every 2 kg/m^2 increase in BMI though not statistically significant (RR=1.08 per 2 kg/m^2 increment, 95% CI: 0.99, 1.18). This study only adjusted for age, family history of prostate cancer and socioeconomic status.[27] The inconsistency observed between this study and the studies in Sweden and Netherlands could be due to the inconsistencies in

the control of potential confounding factors. The current study has evaluated and controlled for an extensive number of potential confounding factors.

This study found a non-statistically significant decreased risk of developing prostate cancer in both overweight and obese men at age 18 when BMI was categorized. These findings are similar to the results from the most recent prospective study that used over 280,000 men who participated in the NIH-AARP study that showed non-significant decreased risk with BMI ≥25 kg/m^2 at age 18 (RR=0.93, 95% CI: 0.84, 1.02) but there was a trend of increased risk with extraprostatic cancer (RR=1.15, 95% CI: 0.90, 1.47) and decreased risk with localized cancer (RR=0.89, 95% CI: 0.80, 0.99) compared to BMI <18.5 kg/m^2.[7] A population-based case-control study conducted in California reported that men between ages 20 and 29 years have a decreased prostate cancer risk (OR=0.53, 95% CI: 0.28, 1.00) and BMI ≥ 30 kg/m^2 (OR=0.40, 95% CI: 0.20, 0.81) compared to BMI <25 kg/m^2.[35] Giovannucci et al. have also shown similar findings in their analysis of the Health Professionals follow-up study. They reported that BMI ≥ 26 kg/m^2 compared to BMI <20 kg/m^2 at age 21 was inversely associated with prostate cancer risk but this association was not statistically significant (RR=0.87, 95% CI: 0.67, 1.12). Further BMI ≥ 26 kg/m^2 was associated with significant decreased risk in advanced prostate cancer (RR=0.53, 95% CI: 0.33, 0.86) compared to BMI <20 kg/m^2 and BMI 24-25.9 kg/m^2 was associated with significant decreased risk in metastatic prostate cancer compared to BMI <20 kg/m^2 (RR=0.46, 95% CI: 0.27, 0.81).[28]

Although this study was consistent with some studies described above, the finding of this study was contradictory with other studies. Schuurman et al. in the prospective Netherlands cohort study that examined about 60,000 men reported that men with BMI ≥

25 kg/m^2 at age 20 compared to those with BMI <19 kg/m^2 were 1.33 times more likely to develop prostate cancer (RR=1.33, 95% CI: 0.81, 2.19).[27] A cohort study of the participants from the Harvard alumni health study with anthropometric measurements measured at age 18 showed a non statistical significant increased risk of developing prostate cancer among men with BMI ≥ 25 kg/m^2 compared to BMI < 20 kg/m^2 (RR=1.17, 95% CI: 0.40, 1.85).[23] The follow-up Norwegian study on 950,000 men measured height and weight between 20-74 years also reported a non-statistically significant risk of prostate cancer. The study showed that men in the ages 20-29 years with BMI ≥ 30 kg/m^2 were 1.22 times more likely to develop prostate cancer compared to men with BMI < 18.50 kg/m^2 (RR=1.22, 95% CI: 0.69, 2.17).[13] The discrepant findings between our study and these studies could be due to limited control for confounding in these past studies. It is important to note that though some of the past studies studying the association between early-onset obesity and prostate cancer were prospective cohort studies, most of the height and weight data collected for the early ages are usually self-reported and therefore subject to the same problems as a retrospective study.

While this study found a statistically significant association between BMI at age 18 and risk of prostate cancer when BMI was analyzed as continuous variable, the association was lost when BMI was categorized. This could be attributed to the loss of information when the variable was categorized.

The current study observed that there was a 3% decrease in the odds of prostate cancer risk for a unit increase in BMI when current BMI was examined as a continuous variable but it was not statistically significant (OR=0.97, 95% CI: 0.92, 1.02). There was only one other study that evaluated baseline BMI as continuous variable and they found

no association between 2 kg/m^2 increase in BMI and prostate cancer risk (RR=1.00, 95% CI: 0.92, 1.07). This study only adjusted for age, family history of prostate cancer and socioeconomic status.[27]

Our study showed that there was significant interaction between age and current BMI on prostate cancer risk when BMI was evaluated as a categorical variable. There was a trend towards decreased risk of prostate cancer with the overweight and obese men in the different age groups except the overweight men in 60 years or younger age group. This finding was similar to the results observed by Giovannucci et al. However, the study by Giovannucci et al. showed a statistically significant decreased prostate cancer risk among men less than 60 years old in the two obese categories 27.5-29.9 kg/m^2 (RR=0.49, 95% CI: 0.32, 0.73) and ≥30kg/m^2 (RR=0.52, 95% CI: 0.33, 0.83) categories compared to men in lower BMI category 23-24.9 kg/m^2.[8] This difference could be attributed to the fact that Giovannucci et al. conducted a prospective cohort study with over 50,000 participants and also used six categories to define BMI.

The associated metabolic syndrome observed in obesity may be an explanation for the observed association between BMI and risk of prostate cancer. Obesity is associated with diabetes later in life and they also occur together in metabolic syndrome. Diabetes has been reported to be associated with lower risk of developing prostate cancer due to decreased insulin levels and decreased IGF-1 activity.[30, 46, 47] This may be a reason for the protective effect observed in this study. But this study did not collect information on history of diabetes.

There are several proposed biological and hormonal risk factors for prostate cancer that could explain the observed association between increased BMI and risk of

prostate cancer. One of these factors is increased insulin and IGF-1 that may be associated with obesity. Obesity is associated with endocrinal imbalances leading to insulin resistance that causes compensatory hyperinsulinemia and increased IGF-1. Studies have shown association between IGF-1 and increased prostate cancer risk.[48, 49, 50, 51, 52, 53]

Another risk factor that may explain the observed association between BMI and risk of prostate cancer may also be the decreased levels of testosterone. Testosterone is needed for normal prostate cancer epithelium differentiation. But obesity decreases the serum testosterone and increases the estrogen levels. The increased estrogen level is also due to peripheral conversion of serum testosterone into estradiol.[54] Further, the estradiol inhibits the pituitary-hypothalamic axis causing decreased testosterone levels.[54] Obesity also reduces the sex hormone-binding globulin that decreases the serum testosterone levels.[55] Studies have shown that lower testosterone levels are associated with increased prostate cancer risk.[56, 57]

The third risk factor that is implicated in prostate cancer risk is leptin; a cytokine and polypeptide hormone that is produced by the adipocytes and maintains the body weight is implicated in prostate cancer risk. However, it is important to note that studies have produced mixed findings with some showing positive association and others showing no significant association between leptin and the risk of prostate cancer..[58, 59, 60, 61, 62, 63] However, this study was unable to confirm these proposed associations as these biological factors were not measured.

There are other proposed non-biological causes for the apparent decreased risk of prostate cancer with obesity. Two studies have shown that obese men are more likely to

get PSA screening.[64, 65] However, obese men have low PSA levels making the detection of early cancers through PSA screening difficult[66, 67, 68] and making them more likely to be diagnosed in later advanced stages after symptoms appear. The reason for the low PSA levels may include that obese men have high plasma volume causing hemodilution and therefore low PSA levels. Also prostate cancer is an androgen-dependent tumor and have been shown to be associated with low testosterone levels. The low testosterone levels may also cause the low PSA levels as testosterone is needed to produce PSA.[69] Our study population may include more early stage cancers causing the apparent protective effect however stage and grade information was not collected to confirm this hypothesis.

Obese men may also less likely to be diagnosed with low grade cancers because of the difficulty to conduct digital rectal examinations (DRE) in them though no studies support this theroy. DRE, biopsy and PSA screening are the main modalities to diagnose prostate cancer. Obese men have larger prostates that have been shown in studies.[70, 71] This makes the routine biopsies very difficult to diagnose the cancer and it can be easily missed. Therefore it is recommended to correct the PSA levels for obese men by multiplying PSA level by a factor of 1.05 and also taking two additional cores in the biopsy to make sure the cancer is not missed.[69]

Potential strengths of this study include collecting height and weight information both at age 18 and current using standardized validated questionnaires, good response rate to mail surveys, and thorough collection of data and control of known and potential confounders. Despite the above strengths this study also presents with some limitations. Limitations include that height and weight information was self-reported and there is a possibility of misclassification of the BMI data. Study by Stevens et al. have shown that

reported and measured weight both current and four years prior are highly correlated (correlation coefficient 0.979 and 0.935) but decreased for weight 28 years ago (correlation coefficient 0.822).[72] Participants in the lower quartile of BMI overestimated their weight and those in the higher quartile of BMI underestimated their weight.[72] It is likely that the current study could have overestimated the association since cases may have over reported the exposure while controls may have under reported it. Crude estimates were calculated using the proportion of obesity in cases and controls from the Prostate cancer prevention trial data.[73] This gave us results consistent to estimates obtained in the current study. There is a potential for recall bias as the study participants have been recalling weight and height information at age 18. But if the cases recall information differently than the controls that would have caused overestimation of the estimates but the current study showed protective effect.

This study used BMI instead of other measure of central obesity including waist to hip ratio. It is believed that in elderly there is a shift in fat from periphery to center that can cause a change in waist to hip ratio without changing the BMI. This can cause an underestimation of the estimates and show a spurious decreased prostate cancer risk. Measuring BMI is easy and studies have shown consistent findings whether they used BMI or waist to hip ratio.[8] Clinic controls were used and they may be different from the general population controls by the fact that they attended the urology clinic. They may share similar risk factors as the cases and may underestimate the association between obesity and prostate cancer risk. But patients with any urological cancer and prostate-related problem were excluded and controls were selected from a variety of diagnosis to reduce misclassification of controls. Since the cases were selected from this clinic, it is a

preferred population to select the controls from the same clinic to be comparable. This study was able to obtain a 37% response rate (53% among cases and 29% among controls). There may be a difference between the responders and non-responders, however, data on non-responders were not available for further analysis. It is possible that non-responders were less healthy than the responders underestimating the association. The current study was conducted in a large urology clinic and there is a possibility that patients from other locations may be referred to this clinic. This can cause an overestimation of the association. But we do not expect differential referral patterns between cases and controls as both of these groups were urology patients.

The present study showed that there was an association between obesity at age 18 and prostate cancer risk. It is important to continuously monitor and study the lifecycle of obesity at early ages in a large prospective study to understand the stage of obesity associated with prostate cancer risk. Obesity has other deleterious effects on heath and findings of this study should be interpreted with caution. Further studies are needed to explore the biological factors influencing the association of increased BMI and risk of prostate cancer, especially in the early ages of life.

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Table 1: Characteristics of the study population

	Cases (%)	Controls (%)	Total (%)
Age (Years)			
≤60	70 (13.2)	375 (59.7)	445 (38.4)
61-70	183 (34.4)	175 (27.9)	358 (30.9)
>70	279 (52.4)	78 (12.4)	357 (30.8)
Race			
White	474 (81.0)	563 (83.0)	1037 (82.1)
African American	63 (10.8)	63 (9.3)	126 (10.0)
Hispanic	40 (6.8)	33 (4.9)	73 (5.8)
Other	8 (1.4)	19 (2.8)	27 (2.1)
Marital status			
Married	498 (83.7)	557 (82.0)	1055 (82.8)
Divorced	90 (15.1)	95 (14.0)	185 (14.5)
Never Married	7 (1.2)	27 (4.0)	34 (2.7)
Education			
<Grade 12	80 (13.8)	41 (6.2)	121 (9.8)
Grades 12 or GED	113 (19.5)	147 (22.2)	260 (21.0)
Some college	126 (21.8)	172 (26.0)	298 (24.0)
College graduate	260 (44.9)	301 (45.5)	561 (45.2)
Household income			
< $25,000	69 (14.0)	55 (9.0)	124 (11.2)
$25,000 to < $50,000	132 (26.8)	107 (17.5)	239 (21.7)
$50,000 to < $75,000	95 (19.3)	134 (21.9)	229 (20.7)
$75,000 to < $100,000	74 (15.0)	100 (16.4)	174 (15.8)
≥ $100,000	123 (25.0)	215 (35.2)	338 (30.6)
BMI			
≤24.99	178 (30.5)	145 (21.6)	323 (25.7)
25-29.99	281 (48.2)	302 (44.9)	583 (46.4)
≥30	124 (21.3)	226 (33.6)	350 (27.9)
BMI at 18			
≤24.99	438 (85.2)	465 (77.6)	903 (81.1)
25-29.99	68 (13.2)	119 (19.9)	187 (16.8)
≥30	8 (1.6)	15 (2.5)	23 (2.1)
FH of Prostate cancer			
Yes	154 (34.4)	91 (15.9)	245 (24.0)
No	294 (65.6)	480 (84.1)	774 (76.0)
Moderate activity (in days per week)			
0	82 (15.1)	106 (16.6)	188 (15.9)
1-2	86 (15.8)	124 (19.4)	210 (17.8)
≥3	377 (69.2)	408 (64.0)	785 (66.4)
Alcohol (drinks per day)			
0	203 (39.1)	174 (28.8)	377 (33.5)
1-2	285 (54.9)	391 (64.6)	676 (60.1)
≥3	31 (6.0)	40 (6.6)	71 (6.3)
Smoking			
Current smoker	43 (7.2)	87 (12.7)	130 (10.1)
Former smoker	62 (10.3)	46 (6.7)	108 (8.4)

	Cases (%)	Controls (%)	Total (%)
Non-smoker	495 (82.5)	553 (80.6)	1048 (81.5)
Fruits and Vegetables (servings per day)			
<2	145 (25.3)	208 (31.1)	353 (28.4)
2-4	264 (46.1)	305 (45.6)	569 (45.8)
>4	164 (28.6)	156 (23.3)	320 (25.8)
Milk (servings)			
Never	52 (9.0)	60 (9.2)	112 (9.2)
At least 1 time per week	328 (57.0)	397 (61.2)	725 (59.2)
≥1 time per day	195 (33.9)	192 (29.6)	387 (31.6)
Vitamin intake			
Yes	390 (66.0)	418 (61.8)	808 (63.8)
No	201 (34.0)	258 (38.2)	459 (36.2)
Vasectomy			
Yes	155 (27.4)	193 (29.0)	348 (28.3)
No	411 (72.6)	473 (71.0)	884 (71.8)
STD			
Yes	50 (8.6)	84 (12.4)	134 (10.7)
No	530 (91.4)	592 (87.6)	1122 (89.3)

Table 2: Association of BMI and prostate cancer

	COR*	AOR** for Current BMI (categorical)	AOR** for Current BMI (continuous)	AOR** for BMI at age 18 (categorical)	AOR** for BMI at age 18 (continuous)
BMI at 18					
≤24.99	1.00			1.00	
25-29.99	0.61 (0.44, 0.84)			0.60 (0.35, 1.05)	
≥30	0.57 (0.24, 1.35)			0.62 (0.12, 3.08)	
	P trend 0.002			*P* trend <.0001	
BMI at 18 (continuous)	0.94 (0.91, 0.97)				0.93 (0.87, 0.98)
BMI					
≤24.99	1.00				
25-29.99	0.76 (0.58, 1.00)				
≥30	0.45 (0.33, 0.61)				
	P trend <.0001				
BMI (continuous)	0.94 (0.92, 0.96)		0.97 (0.92, 1.02)		
FH of Prostate cancer					
Yes	2.76 (2.05, 3.72)	3.20 (1.91, 5.36)	3.45 (2.16, 5.50)	2.85 (1.77, 4.58)	2.99 (1.91, 4.69)
No	1.00	1.00	1.00	1.00	1.00
Moderate activity (in days per week)					
0	1.00	1.00	1.00	1.00	1.00
1-2	0.90 (0.60, 1.34)	1.11 (0.51, 2.39)	0.90 (0.44, 1.84)	1.02 (0.49, 2.09)	0.86 (0.44, 1.69)
≥3	1.19 (0.87, 1.65)	1.03 (0.54, 1.97)	0.87 (0.48, 1.60)	1.16 (0.64, 2.10)	1.07 (0.62, 1.87)
Alcohol (drinks per day)					
0	1.00	1.00		1.00	1.00
1-2	0.63 (0.49, 0.81)	0.94 (0.57, 1.55)		1.00 (0.63, 1.60)	1.02 (0.66, 1.56)
≥3	0.66 (0.40, 1.11)	0.69 (0.28, 1.70)		1.00 (0.40, 2.51)	0.96 (0.41, 2.26)
Smoking					
Current smoker	0.55 (0.38, 0.81)				
Former smoker	1.51 (1.01, 2.25)				
Non-smoker	1.00				

	COR*	AOR** for Current BMI (categorical)	AOR** for Current BMI (continuous)	AOR** for BMI at age 18 (categorical)	AOR** for BMI at age 18 (continuous)
Fruits and Vegetables (servings per day)					
<2	1.00	1.00	1.00	1.00	
2-4	1.24 (0.95, 1.62)	0.91 (0.53, 1.54)	1.10 (0.68, 1.77)	0.98 (0.60, 1.61)	
>4	1.51 (1.11, 2.05)	1.18 (0.63, 2.20)	1.20 (0.68, 2.12)	1.05 (0.59, 1.88)	
Milk (servings)					
Never	1.00	1.00	1.00	1.00	
At least 1 time per week	0.95 (0.64, 1.42)	0.62 (0.30, 1.30)	0.71 (0.36, 1.37)	0.83 (0.40, 1.73)	
≥1 time per day	1.17 (0.77, 1.79)	0.73 (0.34, 1.57)	0.97 (0.48, 1.94)	1.03 (0.48, 2.20)	
Vitamin intake					
Yes	1.20 (0.95, 1.51)				
No	1.00				
Vasectomy					
Yes	0.92 (0.72, 1.19)	0.96 (0.60, 1.52)	1.07 (0.70, 1.64)	0.94 (0.61, 1.45)	
No	1.00	1.00	1.00	1.00	
STD					
Yes	0.67 (0.46, 0.96)	0.92 (0.47, 1.80)	1.07 (0.59, 1.96)	1.00 (0.53, 1.89)	
No	1.00	1.00	1.00	1.00	
Age (Years)					
≤60	1.00		1.00	1.00	1.00
61-70	5.60 (4.03, 7.78)		7.71 (4.84, 12.30)	8.52 (5.23, 13.88)	8.01 (5.07, 12.66)
>70	19.16 (13.39, 27.40)		29.03 (16.25, 51.84)	23.82 (13.67, 41.51)	23.79 (14.20, 39.84)
Race					
White	1.00	1.00	1.00	1.00	1.00
African American	1.19 (0.82, 1.72)	1.85 (0.78, 4.40)	2.39 (1.15, 4.94)	2.26 (0.93, 5.50)	1.86 (0.87, 3.98)
Hispanic	1.44 (0.89, 2.32)	0.46 (0.13, 1.61)	0.78 (0.26, 2.35)	0.84 (0.26, 2.71)	1.04 (0.37, 2.96)
Other	0.50 (0.22, 1.15)	0.88 (0.21, 3.65)	0.87 (0.23, 3.37)	0.78 (0.18, 3.39)	0.63 (0.16, 2.54)

	COR*	AOR** for Current BMI (categorical)	AOR** for Current BMI (continuous)	AOR** for BMI at age 18 (categorical)	AOR** for BMI at age 18 (continuous)
Marital status					
Married	1.00	1.00			
Divorced	1.06 (0.78, 1.45)	1.42 (0.71, 2.85)			
Never Married	0.29 (0.13, 0.67)	0.21 (0.02, 2.17)			
Education					
<Grade 12	1.00	1.00	1.00	1.00	
Grades 12 or GED	0.39 (0.25, 0.62)	0.55 (0.18, 1.70)	0.84 (0.31, 2.27)	0.66 (0.24, 1.82)	
Some college	0.38 (0.24, 0.58)	0.63 (0.21, 1.92)	0.94 (0.35, 2.53)	0.66 (0.24, 1.79)	
College graduate	0.44 (0.29, 0.67)	0.86 (0.28, 2.60)	1.30 (0.48, 3.49)	0.93 (0.35, 2.44)	
Income					
Less than $25,000	1.00	1.00	1.00		
$25,000 to less than $50,000	0.98 (0.64, 1.52)	0.89 (0.35, 2.27)	0.96 (0.41, 2.24)		
$50,000 to less than $75,000	0.57 (0.36, 0.88)	0.56 (0.21, 1.52)	0.61 (0.25, 1.48)		
$75,000 to less than $100,000	0.59 (0.37, 0.94)	0.88 (0.32, 2.46)	0.88 (0.36, 2.17)		
$100,000 or more	0.46 (0.30, 0.69)	0.81 (0.30, 2.21)	0.83 (0.35, 1.99)		

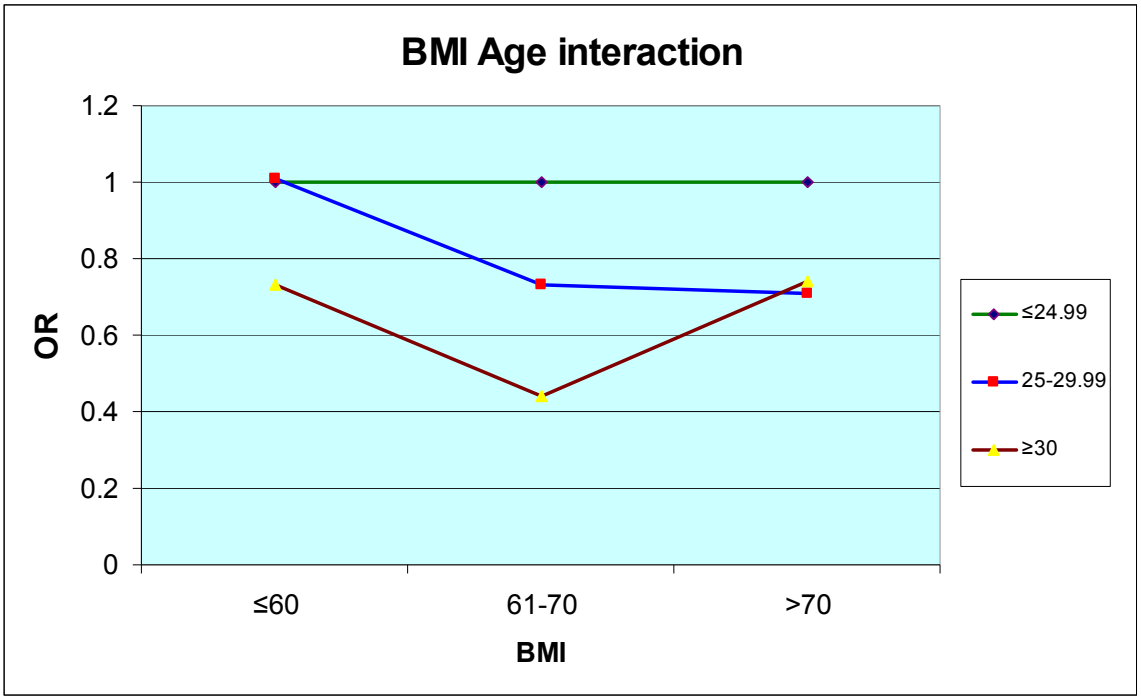
*COR – Crude odds ratios

**AOR – Adjusted odds ratios

Table 3: Interaction between current BMI and age

	BMI		
Age	≤ 24.99	>24.99 and ≤29.99	>29.99
≤60	1.00	1.01 (0.59, 1.74)	0.73 (0.38, 1.40)
61-70	1.00	0.73 (0.34, 1.57)	0.44 (0.18, 1.10)
>70	1.00	0.71 (0.27, 1.87)	0.74 (0.22, 2.56)

Figure 1: Interaction between current BMI and age



APPENDIX A

Detailed Description of Studies included in the Meta-Analysis

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
Roach et al, 2003[23]	Radiation Therapy Oncology Group (RTOG) Randomized trials - 4 consecutive prospective randomized prostate cancer trials (RTOG 8531, 8610, 7506 and 7706)	4 phase III randomized trials performed between 1975 and 1992	11 years and 6 years median follow-up in early (RTOG 7506 and 7706) and late (RTOG 8531 and 8610)studies respectively	2012 men	Treated for clinically localized prostate cancer with external beam radiotherapy with or without hormonal therapy (both short-term and long-term).	Overall survival and prostate cancer-specific survival	Unadjusted estimates 1.24, p=0.04 for overall survival and 1.41, p=0.016 for disease-specific survival, Adjusted estimates 1.17, 95% CI 0.96-1.44, p=0.13 for overall survival and 1.26, 95% CI 0.96-1.67, p=0.1 for disease-specific	Treatment - type radiotherapy with or without short-term or long-term hormonal therapy and Risk group	

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
							survival		
Thompson et al, 2001[24]	Southwest oncology group study (SWOG) 8894, Randomized phase III trial – double blinded randomized trial	December 15, 1989 to September 15, 1994	Median follow-up for African-American men was 5.5 years (4.1-9.3 years) and for White men was 6.7 years (3.8-9.3 years)	1263 men including 975 White and 288 African-American men. Final analysis for cox regressio n had 198 African-American men and 718 White men	Randomized phase III trial that compared orchiectomy with or without flutamide in men with metastatic prostate cancer	Overall survival	Unadjusted estimate 1.38 (1.17-1.64), and adjusted estimate 1.23 (1.04-1.47), p=.018	Age, extent of disease, bone pain, performance status, treatment arm, PSA levels, Gleason score	

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
Crawford et al, 1990[28]	Five cooperative groups including the National Prostatic cancer project, the Southwest oncology group (SWOG), the Northern California oncology group, the North central cancer group and the Mid-Atlantic oncology program, Multi-institutional placebo-controlled, double-blind, randomized clinical trial	Patients recruited from January 1985 to April 1986		603 patients (303 were randomly assigned to receive leuprolide and flutamide and 300 to receive leuprolide and placebo)	To compare the efficacy of combined androgen blockade with leuprolide and flutamide to that of leuprolide and placebo in histologically confirmed stage D2 metastatic prostate cancer that had been previously untreated at this stage	Overall survival			Survival curve for overall survival

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
Halabi et al, 2006[25]	Data from 8 multi-institutional trials performed by CALGB from 4 phase III and 4 phase II clinical trials, Retrospective analysis of Clinical trial data	Clinical trials performed by CALGB between 1992 and 2002		1,194 men	With metastatic hormone refractory prostate cancer from 4 phase III and 4 phase II clinical trials performed by CALGB between 1992 and 2002 – had progressive adenocarcinoma of the prostate after androgen ablation with castrate testosterone.	Overall survival and prostate cancer-specific survival	0.77, 95% CI 0.65-0.92, p=0.004 for overall survival and 0.76, 95% CI 0.63-0.92, p=0.006 for disease-specific survival	Age, performance status, visceral disease, prior radiotherapy, Gleason sum, body mass index, hemoglobin, testosterone, docetaxel, alkaline phosphatase, years since diagnosis, PSA, LDH	
Du et al, 2006[10]	11 SEER areas including metropolitan areas of San Francisco/Oakland, Detroit, Atlanta, Seattle, Los Angeles county, San Jose-Monterey area, States of Connecticut, Iowa, New Mexico, Utah and Hawaii, Retrospective Cohort study	Diagnosed between 1992 and 1999	Till December 31, 2002 – upto 11 years follow up	61,228 men including 53,764 Whites (non-Hispanic Whites), 6,321 African Americans (non-Hispanic blacks) and 1,143 Hispanics	Diagnosed with local/regional stage prostate cancer at age 65 years or older	Overall survival and prostate cancer-specific survival	1.01 (0.97-1.06) for Overall mortality and 1.17 (0.99-1.37) for prostate cancer-specific mortality	Age, comorbidity, AJCC stage, Gleason score, year of diagnosis, SEER region, surgery and radiation, hormone and chemotherapy, composite SES (education, poverty and income)	Survival curves for overall and prostate cancer-specific survival

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
				.					
Tewari et al, 2006[26]	Henry Ford health system, MI, Retrospective Cohort study	Diagnosed between 1980 and 1997		3159 men	With biopsy-confirmed clinically localized prostate cancer in men 75 years of age or younger treated either conservatively or by definitive treatment (radiotherapy or radical prostatectomy)	Overall survival and prostate cancer-specific survival	1.02, 95% CI 0.88-1.19, p=0.766 for overall survival and 1.11, 95% CI 0.87-1.41, p=0.424 for disease-specific survival	Age at diagnosis, SES, Charlson score, biopsy grade of tumor, year of diagnosis	

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
Zagars et al, 1998[29]	University of Texas M.D. Anderson cancer center, Retrospective Cohort study	Receiving external radiation between 1987 and 1996	Median follow-up of 42 months	1,201 men (116 African American and 1,085 White men)	With T1-T3, N0/NX, M0 (clinically localized) prostate cancer receiving definitive external-beam radiation	Overall survival			Survival curve for overall survival
Freeman et al, 2004[27]	4 academic medical centers in the Chicago area (2 private university medical centers and 2 department of veterans affairs medical centers with university affiliations), Retrospective Cohort study	Diagnosed between January 1, 1986 and December 31, 1990	Till December 31, 2000	864 patients (479 university and 385 VA)	All cases of adenocarcinoma of the prostate	Overall survival and prostate cancer-specific survival	1.75 (1.33, 2.29, P<.001) for overall survival and 1.84 (1.22, 2.79, P=.004) for prostate cancer-specific mortality	Age, Charlson comorbidity score, tumor differentiation stage, first-course treatment	
Fowler et al, 2000[12]	Veterans affairs medical center in Jackson, Mississippi, Retrospective Cohort study	Diagnosed between Jan 1, 1982 and Dec 31, 1992	Median follow-up from date of diagnosis 112 months (range 60 to 182)	524 African American and 396 White men	Diagnosed with prostate cancer	Overall survival and prostate cancer-specific survival	1.23 (0.91, 1.69), p=0.17 for cause-specific survival for stage T1b-2 cancer:	Age, Gleason score, treatment status	Survival curves for cause-specific survival for T3-4 and metastatic cancers

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
Hart et al, 1998[35]	Wayne state university, Gershenson radiation oncology center, Detroit, MI, Retrospective Cohort study	Treated from January 1980 to December 1993	Mean and median follow-up were 26 and 35 months respectively (range 1 to 171 months).	996 patients (425 Whites and 571 African American s)	Patients treated curatively with external beam irradiation for carcinoma of the prostate	Overall survival and prostate cancer-specific survival			Survival curve for cause-specific survival
Iselin et al, 1998[34]	Duke University, NC, Retrospective Cohort study	Surgery between January 1970 and December 1996	Median follow-up 4 years for overall population (n=1319) and 2.7 years for PSA era population (n=872).	1,319 patients (115 African-American and 1,204 White males)	With localized prostate cancer treated with radical perineal prostatectomy for cT1-2N0M0 prostate cancer. Prior to January 1993, each patient underwent staging pelvic lymphadenectom y and thereafter only those patients with PSA >25ng/ml and/or whose Gleason sum were 8, 9 or 10 underwent lymphadenectom y	Carcinoma-associated survival	1.29 (0.71, 2.344), p=0.4 for unadjusted carcinoma specific death, 1.215 (0.667, 2.212), p=0.52 for adjusted carcinoma specific death	Gleason sum at surgery, pathologic stage and age	

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
Berry et al, 1979[30]	Duke comprehensive cancer center, Retrospective Cohort study of a phase II protocol	Study done between May 1973 and September 1977.		88 patients	With hormone-resistant stage IV prostatic carcinoma studied according to phase II protocol which used a five-drug chemotherapy program.	Overall survival			Survival curve for overall survival
Optenberg et al, 1995[7]	US Department of Defense tumor registry, Retrospective Cohort study	Diagnosed between 1973 and 1994	Mean crude follow-up was 78.6 months (6.6 years)	1606 newly diagnose d prostate cancer patients	US Department of Defense tumor registry patients with prostate cancer	Overall survival	0.644 (0.396-1.036) for overall survival for distant stage cancer	Age, stage, grade, wait time	Survival curve for overall survival
Kim et al, 1995[31]	Eastern Virginia medical school, Norfolk, VA, Retrospective Cohort study	January 1975 to December 1989		646 patients (489 White and 157 African American men)	With histologically proved stage A2, B and C adenocarcinoma of the prostate who underwent definitive radiation therapy.	Overall survival and prostate cancer-specific survival			Survival curves for overall and prostate cancer-specific survival

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
Brawn et al, 1993[5]	Veterans administration medical center, Temple TX, Retrospective Cohort study	1969-1990, survival info determined in patients diagnosed from 1969-1985 (525 patients-382 White and 143 African American men)	5 years	861 patients with prostate cancer with survival info on 525 patients (382 White and 143 African American men)	Had histologic confirmation of prostate cancer and did not have additional malignancies that might have influenced their survival.	Overall survival			Survival curve for overall survival
Aziz et al, 1988[32]	SUNY health science center at Brooklyn and Kings county hospital center, Retrospective Cohort study	Treated between 1970 and 1983		117 patients (61 African American and 56 White)	Treated by radiation for carcinoma of the prostate	Overall survival			Survival curve for overall survival
Hussain et al, 1992[33]	State university of New York health science center at Brooklyn and Kings county hospital, Retrospective Cohort study	Treated between 1980 and 1990		670 (462 African American, 186 White and 22 other races)	Patients with histologically confirmed adenocarcinoma of the prostate treated with curative and palliative external beam radiation	Overall survival			Survival curve for overall survival

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
					therapy, surgery or both.				
Dayal et al, 1982[8]	MCV/VCU tumor registry, City of Richmond, Retrospective Cohort study	Admitted between 1968 and 1977		99 White and 292 African American patients		Overall survival			Survival curve for overall survival
Dayal et al, 1985[9]	Centralized cancer patient data system (CCPDS) that collects data from 11 comprehensive cancer centers, Retrospective Cohort study	Diagnosed between July 1977 and October 1981	till June 1984	2513 patients (1481 Whites and 1032 African Americans)		Overall survival	1.13, p=0.14	Age and SES (education and income level)	

Study	Study setting and design	Study years	Length of follow-up	Sample size	Population characteristics	Survival type	HR (95% CI)	Controlled for	KM survival curves
Powell et al, 1995[6]	Allen Park Veteran affairs medical center at Wayne county, MI, Retrospective Cohort study	Diagnosed between 1973 and 1992	5 years	358 White and 383 African American, survival analysis done on 340 patients (160 White, 180 African American)	Histologically confirmed newly diagnosed prostate cancers between 1973 and 1992 and data collected through metropolitan Detroit cancer surveillance system (MDCSS) member of SEER program	Overall survival			Survival curve for overall survival

APPENDIX B

Data abstraction form

Part I: Cover Sheet

ID Number:

Reviewer 1:
Reviewer 2:

Author(s):

Title:

Journal of Publication and date:

Peer reviewed:

Yes
No
Unknown

ID Number: Reviewer 1:
Reviewer 2:

Part II: Criteria for Selection of Articles

Studies will be selected for inclusion if all of the following are answered in the affirmative.

1. Sources for selected articles: Computerized search from Medline/Web of Science/Psycinfo/CINAHL and/or relevant articles referenced in the papers identified by computerized search.
    a. Yes
    b. No
    c. Other
    d. Unknown
2. The year of journal publication was during January 1968 – December 2007.
    a. Yes
    b. No
    c. Unknown
3. The type of study design was either a prospective or retrospective cohort study/case-control study or clinical trial.
    a. Yes
    b. No
    c. Unknown
4. The study participants had localized (stages I and II) or advanced (stages III and IV) prostate cancer.
    a. Yes
    b. No
    c. Unknown
5. Race (Caucasian/African American) was the main exposure or at least one of the exposure variables.
    a. Yes
    b. No
    c. Unknown
6. Survival (All-cause or cause-specific) was the outcome or at least one of the outcomes.
    a. Yes
    b. No
    c. Unknown
7. Article
    a. Accepted
    b. Rejected

ID Number: Reviewer 1:
Reviewer 2:

Part III: Data Extraction Form

1. Study location:
2. Study name:
3. Study type:
4. Data source:
5. Cohort characteristics:
    a. Age:
    b. Race:
        i. White
        ii. Black
        iii. Other
    c. Stage of cancer: (TNM/AJCC/Jewett)
        i. Localized
        ii. Regional
        iii. Advanced
    d. Grade of cancer or Gleason score:
        i. Grade I (well differentiated)
        ii. Grade II (moderately differentiated)
        iii. Grade III (poorly differentiated)
        iv. Grade IV (undifferentiated and unknown)
6. Number of subjects (sample size):
7. Year of prostate cancer diagnosis:
8. Length of follow-up (years):
9. Races assessed:
    a. White
    b. Black

c. Hispanic
d. American Indian
e. Asian
f. Other

10. Survival status assessed:
    a. All-cause survival
    b. Prostate cancer-specific survival

11. Other covariates assessed:

12. Covariates controlled for:
    a. Age
    b. Race
    c. Stage
    d. Grade
    e. SES (education and income level)
    f. Comorbidity
    g. Year of diagnosis
    h. Treatment
    i. Geographic area
    j. Marital status
    k. Preoperative PSA level
    l. Gleason score

13. Result:
    a. Kaplan-Meier survival curves: ----------

    b. 5-yr relative survival : ----------

    c. Hazard ratio: ----------

APPENDIX C

Case-control study questionnaire

Prostate Health Study

Instruction: Please complete the following questions to the best of your knowledge. Please check the box or fill the blanks corresponding to the appropriate response.

1. In the table below, please indicate which of your biological (blood-related) family members have been diagnosed with cancer, what kind of cancer they had, and how old they were when they were diagnosed. Also please tell us about any cancer you have had.

Relative (or self)	**Is this relative on your mother or your father's side of the family?**		**Kind of cancer**	**Age diagnosed**	**Died from cancer?**
	Mother's side	*Father's side*			
Example: Grandmother	[X]	[ ]	*Colon*	*54 Years*	*No*
Example: Uncle	[ ]	[X]	*Unknown*	*Unknown*	*Yes*
	[ ]	[ ]			
	[ ]	[ ]			
	[ ]	[ ]			
	[ ]	[ ]			
	[ ]	[ ]			
	[ ]	[ ]			
	[ ]	[ ]			
	[ ]	[ ]			
	[ ]	[ ]			

2. About how much do you weigh without shoes?
   _ _ _ _ Weight
   (pounds)
   ❑ Don't know / Not sure

3. About how tall are you without shoes?
   _ _ / _ _ Height
   (f t / inches)

- ❑ Don't know / Not sure

4. What was your weight at age 18?
   _ _ _ _ Weight
   (pounds)
   - ❑ Don't know / Not sure

5. Within the last 20 years (exclude illness):
   a. What was your: Minimum weight _ _ _ _ lbs ⇨ At what age? _ _ _ age

      Maximum weight _ _ _ _ lbs ⇨ At what age? _ _ _ age

   b. Within the last 20 years, how many times did you lose each of the following amounts of weight on purpose (exclude illness):

5-9 lbs	O 0 times	O 1-2 times	O 3-4 times	O 5-6 times	O 7+ times
10-19 lbs	O 0 times	O 1-2 times	O 3-4 times	O 5-6 times	O 7+ times
20-49 lbs	O 0 times	O 1-2 times	O 3-4 times	O 5-6 times	O 7+ times
50+ lbs	O 0 times	O 1-2 times	O 3-4 times	O 5-6 times	O 7+ times

6. On an average, how many days per week do you do moderate activities (such as brisk walking, bicycling, vacuuming, gardening or anything else that causes some increase in breathing or heart rate) for at least 30 minutes at a time?
   _ _ Days per week
   - ❑ Do not do any moderate physical activity for at least 30 minutes at a time
   - ❑ Don't know / Not sure

7. On an average, how often did you drink any type of alcoholic beverage? How many days per week, per month or per year did you drink? (Select only one response)
   _ _ days per week
   _ _ days per month
   _ _ days per year
   - ❑ Don't drink
   - ❑ Don't know/not sure

8. On those days that you drank alcoholic beverages, on the average, how many drinks did you have?
   _ _ _ _ number of drinks
   - ❑ Don't know/not sure

If you are a current or former smoker, answer the following questions and if you are a non-smoker, skip to question number 12.

9. If you are a current smoker, how long have you been smoking?
   _ _ number of years
   - ❑ Don't know / Not sure

10. Do you now smoke cigarettes every day, some days, or not at all?
    - ❑ Every day
    - ❑ Some days
    - ❑ Not at all
    - ❑ Don't know / Not sure

11. On average, about how many cigarettes a day do you smoke? (1 pack = 20 cigarettes)
    _ _ number of cigarettes
    - ❑ Varied
    - ❑ Never smoked cigarettes regularly
    - ❑ Don't know/not sure

12. On an average, when you go outside on a warm sunny day for more than one hour, how often do you stay in the shade? (this has to be considering your past practices)
    - ❑ Always
    - ❑ Most of the time
    - ❑ Sometimes
    - ❑ Rarely
    - ❑ Never
    - ❑ Don't go out in the sun
    - ❑ Don't know/not sure

13. On an average, when you go outside on a warm sunny day for more than one hour, how often do you wear a baseball cap or sun visor? (this has to be considering your past practices)
    - ❑ Always
    - ❑ Most of the time
    - ❑ Sometimes
    - ❑ Rarely
    - ❑ Never
    - ❑ Don't go out in the sun
    - ❑ Don't know/not sure

14. On an average, when you go outside on a warm sunny day for more than one hour, how often do you wear a long sleeved shirt, long pants or other clothing that reaches the ankles? (this has to be considering your past practices)
    - ❑ Always
    - ❑ Most of the time
    - ❑ Sometimes
    - ❑ Rarely
    - ❑ Never
    - ❑ Don't go out in the sun
    - ❑ Don't know/not sure

15. On an average, when you go outside on a warm sunny day for more than one hour, how often do you use sunscreen? (this has to be considering your past practices)
    - ❑ Always
    - ❑ Most of the time
    - ❑ Sometimes
    - ❑ Rarely
    - ❑ Never
    - ❑ Don't go out in the sun
    - ❑ Don't know/not sure

16. On an average, how often do you drink fruit juices such as orange, grapefruit or tomato? (this has to be considering your past practices, select only one response)
    - _ _ per day
    - _ _ per week
    - _ _ per month
    - _ _ per year
    - ❑ Never
    - ❑ Don't know/not sure

17. On an average, not counting juice, how often do you eat fruit? (this has to be considering your past practices, select only one response)
    - _ _ per day
    - _ _ per week
    - _ _ per month
    - _ _ per year
    - ❑ Never
    - ❑ Don't know/not sure

18. On an average, how often do you eat green salad? (this has to be considering your past practices, select only one response)
    _ _ per day
    _ _ per week
    _ _ per month
    _ _ per year
    ❑ Never
    ❑ Don't know/not sure

19. On an average, how often do you eat carrots? (this has to be considering your past practices, select only one response)
    _ _ per day
    _ _ per week
    _ _ per month
    _ _ per year
    ❑ Never
    ❑ Don't know/not sure

20. On an average, not counting carrots, potatoes or salad, how many servings of vegetables do you usually eat? (Example: A serving of vegetables at both lunch and dinner would be two servings.) (this has to be considering your past practices, select only one response)
    _ _ per day
    _ _ per week
    _ _ per month
    _ _ per year
    ❑ Never
    ❑ Don't know/not sure

21. On an average, how often did you have milk, either to drink or on cereal? (Include skim, no-fat, low-fat, whole milk, buttermilk, lactose-free milk, chocolate or other flavored milks) (this has to be considering your past practices, select only one response)
    ❑ Never
    ❑ 1-2 times per week
    ❑ 3-4 times per week
    ❑ 5-6 times per week
    ❑ 1 time per day
    ❑ 2 times per day
    ❑ 3 times per day
    ❑ 4 times per day
    ❑ 5 or more times per day
    ❑ Don't know/not sure

22. On an average, do you take any vitamin or mineral supplements of any kind? (this has to be considering your past practices)
    - ❑ Yes
    - ❑ No
    - ❑ Don't know/not sure

23. On an average, how long have you used multi-vitamins.? (this has to be considering your past practices, select only one response)
    _ _ months
    _ _ years
    - ❑ Don't know/not sure

24. Did you ever have a vasectomy?
    - ❑ Yes
    - ❑ No
    - ❑ Don't know / Not sure

25. Have you ever had a sexually transmitted disease like syphilis, gonorrhea, Chlamydia, genital herpes or warts?
    - ❑ Yes
    - ❑ No
    - ❑ Don't know / Not sure

26. How old are you? _ _ _Years

27. Which one or more of the following would you say is your race? (Check all that apply)
    - ❑ Non-Hispanic White
    - ❑ Hispanic White
    - ❑ Non-Hispanic Black or African American
    - ❑ Hispanic Black or African American
    - ❑ Asian
    - ❑ Native Hawaiian or Other Pacific Islander
    - ❑ American Indian or Alaska Native
    - ❑ Other [specify]_____
    - ❑ Don't know/not sure

28. What is your marital status?
    - ❑ Married
    - ❑ Divorced
    - ❑ Widowed
    - ❑ Separated

- ❑ Never married
- ❑ A member of an unmarried couple

29. What is the highest grade or year of school you completed?
    - ❑ Never attended school or only attended kindergarten
    - ❑ Grades 1 through 8 (Elementary)
    - ❑ Grades 9 through 11 (Some high school)
    - ❑ Grade 12 or GED (High school graduate)
    - ❑ College 1 year to 3 years (Some college or technical school)
    - ❑ College 4 years or more (College graduate)
    - ❑ Don't know/not sure

30. What is your current occupation?
    - ❑ Employed for wages
    - ❑ Self-employed
    - ❑ Out of work for more than 1 year
    - ❑ Out of work for less than 1 year
    - ❑ A Homemaker
    - ❑ A Student
    - ❑ Retired
    - ❑ Unable to work

31. Is your annual household income from all sources?
    - ❑ Less than $10,000
    - ❑ 10,000 to less than $15,000
    - ❑ $15,000 to less than $20,000
    - ❑ $20,000 to less than $25,000
    - ❑ $25,000 to less than $35,000
    - ❑ $35,000 to less than $50,000
    - ❑ $50,000 to less than $75,000
    - ❑ $75,000 to less than $100,000
    - ❑ $100,000 or more
    - ❑ Don't know / Not sure

VITA

Gayathri Sridhar was born in Trichy, India on May 15, 1972. She is a US citizen. Gayathri received her Bachelors degree in Medicine and Surgery from P.S.G Institute of Medical Sciences and Research, Coimbatore, India in 1995. After practicing for a few years in India, she came to the US and obtained the MPH degree from University of North Texas Health Science Center at Fort Worth, TX in 2000. Then she worked in a variety of settings including state department of health, pharmaceutical company and academia. She started the PhD program in Epidemiology at VCU in 2004. While pursuing the doctoral degree in Epidemiology, Gayathri worked as a teaching assistant and research assistant in the Department of Epidemiology and Community Health and Virginia Premier Health Plan. The she started working as a Health Information Consultant at HMC.