1. a. Full Title:

Contributions of Hypertension to Prostate Cancer Risk and Racial Disparities.

b. Abbreviated Title (Length 26 characters):

Hypertension and Prostate Cancer.

2. Writing Group:

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3. **Timeline:** Writing and analysis to begin immediately.
4. Rationale

African-American men (AAM) are disproportionately burdened by both hypertension and prostate cancer (PCa) and their complications. We propose to investigate whether hypertension influences the risk of PCa, especially lethal and fatal disease, overall and in particular in AAM, in ARIC.

Hypertension: Clinically, hypertension may be defined as that level of blood pressure at which the institution of therapy reduces blood pressure–related morbidity and mortality [1]. Current clinical criteria for defining hypertension generally are based on the average of two or more seated blood pressure readings during each of two or more outpatient visits [2]. A recent classification [3], recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is a common occurrence among the elderly.

Racial disparities in prostate cancer: Prostate cancer remains the most common form of cancer affecting men in the Western Hemisphere. In 2017, 161,360 new cases of PCa are expected to occur in the United States and 26,730 deaths are expected nationwide [4]. The mortality rate is 130% higher among AAM than Caucasian American men (CAM) [5, 6]. This trend is not new nor changing, as data from 1975 to 2007 indicates that the higher mortality rates of PCa among AAM has not narrowed when compared to CAM [7].

The disparity in PCa outcomes within the United States has been attributed to several factors [8-10], including differences in socioeconomic status and lifestyle exposures, access to healthcare, racial and ethnic discrimination, language and cultural barriers, and a delayed disease diagnosis in socioeconomically deprived communities [11]. These may contribute to or compound health delivery disparities as AAM, relative to CAM, are less likely to undergo primary definitive treatment when grouped by National Comprehensive Cancer Network-based risk groups, have more advanced disease when first diagnosed with cancer, show faster tumor volume growth, present with higher plasma prostate specific antigen (PSA), and exhibit more adverse pathological findings in radical prostatectomy specimens [12], when compared to CAM [reviewed in [13] and [14]].

Since these data are related to the biology of PCa, they suggest that cellular and molecular mechanisms contribute to PCa health disparities [10, 11, 14, 15]. An unmet need on this matter is our understanding of the biological basis of aggressive disease in minorities. Increased knowledge will provide researchers and clinicians with better prognostic and therapeutic tools to reduce the disproportionate effects of PCa in AAM.

Association between hypertension and prostate cancer risk: Arterial hypertension has been associated with increased risk of PCa in some but not all studies based on recent meta-analyses [16]. Some studies support that elevated blood pressure is associated particularly with prostate cancer that is advanced at diagnosis [17], including metastatic to the bone [18], and with prostate cancer mortality [18, 19]. With respect to systolic and diastolic blood pressure, among the few cohort studies that have been conducted, results have not been consistent. For example, blood pressure measured at baseline was not associated with prostate cancer mortality in a UK Whitehall cohort study of almost 18,000 men with 40 years of follow-up [20]. In the Swedish Construction Workers cohort, quintiles of both systolic and diastolic blood pressure were
inversely associated with total prostate cancer incidence, but were possibly positively associated with more aggressive prostate cancer [21]. Both of these cohort studies used baseline blood pressure only, which may have led to measurement error of usual blood pressure over long-term follow up, especially for men in the Swedish study in which blood pressure was measured when the men were on average 35 years old. Taken together, the literature remains somewhat inconsistent. Use of data with repeated measures over time, including blood pressure taken by trained staff, and analysis conducted separately by disease aggressiveness may help clarify these associations.

**Tumors and hypertension share a common biological pathways:** Shared biological pathways have been discussed previously [22]. 1) Inositol triphosphate and cytosolic calcium are increased both in hypertension and in the early stages of cell proliferation. 2) Carcinogen binding has been seen in the lymphocytic DNA of hypertensive patients. 3) Angiotensin II, catecholamines, vasopressin, and insulin are neurohormones that are involved in blood pressure regulation and are also mitogenic. For instance, angiotensin II, not only induces hyperplasia or hypertrophy in cultured vascular smooth muscle cells, it does so in other tissues of epithelial origin [23]. Particularly relevant to our proposed study, angiotensin II stimulated proliferation of PCa cells by regulating cross-talk between stromal cells and cancer cells [24]. The available evidence therefore suggests the involvement of the angiotensin system in hallmarks of cancer. We postulate that increase of our knowledge of the shared biological basis underlining prevalence hypertension and tumorigenesis will help us to identify novel molecular biomarkers and therapeutic targets for PCa.

**Anti-hypertensives and prostate cancer:** Study of the effect of anti-hypertensive drugs on risk of cancer is a matter of current discussion. This is illustrated by a recent meta-analysis of antihypertensive drug trials showing studies reporting on cancer, including PCa, as a safety outcome [25]. With respect to observational studies, according to a study done in Sweden there was no clear association between the use of antihypertensive drugs and PCa overall, however, captopril [angiotensin converting enzyme (ACE) inhibitor] users showed a lower risk of subsequent PCa [26]. The results of a Canadian study suggest that beta blockers (BBs) and long-term use of angiotensin blockers (ABs) may prevent PCa whereas calcium channel blockers or ACE inhibitors do not influence PCa risk [27]. With respect to in vitro studies, angiotensin-converting enzyme inhibitors and angiotensin I receptor (AT1R) antagonists – that block AngII production or action have beneficial effects on various aspects of cancer, including tumor progression, vascularization and metastasis [28]. When taken together, these studies indicate that different classes of antihypertensive drugs may have different associations with prostate cancer.

**Hypertension, blood pressure, and prostate cancer in ARIC:** The association between hypertension as one of the components of metabolic syndrome and PCa has been studied in the ARIC study previously with cases through 2000 [29]. High (vs. low) blood pressure was defined as ≥130 mmHg systolic or ≥85 mmHg diastolic or self-reported antihypertensive medication use. 37.4% of the cohort was classified as having high blood pressure. No association was observed. However, this association was not studied separately in AAM and CAM, the study only addressed total PCa not disease with an aggressive phenotype (information on lethal and fatal
PCa is now available), the number of total PCa cases was small (385 cases through 2000; now there are 834 cases with follow-up through 2012). Also, particular classes of drugs used to treat hypertension were not studied in association with PCa.

Thus, to follow-up on that prior work, we propose to study the association of a) diagnosed hypertension (including use of an anti-hypertensive drug), b) blood pressure among those not taking an anti-hypertensive drug, and c) use of particular classes of antihypertensive drugs is associated with total, lethal, and fatal PCa overall and separately in AAM and CAM.

5. Main Hypothesis/Study Questions:

**Overarching hypothesis:** Hypertension is associated with an increased risk of PCa especially with an aggressive phenotype, and that this association is stronger in AAM than CAM (e.g., effect modification). Alternatively, we hypothesize that the association between PCa and hypertension is the same in both AAM and CAM, but the higher prevalence of hypertension in AAM results in a greater public health impact in AAM.

**Specific Aims:**

Among men participating in ARIC, we will assess:

**Aim 1:** Whether diagnosis of hypertension is associated with risk of total, lethal, and fatal PCa overall and in AAM and CAM.

**Aim 2:** In men without a diagnosis of hypertension, whether blood pressure (normal, pre-hypertension, hypertension) is associated with risk of total, lethal, and fatal prostate cancer overall and in AAM and CAM.

**Aim 3:** Whether use of anti-hypertensive medications (any and by class) is associated with risk of total, lethal, and fatal PCa overall and in AAM and CAM.

If we observe a positive association between hypertension and PCa risk, we will

- Using competing risk models, we will estimate the absolute risk of total, lethal, and fatal PCa in men with and without a diagnosis of hypertension separately in AAM and CAM.

If we observe a positive association between hypertension and PCa risk, but the association does not differ by race, to address the alternative hypothesis, we will

Estimate the partial population attributable risk percent (PAR%) for a diagnosis of hypertension and PCa separately in AAM and CAM.

**Relevance:** If our hypotheses are borne out, our findings would support the development of tailored approaches to the prevention and control of hypertension in AAM, including to decrease the disproportionate burden of PCa with a lethal phenotype in the African-American community.
Our team, which includes laboratory scientists, would pursue studies with further focus on identification, validation, and experimental physio-pathological assessment of potentially relevant biomarkers. Also, we will pursue identification of molecular targets for anti-hypertensive driven PCa prevention. Our study has the promise to advance minority-specific precision medicine in PCa. Eventually, these studies may lead to the identification of innovative primary and secondary prevention measures for minority populations.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: Prospective cohort study design

Study population: Men in ARIC. Inclusion/exclusion criteria: We will use the 2012 PCa case file, which has exclusions for history of cancer at baseline and for lack of consent for non-CVD research.

Outcome variables: We will use the 2012 PCa case file. It includes incident, first primary, invasive PCa cases ascertained from after baseline to 2012. Incident cases were ascertained by linkage with state cancer registries in Minnesota, North Carolina, Maryland and Mississippi, and supplemented by active surveillance of the cohort, which includes recording of hospital discharge codes for all participants. The 2012 case file also includes deaths from PCa as the underlying cause from baseline to 2012 (irrespective of whether the death from a first or subsequent primary), which were ascertained from death certificates. The 2012 case file also includes lethal prostate cancer, which is defined as diagnosis with an incident first primary prostate cancer that was metastatic or that resulted in death.

Exposure Variable: Hypertension will be defined from measured blood pressure (Visits 1-4) or use of anti-hypertensive drugs (as described using variables HYPERET04 and HYPERT05 in exam derived variable dictionaries.

Covariates: Covariates will include baseline demographics (age, race, study site, education) and Visit 3 family history of PCa (only time reported); Visit 1-4 anthropometrics (measured weight, height, waist hip circumference, calculated BMI), lifestyle (smoking, inactivity), history of diabetes, history of hypercholesterolemia, use of statins drugs, aspirin, and non-aspirin NSAIDs, use of and access to care.

Statistical analysis

We will begin follow-up at baseline and end on 12/31/2012. We will use Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence interval (CI) of total PCa, lethal, and fatal PCa associated with hypertension measures. We will repeat these analyses stratified by race. In model 1, we will adjust for age, race*field center, and education. In model 2, we will additionally adjust for purported PCa risk factors: height (continuous), updated cigarette smoking status (never, former smoker quit 10+ years ago, recent smoker [current or quit <10 years ago]), obesity (BMI [updated, continuous], waist [updated, continuous]), physical activity (quintiles of leisure index), updated history of diabetes, and family history of PCa (Visit 3 information, yes, no,
unknown). We will also determine whether other covariates may be confounders including history of hypercholesterolemia, and use of statins drugs, aspirin, and non-aspirin NSAIDs. Because access to care may determine whether a man is screened for high blood pressure and is prescribed an anti-hypertensive drug, we will stratify by variables indicative of use of and access to care.

If we observe a positive association between hypertension and PCa risk, we will use competing risk models to estimate the absolute risk of total, lethal, and fatal PCa in men with and without a diagnosis of hypertension separately in AAM and CAM. We will use two approaches (1) a cause-specific hazard modeling to estimate cause-specific hypertension effects on PCa in the presence of other substantial competing events (death, CVD), and (2) a subdistribution hazard approach (Fine-Gray) to estimate hypertension effects on cause-specific incidence curves.

With 834 cases and about 6,600 men, if the prevalence of hypertension is 37%, then for a 2-sided test with alpha=0.05 and power=80%, we can detect as statistically significant an RR of incident total prostate cancer of 1.27 or greater overall and 1.75 in AAM and 1.34 in CAM. For lethal or fatal disease overall the minimum detectable RR is 1.95. Thus, we likely have sufficient power to detect moderate associations or larger overall and in AAM and CAM. We will not have sufficient power to detect modest associations. By race, we will only be able to detect large association with lethal/fatal disease.

The counts for incident total, lethal and fatal PCa through 2012 demonstrate enough power to work on our proposed aims and also serve to be appropriate when subgroup analyses (e.g., by race) is carried out. The counts have a good power demonstrating a difference in incidence of total, lethal and fatal PCa between hypertensive AAM and hypertensive CAM. Also as almost a third of the ARIC participants who are hypertensives are on anti-hypertensive medications [30] there is enough power to carry out the third aim of our proposal finding the association in total, lethal and fatal PCa.

7. a. Will the data be used for non-CVD analysis in this manuscript? Yes

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? Yes

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? No
8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the website at: http://www.cscs.unc.edu/ARIC/search.php

Yes

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)? Proposal # 1078

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes (ancillary studies to ascertain cancer cases)

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* 2011.07, 1995.04)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscs.unc.edu/ARIC/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu.
References