FOX CHASE CANCER CENTER
TEMPLE HEALTH

Protocol Title
Nicotine Dependence and Lung Cancer Genetics in African Americans

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1.0 Introduction

Racial differences in the burden of lung cancer persist despite significant nationwide efforts to promote smoking cessation. A higher incidence of lung cancer is notable among African American (AA) in comparison to Whites, and this has not changed for more than a decade.[1] Despite the fact that AAs smoke fewer cigarettes per day than Whites,[2,3] they are less likely to stop smoking and are more likely to engage in deeper and longer inhalations.[4-7] Although access to health care and other systemic and socio-economic barriers contribute substantially to these problems, biological factors continue to be a critical contributor to lung cancer disparities.[8] In particular, research by the study investigators and others [9-11] (see also preliminary work section) have raised the intriguing possibility that differences between AA and Whites may be attributable to genetic factors that may be contribute to poorer metabolism of tobacco-related carcinogens and increased risk of addiction.[12-14]

2.0 Objectives

Aim 1: Identify ancestry-informative variants in tobacco metabolism and detoxification pathway genes that correlate with metabolic/detoxification capacity in AA smokers.

Aim 2: Identify ancestry-informative variants in tobacco addiction pathway genes that correlate with measures of nicotine dependence in AA smokers.

Aim 3: Explore the possibility that genetic feedback about increased lung cancer risk associated with African American ancestry may influence perceived risk, cancer worry, acute psychological distress, and motivation to quit.

3.0 Background/Rationale

Genetics, race, tobacco-related carcinogen metabolism, and addiction. Two prominent groups of potent tobacco carcinogens are benzo[a]pyrene and tobacco-specific nitrosamines such as N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). NNK is reduced in the body to NNAL and activated by Phase I enzymes to a reactive metabolite that alkylates DNA or is further detoxified by Phase II enzymes in the *UGT* pathway to NNAL – glucuronide (NNAL-Gluc). Phase III enzymes (ABC transporters) are known to efflux Phase II conjugates from cells to enable excretion from the body. NNAL is a potent carcinogen in rats.[15,16] Studies demonstrate that urinary NNAL-Gluc:NNAL ratio, a measure of an individual's metabolism and detoxification capacity, is higher in Whites compared to AA,[13,14] suggesting racial differences in metabolic activation/detoxification of tobacco smoke carcinogens. Genetic polymorphisms have been described for a number of Phase I, II/III enzymes involved in the metabolism of tobacco and efflux of carcinogens. Many of these polymorphisms have been linked to phenotypic differences in protein activity or expression and are likely to be a major source of inter-individual variation in susceptibility to tobacco carcinogenesis and thus increased lung cancer risk.[17-23] Levels of urinary NNAL metabolites can be influenced by polymorphisms in the Phase I and II genes,[24,25] highlighting the importance of genetic variants in tobacco metabolism and carcinogenesis.

Interestingly, the association of genetic variants in Phase I/II/III genes with the metabolism and efflux of tobacco smoke carcinogens from cells may prove to be dependent on race, because the frequency of these polymorphisms varies among racial/ethnic groups.[26] Our preliminary data presented below also provides further support by demonstrating that in Phase I/II/III genes,

polymorphisms with varied frequencies between AA and Whites (i.e., Ancestry Informative Markers [AIMs]) are predicted to be biologically important and could influence the expression and function of these genes. Less well studied are ancestry informative polymorphisms related to addiction. Although a number of studies have identified associations between a variety of genetic polymorphisms and addiction and smoking-related outcomes,[11, 27,28] no study to date has specifically investigated effects of ancestry-informative markers on addiction and smoking behavior in AA smokers.

Clinical relevance of genetic risk information. One potentially important clinical application of genetic testing for lung cancer risk is the provision of test feedback to smokers in the hopes of encouraging cessation. Accumulating research in this area has yielded mixed results, with recent meta-analyses suggesting that genetic feedback about increased lung cancer risk can result in significant short-term improvements in smoking cessation, but no long-term changes.[29] These findings are perhaps not surprising, given the poor long-term smoking cessation success rates, even with available treatments. Experimental studies that systematically manipulate risk information and assess immediate outcomes that are relevant to behaviour change (e.g., worry, perceived risk, motivation to quit) might provide a clearer and more accurate picture of the utility of genetic testing feedback in presenting a "teachable moment" in which to intervene to encourage behaviour change. Consistent with this possibility, Consultant Lipkus and colleagues[30] conducted an experimental study in which hypothetical lung cancer genetic risk information was manipulated, and they found that high-risk information caused immediate increases in motivation to quit smoking. Our pilot data from AA current smokers also confirms this. Similarly, other experimental studies using hypothetical risk information as a model found that genetic risk feedback resulted in immediate increases in worry and perceived risk.[31, 32] Overall, the literature suggests that experimental studies of hypothetical risk can be a useful tool in understanding the short-term effects of receiving genetic risk information. What has not yet been examined is the possibility that adding personally relevant information to the feedback can enhance effects. Feedback regarding genetic ancestry may thus also have a significant impact on perceived risk, worry, and motivation to quit. Based on empirical and theoretical models of heath literacy and numeracy advanced by Consultant Lipkus and others,[33, 34] the proposed study will explore the potentially important contribution of personally relevant quantitative information to key motivational outcomes related to behaviour change. For example, AA smokers who are informed that their genetic ancestry is in fact highly concordant with AA heritage may be particularly concerned about genetic risks that have been shown to be overrepresented in AAs. Conversely, those who learn that they have low levels of genetic concordance with AA heritage may then self-identify less strongly as AA, resulting in lower concern for genetic risks that are overrepresented in AA smokers. To date, no study has investigated this intriguing possibility**.**

4.0 Study Design

This is a multi-centered study being conducted at the following centers:

Fox Chase Cancer Center (FCCC) by the lead investigator, Camille Ragin, PhD, MPH. FCCC will serve as the coordinating center for this study.

CUNY Hunter College under the direction of Joel Erblich, PhD, MPH will conduct community based research initiatives and recruit study participants from the community.

Icahn School of Medicine at Mount Sinai with Claudia Henschke, MD will obtain IRB approval, recruit subjects and execute the protocol at Mount Sinai.

We will enroll 360 AA smokers, 180 from clinic-based settings in Philadelphia and NYC that serve smokers and 180 from the general community in Philadelphia and NYC. This recruitment strategy will provide a regionally-diverse sample with an increased range of smoking and dependence levels, which will enhance generalizability, as well as power to detect hypothesized genetic effects. To ensure that the demographics of both clinic and community-based samples are balanced, both subgroups will be matched on age and gender.

Subjects that had participated in protocol 14-814, PI Ragin's cohort of cancer-free individuals and indicated they would like to be contacted for possible participation in future research will be offered an opportunity to enroll in this study. These participants will complete the intervention aspect of the study and we anticipate they will help us to reach our recruitment goals. This protocol enrolled subjects in NYC and Philadelphia. It also allowed those enrolled to be notified of other cancer related studies led by Ragin and/or her collaborators.

Recruitment and study setting: Philadelphia and NYC are racially diverse, with AAs comprising a large portion of the general populations. This proposed study will leverage on our existing cohort (CAP3) infrastructure, as well as the considerable resources of the Mount Sinai Health System, with which we have partnered to enhance recruitment.

4.1 *Subject Recruitment and Data Collection*

Face-to-face: As previously described in IRB 11-880, study subjects will be recruited from various locations throughout the metropolitan area of the aforementioned study cities (for example, stores, shops, community centers, senior centers, health fairs etc.). Based on results from protocol 11-880, we have determined that "on-site" (face-to-face) recruitment from various locations throughout the Philadelphia metropolitan area works best for control recruitment; subsequently, we will use this method as the primary recruitment method for this study. Primary care and specialty clinics within TUHS (e.g. ENT and Pulmonary clinics) to identify current smokers. We will also utilize study flyers (attached in recruitment section) throughout the TUHS with the contact information for study staff. If the individual calls in we will answer any questions and schedule their enrollment during their next appointment at a TUHS clinic.

After informed consent is obtained Mouthwash/Saliva samples will be collected at the completion of the study questionnaire. Participants will be supplied with a 50 mL falcon tube containing 10ml of scope. Participants will be instructed to gargle while tilting to the back of the throat for 30-60 seconds before spitting it back into a separate tube. Participants will be required to have refrained from eating and drinking at least 30 minutes prior to performing the mouthwash rinses. All mouthwash samples will be transported at 4 degrees Celsius (on ice packs) to the laboratory where they will be processed. All samples will be labeled with a unique ID number corresponding to the questionnaire but without personal identifiers. For urine collection, study staff will instruct the participant on how to conduct a clean catch urine sample and the participant will self-collect in nearest rest room.

All participants with a history of cancer screening (e.g. Pap test, breast mammography [females], PSA and/or DRE [males], oral or skin cancer screening, etc.) within the past 12 months will be asked to sign an authorization to request information from another facility. We will use the standard authorization form used by Fox Chase

Cancer Center (FCCC) (attached), which authorizes the research study staff to request cancer screening results from another health care facility/medical provider. The signed authorization form will be sent along with a memo outlining the specific cancer screening result that would be requested. All reports will be de-identified upon receipt and labeled with the participants study ID number. The cancer screening results will be collected in order to confirm self-reported cancer status.

All study materials will be labeled with a unique ID and no PHI. Maintenance of participant confidentiality is discussed in detail within the "Risk to Participants" section of this document.

For Aim 3: Participants recruited through Aims 1 and 2 at each of the two study sites will be randomly assigned to one of four conditions, in a 2 x 2 fully-crossed between-groups factorial design. In one group ("High Risk, High Ancestry [HRHA]"), participants will be asked to consider a hypothetical scenario in which genetic test results reveal that: 1) they carry genotypes that place AA smokers at a particularly high (~50%-80%) risk for the development of lung cancer, and 2) their profile of AIMs reflects a particularly high concordance with AA heritage (~90%). In a second group ("Low Risk, Low Ancestry [LRLA]"), participants will be asked to consider a scenario in which genetic test results reveal that: 1) they are at normal (~7%-10%) risk for the development of lung cancer, and 2) their profile of AIMs reflects a particularly low concordance with AA heritage (~10%). The final two groups will receive "High Risk, Low Ancestry (HRLA)" and "Low Risk, High Ancestry (LRHA)" hypotheticals, respectively. Participants will be block randomized by age and gender to one of four groups following the 2 (Risk) x 2 (Ancestry) design. To increase feasibility, randomization will be conducted independently at all sites. Following randomization, participants will be presented with a brochure describing the nature of two hypothetical genetic tests, one which assesses lifetime risk for the development of lung cancer in AA smokers, and one which characterizes the degree of a participant's genetic concordance with AA ancestry. The brochure will be explained in a standardized fashion to the participants by the graduate student trainees. Participants will then be given the hypothetical feedback according to their randomized condition (HRHA, HRLA, LRHA, LRLA), followed immediately by the post-feedback assessments (see Measures). Participants will then be debriefed, offered a $30 gift card, and thanked for their participation.

Intervention Administration: The intervention will be administered by graduate student trainees. They will be trained to administer the brochure and feedback in a standardized fashion. Dr. Erblich will train the graduate students in the administration of the hypothetical genetic feedback and the collection of questionnaire data during the post-feedback assessment. The trainees will practice with each other until they achieve proficiency. Dr. Erblich will also personally observe the first five participant interactions in both NYC and Philadelphia, as well as a random selection of later interactions (n=10) to ensure intervention fidelity. Additional training will be conducted as necessary to ensure fidelity to the intervention.

To address Aim 3, we will administer the following well-established questionnaires, all of which have excellent psychometric properties. The questionnaires are brief, so as not to create undue participant burden. Numeracy, an important predictor of response to risk information, will be assessed using the 7-item Subjective Numeracy scale (SNS), developed by Fagerlin and colleagues. Self-perception of Ancestry Scale (a personal

estimation of the genetic proportion of African ancestors) will be assessed using a measure described and validated by Ruiz-Linares et al.

Post-Feedback Assessment: Motivation to quit will be assessed using the Motivation to Quit Smoking Scale (MTSS), which has been found to be a strong predictor of quit attempts.74,75 Perceived risk of lung cancer will be assessed using an established face-valid perceived risk scale developed and used by PI Erblich in previous work. Cancer worry will be assessed using the well-established 4-item Cancer Worry Scale. Psychological distress will be measured using the BSI-18. For all assessments, participants will be instructed to respond based on how they believe they would feel if they actually received the genetic information that was presented to them.

Projected Recruitment: The number of participants that will be enrolled into this study will be 180 for 3 years (approximately 60 patients per year, per site).

Number of subjects per year projected at FCCC	Total number of subjects at FCCC	Number of subjects nationally or internationally (if applicable	Number of subjects at collaborating institutions (if applicable)
Up to: 60	Up to:180	360	180

4.2 *Inclusion and exclusion criteria*

Key Inclusion Criteria:

1. Men and women age 18 years and older and able to speak and read English
2. Must be in good health and not knowingly have a cancer at the time of study inclusion

Key Exclusion Criteria:

1. Head and Neck cancer diagnosis at the time of the oral cancer screening
2. Low DNA quantity found in mouthwash/saliva sample
3. Incomplete questionnaire data
4. Cancer diagnosis within the last 2 years

5.0 Risks to Participants

Risk to the subject is breach of confidentiality. In order to minimize this risk, all information obtained from or for this research study will be kept as confidential as possible. Identification of questionnaire data and saliva specimens will be assigned a coded study number and files will be kept secure.

6.0 Potential Benefits to Participants

No direct benefit will be gained by subjects, except for the satisfaction they might experience by participating in a medical research study. Benefits to society will be those associated with a better understanding of the effects of ancestry on motivation to quit smoking and screen for lung cancer.

7.0 Provisions to Maintain the Confidentiality of Data
All specimens and associated data (questionnaire, cancer screening results, urine specimen, as well as mouthwash samples) will be stored with a unique ID only and not with subject identifiers. Identifiable information will never be placed on specimens or associated data (laboratory or questionnaire data).

8.0 Costs to Participants
Not Applicable

9.0 Consent Process
On-Site Recruitment: Local Information tables will be set up in various locations such as senior centers, community recreation centers, churches, community health fairs and neighborhood block meetings. The information table will be manned by research staff who will explain the research studies conducted in the Ragin Lab and the purpose of the participant recruitment.

Recruitment initiated by Phone-Call: Research staff will call participants that enrolled in 14-814 and indicated their interest in future research opportunities and briefly describe the study objectives and rationale. The research staff will answer all questions asked by the potential participant and an invitation will be extended to participate in this study. If he/she agrees to enroll in this study, they will sign an informed consent document, questionnaires will be administered, and biological samples will be collected by trained research staff.

As part of the informed consent process, all participants recruited in this study that have not been enrolled in 14-814 will be given an opportunity to join the 14-814 registry study. On-Site Recruitment as described in section 9.0 of that protocol will be followed.

10.0 Off-Study Criteria
Participants will only be removed from the study if a cancer diagnosis is made at the time of the oral cancer screening or if the participant is re-contacted for other research opportunities within the Ragin Lab and they had a cancer diagnosis subsequent to joining the study.

11.0 Drugs and Devices
Not Applicable

12.0 Multi-Site Research Study
This study will be conducted at sites across the northeastern region of the country. Survey data and biological specimens collected from NYC and Philadelphia, will be housed at FCCC.
In an effort to minimize a breach in participant confidentiality, all site-PIs and their respective team members will: provide current Human Subjects Training and be given access to both Presage Lite and REDCap, where they will securely enter patient information and complete study related questionnaires. Paper copies are also available for back up if needed. Scanned copies of signed consent forms will be emailed to the study coordinator at FCCC using HIPAA compliant networks and stored in a password protected file on FCCC stored on a HIPAA compliant institutional network drive. Only coded bio-specimens will be sent to FCCC where all laboratory procedures will take place.

Adverse events that take place at an external site will first be reported to the respective site's IRB followed by FCCC's IRB. All study findings will be reported under the blanket of the African Caribbean Cancer Consortium, a collaborative research group where Dr. Ragin is the PI.

13.0 Statistical Analysis

Aim 1: Variance stabilizing and normalizing transformations will be applied when appropriate. Descriptive statistics for demographic variables will be presented. The range and mean concentrations of free (NNAL), conjugated (NNAL-Gluc) and total (NNAL+NNAL-Gluc) biomarkers will be summarized by genotype. These concentrations as well as the ratio of NNAL-Gluc:NNAL concentrations will be correlated with each AIM after adjusting for smoking dose (pack-years), age and recruitment setting (clinic vs. community) using analysis of variance. A similar analysis will be done by correlating these variables with each haplotype block. In addition, multiple linear regression will be used to correlate NNAL concentration with proportion of African ancestry after adjusting for smoking dose, age and recruitment setting. To account for multiple testing, the Benjamini-Hochberg (BH) method will be used to control the false discovery rate (FDR). All tests will be two-sided and tests with FDR ≤ 10% will be considered to be statistically significant.[35]

Sample Size and Power: With 360 samples split in a 1:3 ratio between the minor and major allele groups, we will have 80% power to detect an effect size of 0.45 in mean NNAL concentration (total) between the groups using a two-sided test at a significance level of 0.005. This computation is based on a standard deviation of 1 for NNAL concentrations (on the log2-scale) from pilot studies. An effect size of 0.45 corresponds to a 1.37-fold change in NNAL concentration between groups. Similarly, with 360 samples split in a 1:3 ratio between the minor and major allele groups, we will have 80% power to detect an effect size of 1.09 in mean NNAL concentration ratio between the groups using a two-sided test at a significance level of 0.005. This computation is based on a standard deviation of 2.44 for NNAL concentration ratios (on the log2-scale) from pilot studies. An effect size of 1.09 corresponds to a 2.13-fold change in NNAL expression between groups. A significance level of 0.005 results in 1 false discovery per 200 non-differentially expressed SNPs.

Aim 2: For each SNP, nicotine dependence (as determined by high-very high FTND scores: 6-10) will be modeled using genotype after adjusting for smoking dose (pack-years), age and recruitment setting using logistic regression (LR). Sensitivity, specificity and prediction accuracy (along with 95% confidence bounds) will be used to characterize the precision of binary predictions from LR. Multiple linear regression will be used to correlate the proportion of African ancestry with FTND score (low vs. high) after adjusting for smoking dose, age and recruitment setting. All tests will be two-sided and the Benjamini-Hochberg method will be used to account for multiple testing.[35] Secondary outcomes will include cigarettes per day, age at initiation, and intention to quit. To account for the potentially large number of SNPs resulting from this univariate analysis, penalized logistic regression (PLR) will be used to develop a prediction model for nicotine dependence using these SNPs.[36] PLR has been demonstrated to have excellent power to identify covariate effects as well as superior prediction accuracy compared to competing methods like Classification and Regression Trees and Multifactor Dimensionality Reduction.[37-40] Sensitivity, specificity and prediction accuracy (along with 95% confidence bounds) will be used to characterize the precision of binary predictions from PLR. AUC curves (along with 95% confidence bounds) will be used to characterize the predictive value of models from these methods. A participant whose predictive probability is > 0.5 will be classified as having high nicotine dependence; however, alternative thresholds will also be evaluated in this

analysis. In addition, the performance of each model will be evaluated using leave-one-out cross validation. All computations will be performed using R statistical language and environment.[41]

Sample Size and Power: With 180 subjects each in the low-medium (scores 0-5) and high-very high (scores 6-10) nicotine dependence groups, we will have 80% power to detect a difference in the range of 0.14-0.19 (in minor allele frequency between groups in SNPs of interest) at the 0.005 significance level. This calculation assumes a 10-40% minor allele frequency in the low nicotine dependence group.

Aim 3: Variance stabilizing and normalizing transformations will be applied to the data as appropriate. Analysis of variance will be used to identify the individual and interaction effects of factors on each outcome measure. The Benjamini-Hochberg FDR method[56] will be used to adjust for multiple tests involving each factor or interaction across the various outcome measures, and each test with an FDR ≤ 10% will be considered significant. The primary study analyses will be a 2 (Risk) x 2 (Ancestry) factorial ANOVA. With this statistical approach, we will be able to test for main effects of Risk and Ancestry, as well as Risk x Ancestry interactions. The primary outcome measure will be motivation to quit; perceived risk, cancer worry, and psychological distress will serve as secondary outcomes. In addition to this primary analysis, we will also consider including covariates (e.g., demographics, numeracy, FTND, study site, gender, age) to control for external sources of variation. Finally, we will be able to explore possible moderating effects of these covariates. Although of course, the proposed study is not powered to detect such effects, such exploratory findings may be important when deciding next steps in formally utilizing the results to develop interventions aimed at increasing knowledge of genetic lung cancer risk.

Sample size and power: Power computations for this aim are based on the 2 x 2 factorial design described above. With 90 participants per experimental condition (combination of genetic risk and ancestry), we would be able to detect an effect size of 0.685 due to genetic risk or ancestry at a significance level of 0.0125 with 80% power. Similarly, we would be able to detect an effect size of 0.895 due to an interaction between genetic risk and ancestry at a significance level of 0.0125 with 80% power.[42] A significance level of 0.0125 has been used to account for the four outcome measures of interest in this aim and the calculations are based on a standard deviation of 1.37 for motivation to quit smoking from the literature.[43]

14.0 Data Safety Monitoring Plan

The PIs and Co-Is have the responsibility to oversee data handling, safety and issues of confidentiality, and has the responsibility to train research team members in procedures for safeguarding the well-being of human subjects and the confidentiality and correct handling of data as well as data storage. The PIs are responsible for monitoring protocol conduct and reporting to the Institutions' Data & Safety Monitoring Board (DSMB) any adverse events related to study procedures. The PIs will also be responsible for reviewing and completing the adverse event assessment.

15.0 Adverse Events

In accordance with FCCC guidelines, this protocol will employ the following mechanisms for adverse event reporting: 1) alert the FCCC review committees of any and all reports of adverse events; 2) inform all members of the study team of any all reports of adverse events. If 3 or

more adverse events are reported, the study team will assess potential causes of the adverse events and, if events are clearly linked to study participation, discontinue the study.

16.0 Quality Assurance Procedures and Participant Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations required a signed subject authorization informing the subject of the following: The protected health information (PHI) that will be collected from patient; who will have access to that information and why; who will use or disclose that information; the rights of a research subject to revoke their authorization or use their PHI. In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information prior to the revocation of subject authorization. To ensure confidentiality identifier will be recorded and used with electronic data collected and all records will be secured in a locked location.

All participants will be screened for eligibility using a checklist created for this study and the Principal Investigator will regularly audit accrual to ensure that participants meet eligibility criteria. In addition, the Principal Investigator will regularly audit the study files to ensure that questionnaires completed by participants contain all study items. Lastly, in order to protect confidentiality, all data will be numerically coded and will contain no other identifying factors. Information linking the numeric codes to the participant's name will be kept in a secured file cabinet in a secured office. In addition, computer data files will be stored on password-protected computers.

17.0 Participant Informed Consent

See separate Informed consent document

18.0 References

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