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Variations in prostate biopsy recommendation and acceptance confound evaluation of risk factors for prostate cancer: Examining race and BMI

Catherine M. Tangen[a,*], Jeannette Schenk[b], Cathee Till[a], Phyllis J. Goodman[a], Wendy Barrington[c], M. Scott Lucia[d], Ian M. Thompson[e]

[a] From the SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA, United States
[b] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, United States
[c] Department of Psychosocial and Community Health, The University of Washington, Seattle, WA, United States
[d] Department of Pathology, The University of Colorado Denver School of Medicine, Denver, CO, United States
[e] The Cancer Therapy and Research Center, Christus Santa Rosa Medical Center, San Antonio, TX, United States

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ABSTRACT

Background: Prostate cancer is ubiquitous in older men; differential screening patterns and variations in biopsy recommendations and acceptance will affect which man is diagnosed and, therefore, evaluation of cancer risk factors. We describe a statistical method to reduce prostate cancer detection bias among African American (n = 3398) and Non-Hispanic White men (n = 22,673) who participated in the Selenium and Vitamin E Cancer Prevention trial (SELECT) and revisit a previously reported association between race, obesity and prostate cancer risk.

Methods: For men with screening values suggesting prostate cancer but in whom biopsy was not performed, the Prostate Cancer Prevention Trial Risk Calculator was used to estimate probability of prostate cancer. Associations of body mass index (BMI) and race with incident prostate cancer were compared for observed versus imputation-enhanced outcomes using incident density ratios.

Results: Accounting for differential biopsy assessment, the previously reported positive linear trend between BMI and prostate cancer in African American men was not observed; no BMI association was found among Non-Hispanic White men.

Conclusions: Differential disease classification among men who may be recommended to undergo and then consider whether to accept a prostate biopsy leads to inaccurate identification of prostate cancer risk factors. Imputing a man's prostate cancer status reduces detection bias. Covariate adjustment does not address the problem of outcome misclassification. Cohorts evaluating incident prostate cancer should collect longitudinal screening and biopsy data to adjust for this potential bias.

1. Introduction

The identification of risk factors and preventive strategies for prostate cancer by epidemiologic and other studies has a major impact, affecting how clinicians select patients for prostate biopsy and treatment and what steps patients take to reduce their disease risk. As detectable prostate cancer is almost ubiquitous in aging men, illustrated by the 15% risk of prostate cancer in men over age 55 undergoing a 6-core prostate biopsy with low PSA and a normal digital rectal exam, biases in selecting whom to biopsy could have profound and potentially adverse implications on populations of men at risk for prostate cancer [1,2]. While seemingly a trite concept, as prostate cancer is so common and asymptomatic during a decade or more of sojourn [3,4], for a man to receive a prostate cancer diagnosis, he must be screened with PSA, recommended to undergo biopsy, and agree to have a biopsy. We previously observed that a broad range of factors affected patients' likelihood of biopsy [5]. Younger or married men, those with a family history of prostate cancer or with BPH, were more likely to undergo biopsy. A higher BMI, diabetes, or previous or current smokers were less likely to undergo biopsy. When accounted for, using the unique resource of the PCPT in which all men were recommended to undergo biopsy, we found that the magnitude and, in some cases, the direction of risk factors were significantly changed. An important example was aspirin that, without adjustment for biopsy, was associated with a 34% reduction of prostate cancer risk; by comparison, after adjustment, prostate cancer risk was actually increased by 20–23%. Following our

* Corresponding author.
E-mail address: ctangen@fredhutch.org (C.M. Tangen).

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observation, the 19,114-subject ASPREE randomized trial confirmed a 31% increased risk of cancer death in subjects receiving aspirin [6]. Unidentified confounders in observational cohorts can make it difficult to obtain unbiased estimates of risk factor – cancer associations. In a recent comparison, investigators found no significant correlation between the hazard ratio estimates reported by observational studies and randomized trials [7].

In 2015, Barrington et al examined the joint BMI and race association in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a study evaluating vitamin E and selenium for cancer prevention. No association between BMI and prostate cancer incidence was found in non-Hispanic white (NHW) men, but a positive linear trend for BMI was seen in African American (AA) participants (NWH trend $p = 0.63$, AA trend $p = 0.03$) [8]. While investigators acknowledged possible bias due to screening and election of biopsy, possible direction or magnitude was not discussed.

Because prostate cancer is highly-prevalent in aging men, if any given risk factor increases the likelihood of biopsy, even if there is no true association, men with the risk factor will appear to have increased risk simply due to the bias caused by a greater likelihood of biopsy.

Given these observations, we re-examined the relationship between race and BMI and risk of prostate cancer in SELECT, to assess whether accounting for differential biopsy referral and acceptance rates changed associations between BMI, race and prostate cancer as earlier reported.

2. Methods

Details of the SELECT trial design and results have been previously published. [9–11] From 2001–2004, 35,533 men 55 years or older ($\geq$50 for AA men) were recruited from 427 study sites in the US, Canada and Puerto Rico and randomized to selenium, vitamin E, the combination or neither in a double-blind fashion. Eligibility included a PSA less than 4 ng/ml and a normal DRE. At the time of study closure, the median follow-up was 5.5 years. Participants underwent annual PSA and DRE screening and received biopsy recommendations according to local standard of care and the participant's preference. The primary endpoint for SELECT was time from randomization to prostate cancer diagnosis.

We first evaluated whether receipt of a biopsy (regardless of outcome) varied by race and BMI. Using a proportional hazards model, we estimated the hazard ratio (HR) for each BMI and race group compared to NHW lowest BMI group, the same reference group as the original report, in terms of time to first on-study biopsy. The model adjusted for study arm, age, family history of prostate cancer and longitudinal PSA and DRE as time-dependent covariates. Men without a biopsy were censored at last contact.

Next, we evaluated the association of BMI and race with prostate cancer accounting for differential biopsy patterns. Significant differences between the originally reported associations of BMI and race and prostate cancer based on observed biopsies compared to those that mimic uniform biopsy recommendations and acceptance would suggest that detection bias is present.

For these analyses, we assumed a man who had a negative biopsy during SELECT was cancer-free for the remainder of the trial. For those without a prostate cancer diagnosis or negative biopsy, we used a man's estimated probability of prostate cancer under two scenarios to account for lack of biopsy. Because AA men could enter SELECT at 50 years versus 55 for NHW, we adjusted for age as the single covariate in our models. Although more complex models could be considered, we wanted to keep the models relatively simple to focus on the comparisons across approaches.

To estimate probability of prostate cancer for those without a biopsy we used the PCPT risk calculator [12]. In that trial, from 1994 to 1997, 18,880 eligible men were randomized to receive finasteride or placebo. The primary endpoint was period prevalence of prostate cancer at 7 years. The design [13], conduct [14] and primary results [15] have been published. Men who had not been diagnosed with prostate cancer during the trial were recommended to undergo an end-of-study prostate biopsy regardless of PSA or DRE results. Due to this unique feature, differential biopsy detection bias was minimized [16]. We used the risk calculator developed for the placebo arm [12].

The data inputs for the PCPT risk calculator are: age, PSA and DRE status within the prior year, family history, prior negative biopsy, and race. Men with larger BMI may have hemo-dilution of PSA [17]. Liang et al estimated BMI-adjusted PSA factors using PCPT data. We used adjusted PSA values in the PCPT risk calculator [18].

Our approach differed slightly from Barrington et al. [8]. NHW men in the lowest BMI category remained the reference group with the same BMI cut-points. However, incidence density ratio (IDR) is the measure of association instead of a HR from a proportional hazards model. The ID endpoint allows a man's outcome to be something other than a 0 (no cancer) or 1 (prostate cancer). The ID for a group is the sum of incident prostate cancers divided by the sum of total person-years at risk [19]. For data from an exponential distribution, the ID is an efficient estimator for the hazard parameter, but it can also more generally serve as a useful descriptive statistic for time-to-event data [20]. An ID was calculated for each of the 30 BMI (5), race (2) and age group (3) combinations, and ID ratios (IDRs) were formed using ID of NHW lowest BMI as the reference group. IDRs can be interpreted as a measure of association analogous to a HR.

After estimating ID's for each BMI, race and age cross-classification, the corresponding estimated covariance matrix of the cell-specific ratio estimates was computed via a first-order Taylor series approximation of the deviations of the estimates from their expected values [21]. Nine BMI/race IDRs adjusted for age group were estimated, along with standard errors and 95% confidence intervals. The GENMOD procedure in SAS was used to estimate IDRs by specifying Poisson regression. (SAS version 9.4).

Three approaches were used for estimating a man's ID; a standard approach and two sensitivity analysis strategies.

Standard (unadjusted) Approach: This is analogous to a proportional hazards analysis of observed incident prostate cancer where, in the absence of a diagnosis, a man is assumed to be disease free. The numerator equals 1 for a prostate cancer diagnosis; otherwise equals 0. His time at risk (denominator) is days from randomization to diagnosis or last contact.

Sensitivity analysis #1: For-cause Imputation of Biopsy Result: We estimate a man's probability of prostate cancer at his first for-cause screening value (i.e., PSA $\geq$ 4.0 ng/ml or suspicious DRE) but no biopsy. The man's ID indicator (numerator) is the estimated probability of prostate cancer, and his at-risk time (denominator) is the time to first for-cause screening. A man with a diagnosis of prostate cancer, a man with only a negative biopsy on study, or a man who had no "for-cause" screening had their ID handled the same as the Standard Approach.

Sensitivity analysis #2: Imputation for All Non-Biopsied: If a man had no study biopsy and no for-cause screening, we estimate his probability of prostate cancer when he exited the trial. Others follow sensitivity analysis #1.

For estimation of prostate cancer probability, we performed multiple imputation of the predicted probability, using the standard error provided from the PCPT risk calculator.

3. Results

There were 22,673 NHW and 3398 AA men from SELECT that were evaluable for this analysis. AA men tended to be younger (median 58 years) compared to NHW men (median 62). Other characteristics are summarized in Table 1, stratified by race and BMI. AA men had higher BMI ($p < 0.001$) than NHW men, and were more likely to be hypertensive, diabetic, and current smokers. Both hypertension and diabetes increase with BMI. The numbers of PSA and DRE screens were similar across BMI and race categories. Approximately 85% of all

Table 1
Baseline and On-study Characteristics of SELECT Participants Stratified by BMI and Race for N = 26,071 Men.

Race	Participant Factors At Study Entry	BMI Category of Subject				
		BMI 18.0–24.9	BMI 25.0-27.4	BMI 27.5–29.9	BMI 30.0–34.9	BMI 35.0–50.0
NHW	Sample size	4555 (20.1%)	6140 (27.1%)	5153 (22.7%)	5092 (22.4%)	1733 (7.6%)
AA	N (%)	638 (18.8%)	749 (22.0%)	688 (20.2%)	897 (26.4%)	426 (12.5%)
NHW	Current Smoker %	7.3%	5.5%	4.8%	4.6%	5.4%
AA		32.4%	18.7%	16.0%	12.2%	10.8%
NHW	Heavy Alcohol Use %	2.0%	2.3%	2.5%	2.0%	2.3%
AA		3.3%	2.8%	1.3%	1.9%	1.9%
NHW	Hypertension %	19.5%	25.3%	32.1%	41.7%	52.6%
AA		44.7%	43.7%	51.9%	57.2%	69.0%
NHW	Diabetes %	3.6%	4.9%	7.7%	11.9%	18.2%
AA		10.7%	14.0%	16.0%	19.8%	31.0%
NHW	Family History of Prostate Cancer %	18.7%	20.7%	20.0%	20.0%	19.8%
AA		16.3%	20.4%	18.3%	17.7%	19.7%
NHW	Prior Negative	11.3%	11.3%	10.8%	11.2%	8.8%
AA	Biopsy Before SELECT %	4.9%	7.3%	5.8%	7.4%	6.3%
Participant Factors <u>On-Study</u>						
NHW	# of DREs per Person-Year	0.89	0.88	0.87	0.86	0.82
AA		0.86	0.86	0.86	0.86	0.84
NHW	# of PSA Screens per Person-Year	1.20	1.20	1.19	1.18	1.15
AA		1.19	1.18	1.18	1.17	1.17
NHW	Median PSA just prior to biopsy	3.50	3.58	3.64	3.40	3.34
AA		3.89	3.40	3.70	3.85	3.80
NHW	% with at least 1 on-study biopsy	17.4%	17.4%	16.5%	15.1%	13.7%
AA		17.6%	20.2%	17.7%	17.5%	18.5%

NHW = non-Hispanic white, AA = African American, DRE = digital rectal exam, PSA = prostatic specific antigen, BMI = body mass index.

SELECT men had PSA testing and 70% underwent DRE annually [7]. More NHW men underwent a negative prostate biopsy *prior* to entering SELECT (range: 8.8%–11.3%) compared to AA men (range: 4.9%–7.4%), suggesting more intensive pre-trial screening in the NHW group.

Table 2 provides the likelihood of getting a prostate biopsy by race and BMI. AA men were more likely to undergo an on-study biopsy, but no correlation with BMI. In the NHW group, the highest two BMI groups were significantly less likely to undergo a biopsy compared to the lowest BMI group. After accounting for age, family history and longitudinal PSA values and digital rectal exam status, race and BMI played a role in who was recommended for and accepted a prostate biopsy.

In Table 3 we provide the number of prostate cancer diagnoses and person-time at risk for each BMI and race group. In column 3, the covariate adjusted BMI and race HRs for incident prostate cancer from the Barrington et al report show the positive linear trend between BMI and prostate cancer in the AA group (p = 0.03), but not in the NHW group (p = 0.63) [8]. In column 4, the same model is adjusted for only age group to have a comparator for our IDR analysis. Columns 5–7 report the IDRs using the Standard Approach and 2 sensitivity analyses. As expected, the corresponding HRs (column 4) and Standard Approach IDRs (column 5) are very comparable and found an *inverse* linear association between BMI and prostate cancer in the NHW group (p = 0.035), and among AA men there was a higher risk of prostate cancer in the top four BMI groups but no obvious linear trend (IDRs range 1.45–1.60, trend p = 0.15).

Imputing at the first for-cause screening to mimic uniform prostate cancer ascertainment across groups (sensitivity analysis #1, column 6), AA and NHW men in the lowest BMI group (< 25.0) have similar risk of prostate cancer (IDR = 0.99). AA men in BMI groups 2–5 have elevated risk of prostate cancer (IDRs 1.32, 1.21, 1.25, 1.30, respectively) compared to NHW in the lowest BMI group but no linear trend is apparent (trend p = 0.24), and IDRs are closer to the null compared to the Standard Approach. NHW men had a significant *inverse* association between BMI and prostate cancer (trend p = 0.004). The relationship between BMI and prostate cancer was the opposite direction for NHW men. Fig. 1 shows the trends for the unadjusted and for-case screening adjustment by race and BMI group.

Imputing for everyone without an on-study biopsy (sensitivity analysis #2, column 7) the inverse linear trend in the NHW group disappears (trend p = 0.54), suggesting biopsy bias appears to be operational in the NHW group too, and most IDR estimates for NHW and AA BMI groups moved closer to the null compared to "for-cause" only imputation (sensitivity analysis #1).

Because the multiple imputation approach had almost no effect on confidence intervals, only the single imputation results are reported.

Table 2
Time to First Biopsy Regardless of Prostate Cancer Outcome in a Cox Regression Model, Stratified by Race and BMI Category.

Risk Factor	Time to First Biopsy, Censor at Last Contact Date	
	Hazard Ratio* (95% CI)	p-value*
Race x BMI Classification		
NHW BMI 1	*Reference group 1.0*	
NHW BMI 2	1.02 (0.98, 1.07)	0.35
NHW BMI 3	0.98 (0.94, 1.03)	0.40
NHW BMI 4	0.90 (0.86, 0.94)	< 0.0001
NHW BMI 5	0.81 (0.76, 0.87)	< 0.0001
AA BMI 1	1.19 (1.09, 1.30)	0.0001
AA BMI 2	1.17 (1.07, 1.27)	0.0004
AA BMI 3	1.09 (1.00, 1.20)	0.049
AA BMI 4	1.03 (0.95, 1.12)	0.48
AA BMI 5	1.15 (1.03, 1.28)	0.015

Grp 1: BMI 18.0–24.9, Grp 2: BMI 25.0–27.4, Grp 3: BMI 27.5–29.9, Grp 4: BMI 30.0–34.9, Grp 5: BMI 35.0–50.0.

* Adjusted for selenium, vitamin E supplement arms, age, family history and longitudinal PSA and DRE status.

Table 3
Adjusted Incidence Density Ratios and Adjusted Hazard Ratios from the SELECT Trial, Modeling Time to Prostate Cancer.

Col.	1	2		3	4	5	6	7
		Observed Incident Cases and Person Years at-risk^^		Hazard Ratio from original JAMA Oncology, Barrington et al**	Hazard Ratio from Proportional Hazards Model*	Standard Approach Incidence Density Ratio*,	Sensitivity Analysis #1: Imputing at 1st For-Cause Screening *	Sensitivity Analysis #2 Imputing at 1st For-Cause screening or End of Study*
Race	BMI Group	*Prostate Cancer (N)*	PY	HR (95% CI)**	HR* (95% CI)*	IDR* (95% CI)*	IDR* (95% CI)*	IDR* (95% CI)*
NHW	1 (ref)	289	24,599	1.0	1.0	1.0	1.0	1.0
	2	438	33,194	1.12 (0.97, 1.30)	1.12 (0.97, 1.30)	1.12 (0.97, 1.30)	1.09 (0.96, 1.23)	1.07 (0.99, 1.16)
	3	333	27,802	1.04 (0.89, 1.22)	1.02 (0.87, 1.19)	1.02 (0.87, 1.19)	0.99 (0.87, 1.13)	1.02 (0.94, 1.11)
	4	299	27,572	0.96 (0.82, 1.13)	0.92 (0.78, 1.08)	0.92 (0.78, 1.08)	0.90 (0.79, 1.03)	1.02 (0.94, 1.11)
	5	94	9,284	0.94 (0.74, 1.19)	0.87 (0.69, 1.10)	0.87 (0.69, 1.10)	0.84 (0.69, 1.01)	1.11 (0.99, 1.24)
Linear Trend Across NHW BMI Groups				P = 0.63	p = 0.035	p = 0.035	p = 0.004	P = 0.54
AA	1	39	3167	1.28 (0.91, 1.80)	1.14 (0.81, 1.59)	1.12 (0.80, 1.57)	0.99 (0.74, 1.32)	1.02 (0.85, 1.23)
	2	63	3797	1.67 (1.27, 2.21)	1.53 (1.16, 2.01)	1.51 (1.15, 1.98)	1.32 (1.04, 1.67)	1.17 (0.99, 1.37)
	3	57	3531	1.64 (1.23, 2.19)	1.47 (1.10, 1.95)	1.45 (1.09, 1.93)	1.21 (0.94, 1.55)	1.14 (0.96, 1.35)
	4	73	4593	1.68 (1.29, 2.18)	1.47 (1.14, 1.90)	1.46 (1.12, 1.89)	1.25 (1.00, 1.57)	1.17 (1.01, 1.36)
	5	37	2116	1.90 (1.34, 2.70)	1.63 (1.15,2.29)	1.60 (1.14, 2.26)	1.30 (0.95, 1.77)	1.28 (1.05, 1.57)
Linear Trend Across AA BMI Groups				P = 0.03	p = 0.15	p = 0.15	p = 0.24	P = 0.092

BMI Categories: Grp 1: 18.0–24.9, Grp 2: 25.0–27.4, BMI 27.5–29.9, BMI 30.0–34.9, BMI 35.0–50.0.

** Reported from paper, adjusted for age, education, diabetes mellitus, family history of prostate cancer, current smoking and trial supplement arm, PY = person-years at risk, HR = hazard ratio, IDR = incidence density ratio, AA = African American, NHW = Non-Hispanic White.

* Adjusted for age group.

^^ time to prostate cancer or last contact date summed across race and BMI categories.

4. Discussion

One could argue that differences in physician recommendations for biopsy or patient acceptance of biopsy are completely appropriate. For the former, they may be based on unmeasured risk factors (e.g., subtleties in DRE or risk of biopsy complications) and, for the latter, reflecting patient preferences. Unfortunately, these biases will affect the interpretation of other risk factors for prostate cancer. We previously reported that, accounting for PSA and DRE screening, men on SELECT with co-morbid conditions were less likely to undergo a biopsy [7]. These health conditions were more prevalent among AA men, and the prevalence often correlated with increasing BMI. Although screening was relatively uniform for all men on SELECT, it appears that screening *prior to* SELECT was more intensive among NHW men perhaps causing a delay in the conduct of on-study biopsies in the NHW group. AA men also had a greater risk of dropping out of the study early [22]. A

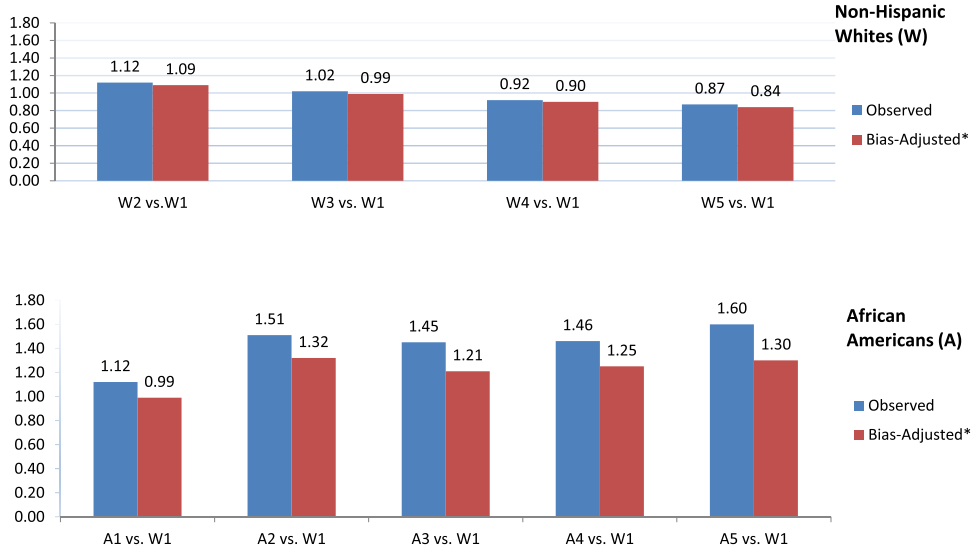

Fig. 1. Incidence Density Ratio Estimates for Prostate Cancer Incidence, Stratifying on Race and BMI Categories, Lowest Non-Hispanic White BMI Group (W1) is the Reference Group.
*Bias-adjusted for those with elevated PSA or suspicious DRE but no biopsy (sensitivity analysis #1).

number of these factors could differentially impact disease assessment, and it is difficult to anticipate the direction of the net bias.

The PCPT risk calculator was developed externally to SELECT, incorporating end of study biopsy results that minimized detection bias. It has been externally validated in a number of cohorts. [23,24] An additional feature of the PCPT risk calculator is that it calculates a man's risk of high grade prostate cancer. By applying the methods described in this paper, an investigator could use that endpoint instead of or in addition to all incident prostate cancer. Other prostate cancer risk calculators are based on groups of men who were recommended for and accepted biopsy based on abnormal DRE or elevated PSA. Use of these other risk calculators would propagate the biopsy detection bias. We evaluated the impact of substituting the probability of prostate cancer for men who did not undergo prostate biopsy on the association of BMI, race and prostate cancer. Our results suggest that the HRs from the multivariate PH model from the original Barrington et al paper [8] over-estimate the risk of prostate cancer in AA men with higher BMI, and there is no evidence of a linear trend. However, we find that AA men with a BMI $\geq$ 25.0 have a 14–30% greater risk of prostate cancer compared to NHW men with BMI $<$ 25.0, or alternatively, AA and NHW men with a BMI $<$ 25 have similar risk of prostate cancer.

There are possible limitations to this study. Although we adjust for age group, there may be other useful covariates. The Barrington analysis [8] adjusted for age, education, diabetes mellitus, family history of prostate cancer, current smoking status, and SELECT trial arm. However, such extensive covariate control has the potential to increase net bias even when the covariates would have been confounders under perfect classification, and even if covariates are determinants of classification. Bias due to misclassification cannot be adequately dealt with by the methods used for control of confounding." [25]

We defined a for-cause screening rule to impute probability of prostate cancer. The PSA cutoff for biopsy level of 4.0 ng/mL could be disputed. We selected this level as it was the cutoff used in SELECT and PCPT and the most commonly-employed threshold for biopsy recommendation. Other for-cause PSA cutoffs could be employed to best match the screening patterns of a given cohort.

There are several approaches for missing cohort data. Structural modeling approaches to selection bias have been proposed where "selection bias" can encompass bias from inappropriate selection of controls, bias from differential loss-to-follow-up, non-response bias, among others [26–28]. Sometimes correction can be accomplished by a generalization of inverse-probability weighting or stratification, assuming outcomes are missing at random (MAR): missingness can be modeled using some observed covariates. There are situations in which MAR is questionable, and the missingness may be non-ignorable (NI): the missing data mechanism is related to the missing values and cannot be modeled with observed covariates. Some aspects of differential biopsies may introduce a NI pattern of missingness. Our method using an external calculator to estimate prostate cancer probability for those without a biopsy is one approach to minimize the NI missing data challenge. We do not use the observed covariable correlations with prostate cancer from SELECT to calculate biopsy outcomes as this would not reduce bias.

Our analysis identified factors that are differentially distributed by race and BMI. Most (e.g., smoking, hypertension, and diabetes) are related to life expectancy (and the perceived potential benefit of an earlier detection of prostate cancer, and its subsequent treatment). These factors could also be related to risk of biopsy complications. The source of the bias could be the patient's decision, the treating physicians' decision, or both. These biases likely confound previous attempts to link obesity with the risk of prostate cancer. Our analysis confirms AA men's higher risk of prostate cancer, but, after accounting for differential detection bias, the role of BMI is not as clear.

Differential biopsy ascertainment may play a role in evaluating the association of many potential risk factors and prostate cancer including diabetes, statin use, vitamin D levels and physical activity, to name a few. To analytically minimize this differential detection bias, cohorts need to collect more detailed individual screening and biopsy data.

Author contribution

Title: A Method for Reducing the Impact of Differential Prostate Biopsy Bias Using an Example of Race and Body Mass Index with Prostate Cancer Incidence

Authors: Catherine M. Tangen, Jeannette Schenk, Cathee Till, Phyllis J. Goodman,

Wendy Barrington, M. Scott Lucia, Ian M. Thompson

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All co-authors contributed to the methods, conclusions and writing of this paper. They have all made scientific contributions, and they have reviewed the most current version of the manuscript.

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Declaration of Competing Interest

The authors declare no potential conflicts of interest.

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