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TITLE: Evaluation of Feasibility for a Case-Control Study of Pituitary-Ovarian Function in Premenopausal Women with Breast Cancer

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13. ABSTRACT (Maximum 200 Words) Background: Postmenopausal women with elevated estrogens are at an increased risk of breast cancer, but an association of estrogens with breast cancer in premenopausal women has not been clearly established. Objective/Hypothesis: We will evaluate the feasibility of a case-control study that uses gonadotropin releasing hormone (GnRH) agonist stimulation tests to compare pituitary-ovarian function in premenopausal women with breast cancer with unaffected controls. Hypotheses to be tested in the full-scale study are: 1) premenopausal women with breast cancer secretes more luteinizing hormone (LH) and follicle stimulating hormone (FSH) in response to GnRH compared to controls; 2) premenopausal women with breast cancer secrete more estradiol and testosterone in response to gonadotropins, and this is related to their higher insulin like growth factor -1 (IGF-1) levels compared to controls; 3) increased estradiol production in premenopausal women with breast cancer is due to increased enzyme activity at a specific step in steroidogenesis. Specific Aims: Specific aims of the feasibility study are: 1) determine the feasibility of a full-scale study; 2) gather preliminary data on basal and GnRH stimulated serum levels of LH, FSH, estradiol, and testosterone in women with breast cancer compared to controls. Study Design: A case-control study will be conducted at FCCC.				
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Introduction: Elevated serum levels in postmenopausal women have been shown to increase the risk of breast cancer. However, the association of serum estrogens with breast cancer in premenopausal women has not been established. The purpose of this study is to determine the safety and feasibility of conducting a case-control study that uses gonadotropin releasing hormone (GnHR) stimulation tests to evaluate the sensitivity of the hypothalamic pituitary ovarian (H-P-O) axis in premenopausal women with breast cancer compared to unaffected premenopausal women. The full-scale study will determine if: 1) the anterior pituitary of premenopausal women with breast cancer secretes more luteinizing hormone (LH) and follicle stimulating hormone (FSH) in response to GnRH compared to controls; 2) the ovaries of premenopausal women with breast cancer secrete more estradiol and testosterone in response to gonadotropins, and this is related to their higher insulin like growth factor -1 (IGF-1) levels compared to controls; 3) increased estradiol production by the ovaries in premenopausal women with breast cancer is due to increased enzyme activity at a specific step in steroidogenesis.

Body: Research accomplishments are described for each task outlined in the approved statement of work.

Task 1: Prepare for data collection, Months 1-2

- a. Finalize data collection protocol and forms. This activity has been completed and all questionnaires have been approved by both the FCCC IRB and the DOD IRB.
- b. Finalize database design and data entry screen. This activity has been completed.
- c. Hire and train program coordinator. This activity has been completed, but changes in personnel have delayed progress. These personnel changes have been motivated by career decisions, Leigh Coakley completed nursing school and left to take a nursing position at a local hospital, and Chris Chatham, who replaced Leigh, left soon after to take another better paying position. Deb Riordan assumed the study coordinator position April 21, 2003, completed all human subjects and HIPPA training for certification and has been trained in all aspects of the study. We also have added a senior clinical research coordinator, Cecilia McAleer BS, CCRP, who works in the FCCC protocol office and has extensive experience in conducting clinical studies at FCCC. She is responsible for coordinating participant scheduling, preparing treatment orders, and ensuring that the appropriate staff are notified to collect and process the blood specimens. She will also assist with administering questionnaires and ensuring that all necessary forms are completed. She also has been trained in all aspects of the study.

Task 2: Identify and recruit participants, Months 2-6

- a. Search the FCCC Tumor Registry and Health Information Management System (HIMS) to identify potential cases and benign breast disease controls. The FCCC IRB required that we conduct the study in phases – recruiting and conducting GnRH stimulation tests in healthy premenopausal women during the first phase and conducting GnRH stimulation tests in premenopausal women treated for stage 0 or stage 1 breast cancer who did not receive any chemotherapy and who completed

- adjuvant therapy at least one year earlier during the second phase. Because we are currently recruiting healthy controls for phase 1, via advertisements and posters that have been approved by the FCC and DOD IRB's, this activity has not been initiated.
- b. Obtain physician approval to contact cases and benign breast disease controls. For the reasons described above under (a), this activity has not been initiated.
 - c. Identify one friend control who is eligible and agrees to participate for each case. Friend controls have been replaced with healthy community controls because of the IRBs concerns about asking cases to identify friends who did not have breast cancer.
 - d. Send approximately 50 letters. Letters have been sent to 53 women.
 - e. Perform approximately 50 telephone interviews. As of May 28, 2003, 59 interested, premenopausal women have called in to obtain more information about the study. Sixteen women were not eligible for participation based on the preliminary screening questionnaire approved by the FCCC and DOD IRBs. Eleven women were no longer interested once they received more information about the study. Twenty-one women were potentially eligible based on the screening interview completed over the phone. An additional eleven women were sent study materials and will be recontacted to determine their interest in the study and potential eligibility.
 - f. Trace approximately 5 participants who moved. No participants have taken part in the study, therefore, this activity has not been initiated.

Task 3. Conduct data collection visits, Months 3-8. We are waiting for DOD IRB approval of changes to the protocol submitted in June 2003 before beginning data collection visits. These changes have been approved by the FCCC IRB.

- a. Administer 27 questionnaires.
- b. Measure heights and weights of 27 participants.
- c. Perform 27 GnRH stimulation tests, collect and store serum specimens
- d. Isolate DNA from lymphocytes for 27 participants and store
- e. Key and verify data

Task 4. Create a serum pool for laboratory quality control, Month 8. This task will be done when we get closer to conducting laboratory analyses.

Task 5. Measure LH, FSH, estradiol, testosterone, IGF-1, and IGFBP-3 concentrations in serum from 27 participants, Months 9-10. This task will be done after the GnRH stimulation study.

Task 6. Analyze data and write reports, Months 11-12. This task will be completed in the future.

- a. Perform statistical analyses
- b. Write final report
- c. Begin writing grant proposal for full scale study

Key Research Accomplishments:

- a. Our goal for the first phase of the study is to recruit 10 women.
- b. We have identified 21 women who are interested in participating and are potentially eligible.
- c. An additional 11 women have been sent study materials and will be recontacted to determine their interest in the study and potential eligibility.

Reportable Outcomes: None at this time.

Conclusions: This is an interim report for a pilot study. Based on our experience to date, it appears that we will be able to recruit healthy controls for a full scale case-control study that uses gonadotropin releasing hormone (GnRH) stimulation to determine sensitivity of the hypothalamic pituitary ovarian (H-P-O) axis in premenopausal women with breast cancer compared to unaffected premenopausal women. The full-scale study will also evaluate whether differences in serum IGF-1 and IGFBP-3 contribute to observed differences in ovarian steroidogenesis in premenopausal women with breast cancer and controls. Furthermore, it will determine if increased production of estrogens in premenopausal women with breast cancer following GnRH stimulation is related to increased enzyme activity at a specific step in the steroidogenesis pathway. Identification of the hormonal cause for breast cancer in premenopausal women could ultimately lead to detection of populations at increased risk, approaches to screening for women at high risk, and/or chemopreventive strategies that target the responsible enzyme or regulatory protein.

References: None at this time.

Appendices: None at this time.