Barriers to Obtaining Sera and Tissue Specimens of African-American Women for the Advancement of Cancer Research

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Supplementary Issue: Health Disparities in Women

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ABSTRACT: African-American women, a historically understudied and underserved group, have increased risk for triple-negative breast cancer and obesity-associated disease. Obesity-associated metabolic diseases share a common link of low grade chronic inflammation, but not all obese women have metabolic disturbances or are inflamed. One goal of our ongoing research is to identify blood biomarkers that can predict increased risk of breast cancer in women who have obesity or metabolic dysfunction. However, vulnerable populations that stand to benefit most from advances in biomedical research are also underrepresented in research studies. The development of effective, novel approaches for cancer prevention and treatment will require significant basic medical research effort to establish the necessary evidence base in multiple populations. Work with vulnerable human subjects at a safety net hospital enabled us to comment on potential obstacles to obtaining serological and tissue specimens from African-American women. Here, we report some unexpected barriers to participation in our ongoing research study that might inform future efforts.

KEYWORDS: obesity, African-American women, cardiometabolic risk, inflammatory biomarkers

SUPPLEMENT: Health Disparities in Women

CITATION: Strissel et al. Barriers to Obtaining Sera and Tissue Specimens of African-American Women for the Advancement of Cancer Research. *Clinical Medicine Insights: Women's Health* 2016:9(S1) 57–61 doi:10.4137/CMWH.S34698.

TYPE: Original Research

RECEIVED: January 28, 2016. **RESUBMITTED:** June 8, 2016. **ACCEPTED FOR PUBLICATION:** June 13, 2016.

ACADEMIC EDITOR: Nicole Powell-Dunford, Editor in Chief

PEER REVIEW: Twelve peer reviewers contributed to the peer review report. Reviewers' reports totaled 2,943 words, excluding any confidential comments to the academic editor.

FUNDING: This work was supported by grants from the National Institutes of Health (T32 AI089673, DAN, DK090455 and U01 CA182898, GVD; Boston Medical Center Carter Disparities Fund, NK). The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: No potential conflicts of interest relevant to this article were reported. GVD is the immediate past chair of the Obesity and Cancer Section of The Obesity Society; the investigators are recipients of research grants from the National Institutes of Health; and support from both The Obesity Society and the American Association of Immunologists. None of these organizations had any role in the preparation or content of this report. The authors take sole responsibility for the opinions expressed herein.

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Paper subject to independent expert single-blind peer review. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE).

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Introduction

African-American women, a population with high rates of obesity, experience higher risk of poor-prognosis triple-negative breast cancer and higher mortality rate than White women.[1–3] To help address this disparity, researchers need access to blood and tissue specimens. However, traditionally disadvantaged patients such as African-Americans frequently distrust researchers, making subject enrollment and retention difficult.[4] Environmental stressors that compound problems of recruitment and study retention for vulnerable subjects include: (1) living in public housing in US inner cities, (2) family environments that rely on public support to augment low-wage jobs, (3) living in neighborhoods with high rates of violent crime and social isolation, or (4) reduced participation in the health-care system.[5]

Stressful urban environments can make outdoor physical activity rare and promote sedentary behaviors, which can lead to obesity.[6] Insulin-resistant obesity features chronic systemic[7] and local inflammation of adipose tissue,[8] which has been linked to breast cancer outcomes.[9] However, not all obesity is alike with respect to disease risks. A quarter of obese adults remain relatively metabolically healthy, despite obesity. These subjects, who lack markers of inflammation,[10–12] are protected from cardiometabolic comorbidities of obesity[13] and from obesity-associated cancer risks.[14]

We do not fully understand the mechanistic relationship between obesity-driven inflammation and breast cancer outcomes, or why some women become inflamed and others do not, even when both are equally obese. The goal of our ongoing research is to identify inflammatory biomarkers that associate with metabolic status—metabolically unhealthy subjects versus metabolically healthy obese (MHO) subjects—and can predict future breast cancer risk in African-American women. To accomplish this goal, we are currently conducting a multidisciplinary, cross-sectional study to measure immunometabolic variables in African-American women at

Boston Medical Center (BMC), who present for elective breast reduction mammaplasty. The obstacles encountered while conducting these studies shed light on barriers to study participation and specimen collection of underserved or minority populations. Ultimately, our experience with recruitment and study participation of African-American women can inform future research effort.

Methods

Participants and recruitment. All procedures are approved by the Institutional Review Board of Boston University Medical Center in accordance with the Declaration of Helsinki. The investigation into barriers for enrollment is an IRB approved use of our data. All subjects provide informed consent. Potential subjects are recruited from obese patients who were presented for elective breast reduction surgery in the BMC Division of Plastic and Reconstructive Surgery, Boston University School of Medicine. Inclusion criteria are body mass index (BMI) $>$ 30 kg/m^2. Qualified subjects with hypertension (systolic blood pressure [sBP] 140–159 mmHg, diastolic blood pressure [dBP] $>$ 85 mmHg), elevated fasting triglyceride (TG) (>1.70 mM), and type 2 diabetes (T2D) (glycated hemoglobin [HbA1c] $>$ 6.5%) are included. Exclusion criteria for subjects are acute infectious illness or fever within two weeks prior to surgery, type 1 diabetes, autoimmune disease, cancer, poorly controlled hypertension (BP $>$ 160/100), atherosclerotic cardiovascular disease (CVD), stroke, blood disorders, or other serious illness. Patients are first contacted by the Department of Plastic and Reconstructive Surgery and recruited through clinical staff. There are no additional contacts apart from review of the consent form, and agreement or disagreement to participate. Subjects may either agree or not, in the form of checkoff boxes on the consent form to the following: to be contacted for future studies, to the banking of their tissue, for tissue RNA analysis, and to self-identify as African-American or mixed race, Latina or Hispanic ethnicity.

Recruitment methods employed are based on practical considerations and our surgical collaborator's preference. During initial consultation, surgeons identify potential subjects two to three weeks in advance of their surgical procedure date and provide an information sheet to inform them about the study. The potential subject may then indicate her interest, and if she wishes, is invited to meet privately with the clinical coordinator to learn more about the study and proceed with the consent process. Nursing staff provide an advance list of scheduled surgeries to the clinical coordinator, who then consults the electronic medical record to determine patient eligibility to enroll and to obtain date of surgery, type of procedure, and surgeon's name. The study coordinator de-identifies and records this information using a randomly assigned identification number. The clinical coordinator then approaches potential eligible subjects at a presurgical follow-up visit, or when the patient arrives on the day of surgery, to ask if they might be or are still interested in participating. Collected information of noneligible subjects, or subjects excluded for scientific reasons, is destroyed.

Study design/sample/data collection and analysis. Breast adipose tissue was resected during surgery and under anesthesia. A portion of the normally discarded tissue and axillary subcutaneous adipose tissue (when available) was used for research purposes. Blood samples were collected from an established line prior to surgery. Blood was used for measurements of circulating factors that change in response to metabolism and health status (eg, insulin or HbA1c). Prevalence data were obtained from study records and by the study coordinator's verbal recall of subject interviews. Female subjects (BMI $\geq$ 30 kg/m^2) were classified into either an unhealthy obese group (diagnosis of type 2 diabetes, blood HbA1c $>$ 6.5%, and hypertension, BP $>$ 130/85) or a healthy obese group (neither type 2 diabetes nor hypertension), based on medical record or blood measures.

Results

We were able to enroll a total of 18 subjects in this study. Approximately 50% of subjects approached by clinical coordinators for study enrollment denied participation. The 50% response rate to study enrollment contributed to low study enrollment. In addition, the number of MHO women seen in the plastic surgical practice was much higher than indicated in a preliminary review of hospital statistics. A majority of subjects had BMI $>$ 35 kg/m^2, but only one subject had type 2 diabetes. African-American women were younger than anticipated. Young age likely contributed to better metabolic health (Table 1).

Three subjects who appeared to fit the racial/ethnic category for eligibility chose not to self-identify as African-American. Because achieving target enrollment and retention

Table 1. Prevalence of metabolically healthy obese and metabolically unhealthy obese AA women

	SUBJECTS PER GROUP	
	MHO (N = 17)	MUO (N = 1)
Age group (years)		
<20	1	0
20 to 39	7	0
40 to 59	9	1
≥60	0	0
BMI group (kg/m^2)		
Normal weight, 18.5–24.9	2	0
Overweight, 25–29.9	5	0
Class I obesity, 30.0–34.9	10	1
Class II obesity, 35–39.9	0	0
Class III obesity, ≥40.0	0	0

Abbreviations: AA, African-American; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

of subjects is a challenge for research studies,[15] we wanted to understand why some subjects preferred not to self-identify as Black or African-American. Of the 21 subjects who had indicated interest to enroll, 18 did self-report as African-American or Black race. Medical records for the three subjects who declined showed country of origin to be the United States, South Africa, or Cape Verde. Declination to self-report race/ethnicity by subjects reduced the study population by three. However, the study is limited because subjects were not interviewed further to understand their reasons not to self-identify.

Four subjects declined blood collection and six declined axial adipose tissue collection, even though Health Insurance Portability and Accountability Act protections were well described during the consent process, including the concept that no extra sample would be taken. Due to the difficulty of obtaining consent for blood or tissue for RNA, we utilized qualitative interviews and assessed responses of enrolled subjects to the choices in the study consent form, to better understand why subjects declined participation for certain aspects of the study. Subjects mentioned, "Are they going to make the cuts bigger to take out extra tissue?" or "I don't want anyone to follow me or to find me". Five of the six subjects who declined consent for axial tissue also declined medical record assessment. Subjects who declined blood collection also declined both RNA analysis and medical record assessment (Table 2). Subjects generally declined medical record examination (12 of 18), suggesting a mistrust about the intended use of materials and records, particularly Health Insurance Portability and Accountability Act-protected information. The declined consent for both blood and medical record examination of four of the study subjects prevented our assessment of their metabolic status, which prevented assignment to either a control or experimental group, narrowed the study population, and reduced statistical power.

Overall, the low number of subjects currently enrolled in the study significantly hindered data analysis. Basic multivariate analyses (supervised hierarchical clustering, multiple regression analysis, or principal component analysis) to evaluate differences in cytokine profiles between metabolically unhealthy obese (MUO) and MHO groups were not possible. Fewer enrollment limited data analysis to assess the association of cytokine signatures with overall metabolic risk.

Discussion

We are concerned that the African-American women most at-risk for obesity-associated inflammation, metabolic disease, and obesity-driven breast cancer were not well represented among the study population. Obese patients with comorbid type 2 diabetes and hypertension were infrequent candidates for this elective surgery. It is likely that the elective nature of breast reduction surgery selects for healthier women, who already have resources and insurance to consider this surgical option. Clinical colleagues have indicated that metabolically unhealthy obese women are likely seen in the

Table 2. Prevalence of declined consent for specific use of surgical tissue or other among the 18 enrolled subjects.

SUBJECT #	DECLINED CONSENT OF BREAST FAT TISSUE	DECLINED UNDERARM FAT	DECLINED BLOOD COLLECTION	DECLINED RNA ANALYSIS	DECLINED MEDICAL RECORD EXAMINATION
1		X	X		X
2					X
3		X			X
4					
5					X
6		X			X
7		X			X
8					
9			X		X
10					
11		X			X
12					
13		X	X	X	X
14					
15					X
16					
17			X	X	X
18					X
Total	0/18	6/18	4/18	2/18	12/18

diabetes outpatient service, or may not receive medical care at all. Therefore, it is unlikely that we or others will be able to study breast adipose tissue characteristics in these at-risk individuals. Nonetheless, we may be able to leverage what we have learned about inflammatory cytokine profiles matched to breast adipose tissue for healthier subjects and extrapolate risk using blood only. However, this approach is contingent on the participation of all ethnic groups in a prospective clinical trial, in which the biomarkers will be tested. Due to varying cancer and cardiometabolic risk among ethnic groups, risk extrapolations from one population to another may not only be inaccurate but also detrimental.

The consent process must be optimized to minimize negative reactions from potential participants. It is imperative to emphasize the purpose and benefits of the study, the rigorous protection of personal information, and any changes to the standard of care. Altruism was recently identified as a positive motivator for study enrollment and tissue donation.[16,17] Willingness to donate saliva and/or blood was based upon subjects' understanding of the purpose of the study and the idea that future patients could potentially receive improved treatment.[17]

The use of a culturally competent clinical coordinator may also help to dissipate long-held, negative perceptions associated with research in minority populations.[18] Matching the ethnic and racial background of the clinical coordinator to the target population is another approach that may aid in recruitment and retention of minority populations. Our study employed three different clinical coordinators, one of whom shared the race/ethnicity of the target population. Last, our results also lead us to speculate that studies that rely on self-identification of race and ethnicity could benefit from diversified options for self-reporting.

Understanding how breast cancer risk assessment and screening may be improved for African-American women is critical. Research efforts have demonstrated that despite high rates of current mammography screening, breast cancer mortality for African-American women is still significantly higher than for White women.[19–21] Reducing this disparity will be dependent on diminishing barriers to research participation for African-Americans and other minority groups.

Barriers to participation in medical research are multifactorial[22] and complex,[23–26] such as environmental pressures of living with economic insecurity combined with the stressors of subtly pervasive racism.[27] Deeply rooted reasons for mistrust of the scientific community can thrive among individuals, families, neighborhoods, communities, and populations.[28] From Tuskegee to Henrietta Lacks, the scientific community has created an entrenched research environment that can be understandably challenging for African-Americans to embrace. Lead contamination of the public water supply in Flint, Michigan, where an African-American majority population has felt consistently lied to by public officials, has continued to undermine trust in public health authorities.[29] Damaged trust hinders critical scientific discoveries, especially when reluctance extends to tissue sample donation.[30] For example, the 19.4% difference between the number of subjects reporting interest to participate in a study and the number of actual tissue donations arises in part from subject privacy concerns.[17,31] Given these trends, reducing persistent barriers due to mistrust may require additional study,[31] building trust, and community outreach and education.[17,32–35] Community-based approaches have shown promise for increasing enrollment in cancer research studies, as well in participation in tissue banking efforts.[17,36] These endeavors are worth the time and resources to ensure proper and true informed consent that addresses past injustices.

Based on our experience, future study design will take into account the potential barriers to study enrollment and participation. However, reluctance to participate in blood-based screening may be expected to continue, despite the promised benefit for improved risk assessment in a vulnerable population. The effort to understand, define, and then inform national decision-making must continue to ensure equal participation and equal access to medical advancements.

Acknowledgments

We thank the Boston Medical Center (BMC) patient population for their willingness to participate as research subjects in this disparities-focused research, as well as the physicians, nursing and administrative staff, and past study coordinators, Brianna Krafcik-Morgan and Victoria Lattanzi. We thank our immunology colleagues, particularly Dr. Barbara Nikolajczyk, for support and thoughtful comments, as well as the American Association of Immunologists, particularly Dr. Jennifer Meyers, for programmatic interest in obesity-associated inflammatory biomarkers and mechanism. We are grateful for the ongoing support and enthusiasm of our colleagues in disparities research, including Drs. Deborah Bowen (University of Washington), Renée Boynton-Jarrett (BMC Pediatrics), and Carla Boutin-Foster (Weill Cornell Medical College). We thank obesity researchers at Boston University School of Medicine, particularly Dr. Caroline Apovian, and the leadership of The Obesity Society for their vision and commitment to eliminate health disparities in obesity medicine.

Author Contributions

Performed experiments: KJS. Researched data: KJS, DAN, and MC-C. Wrote the manuscript: KJS, DAN, NK, and GVD. Provided funding and supervised the study as the principal investigator: GVD. All the authors have reviewed the manuscript and took responsibility for the integrity of the data, interpretation and the accuracy of the analysis.

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