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TITLE: Mammographic Breast Density in a Cohort of Medically Underserved Women

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## **Introduction**

The purpose of this HBCU/MI Partnership Training Award is to train Meharry Medical College (MMC) faculty to conduct independent breast cancer research by collaborating with faculty from Vanderbilt University Medical Center (VUMC). Three MMC faculty will undergo intensive training supervised by three VUMC faculty during year 1 with additional training taking place in subsequent years. To reinforce training, faculty from MMC and VUMC will conduct a case-control study of mammographic breast density to investigate its' association with obesity and insulin resistance in years 2 through 4. Cases (n=150) whose breasts are in the upper quartile of breast density and controls (n=850) whose breast are in the lowest three quartiles of breast density, will be recruited from the MMC Center for Women's Health Research which serves a medically underserved population. Specific aims are: 1) to assess mammographic breast density through digital mammograms; for a sample of women we will also assess mammographic breast density through film mammograms to determine the diagnostic accuracy of digital versus film mammogram, 2) to obtain information on breast cancer risk factors including health literacy, and to collect anthropometric measurements and fasting blood, 3) to assay blood for select hormones and growth factors, 4) to perform statistical analyses to determine the associations between obesity and insulin resistance and mammographic breast density, and 5) to evaluate patients' ability to understand their mammogram findings as they are explained by their medical provider.

## **Body**

As indicated in the Statement of Work (Appendix), this project is occurring in two phases, the training phase (year 1) and the investigation phase (years 2 through 4). We completed all training tasks during the first year of the project; however, Dr. Corey Jones an MMC co-investigator has left Meharry. Dr. Jones who was taking coursework toward completion of the Master's of Science in Clinical Investigation degree was replaced by Dr. Heather O'Hara, a Preventive/Occupation Medicine physician with a Master's of Science in Public Health, effective September 18, 2012. Ongoing training tasks include the attendance of MMC investigators at workshops and conferences, and Institutional Review Board (IRB) approval of the Mammographic Breast Density Project. Dr. Sanderson presented a poster at the Society for Epidemiologic Research conference and has submitted a manuscript from the poster for review (Appendix includes abstract using data from Dr. Sanderson's previous study DAMD17-03-1-0274), and Dr. Khoder attended the American Society for Clinical Oncology conference. We obtained continuing Institutional Review Board (IRB) approval for the project from MMC on 8/24/2012, VUMC on 5/1/2012, and the Department of Defense (DOD) on 8/24/2012.

During the second year of the project we moved from the training phase into the investigation phase. The study team has met on a monthly basis and the investigative team (Drs. Sanderson, O'Hara, and Khoder from MMC and Drs. Dupont, Shu and Peterson from VUMC) has met on a quarterly basis. Between January and September, 2012 we completed subject recruitment and data collection of 244 women (Appendix includes table of response rates). We partially completed investigation tasks 2 through 5 by quantitating mammographic breast density measurement; recruiting subjects and collecting data; assessing health literacy; and processing blood samples, taking body measurements and performing assays. We partially completed investigation tasks 7 and 8 by conducting ongoing quality assurance audits to ensure patient safety and integrity, and conducting interim analyses.

During the third year of the project, we will continue with the investigation phase. Drs. Sanderson, O'Hara and Khoder will attend workshops and conferences when possible. We will partially complete investigation tasks 2 through 5, and 7 and 8. Investigation tasks 6 and 9 will be completed in subsequent years.

### **Key Research Accomplishments**

- Completed ongoing training task by Drs. Sanderson and Khoder attending and/or presenting posters at workshops and conferences.
- Completed ongoing training task by obtaining continuing IRB approval from three entities.
- Partially completed investigation tasks 2 through 5 by recruiting subjects and collecting and processing data (digital mammograms, blood, body measurements, questionnaires including health literacy).
- Partially completed investigation tasks 7 and 8 by conducting quality assurance audits and interim analyses.

### **Reportable Outcomes**

#### 1) Manuscripts

Not applicable

#### 2) Abstracts

Sanderson M, Perez A, Weriwoh ML, Alexander L, Peltz G, Agboto V, Jones CD, Khoder W. Perinatal factors and breast cancer risk among Hispanics. Am J Epidemiol 2012;175:S6.

#### 3) Grants

Not applicable

### **Conclusions**

The overall goal of this proposed HBCU/MI Partnership Training Award is to strengthen the existing collaborative relationship between the minority institution, MMC, and the collaborating institution, VUMC. The investigators from MMC and VUMC have mutual interests in studying the interplay of lifestyle and molecular factors on breast cancer risk as measured by its precursor, mammographic breast density. High mammographic breast density is comparable in its predictive magnitude of risk to historically well-established breast cancer risk factors. The biological basis for the association between higher percentage of density and risk of breast cancer is not clear but may be related to increased stroma and glandular tissue in dense breasts through estrogen exposures or production of certain growth factors including insulin-like growth factor-I (IGF-I) or adipokines such as leptin. Very few studies have focused on obesity and insulin resistance as they relate to mammographic breast density. We hypothesize that: 1) obesity and insulin resistance, defined as high levels of C-peptide, will be positively associated

with high mammographic breast density, and 2) these associations will be more pronounced among women with high levels of IGF-I and high levels of leptin.

This project will establish associations between some lifestyle and molecular factors and mammographic breast density; known to be linked to subsequent breast cancer, especially in minority and medically underserved women. By identifying biomarkers that influence mammographic breast density in minority women, this project may provide therapeutic targets for new prevention strategies in this population. While faculty from VUMC has expertise in breast cancer research, faculty from MMC has strong ties with minority communities in Nashville and Davidson County. To date, limited breast cancer research has been conducted at MMC. By partnering together, MMC and VUMC hope to build infrastructure to conduct population-based case-control studies of breast cancer at MMC, and to establish an outstanding collaborative breast cancer research program.

### **References**

Sanderson M, Perez A, Weriwoh ML, Alexander L, Peltz G, Agboto V, O'Hara H, Khoder W. Perinatal factors and breast cancer risk among Hispanics. (under review)

**Statement of Work**Phase 1: Training Phase (Year 1)

**Task 1:** (Drs. Sanderson, Khoder, Jones, Richard-Davis, Disher, Sanderson, Dupont, Peterson and Shu)

- 1a. Drs. Sanderson, Khoder and Jones audit courses at Summer Research program at University of Michigan (months 6-7).
- 1b. Dr. Jones begins the Meharry Medical College, Master's of Science in Clinical Investigation Program (months 1-30).
- 1c. Consult with advisory board and health providers in the Center for Women's Health Research (CWHR) to design a cross-sectional study for measurement of mammographic breast density, related hormones and health literacy (months 1-3).
- 1d. Develop and finalize study protocol for recruitment of participants (months 1-6).
- 1e. Develop and finalize study protocol for obtaining analog screening mammograms and digital mammograms (months 1-3).
- 1f. Finalize advertisements for contacting participants, questionnaires, and other data collection forms (months 1-3).
- 1g. Order supplies for blood collection and processing, order supplies for performing assays (months 5-6).
- 1h. Create and finalize quality assurance audit forms to ensure safety of participants and integrity of all data (months 4-6).
- 1i. Update IRB protocols, informed consent documents, and HIPAA waivers for IRB submission (months 4-6).
- 1j. Generate standard operating procedures manual to reflect all aspects of study procedures (months 4-6).
- 1k. Work with Dr. Dupont to modify accrual database to include scripts and screening forms, and allow accrual and productivity reports to be generated (months 7-12).
- 1l. Work with the project coordinator to create REDCAP database for entry of study data (months 7-12).

Phase 2: Investigation Phase (Years 1 through 4)

**Specific Aim 1)** to assess mammographic breast density through digital mammograms; for a sample of women we will also assess mammographic breast density through analog mammograms to determine the efficacy of digital versus analog mammogram;

**Specific Aim 2)** to obtain information on breast cancer risk factors including health literacy, and to collect anthropometric measurements and fasting blood;

**Specific Aim 3)** to assay blood for select hormones and growth factors;

**Specific Aim 4)** to perform statistical analyses to determine the association between obesity and insulin resistance and mammographic breast density;

**Specific Aim 5)** to evaluate patients' ability to understand their mammogram findings as they are explained by their medical provider.

**Task 2:** (Drs. Sanderson, Dupont, Disher, Khoder)

Quantitate mammographic breast density measurement, Months 1-42.

- 2a. Work with Dr. Disher to refine protocols for mammographic density analyses (months 1-12).
- 2b. Work with Dr. Disher to observe Cumulus computer program to quantify breast density (months 7-12).
- 2c. Coordinate flow of digital mammography data from the Center of Women's Health Research to Dr. Disher for quantitation (months 7-42).
- 2d. Assess breast density of mammograms using digital quantitative analysis to obtain the percentage of the breast occupied by breast tissue (months 7-42).

**Task 3:** (Drs. Sanderson, Jones, O'Hara, Disher)

Recruit subjects and collect data, Months 7-42.

- 3a. Screen and recruit potentially eligible women for digital mammography study at the Center for Women's Health Research (1,000 patients total) (months 7-42).
- 3b. Administer questionnaire (months 7-42).
- 3c. Perform standardized body measures; weight, height, skinfold thickness, and waist and hip circumference (months 7-42).
- 3d. Collect blood samples and transport to Vanderbilt molecular epidemiology laboratory for storage and processing (months 7-42).
- 3e. Order additional supplies as needed (months 7-42).

**Task 4:** (Drs. Jones, O'Hara, Khoder and Peterson) Months 7-42.

- 4a. Administer Short Test of Functional Literacy in Adults (S-TOFHLA) to study participants (months 7-42).
- 4b. Score S-TOFHLA instruments and categorize levels of patient's health literacy (months 7-42).

**Task 5:** (Drs. Sanderson, Jones, O'Hara, Khoder and Shu)

Process blood samples, measurements and perform stated assays, Months 7-42.

- 5a. Supervise research staff in acquisition and analysis of data (months 7-42).
- 5b. Separate serum, plasma and clot in blood sample and store at -80°C (months 7-42).
- 5c. Transport biospecimens to the Vanderbilt University molecular epidemiology laboratory for processing and analysis (months 7-42).

**Task 6:** (Drs. Khoder, Disher and Dupont) Months 7-42.

- 6a. Obtain analog mammography films and digital mammography films for each participating patient for rating of quantitative breast density by interpretation (months 7-42).
- 6b. Calculate the sensitivity and specificity of each modality for detecting mammographic breast density (months 7-42).
- 6c. Perform statistical analyses to account for multiple comparisons in breast density subgroups (months 40-42).

**Task 7:** (Drs. Sanderson, Jones, O'Hara, Khoder , Dupont)

Conduct ongoing quality assurance audits to ensure patient safety and data integrity, Months 7-48. Twice monthly monitoring of activities (number of screening phone calls logged, number and type of contacts with potential or actual participants, progress with data entry, etc.).

- 7a. Twice monthly monitoring of study accrual (months 7-42).
- 7b. Continuous monitoring/reporting of potential adverse events (months 7-48).
- 7c. Monthly audits to verify study staff adherence to standard operating procedures (months 7-48).

**Task 8:** (Drs. Sanderson, Jones, O'Hara, Khoder, Shu, Dupont, Peterson)

Conduct interim analyses, Months 12-48.

- 8a. Perform interim statistical analysis (months 12-18, months 24-30, months 36-42).
- 8b. Preparation and submission of abstracts reflecting findings to date (months 36-48).
- 8c. Creation and submission of annual reports to funding agency (months 12, 24, 36).

**Task 9:** (Drs. Sanderson, O'Hara, Khoder, Shu, Dupont, Peterson)

Final analyses and dissemination of data, Months 22-48.

- 9a. Begin final statistical analyses (months 40-48).
- 9b. Preparation and submission of final report to funding agency (months 48).
- 9c. Preparation and submission of abstracts and manuscripts reflecting final results (months 40-48).

**Perinatal factors and breast cancer risk among Hispanics.**

M. Sanderson, A. Pérez, M.L. Weriwoh, L. Alexander, G. Peltz, V. Agboto, C.D. Jones, W. Khoder

We assessed whether perinatal factors were associated with breast cancer among Hispanics, a group with fairly low incidence rates of breast cancer. We used data from a case-control study of breast cancer among Hispanics age 30 to 79 conducted between 2003 and 2008 on the Texas-Mexico border. In-person interviews were completed with 188 incident breast cancer cases ascertained through surgeons and oncologists, and 974 controls who were designated as high-risk (n=510) and low-risk (n=464) for breast cancer (with respective response rates of 97%, 83% and 74%). Multiple imputation and multinomial regression were used for data analysis. After adjustment for age, menopausal status and mammography screening, relative to birthweight 2,500-3,999 grams, there were non-significant decreases in breast cancer risk for birthweight of  $\geq 4,000$  grams (high-risk controls odds ratio [OR] 0.75, 95% confidence interval [CI] 0.39-1.41; low-risk controls OR 0.61, 95% CI 0.32-1.18). Non-significant reductions in breast cancer risk were also seen for preterm birth (high-risk controls OR 0.30, 95% CI 0.07-1.26; low-risk controls OR 0.30, 95% CI 0.06-1.41). Although based on small numbers, twins were at substantially increased breast cancer risk (high-risk controls OR 2.02, 95% CI 0.74-5.54; low-risk controls OR 6.07, 95% CI 1.50-24.5). Our results tended to differ from previous studies of this topic perhaps due to the different hormonal milieu among Hispanics relative to Caucasians, African Americans and Asians in whom all previous studies of this topic have been conducted. Confirmation of our findings in larger studies may assist in determining how hormonal mechanisms responsible for breast cancer differ by race/ethnicity.

**Response numbers through 10/15/2012****Women who Called/Contacted by Study Staff by Month of Entry into Study<sup>a</sup>**

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Total
Total contacted	49	40	37	39	47	49	107	70	7	5	450
Eligible	46	40	31	33	39	40	75	59	7	5	375
Ineligible	3	0	6	5	8	8	15	7	0	0	52
Pending eligibility	0	0	0	1	0	1	17	4	0	0	23

**Reasons Ineligible by Month of Entry into Study<sup>a</sup>**

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Total
Total Ineligible	3	0	6	5	8	8	15	7	0	0	52
Past participant	1	0	3	1	2	2	2	2	0	0	13
Age	0	0	1	0	3	2	1	1	0	0	8
Hx of cancer	1	0	1	2	0	1	5	1	0	0	11
Hx breast surgery	0	0	0	1	2	2	2	2	0	0	9
Current breast problem	1	0	1	1	1	1	5	1	0	0	11

**Status of Eligible Participants by Month of Entry into Study<sup>a</sup>**

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Total
Total Eligible	46	40	31	33	39	40	75	59	7	5	375
Completed	39	30	26	24	28	33	50	21	0	0	251
Appt pending	0	0	0	1	0	0	4	27	7	5	44
Missed appt	1	3	3	5	7	6	18	11	0	0	54
Refused	4	4	2	1	3	1	2	0	0	0	17
Ill or disabled	1	1	0	0	1	0	1	0	0	0	4
Wrong number	1	2	0	1	0	0	0	0	0	0	4
No response x 10	0	0	0	1	0	0	0	0	0	0	1

<sup>a</sup> Twelve women who were contacted in December are included in January numbers.

**Among Completed Interviews/Mammograms by Month Completed<sup>a</sup>**

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Total
Completed Interviews	22	21	22	30	30	34	42	27	16	7	251
Avg Time Elig-Intvw (days)	8	17	30	32	20	23	24	19	39	54	24
Mammograms											
Normal mammograms	22	20	18	26	31	31	37	22	15	0	218 <sup>b</sup>
Abnormal mammograms	0	1	4	4	3	3	5	5	0	0	25
Results pending	0	0	0	0	0	0	0	0	0	4	4

**Among Completed Interviews/Mammograms by Month Completed**

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Total
Age (mean)	51.7	50.2	49.5	51.1	50.7	50.8	52.4	50.1	50.8	56.3	51.1
Spanish-speaking	2	10	5	5	2	4	1	0	0	0	29
Race <sup>c</sup>											<b>Total (%)<sup>c</sup></b>
African-American	16	4	12	16	16	17	23	17	12	5	138 (55.4)
White	1	3	4	8	7	9	16	8	4	2	62 (24.9)
Hispanic	3	10	5	5	4	7	2	1	0	0	37 (14.9)
Native-American	0	0	0	0	1	0	0	1	0	0	2 (0.8)
Other	2	3	1	1	2	0	0	0	0	0	9 (3.6)
Don't Know	0	1	0	0	0	0	0	0	0	0	1 (0.4)

<sup>a</sup> Twelve women who were contacted in December are included in January numbers.

<sup>b</sup> One woman had mammogram has not returned for interview; 5 women completed interview are pending mammogram.

<sup>c</sup> No race data on 2 women whose interviews were stopped; other race includes: African-American/Native American (3), White/African-American/Native American (2), White/African-American (1), African-American/Hispanic (1), Native American/Jewish (1), Black - from Dominican Republic (1)