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TITLE: Bone Mineral Density, Sex Steroid Genes, Race and Prostate Cancer Risk

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The goal of this project is to determine whether bone mineral density (assumed to be an integrated marker of sex steroid hormone exposure) is a risk factor for prostate cancer; and (2) to identify prostate cancer susceptibility alleles among genes in the sex steroid pathway. To address these aims, we are undertaking a case-control study of African American and Caucasian men in Pittsburgh, PA and Birmingham, AL. As of 7/31/04, 163 Caucasian and 19AA cases, 159 Caucasin and 14 AA controls with PSA <3.0 ng/mL frequency matched by age and race to Hip, spine and total body BMD is measured by Dual-energy X-ray Absorptiometry (DXA) on all participants. Blood specimens have been used to isolate DNA on 255 subjects. Polymerase Chain Reaction (PCR) techniques are being used to determine allelic distributions of genotypes for sex steroid metabolism, biosynthesis and action genes. Risk factor data are obtained by an in-person interview and are immediately scanned into the study database. Caucasian recruitment has been completed. AA recruitment is ongoing. Upon completion of AA recruitment and data collection, we will evaluate the role of BMD and candidate genotypes in prostate cancer risk by race. We will further examine the interaction between BMD and genotypes to evaluate the hormonal environment - gene interaction and its effect on prostate cancer risk.
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INTRODUCTION:
The goal of this project is to determine whether bone mineral density (assumed to be an integrated marker of sex steroid hormone exposure) is a risk factor for prostate cancer; and (2) to identify prostate cancer susceptibility alleles among genes in the sex steroid pathway. To address these aims, we are undertaking a case-control study of African American and Caucasian men in Pittsburgh, PA and Birmingham, Alabama. Cases are 100-150 African American and 150 Caucasian men with histologically-confirmed prostate cancer. Controls are age and race frequency-matched men who have a prostate specific antigen (PSA) level < 3.0 ng/mL. Hip, spine and total body body mass index (BMD) is measured by Dual-energy X-ray Absorptiometry (DXA). Blood is used to obtain DNA. Polymerase Chain Reaction (PCR) techniques will be used to determine allelic distributions of genotypes for sex steroid metabolism, biosynthesis and action genes. Risk factor data are obtained by an in-person interview. Pathology information will be collected using standardized medical abstraction and all pathology will be confirmed by a central pathologist. Upon completion recruitment and data collection, we will evaluate the role of BMD and candidate genotypes in prostate cancer risk by race. We will further examine the interaction between BMD and genotypes to evaluate the hormonal environment – gene interaction and its effect on prostate cancer risk.

BODY:
In this section, we describe our accomplishments according to the Work Plan originally approved:

Task 3 Recruiting of Subjects and Obtaining of Data, Months 6-30

Please see tables 1-3 for summaries to 7/31/04. In short, we have recruited 163 Caucasian cases, 159 Caucasian controls, 19 African American (AA) cases and 14 AA controls. An additional 4 AA cases have been recruited from Alabama.

Task 4 Performance of Laboratory Assays, Months 12-31:

a. Isolate DNA from blood samples
   - DNA was isolated on 255 of the 355 subjects thus far and continues to move forward.
   - DNA was quantitated and diluted to 40ng/ul

b. Assay samples (600) to detect sex steroid related genetic polymorphisms and record results on study forms
   - The following genotyping assays were performed:
     a. AIB1/SRC3 - steroid receptor coactivator 3; CAG (glutamine) repeat polymorphism
     b. CYP11A - cholesterol side chain cleavage enzyme; pentanucleotide repeat [(TTTTA)n] in the promoter
     c. SHBG - pentanucleotide repeat [(TAAAA)n] located in an Alu sequence at the 5' boundary of the promoter
     d. CYP19 - aromatase; intronic tetranucleotide repeat [(TTTA)n]
     e. HSD11B1 - 11-beta hydroxysteroid dehydrogenase; a CA repeat

Task 5 Data Entry, Months 12-32:

a. Enter, verify and clean interview, anthropometric, physical activity, pathology, DXA, and laboratory assay data via the PoP computerized data entry system
- As previously reported, we implemented the questionnaire in TeleForm, so that data entry is ongoing. All data is entered when a subject is interviewed. Thus, data on all subjects recruited to date is already in the study database. We have randomly reviewed 10% of the interview forms and compared the data with the database to ensure accuracy.

**Task 6 Interim Analyses of Data, Months 18-30:**

- Perform interim statistical analyses of data periodically
- See tables 1-3 for data
- A preliminary review of these data suggest that the AA population is less likely to be married and have a lower level of education. This most likely reflects the referral patterns of AA with prostate cancer and the practice from which we recruit our Caucasian subjects (Dr. Joel Nelson, Chair of Urology, University of Pittsburgh Medical Center). These differences will be controlled for in our analyses (by including a variable in our models).

**Overall Study Progress:**
To date, we have completed recruitment of Caucasians in Pittsburgh.

**Pittsburgh Progress:**
We obtained IRB approval from the University of Pittsburgh to commence recruitment of subjects in Pittsburgh. Recruitment began in February 2002. Cases are recruited from all newly diagnosed cases of prostate cancer seen in the practice of Dr. Joel Nelson. Controls are men who have participated in a population-based prostate cancer screening trial (the Prostate, Lung, Colo-rectal and Ovarian (PLCO) Cancer Trial) and are frequency matched to cases by age and race. The summary of recruitment to date is in Table 1. We recruit approximately 4 men per week in Pittsburgh (2 cases, 2 controls), which was in line with the anticipated recruitment schedule. Because interview data is scanned in weekly, we are able to provide interim data analyses. Table 2 summarizes the baseline data on all recruited subjects through July 31, 2004.

**Baltimore Progress:**
We were unable to obtain IRB approval from the DOD Human Subjects Committee for the Baltimore site. We have therefore dropped this site from the study. We invested a great deal of time and effort in trying to launch this study in Baltimore, and are disappointed to not include them in the study because in the preliminary recruitment efforts, approximately 2-3 AA cases per week were being referred into the study.

**Alabama Progress:**
We received DOD IRB approval in early 2004 to commence minority recruitment at the Alabama site. The site is under the supervision of Dr. James Shikany. During the Spring we worked with the Alabama investigators to revise the Manual of Operations for their site and to put into place all the study procedures, including sending data and specimens to Pittsburgh. We also trained the field interviewer to ensure consistency in questionnaire administration. Concurrently, the Alabama investigative team met with urologists in the area to set up recruitment procedures.

As of July, 2004, Dr. Shikany and his staff have set up recruitment in several urology clinics in the Birmingham area, including Dr. Urban at the University of Alabama, Dr. Tully (AL Urology Associates) and Dr. Cohn (St. Vincent’s Medical Center). They are also working to have access to a population seen by an African American urologist at Princeton Medical Center and the local VA hospital. These sources should facilitate recruitment of
cases into the study. Controls will be recruited from healthy men participating in the PLCO trial, as was done in Pittsburgh. As was done in Pittsburgh, control recruitment will begin once case recruitment is well under way.

Since starting recruitment in June, the Alabama site has recruited 4 AA cases (through 7/31/04). This represents only a single clinic in Alabama (Dr. Urban’s). We are hopeful that with the addition of the other clinics, recruitment will increase. Because of the delay in IRB approval and study start, we have received approval to extend the study at no cost for 1 additional year. We have set aside approximately 40% of the initial grant funds to cover this additional year and facilitate AA recruitment. If recruitment appears to go well in Alabama, we will ask for an additional extension to complete recruitment.

Exclusion Criteria
The following are the criteria used to exclude men from participation in this study.
- <40 or >80 years of age
- Inability to consent to medical procedures.
- History of hyper or hypothyroidism, hyperparathyroidism, renal disease, or bone disorders
- History of hypogonadism
- History of Bone Disease/problems – osteoporosis, Paget’s disease, osteomalacia, osteogenesis imperfecta,
- Chronic (>3 months) glucocorticoid therapy
- Use of testosterone supplementation (>3 months)
- Use of bisphosphonate supplementation (>3 months)
- Bilateral hip replacement
- Kidney or liver transplant recipient
- Previous diagnosis of cancer, except basal/squamous cell skin cancer
- Trouble absorbing vit. D, vit. D deficiency, calcium abnormality, brittle bones
- 2 or more non-traumatic fractures over a lifetime or 1 or more non-traumatic fracture in the last year.
- For prostate cancer cases, evidence of bone metastases
- For controls, PSA levels above 3 ng/mL within the last 3 months

Data Collection
The following data are collected on all participants:
- demographics, lifestyle factors and medical history via a ½ hours in-person interview
- hip, spine and total BMD via a DXA scan. Results are abstracted onto a study form
- 35 ml of blood. This is used to isolate DNA for the current study. In addition, the following specimens are banked:
  - serum (8x1mL)
  - plasma (8x1mL)
  - buffy coat
  - clot
- height, weight and hip circumference (measured by study personnel during study visit). Results are recorded on a study form.

Laboratory Assays
All genotyping assays are done in the laboratory of Dr. Robert Ferrell. High molecular weight DNA is extracted from peripheral blood leukocytes by the salting-out procedure. Polymerase Chain Reaction (PCR) and Restriction Fragment Length Polymorphism (RFLP) techniques will be used to identify polymorphisms in
the sex steroid metabolism pathway. Restriction fragment length polymorphisms are genotyped by amplification of the variable site using unique sequence flanking primers, digestion with an appropriate restriction endonuclease, resolution of the fragments on 2% agarose gels and visualization under ultra violet light after ethidium bromide staining. Single nucleotide polymorphisms that do not alter a restriction site are assayed by a modified allele specific oligonucleotide ligation assay. Length polymorphisms are genotyped by amplification using unique sequence flanking primers, one of which is labeled with a fluorescent dye (FAM, HEX or TET; Research genetics, Huntsville, AL). The products are resolved on the ABI 377 automated DNA sequencer (Applied Biosystems, Foster City, CA) and the resulting gel images are analyzed using the GENESCAN software package. These protocols are standard in Dr. Ferrell’s lab. Genotypes are assigned by two independent readers by directly comparing test samples to sequence-verified control samples run on the same gel. Conflicts are resolved by repeat genotyping.

We have tested the laboratory assays on a sample of specimens early in our recruitment. The assays appear to be working.

**BMD Measurements**

Hip, spine and total body BMD will be measured by Dual-energy X-ray Absorptiometry (DXA) using a Hologic QDR-4500A (Hologic, Inc., Waltham, MA) in the Laboratory of Dr. Susan Greenspan. Quality control is assessed by daily quality control scans with the phantom provided by the manufacturer. We will also have a subset of scans (10%) reanalyzed by Synarc, Inc. (Bedford, MA), which provides quality control for large scale studies, including several of Dr. Greenspan’s studies. All DXA results will be recorded on a standard study form for data entry.

**Problems encountered and measures taken:**

Minority recruitment has been very difficult. Because of the new HIPAA regulations, we are unable to identify minority cases as we originally intended in Pittsburgh; thus, our minority recruitment is very low. We are therefore relying on Alabama for minority recruitment.

We have also begun collaborating with Dr. Stephen Thomas of the Center for Minority Health in Pittsburgh. Dr. Thomas recently completed recruitment of AA men into Dr. Greenspan’s study of prostate cancer treatment. Recruitment was highly successful using innovative recruitment techniques, including networks of federally-funded local health care centers. We are hopeful that Dr. Thomas’ established network will help increase minority recruitment in Pittsburgh, supplementing the Alabama minority site.

**KEY RESEARCH ACCOMPLISHMENTS:**

- completed Caucasian recruitment in Pittsburgh
- all Pittsburgh demographic and BMD data are cleaned and ready to be analyzed
- received IRB approval at the Alabama site
- set up all study procedures and trained Alabama personnel
- completed Alabama manual of operations
- begun working with the Center for Minority Health in Pittsburgh to increase AA recruitment in Pittsburgh.
- isolated and quantitated DNA from 255 samples to date, with isolation continuing
- genotyped a subset of specimens on 5 sites
REPORTABLE OUTCOMES:
As stated in the original grant application, we have used this opportunity to collect data and specimens to bank in order to support future studies. For example, we collected data on potential markers of prostate cancer risk including male pattern baldness. These data were analyzed and the results presented at the annual meeting of the American Association for Cancer Research. The abstract appears after tables 1-3.

CONCLUSIONS:
We are pleased with our progress in Caucasian recruitment and the laboratory work, and anticipate the successful completion of this project. We recognize that we are behind in AA recruitment, although we have worked to ensure resources will be available to complete this recruitment over the next 1-2 years. We are working to recruit an additional 75-125 AA cases with controls in Pittsburgh and Alabama. To ensure that geographical differences between the two sites will not confound any results, we will control for recruitment site in all analyses and will likely recruit a small number of Caucasian cases and controls in Alabama. We will also perform separate analyses by recruitment site.

REFERENCES:
None

APPENDICES:
None
Table 1: Summary of Recruitment through 7/31/04, Pittsburgh Site

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Table 3: Summary Demographic Statistics on Controls for Pittsburgh through 7/31/04

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<th>UPMC Controls</th>
<th>Caucasian Controls</th>
<th>AA Controls</th>
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<td></td>
<td>n=173 %</td>
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<td>n=159 %</td>
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<td>Age (yrs) mean</td>
<td>61.66</td>
<td>62.35</td>
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Race
- Caucasian: 159 (91.9%), 158 (95.8%)
- African-American: 14 (8.1%), 7 (4.2%)

Recruitment Site
- UPMC: 165 (95.4%), 158 (99.4%), 7 (50.0%)
- VA: 8 (4.6%), 1 (0.6%), 7 (50.0%)

Education
- <8 yrs: 1 (0.6%), 1 (0.6%)
- 8 to 11 yrs: 4 (2.3%), 4 (2.4%), 3 (1.9%), 1 (7.1%)
- 12 yrs or HS: 38 (22.0%), 36 (21.8%), 33 (20.8%), 5 (35.7%)
- post secondary: 14 (8.1%), 12 (7.3%), 12 (7.5%), 2 (14.3%)
- some college: 35 (20.2%), 32 (19.4%), 31 (19.5%), 4 (28.6%)
- college grad: 31 (17.9%), 30 (18.2%), 29 (18.2%), 2 (14.3%)
- postgraduate: 50 (28.9%), 50 (30.3%), 50 (31.4%)

Marital Status
- never married: 12 (6.9%), 10 (6.1%), 8 (5.0%), 4 (28.6%)
- married: 131 (75.7%), 126 (76.4%), 123 (77.4%), 8 (57.1%)
-widowed: 11 (6.4%), 11 (6.7%), 10 (6.3%), 1 (7.1%)
- divorced: 17 (9.8%), 16 (9.7%), 16 (10.1%), 1 (7.1%)
- separated: 2 (1.2%), 2 (1.2%), 2 (1.3%)

BMD (g/cm²)
- Hip: 173 (1.095), 165 (1.094), 159 (1.094), 14 (1.100)
- Spine Lateral: 113 (0.800), 105 (0.794), 105 (0.794), 8 (0.880)
- Spine PA: 173 (1.107), 165 (1.108), 159 (1.107), 14 (1.105)
- Total Body: 173 (1.172), 165 (1.171), 159 (1.170), 14 (1.193)
- LBM: 173 (63.65), 165 (63.47), 159 (63.60), 14 (64.29)
- % Body Fat: 173 (26.82), 165 (26.70), 159 (26.83), 14 (26.63)
Abstract 1103 in Proceedings of the AACR, Volume 45, March 2004

Claudia C. Leiras, Francesmary Modugno, Joel Weissfeld, Joel Nelson. University of Pittsburgh, Pittsburgh, PA and University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: Elevated androgen levels, and in particular dihydrotestosterone (DHT), are believed to play a causal role in prostate cancer. DHT also regulates hair growth and patterning.

Methods: We examined the association between hair patterning and prostate cancer in an ongoing case-control study of Caucasian men in Pittsburgh, PA. Cases (n=126) were men diagnosed with incident, early stage, primary prostate cancer who had not undergone treatment. Controls (n=70) were community dwelling men with no history of prostate cancer and with a recent PSA level of less than 3.0 ng/mL. All subjects completed a 30 minute standardized, in-person interview. Hair patterns at age 30 and 40 were assessed using the Hamilton Scale of Baldness. Subjects were asked to select the picture that most closely resembled their hair pattern at different ages. We used multivariable logistic regression to assess the relationship between prostate cancer and hair patterns adjusting for current age.

Results: At age 30, 16% of subjects reported vertex (back of head) balding and 8% reported frontal (front of head) balding. At age 40, 29% of men reported vertex balding while the percent of men with frontal baldness remained unchanged. Compared to controls, cases were more likely to report vertex baldness at age 30 (OR=2.93; 90% CI=1.09-7.31). No difference in frontal baldness at age 30 was evident (OR=1.1; 90% CI=0.45-2.7). Results were similar at age 40: OR for vertex balding = 1.23 (90% CI=0.70-2.17); OR for frontal balding = 0.99 (90% CI=0.40-2.45).

Conclusion: These data suggest that vertex baldness, and in particular early onset vertex baldness, may be a biomarker of prostate cancer risk.