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TITLE: Epidermal Growth Factor (EGF) Receptor Intron 1 CA Repeat Polymorphisms in African-American and Caucasian Males: Influence on Prostate Cancer Risk or Disease Progression and Interaction with Androgen Receptor CAG Repeat Polymorphisms

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13. ABSTRACT ***(Maximum 200 Words)***

We are investigating the effect of a polymorphic epidermal growth factor receptor (EGFR) gene intron 1 CA repeat on prostate cancer (CaP) development, alone or in combination with a known androgen receptor gene CAG repeat polymorphism. We will determine the lengths of these repeats in DNA from African-American and Caucasian men with CaP. The data will be analyzed for any correlation using both parameters with clinical outcome (age of onset, rapid progression, or metastasis). A biostatistician has been recruited to the study and a new statistical analysis plan has been developed. A major restructuring of the Cooper Hospital/ University Medical Center Institutional Review Board took place during the past year, and this resulted in a series of required changes in the informed consent form and other delays in obtaining documentation required for the revised human subjects protocol. Thus, the Human Subjects Protocol has not yet been approved by the US Army Medical Research and Materiel Command Human Subjects Research Review Board (USAMRMC HSRRB). Since we have not been given approval to initiate the study, there is no data to report. However, the final pieces have recently come together, and a revised protocol has been submitted to the HSRRB.

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prostate cancer, genetics, molecular biology, gene interactions, transcription familial, hereditary carcinogenesis, polymorphism, research resources

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INTRODUCTION: African-Americans are at increased risk of developing prostate cancer (CaP) relative to whites, and the lengths of two polymorphic repeats in the first exon of the androgen receptor (AR) gene contribute to that risk (Ries *et al*, 1990; Parker *et al*, 1996). The CAG repeat length is best correlated with prostate cancer risk, shorter repeats being associated with higher risk, and the prevalence of the shorter CAG alleles is greatest in African-American men, intermediate in Caucasian, and least in Asian-American men (Faber *et al*, 1989; Irvine *et al*, 1995; Kantoff *et al*, 1998; Pettaway, 1999). However, a multigenic etiology for CaP is likely. A polymorphic CA repeat has been described in intron 1 of the epidermal growth factor receptor (EGFR) gene, and the length of the repeat inversely correlated with transcriptional activity *in vitro* (Chi *et al*, 1992; Gebhardt *et al*, 1999). Preliminary evidence suggests that the CA repeat status affects EGFR content in breast cancer, and that shorter repeats might be a predisposing factor for breast cancer (Buerger *et al*, 2000). The EGFR is also important in regulation of prostatic epithelial and CaP cell growth, and androgen may affect that by increasing the levels of EGFR and its' ligands in CaP cells (Schuurmans *et al*, 1991; Liu *et al*, 1993). Shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, and potentially also by affecting alternative splicing of the EGFR transcript, could synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and promote the development of androgen-independent, metastatic prostate cancer. In collaboration with The Prostate Cancer Risk Assessment Program at Cooper Hospital/ University Medical Center, we will isolate DNA from blood samples from 300 African-American and Caucasian American men with (and some without) prostate cancer. We will determine the length of these two repeats, to determine whether the EGFR CA repeat, alone or in combination with the AR CAG repeat, affects CaP risk. Lymphoblastoid cell lines will be established for a representative subset of these samples, and will be made available to other researchers at the end of this study. The data will be analyzed for any correlation using both parameters with clinical outcome (age of onset, rapid progression, or metastasis).

BODY: Based on USAMRMC recommendation, a biostatistician has been recruited to the study and a new statistical analysis plan has been developed. A major restructuring of the Institutional Review Board of Cooper Hospital/ University Medical Center took place during the past year, and this resulted in a series of required changes in the informed consent form and other delays in obtaining documentation required for the revised human subjects protocol. In response to a recent request by my collaborator, Dr. Joel Marmar, the Cooper Hospital/ University Medical Center IRB now considers the present study (PC001407, funded by award number DAMD17-01-1-0080) to be a sub-study of the Regional Prostate Cancer Registry and Risk Assessment Program at Cooper Hospital/ University Medical Center. The Human Subjects Protocol has not yet been approved by the US Army Medical Research and Materiel Command Human Subjects Research Review Board (USAMRMC HSRRB). Since we have not been given approval to initiate the study, there is no data to report. However, the final pieces have recently come together, and a revised protocol has been submitted to the DOD HSRRB. We are therefore requesting a change in the funding period to reflect the time required to obtain all approvals necessary to initiate the proposed research. The revised

Human subjects Protocol and revised informed consent form are appended. Changes recommended by either the HSRRB or the Cooper Hospital/ University Medical Center IRB are highlighted in color.

KEY RESEARCH ACCOMPLISHMENTS: None, since we have not been authorized to initiate the research.

REPORTABLE OUTCOMES: None.

CONCLUSIONS: Despite tremendous progress in research into the origins of prostate cancer (CaP), there are still many important, unresolved questions about the etiology of this common cancer. Perhaps the most urgent problem facing prostate cancer researchers -- and those with the disease -- is to identify the subset of CaP sufferers whose cancer will progress rapidly. Despite extensive research, no single marker has arisen as a definitive marker of such cancers. Indeed, a multigenic etiology for CaP is extremely likely. Among the candidate genes are those encoding the androgen receptor and the epidermal growth factor receptor (EGFR). The EGFR is clearly important in the regulation of prostatic epithelial and CaP cell growth, and is frequently overexpressed in BPH and CaP cells, but no studies have convincingly demonstrated that it is of great use in predicting the course of a particular CaP case. However, a polymorphic CA repeat has been described in intron 1 of the epidermal growth factor receptor (EGFR) gene, and the length of the repeat has recently been inversely correlated with transcriptional activity *in vitro* (Chi *et al*, 1992; Gebhardt *et al*, 1999). Androgen may also influence the expression of the EGFR by increasing the levels of its' ligands, and perhaps directly in CaP cells (Schuurmans *et al*, 1991; Liu *et al*, 1993). However, the possible contribution of EGFR CA repeat polymorphisms on prostate cancer risk or progression has never been investigated. Shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, and potentially also by affecting alternative splicing of the EGFR transcript, could synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and promote the development of androgen-independent, metastatic prostate cancer. This proposal will both begin to address these possibilities, and provide resources for definitive future studies.

We are looking forward with great anticipation to the approval of the revised human subjects research protocol so that we can initiate this research.

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CORIELL INSTITUTE for Medical Research

HSRRB Log No. A-10414/ PC001407 - " Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat polymorphisms in African-American and Caucasian males: Influence on Prostate Cancer risk or disease progression and interaction with Androgen receptor CAG repeat polymorphisms."

Human Subjects Protocol

1. This grant will utilize specimens and information accrued through The Prostate Cancer Risk Assessment Program, a collaborative project of Cooper Hospital/ University Medical Center and The Coriell Institute for Medical Research. The overall study is entitled "Development of a regional prostate cancer registry & risk assessment program".

2. This protocol does NOT involve the testing of Investigational New Drugs or Devices.

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5. Time required to complete: Expected Start: October 1, 2002
Completion: September 31, 2005

6 - 9. Protocol

a. Research Hypotheses/ Objectives: This study involves the development of a prostate cancer database that will collect data not currently available on prostate cancer patients and their family members. Personal information and blood samples will be collected from all participants, and tissue samples will be collected from participants that undergo medically indicated biopsies or surgeries. Regarding PC001407, I hypothesize that shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, will synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and/ or promote the development of androgen-independent, aggressive prostate cancer. The status of Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat and androgen receptor CAG repeat polymorphisms in African-American and Caucasian males will be determined by PCR analysis of DNA isolated from blood samples. These data will be studied in conjunction with the personal and medical information to determine whether the status of the EGF receptor polymorphism, alone or in combination with the androgen receptor polymorphism, influences the age of ons et or biological characteristics (e.g., hormone dependence, invasiveness, metastasis) of prostate cancer. Further details are described in the included abstract.

b. Study Population: The study population will be comprised of approximately 300 males recruited from individuals who come to Cooper Hospital for the treatment of prostate cancer and via the Prostate Cancer Risk Assessment Program at Cooper Hospital. Cooper Hospital serves primarily Camden County and western Burlington County, New Jersey, and ethnically diverse area with significant African-American, Caucasian, and Hispanic populations.

c. Inclusion and Exclusion Criteria: All subjects recruited will be males in the age range of 35 - 69 years. Carcinoma of the prostate (CaP) is rare among individuals under age 35, whereas prostatic intraepithelial neoplasia (PIN) the presumed precursor of CaP, is very common among men older than 70, so older individuals are less likely to be informative regarding hereditary predisposition. Because the frequency of the various EGF receptor intron 1 CA repeat lengths in African-American men is currently unknown, and since African-American men are at greater risk of prostate cancer than the general population, we will recruit a significant fraction of subjects from the African-American community. Subjects accrued to date under the previously approved Prostate Cancer Risk Assessment Program protocol are ca. 50% African-American and 50% Caucasian.

d. Informed Consent Process: Clinical nursing staff at Cooper Hospital/University Medical Center will explain The Prostate Cancer Risk Assessment Program in lay terms to prospective subjects who come to the weekly screening clinic ("self-recruitment"). The Prostate Cancer Risk Assessment Program is open to men between the ages of 35 and 69 who are African-American, or of any race with a family history of prostate cancer. Prostate cancer patients of Dr. Joel Marmar will also be offered the opportunity to enroll in the study. Individuals uncertain about participation may discuss the study with friends and family members and return at a later time. Interested individuals will then be talked through the informed consent form (appended), with particular attention being focussed on the clauses regarding (a) the choice to be informed of any clinical implications of their results in the context of this or other relevant prostate cancer studies, (b) the risks of participation in the study, and (c) sample donation. Witnesses may be

other clinic personnel or any other individual the subjects choose. As the document is discussed, the subjects and their witnesses will be asked to initial each page to indicate that it has been explained to them, as well as to sign the last page of the document to indicate their agreement to participate in the study. Two copies of the consent form will be completed so that the subjects can keep an original copy.

e. Sample Size: A target of 300 individuals will be sought over the course of 3 years. (The overall target for the Regional Prostate Cancer Registry and Risk Assessment Program is 400 subjects, but the time and funds for PC001407 will allow for analysis of 300.) By recommendation of peer review, a biostatician has been consulted regarding sample size (appended), and will be consulted for subsequent data analyses. EGFR intron 1 CA repeat allele frequencies in the general populations of African-American and Caucasian American men will be determined by analysis of DNA samples from apparently normal individuals in existing Coriell Cell Repository panels.

f. Protocol Design: Male subjects (300) will be recruited from individuals who come to Cooper Hospital for the treatment of prostate cancer and via the Prostate Cancer Risk Assessment Program at Cooper Hospital as described in b - d above. Notices will be published as in the appended Cooper Health system newsletter. After informed consent is obtained as described in (d), subjects will be asked to complete a Health History Questionnaire (appended), and to donate 3 (~10 ml each) tubes of blood. One tube will be used by the hospital for medical diagnosis (e.g., Prostate Specific Antigen level), while the other tubes will be used at the Coriell Institute for Medical Research for (a) extraction of DNA and (b) isolation and cryopreservation of lymphocytes. Blood will be collected no more than once per year for the purposes of this study. The lengths of the EGFR intron 1 CA repeat and the AR CAG repeat will be determined by PCR analysis of the DNA (of the samples accrued to date on a previous protocol, the AR repeat has already been analyzed in several dozen). Epstein-Barr virus-immortalized lymphoblastoid cell lines will be established for individuals representing the possible combinations of these two polymorphisms. These cell lines will be deposited in the National Institute of Aging Repository in the Coriell Cell Repositories, and will be available to other researchers at the end of this study. We will also utilize prostate biopsies, when obtained as part of the subjects' medical care, to examine EGFR and AR expression and initiate prostate cell lines. The specimens, health histories, and clinical information will be encoded as PS### (e.g., PS100, PS101, etc.) by the Cooper Hospital clinical staff, such that all specimens and information received by The Coriell Institute for Medical Research will be separated from subject names. Coriell will receive only coded summaries of the Health History Questionnaires. Any cell lines accepted by the Coriell Cell Repositories for distribution to other researchers will be given new code numbers (e.g., AG00000) to ensure confidentiality. For PS### cell lines to be submitted to the Coriell Cell Repositories, Dr. Joel Marmar's clinical staff will assign new numbers from a list of the next available AG numbers; the list indicating the PS #s corresponding to the new AG numbers will be kept by his office for 4 years after completion of the study.

g. Risks to Subjects: As this is not an interventional protocol, this project poses no greater than minimal risk to participants. Risks noted in the consent form include the risk of discovering a genetic predisposition to cancer, which may cause concern. Subjects may also have concerns even if they are not in the future told that they have a gene alteration that has been linked to an increased risk of prostate cancer. Subjects do not have to agree to have this information revealed to them or their family members. The risks and discomfort associated with giving blood include the possibility of bleeding and bruising. This rarely causes a significant problem.

h. Benefits to Subjects: As noted in the consent form, subjects will not receive any immediate benefits as a result of participation in this study. It is possible that the study will reveal known or novel genetic polymorphisms that would indicate a statistically greater or lesser prostate cancer risk than the general population. This might prompt an individual to have regular screening for prostate cancer, which could affect their prognosis should cancer be discovered. However, such information is more likely to be of use in the future, rather than to subjects recruited in the current study.

i. Roles and Responsibilities of Study Personnel: Local review boards have not found the protocol to be of greater than minimal risk, so no medical monitor has been assigned.

David K. Moscatello, Ph.D. Role: Principal Investigator (PC001407), 40%. Lymphocyte and DNA isolation, analysis of EGFR intron 1 CA repeats, analysis of Androgen receptor CAG repeats, preparation of DNA, RNA, and protein lysates from prostate specimens, immunohistochemistry and western blotting, reverse transcription-polymerase chain reaction (RT-PCR), Southern and Northern blotting, cryopreservation of viable prostate biopsies, and data analysis.
Bender, Patrick K., Ph.D. (Associate Professor and Supervisor, Division of Molecular Biology, Coriell Institute for Medical Research, 5%. Role: Analysis of Androgen Receptor CAG repeats.

Grana, Generosa, M.D., Assistant Professor of Hematology/ Oncology and Medical Director, The Cancer Risk Evaluation Center, Cooper Hospital/University Medical Center, 5%. Role: Medical Director, The Cancer Risk Evaluation Center.

Marmar, Joel, M.D., Professor of Urology and Head, Division of Urology, Cooper Hospital/ University Medical Center, 5%. Role: Procurement of benign and malignant prostate specimens.

Juliette M May, Cooper Hospital/University Medical Center, 25%. Role: Subject recruitment, interviews, blood collection, data entry and encoding.

Nancey Coker, B.A., Technician, Coriell Institute for Medical Research, 50%. Role: Lymphocyte isolation and cryopreservation, DNA isolation, and PCR.

Constantine Daskalakis, Sc.D., Biostatistics section of the Department of Medicine, Thomas Jefferson University, Philadelphia, PA, 5%. Role: Consultant for study design and data analyses.

10. Reporting of serious and unexpected adverse events. This is not an IND or IDE protocol. No medical interventions are proposed. However, there is a remote possibility of a severe adverse event such as excessive bleeding or infection as a result of blood collection. Should such an event occur, Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Deputy for Regulatory Compliance and Quality (301-619-2165) and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days.

11. Description of Protocol Drug(s) or Device(s): Not applicable.

12. Disposition of data: All health history and clinical records will be maintained at Cooper Hospital/ University Medical Center according to their standard procedures. No disposal is contemplated, except for individuals who are withdrawn from the study (either voluntarily or otherwise), in which case the health questionnaires held at Cooper, and samples and associated data held at Coriell will be destroyed. Otherwise, encoded/ tabulated data without personal identifiers of just the subset of samples that will be submitted to the NIA Cell Repository will be maintained in the secure files of The Coriell Institute for Medical Research indefinitely.

13. Modification of the protocol: As this is not an IND/ IDE protocol, no modifications are anticipated, with the possible exception of the recruitment of additional subjects. This might be necessary to achieve statistical validity of possible correlations between the genetic polymorphisms and clinical data. The use of additional methods to recruit subjects might be considered if targets are not met. If this becomes necessary, the revisions, including any proposed new recruiting methods, will be submitted to the Institutional Review Boards of both local institutions, and subsequently to the OTSG HSRRB for approval.

14. Departure from the Protocol: Any departures from the proposed protocol with respect to the consents, questionnaires, or specimens will be submitted to the Institutional Review Boards of both local institutions, and subsequently to the OTSG HSRRB.

15. Roles and Responsibilities of Study Personnel: See (i) above.

16. USAMRMC Volunteer Registry Database: Project judged not greater than minimal risk by local review boards, therefore not applicable.

Signature of Principal Investigator: _____
David K. Moscatello, Ph.D.

Date: _____

STATISTICAL ANALYSIS PLAN

Our analyses will be based on samples obtained from 300 prostate cancer patients (prospectively collected) and from approximately 200 controls (from existing panels). The study's aims are to evaluate
(1) the association between EGFR intron 1 CA repeats and prostate cancer;
(2) the association between AR CAG repeats and prostate cancer; and
(3) the combined (synergistic) effect of EGFR and AR on prostate cancer.

The first two aims pertain to the main effect of each gene, while the third aim focuses on their possible interaction. Preliminary analyses will be based on two-by-two cross-classification tables of each gene with prostate cancer status (case/control). We will estimate and test the (crude) unadjusted odds ratio separately for each gene, using Fisher's exact test and Mantel-Haenszel stratification analysis. We will then model the outcome (prostate cancer case or control status) as a function of both genes via logistic regression. In this multivariable analysis, we will also control for age, race, and other potential confounders.

Finally, we will test the hypotheses of "no multiplicative interaction" and "no additive interaction" between the two genes. Using the long-EGFR/long-AR combination as the referent group, the hypothesis of no multiplicative interaction implies that the joint odds ratio for the short-EGFR/short-AR combination is equal to the product of the two main effects odds ratio (i.e., short-EGFR/long-AR and long-EGFR/short-AR). The test of this hypothesis involves testing the product interaction term; likelihood ratio and Wald tests are straightforward to compute in all statistical packages. The hypothesis of no additive interaction, on the other hand, implies that the joint odds ratio is the sum of the two main effects odds ratios minus one. Although preprogrammed software capabilities do not allow testing of this hypothesis in logistic regression, we have a SAS macro that will allow us to perform the corresponding likelihood ratio and Wald tests.

We have also planned secondary analyses to assess:
1. the effects of the two genes among Caucasian and African-American subjects (i.e., gene-by-race interactions); and
2. the association between the length of the repeats for each gene and cancer recurrence and/or survival (among the prostate cancer cases only).

SAMPLE SIZE AND POWER

Based on previous data, EGFR intron 1 CA repeats show a distribution with 3 peaks in the general population, at 20, 18 and 16 repeats. A smaller number of repeats (<17, approximately 45% in the general population) are hypothesized to be associated with higher risk of prostate cancer. With 300 cases and 200 controls, using a two-tailed Fisher's exact test with alpha of 0.05, we have 84% power to detect an odds ratio of about 1.75 (i.e., short allele in 45% of the controls vs. 59% of the cases).

Similarly, based on previous data, AR CAG short repeats (<20) seem to be present in about 30% of the general population. With 300 cases and 200 controls, using a two-tailed Fisher's exact test with alpha of 0.05, we have 82% power to detect an odds ratio of 1.75 (i.e., short allele in 30% of the controls vs. 43% of the cases).

In terms of the interaction between the two genes, we have good power to detect moderate interactions on both the additive and the multiplicative scale. All power calculations were performed via Monte-Carlo simulation, using the appropriate likelihood ratio tests in logistic regression, with alpha of 0.05.

Assuming main effect odds ratios for each gene of about 1.75, under the "no additive interaction hypothesis", we expect a joint odds ratio of 2.5 (i.e., 1.75+1.75-1) for the comparison of the short-EGFR/short-AR combination with the referent long-EGFR/long-AR combination. In our study, we have power to detect departures from additivity when the synergy factor is 3 or higher (i.e., an odds ratio for the joint effect of 5.5 or higher):

Allele EGFR	Allele AR	Effect type	OR	OR	Power	OR	Power
long	long	refer.	1.00				
long	short	main	1.75				
short	long	main	1.75				
short	short	joint	2.50*	5.5	81%	6.5	91%

(*) Additivity of effect (i.e., no additive interaction)

With the same assumptions of main effect odds ratios for each gene of about 1.75, under the "no multiplicative interaction hypothesis", we expect an odds ratio of 3.06 (i.e., 1.75x1.75) for the comparison of the short-EGFR/short-AR combination with the referent long-EGFR/long-AR combination. In our study, we have power to detect a multiplicative interaction factor of about 3 or higher (i.e., an odds ratio for the joint effect of 9 or higher):

Allele EGFR	Allele AR	Effect type	OR	OR	Power	OR	Power
long	long	refer.	1.00				
long	short	main	1.75				
short	long	main	1.75				
short	short	joint	3.06*	9.2	75%	10.7	85%

(*) Multiplicativity of effect (i.e., no multiplicative interaction)

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Prostate Cancer Risk Assessment

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE OF STUDY: Development of a regional prostate cancer registry & risk assessment program

DEPARTMENT: Cooper Cancer Institute; Coriell Institute for Medical Research (Moscatello)

PRINCIPAL INVESTIGATOR: Joel Marmar, MD

PHONE NUMBER 963-3577

CO-INVESTIGATOR(S): Generosa Grana, MD, Christopher Koprowski, MD, Evan Krisch, MD, David K. Moscatello, Ph.D., Juliette M May

PHONE NUMBER(S):

SUBJECT'S NAME: _____

SUBJECT'S ADDRESS: _____

DATE OF BIRTH: _____

The doctors at the Cooper Health system do research on the nature of diseases and new treatments. This research project is to study the effect of environmental, life styles and genetic causes of prostate cancer. No one can say that you are going to be helped by it. If you have any questions or problems during the study you can call the doctors at the Phone numbers listed at the top of this page and they will try to help you. If you want to know more about their backgrounds, you can get the information from the Medical Staff office at the Cooper Health System. Information on The Coriell Institute for Medical Research or Dr. Moscatello can be obtained at Coriell (403 Haddon Avenue, Camden, NJ 08103) or on the web at http://coriell.umdnj.edu/.

PURPOSE OF STUDY: The Cooper Cancer Institute at Cooper Hospital/ University Medical Center and its collaborators are conducting research on the causes of Prostate cancer to find new methods of prevention, diagnosis and treatment. Prostate cancer is one of the leading causes of cancer among men and is second only to lung cancer. Since prostate cancer is more frequent in African Americans than Caucasians, it is important to recruit men of all races into this study.

This study will involve the development of a prostate cancer database that will collect data not currently available on prostate cancer patients and their family members. Personal information, blood and tissue samples will be collected from participants. Researchers, including scientists at Coriell, who would like to study possible causes of cancer such as genes, lifestyles and environmental factors will use the samples and information. It is estimated that 100 participants a year and approximately 300 participants over a 3 year period will be enrolled in this study.

STUDY PROCEDURE (S): You have been told that during the course of this study, the following will occur: Each participant will be asked to provide lifestyle, medical and family history information and a blood sample. Participants who have had a biopsy, either benign (noncancerous) and/or malignant (cancer) will be asked for a tissue sample. Specifically we will ask you to do the following:

1. Complete a questionnaire on your family history of cancer, as well as medical and lifestyle information. You may refuse to answer any question on the questionnaire that makes you uncomfortable.
2. Donate three tubes of blood (about 2-3 tablespoons) that will be drawn from a vein in your arm. You may be asked to donate blood samples periodically throughout the study, but no more than once per year.
3. If you have had a biopsy, or surgery to remove a tumor, or are scheduled for surgery, we will ask you to complete an authorization form. This form will allow us to obtain copies of your pathology and medical records. It will also allow us to obtain a portion of your fresh tissue or stored tissue (after surgery, tissue samples are stored in wax blocks at the hospital).
4. Complete a follow-up questionnaire each year for four years to update the registry files on your health and to reconfirm your willingness to participate in the study. (Subjects who enroll on the 4th year will receive 1 year follow-up.)

You are eligible for this study because you meet one of the following criteria: 1) you have a diagnosis of prostate cancer or 2) you have a family history of cancer or 3) you are of the African-American race.

It is possible that a genetic link to prostate cancer will be discovered. It is also possible that you will be discovered to have a gene that may be linked to an increased risk of developing prostate cancer. It is your option to be told or not told this information. You are being asked to make that choice in this form by circling the "Yes" or "No" that follow. "Yes" means you want to be told. "No" means you do not want to be told. Please circle and initial your preference.

Yes or No _____initials

If you choose not to be told no other informative action will be taken. However if you choose to be informed and information about you is discovered, a letter asking you to make an appointment with the researchers will be sent to your home. During this appointment, you will be informed of the findings and offered counseling/education on the subject.

BENEFITS: Although you will receive no immediate benefit from your participation in the study, investigators hope that the knowledge gained from future research studies will be of benefit to you, your relatives, and future generations.

RISK AND DISCOMFORTS: The risk of discovering that you have a genetic predisposition to cancer will be discussed with you prior to agreeing to participate in the study. This may cause you concern. You may also have concerns even if you are not in the future told that you have a gene

alteration that has been linked to an increased risk of prostate cancer. You do not have to agree to have this information revealed to you or your family members. Some people are concerned about genetic discrimination by insurance companies and/or employers. We will not release any information about you or your family to an insurance company or employer without your consent. The risks and discomfort associated with giving blood include the possibility of bleeding and bruising. This rarely causes a severe problem.

ALTERNATIVES: The alternative is to not participate in this study.

COSTS/COMEPENSATION: Your participation in this study is free. Any counseling/ education sessions provided to you at Cooper in connection with this study will also be free. The cost of any counseling or education you choose to receive somewhere other than Cooper or not in connection with this study will be your responsibility. You will not be paid for your participation in the study.

SAMPLE DONATION: During this study, you will be asked to provide blood (and prostate, if biopsy or surgery is medically indicated) samples. These samples will be used for isolation of DNA, RNA, and proteins for analysis, immunohistochemical analysis, and for the establishment of cell lines, and may also be used for purposes that are currently unknown. There is a chance that the samples that you are donating under this study may be used in other research studies and may have some commercial value. Should your donated sample(s) lead to the development of a commercial product, the institution(s) or inventor(s) who developed the product will own it and may take action to patent and license the product. The Institute does not intend to provide you with any compensation for your participation in this study nor for any future value that the sample you have given may be found to have. You will not receive any notice of future uses of your sample(s). You are being asked to make the choice in this form by circling the "Yes" or "No" that follow. "Yes" means you agree to allow any sample(s) collected for this study to be used for further research. "No" means you do NOT want your sample(s) to be used for any further research other than this study. Please circle and initial your preference.

Yes or No _____initials

CONFIDENTIALITY: Every effort will be made to maintain the confidentiality of your study records. All identifying markers such as your name and address will be removed from all your information and samples, and a code number will be used instead. The list of names and matching code numbers will be stored securely in a safe and kept separately from the other study information. Only the principal investigator or other hospital personnel he may designate will have access to this list. Your blood and tissue samples labeled with only your code number will be stored securely and indefinitely at the Coriell Institute for Medical Research in Camden New Jersey. Officials of the Cooper Health System, including the Institutional Review Board and the Coriell Institute for Medical Research may inspect sections of your medical records related to this study. If the findings from the study are published, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law. It should be noted that representatives of the U.S. Army Medical Research and Materiel Command, and of Health and Human Services are eligible to review research

records as part of their responsibility to protect human subjects in research. Otherwise your medical record and the information it contains may not be furnished to anyone unaffiliated with the Hospital without your written consent. If your record is used or reviewed for government purposes, your privacy will be protected as much as possible under the laws relating to public revealing of information and the law enforcement responsibilities of the agency. The New Jersey Genetic Act (PL 96, C. 126) regulates genetic testing and also protects against unfair discrimination by both employers and the insurance industry.

CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT: Your participation may be terminated without consent if you are not available to follow-up or the researchers are unable to contact you for further evaluation.

NEW FINDINGS: During the course of the study, you will be told about any new information that may affect your willingness to remain in the study. The risk of discovering that you have a genetic predisposition to cancer will be discussed with you prior to agreeing to participate in the study. You do not have to agree to have this information revealed to you or your family member.

INJURY: If you are injured as a result of participating in this study, treatment will be available at the Cooper Health System. However, this statement does not mean that costs for such treatment will necessarily be free. In the unlikely event of an injury, you or your insurance company will be billed in the customary manner. Furthermore, no provisions have been made for compensation in the event of injury. No money will be provided by the hospital for compensation for a research related injury. If you believe that you have suffered injury or illness due to your participation in this study, you should notify the Executive Vice President for Medical Affairs or her designee at (856-968-3835). A review by a committee will be arranged to determine if the injury or illness is a direct result of participation in this research. You should also contact that person if you have any questions about your rights as a research subject or if you believe that you have not been adequately informed as to the risks, benefits, alternative procedures, or that you are being pressured to continue in this study against your wishes. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator or his representative before you enroll in this study.

VOLUNTARY PARTICIPATION: I voluntarily consent to participate in this study. I do so with an understanding of the possible outcomes that might occur in the course of the study. I have had adequate time to read this form and I understand its contents. I have been given a copy for my personal records.

RIGHT TO REFUSE OR WITHDRAW: I understand that my participation is voluntary and I may refuse to participate or may discontinue my participation at any time, without penalty or loss of benefits to which I am otherwise entitled and without prejudice to my present or future care. I can withdraw by contacting Dr. Joel Marmar's office at the number listed on the first page of this form. I also understand that the investigator has the right to withdraw me from the study at any time. In the event I am no longer participating in the study, blood and tissue samples will be destroyed along with my questionnaire and other materials with my name and code numbers.

Subject's initials _____ Witness's initials _____

INDIVIDUALS TO CONTACT: If I experience side effects or need to discuss any problems or questions concerning my participation in this study, I can contact one of the investigators listed on the first page.

If I have any questions about my rights as a research subject, I can contact:

Carolyn Bekes, MD
Executive Vice President of Medical Affairs
Cooper Health System (856) 968-3835

I have read this entire form, or it has been read to me. I have been informed that I have the right to ask questions, and all of my questions regarding this form or this study have been answered to my complete satisfaction. I agree to participate in this research study. I understand by signing this form that I am not waiving any other legal rights to which I might be entitled. I have been given a copy for my personal records.

SIGNATURE OF SUBJECT

Subject Name: _____ Signature: _____

Witness Name: _____ Signature: _____

Date: _____

INVESTIGATOR'S STATEMENT

I have explained the terms and conditions of this consent form to the above named subject including the risk of discovering a genetic predisposition to cancer and based on this conversation I believe he/she has understood what was discussed.

Investigator's Name: _____ Signature: _____

Date: _____