Award Number: DAMD17-97-1-7111

TITLE: The Relationship Between Endocrine Factors and Breast Cancer Risk

PRINCIPAL INVESTIGATOR: Tanya D. Agurs-Collins, Ph.D.

CONTRACTING ORGANIZATION: Howard University
   Washington, DC 20059

REPORT DATE: September 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
   Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

The views, opinions and/or findings contained in this report are
those of the author(s) and should not be construed as an official
Department of the Army position, policy or decision unless so
designated by other documentation.
**REPORT DOCUMENTATION PAGE**

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

<table>
<thead>
<tr>
<th>1. AGENCY USE ONLY (Leave blank)</th>
<th>2. REPORT DATE</th>
<th>3. REPORT TYPE AND DATES COVERED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>September 1999</td>
<td>Annual (15 Aug 98 - 14 Aug 99)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. TITLE AND SUBTITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Relationship Between Endocrine Factors and Breast Cancer Risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. AUTHOR(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanya D. Agurs-Collins, Ph.D.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard University</td>
</tr>
<tr>
<td>Washington, DC 20059</td>
</tr>
</tbody>
</table>

E-MAIL: TAGURS-COLLINS@FAC.HOWARD.EDU

<table>
<thead>
<tr>
<th>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Army Medical Research and Materiel Command</td>
</tr>
<tr>
<td>Fort Detrick, Maryland 21702-5012</td>
</tr>
</tbody>
</table>

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

The present study is designed to examine the relationships between hyperinsulinemia, insulin-like growth factor-1, central adiposity, maximal adult weight, physical fitness and breast cancer risk in post-menopausal African-American women. The research design is a case-control study of women 55 to 79 years of age. Eligibility criteria for the cases will be newly histologically confirmed primary breast cancer. Both cases and controls will be identified during the same time frame and will come from the same population base. None of the controls will have a previous history of malignant or gynecological conditions that may have the same risk factors in breast cancer. Plasma levels of IGF-1 and insulin will be measured by radioimmunoassay. Central adiposity will be measured as waist-to-hip ratios (WHR). Multiple logistic regression will be used to determine age adjusted odds ratios for tertiles of waist, hip, WHR, maximal adult weight gain and levels of physical activity. Corresponding 95 percent confidence intervals will be based on the logistic regression models.

14. SUBJECT TERMS

central adiposity, physical activity, insulin, breast cancer, insulin-like growth factor-1, waist-to-hip ratio

15. NUMBER OF PAGES 8

16. PRICE CODE Unlimited

17. SECURITY CLASSIFICATION OF REPORT

Unclassified

18. SECURITY CLASSIFICATION OF THIS PAGE

Unclassified

19. SECURITY CLASSIFICATION OF ABSTRACT

Unclassified

20. LIMITATION OF ABSTRACT

Unlimited
FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

Where copyrighted material is quoted, permission has been obtained to use such material.

Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

N/A In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

X For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

N/A In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

N/A In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.
INTRODUCTION

The purpose of the study is to examine the relationships between central adiposity, maximum adult weight gain, physical fitness, hyperinsulinemia, insulin-like growth factors (IGF-1) and breast cancer risk. The majority of the studies that examined the relationship between breast cancer risk and weight used body mass index (BMI) as their measure for weight. However, BMI measures overall obesity and therefore may not be a sensitive indicator for breast cancer risk. Others have proposed that waist-to-hip ratios (WHR) are a more sensitive measure because it is closely related to the metabolic consequences of obesity such as alterations in ovarian hormones, fasting glucose metabolism and growth factors that have been shown to promote breast cancer cell growth. Several studies examined WHR’s in postmenopausal women, but not with an African American population. Moreover, these studies did not determine whether WHR is associated with increased levels of IGF-1. Increased levels of insulin and IGF-I were found to be potent mitogens for the stimulation of growth in human breast cancer cells. Since WHR is believed to be associated with IGF-1 through increased levels of insulin, it is important to document this relationship. Central adiposity, hyperinsulinemia and IGF-1 may be biological markers for breast cancer risk.

Another lifestyle factor that affects breast cancer risk is time of weight gained and physical activity. Instead of measuring weight and physical activity at one point in time, it is more important to measure maximal adult weight gain and physical activity during that period of time when a woman is undergoing hormonal change such as menarche, pregnancy and menopause. Timing of weight gain/change and physical activity with hormonal change is more relevance to risk for postmenopausal breast cancer. It may be possible to prevent or decrease breast cancer risk by maintaining a healthy weight and exercising more during the time of hormonal change. Specifically, this research is expected to show that central obesity is positively associated with increased levels of insulin, IGF-1 and risk for breast cancer. Additionally, we expect to show that increased levels of IGF-1 and maximal adult weight gain are positively associated with the risk for developing breast cancer and to determine the time period for the protective effect of physical activity with breast cancer risk.
BODY

Task 1: Develop and finalize questionnaires for printing.
Study questionnaires were developed and finalized in February 1998.

Task 2: Hiring and Training Staff
After the grant was awarded August 15, 1997, the two positions along with the position
descriptions for medical research assistant and data manager were approved by the University in
October 1997. The positions were advertised and potential candidates were interviewed in November
and December 1997. Two persons were selected and started working on the project in January and
February 1998. In February, they were trained regarding study goals, objectives, protocols,
responsibilities and how to finalize study questionnaires.

Task 3: Recruitment of cases and controls: informed consent; data collection
The research design is a case-control study of postmenopausal women who are 55 to 79 years
of age. Initially, the sample size in the proposal was 50 cases and 50 control. However, after the
revised budget was submitted, DOD asked me to respond to the study weakness cited by the
reviewers. One of the cited study weaknesses was that the sample size was too small to detect a
difference. In response to the reviewer's critic, the sample size was increased from 100 to 244
subjects. The increased is based on 80% power, alpha=0.05 and a relative risk of 2.0 for 122 cases
and 122 controls (35). However, the original grant proposal and revised budget does not reflect this
increase in sample size.

In February 1998, recruitment of patients started at the Howard University Mammography
clinic and at the Georgetown Medical Center in October 1998. A prescreening questionnaire was
developed and administered to potential participants to determine initial eligibility. After the patients
met the prescreening criteria, they are given an appointment to determine final screening criteria.
Once the patients are eligible, they participate in a (1) one-hour data collection interview.

From February 1998 through August 15, 1999, we have recruited 87 postmenopausal women
without breast cancer who are serving as the control subjects and 30 postmenopausal women with
breast cancer. To date we have enrolled 117 patients. The recruitment of women with breast cancer
is slow. There are several reasons for this. First, the recruitment criteria eliminates persons who are
diabetic and who are taking estrogen replacement therapy since the study is measuring insulin-like
growth factor type-1 (IGF-1) and estradiol. In the African-American population, the prevalence of
Type II diabetes is very high among women. It is becoming increasing difficult to find
postmenopausal women who are not taking some form of estrogen replacement therapy. Also, we are
finding a larger number of premenopausal black women with breast cancer when compared to
postmenopausal black women at our institution. Therefore, expanding the recruitment database to
include additional sites to recruit patients for the study is essential. We started recruiting patients from
the Georgetown Medical Center in October 1998. Unfortunately, this institution did not have the
number of minority patients that was predicted. In May 1999, I submitted a proposal to the DC
General Hospital's Institutional Review Board, which has a large minority population-base. We will
start recruiting at this institution in October 1999. The addition of this site will increase the number of breast cancer patients for this project.

The PI sent a letter dated May 17, 1999, requesting a no-cost extension for one year to continue recruiting women into the study. Approval for the extension was granted in August 1999.

**Task 4:** Send Plasma to Laboratory for analysis; work with oncologist to determine primary breast cancer cases.

Plasma samples are drawn into tubes containing ethylene-diaminetetraacetic acid (ETA). The plasma is separated by centrifugation and analyzed by Quest Diagnostics, Inc., which is a commercial laboratory. The research team works very close with the medical oncologist and radiologist within the various institutions.

**Task 5:** Data Entry

All questionnaires have been coded. As women accrue, laboratory and epidemiological data are entered into the software program “Microsoft Excel” for future analyses.

**Task 6:** Data analysis; Final Report

Data analysis and final report will be completed August 2000.

**STATEMENT OF WORK**

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Months</th>
<th>Technical Objectives</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-2</td>
<td>Develop and finalize questionnaires for printing.</td>
<td>Completed</td>
</tr>
<tr>
<td>2</td>
<td>1-3</td>
<td>Hiring and Training Staff</td>
<td>Completed</td>
</tr>
<tr>
<td>3</td>
<td>4-28</td>
<td>Recruitment of cases and controls; informed consent; Data collection</td>
<td>On-going</td>
</tr>
<tr>
<td>4</td>
<td>4-30</td>
<td>Send Plasma to Laboratory for analysis; work with Oncologist to determine primary breast cancer cases.</td>
<td>On-going</td>
</tr>
<tr>
<td>5</td>
<td>4-30</td>
<td>Data Entry</td>
<td>On-going</td>
</tr>
<tr>
<td>6</td>
<td>31-36</td>
<td>Data analysis; Final Report</td>
<td>Not yet Addressed</td>
</tr>
</tbody>
</table>

**KEY RESEARCH ACCOMPLISHMENTS**

- Finalizing study questionnaires
- Hiring of study personnel
- Enrolling 117 African American women
- On-going data entry
CONCLUSIONS

To date, 117 African American women are enrolled in the study. Recruitment for postmenopausal African-American women with breast cancer is slow because of our exclusion criteria which eliminates women with Type II diabetes and women taking estrogen replacement therapy. However, we have taken the necessary steps to broaden our recruitment efforts. We are currently recruiting at the Georgetown University Medical Center and will start recruiting at the DC General Hospital in October 1999. The PI received approval from DOD for a one-time, no cost extension until August 15, 2000 to complete the study. The extension is needed to successfully complete the project by allowing more time to recruit breast cancer cases.