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TITLE: Contribution of AMACR and Phytanic Acid to Prostate Cancer Risk
Among African Americans in North Carolina

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14. ABSTRACT: Several lines of evidence have suggested genetic and dietary differences may be important in PCa, particularly among AA (African American) men. In this study, we aim to test the hypothesis that mutations/sequence variants in the AMACR gene, and dietary intake of foods rich in phytanic acid, increase the risk to PCa among AA men. We will conduct a population based study by ascertaining 250 AA men who have PCa and 250 race, age, and county-matched controls from eight counties of North Carolina. We are in the process of carrying out the 1st task, study subject recruitment, until year 2008. In the past funding year, we have obtained IRB approval and started subject recruitment. We have also contacted other investigators to explore the possibility of expanding our study area. Additionally, we have also submitted two additional grant applications to investigate genetic and environmental risk factors based on this study population. The results from this study, as well as other future studies based on this study population, will greatly increase our knowledge for potential risk factors and suggest potential preventive strategies for prostate cancer in AA men.					
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Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4-6
Key Research Accomplishments.....	6
Reportable Outcomes.....	6-7
Conclusion.....	7-8
References.....	N/A
Appendices.....	N/A
Supporting Data.....	N/A

Introduction

Several lines of evidence have suggested genetic and dietary differences may be important in PCa, particularly among AA men. Specifically, the *AMACR* gene has been implicated by gene expression profiling of tumors, as well as in genetic studies among mostly Caucasian American subjects. Additionally, the *AMACR* gene happens to be required for the metabolism of phytanic acid, which is obtained in the human diet almost exclusively in red meat and dairy products, both of which have been implicated in PCa risk. In this study, our primary goal is to test the hypothesis that mutations/sequence variants in the *AMACR* gene increase the risk to PCa among AA men. Our secondary goal is to test the hypothesis that PCa risk is increased by dietary intake of foods rich in phytanic acid, and that this risk is further increased due to alterations in *AMACR*. To test these hypotheses, we will conduct a population based study by ascertaining an additional 250 AA men who have PCa and 250 race, age, and county-matched controls from eight counties of North Carolina. These can be combined with our existing pilot study population, for a total of ~550 AA men. Our primary aim is to identify the AA spectrum of mutations and sequence variants in *AMACR* and assess their contribution to PCa. Our secondary aim is to preliminarily assess the contribution to PCa risk related to dietary intake of foods rich in phytanic acid, and then explore the interaction effect between *AMACR* and phytanic acid.

Body

The first 25 months (15 Jan 2006 - 14 Feb 2008) of this study will be mainly focused on study subject recruitment. We spent the first 8 months (Jan-Aug) of the funding period working to obtain regulatory approval from the IRB of the USAMRMC (DOD). We then spent two months (Sept-Oct) obtaining approval from the North Carolina Cancer Registry Committee and our local IRB at Wake Forest University School of Medicine, thus allowing us to begin recruitment. The cancer registry began identification of cases for our study in early November, and then reported the first batch of cases to us in late November. We began to recruit these subjects in early December. We hired and trained a new study interviewer in early-mid January, and then enrolled our

first subjects in late January 2007. Through the reporting period ending February 14, 2007, we have recruited 20 cases via The North Carolina Central Cancer Registry, per inclusion and exclusion criteria.

Because of the late start in subject recruitment due to IRB delays, we have also contacted the South Carolina Cancer Registry to discuss the possibility of expanding our study area in case we cannot meet our recruitment goal within study timeline. However, we are currently focused on optimizing our recruitment in North Carolina. The specific accomplishments associated with each task in the Statement of work are detailed in the following section.

Statement of Work

Task 1. To recruit 250 AA men who have PCa and 250 race, age, and county-matched controls from eight counties of North Carolina, in a population based study. These can be combined with our pilot study population, for a total of ~550 AA men. (Months 1-25; 15 Jan 2006 - 14 Feb 2008)

1. We obtained IRB approval from the USAMRMC, the NC Cancer Registry, and the WFU IRB. We then began our subject recruitment starting in December 2007.
2. We identified 20 cases via The North Carolina Central Cancer Registry (NCCCR), per inclusion and exclusion criteria. We expect to receive information for NCCCR identified prostate cancer cases every 3 weeks until we meet our recruitment goal. According to the cancer registry, the number of cases identified each month should steadily increase as more hospitals and physicians offices participate in reporting cases.
3. We hired and trained a new study interviewer.

4. Four subjects have been enrolled as of 14 Feb 2007. Several additional subjects have been scheduled to participate in this study. Per our protocol, we have mailed follow-up letters and phone calls to the remaining cases.

Tasks 2, 3, and 4, will start after all study subjects have been recruited (task 1) during the 3rd year of this study.

Task 2. To identify sequence variant/mutation spectrum of the AMACR gene in AA men (15 Feb 2008 - 14 Apr 2008).

Task 3. To genotype mutations/sequence variants in AMACR among AA men and evaluate their contribution to and association with PCa (15 Apr 2008 - 14 July 2008 Months 26-28)

Task 4. To measure serum levels of phytanic acid and intake of dairy products and meat consumption for each subject, and test whether the these levels increase the risk to PCa among AA men (15 July 2008 - 14 Jan 2009)

Key Research Accomplishments

- Obtained regulatory approval
- Hired and trained new staff
- Initiated subject recruitment

Reportable Outcomes

We have applied two other grant applications based on this study in an attempt to make good use of the effort we have invested in the start-up of this study.

The first grant, “The COX-2/PGE₂ axis as a potential biomarker for cancers”, was submitted to the National Cancer Institute in response to PAR-06-294, Small Grants Program for Cancer Epidemiology (R03). We hypothesized that there are variations in COX-2/PGE₂ axis in the general population, and these variations will influence individual risk to cancer initiation and progression and serve as a biomarker for cancers. We proposed to measure several critical steps of COX-2/PGE₂ cascades in PBMCs collected from 150 study subjects which are a subset of the study population collected in our DOD funded study. The results from this proposed study will provide us with good biomarker candidates for testing in a large-scale prospective study for risk of cancer development and progression.

The second grant, “Dietary fatty acids and genetic variations in fatty acid metabolism/signaling and prostate cancer risk in African Americans” was submitted to the American Institute for Cancer Research, Investigator Initiated Grants. In this proposal, we hypothesize that genetic variations in ω -3/-6 PUFA metabolism and signaling pathways, as well as their interactions with dietary intake of ω -3/-6 PUFAs, affect risk to prostate cancer. We propose to measure serum levels of ω -3 and ω -6 PUFAs in 250 African American (AA) men who have PCa and 250 race, age, and county-matched controls, all of which will be collected in our DOD funded study. We also proposed to genotype the haplotype-tagging SNPs (htSNPs) in critical genes of the ω -3/-6 PUFA metabolism and signaling pathways, and to evaluate the association of these htSNPs with PCa risk alone, or their interaction effects with dietary intake of ω -3/-6 PUFAs on prostate cancer risk..

Conclusion

During the past funding period (15 Jan 2006 – 14 Feb 2007), we have obtained approvals to begin this study and have successfully started our study subject recruitment. We have also explored several possibilities to expand the recruitment area to reach our recruitment goal in a shorter period of time to make up later start in subject recruitment due to IRB approval delays. We are also actively looking for opportunities for additional

studies based on this study population, and have applied for additional funding to study other genetic and environmental risk factors for AA men.

The results from this study, as well as other future studies based on this study population, will greatly increase our knowledge of potential risk factors and suggest for potential preventive strategies for prostate cancer in AA men. These men have the highest risk to develop prostate cancer, and the highest risk to eventually develop aggressive forms of prostate cancer, while also being an understudied group. Therefore, this project fills a vital gap in our understanding of prostate cancer etiology. This study could potentially clarify the diet-gene interactions that lead to prostate cancer. Specifically, this project could lead to genetic testing that would help identify men with increased prostate cancer risk, while at the same time offering these men targeted guidance to reduce this risk by lowering their dietary intake of certain foods such as dairy, red meat, and fatty fish.

References.

None.

Appendices.

None.

Supporting Data.

None.