

SPECIFIC AIMS

Prostate cancer (CaP) is the leading non-cutaneous cancer in US men¹. African Americans (AA) suffer from the highest rates of carcinoma of the prostate (CaP) in the world, with an average (and growing) annual incidence rate of 165 per 100,000 in the period 2004-2008 and 229 per 100,000 in the period 2006-2010^{2,3}. The International Agency for Research on Cancer (IARC) GLOBOCAN program estimates that CaP is also the leading cancer in terms of incidence and mortality in men from Africa and the Caribbean⁴. Therefore, men of African descent around the world suffer disproportionately from CaP compared to men of other races or ethnicities⁵. IARC also estimates that CaP is a growing problem in Africa, with a predicted near doubling of CaP deaths from 55,522 in 2010 to approximately 105,758 deaths by 2030¹, double the number that will be diagnosed in the US in 2030. Furthermore, AA men experience the highest rate of aggressive CaP and CaP-specific mortality of any ethnic group in the US¹. Our understanding of this disparity remains limited. The majority of Sub-Saharan African (SSA) CaP cases are diagnosed with aggressive disease, often at late (usually incurable) stages^{6,7}. In both SSA and AA men, this pattern may be due to a combination of biological aggressiveness and late detection. Thus, there may be common features of CaP etiology in men of African descent that may explain observed mortality patterns. Knowledge gained from studies of CaP in SSA may in turn improve our understanding of aggressive CaP in men of African descent around the world, including AA.

Despite the clear public health implications of CaP in men of African descent, there have been few consistent associations of exposures, genetic susceptibility loci, or environmental factors with CaP etiology in AA. In contrast, CaP has the highest heritability of any major cancer^{8,9}, and many genetic susceptibility loci have been identified in men of European and Asian descent. Numerous genome-wide association studies (GWAS) have been reported (none in exclusively African populations), and most of the GWAS-identified loci have not been replicated in AA. There is a pressing need to identify African-specific alleles and thereby to elucidate the etiology of CaP in AA men. Furthermore, the development of infrastructure that can address CaP genetics in Africa will help build research capacity in Africa to broadly foster cancer research.

To better understand the etiology of CaP in African men, we have initiated a large, multicenter consortium known as “Men of African Descent and Carcinoma of the Prostate” (MADCaP). Using resources of this consortium, we propose to undertake a multicenter study of CaP in SSA addressing the following Aims:

Specific Aim 1: Genetic Susceptibility: Discover novel CaP loci and validate known CaP loci in African men to provide new information about the genetic etiology of CaP.

Aim 1.1. Undertake a genome-wide association study of CaP etiology and aggressiveness in a Pan-African sample set representative of the ancestral origin of African Americans.

Specific Aim 2. Population Genomics: Evaluate how population differentiation and the recent evolutionary history of African and African American populations inform the underlying reasons for the high rates of CaP in African Americans.

Aim 2.1. Identify variants with large allele frequency differences between continents and populations (including ancestry informative markers, AIMS), and evaluate whether these variants are correlated with increased CaP risk and aggressiveness in African and African American men.

Aim 2.2. Evaluate how the evolutionary history of different genomic regions, including genetic “hitchhiking” between CaP susceptibility alleles and locally adaptive alleles at closely linked loci, contributes to population differences in CaP risk in men of African descent.

A synopsis of the approach to be taken is presented in **Table 1**.

Table 1. Overview of Approach

	Specific Aim 1	Specific Aim 2
Sample	Split sample: Phase I discovery set (N=2,099 CaP cases, 2,493 controls); Phase II validation set (N=2,099 CaP cases, 2,493 controls)	N=9,184 CaP Cases and Controls; publicly available genomic data; and whole genome sequence data in multiple African populations from the Tishkoff Lab
Outcomes	CaP case status; CaP aggressiveness metrics	Ethnic population structure; development of ancestry marker panels
Predictors; Confounders	Candidate variants; center, ancestry, age, population, languages spoken	Candidate (GWAS) loci; Gene flow between populations (admixture) population-specific patterns of linkage disequilibrium
Analysis Methods	Contingency table analysis, logistic regression	Population genetic methods that include tests of neutrality and scans of natural selection.