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TITLE: Quasi-Prospective Study of Breast Cancer and Diet

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CONTRACTING ORGANIZATION: University of South Carolina
Columbia, SC 29208

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13. ABSTRACT (Maximum 200 Words)

Conventional breast cancer (BrCA)risk factors explain 50% of variability in disease rates and change in incidence over time. The past two generations of American women have experienced major changes in physical activity, preparing and eating food, and increases in the prevalence of overweight. These factors may exert powerful influences on physiologic processes leading to cancer. This case control study aims to investigate the relationship between physical activity, diet, and adult weight history and breast cancer. Our goal is to recruit 648 incident cases of breast cancer and up 2 controls per case from the Breast Care Centers of the Palmetto Richland and Baptist Hospitals of Palmetto Health /South Carolina Cancer Center (BCC) - services that see a total of about 35,000 mammography screenees each year and in which about 700 women are diagnosed with breast cancer. After obtaining permission from the Human Use Review Office of the USAMRAA (on 30 November 2000) to begin recruitment we finished the run-in process and began recruitment in the Baptist Hospital BCC in spring of 2001. To date, we have recruited 990 subjects. Recruitment at Richland began in May 2002.

14. SUBJECT TERMS
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QUASI-PROSPECTIVE STUDY OF BREAST CANCER AND DIET: Annual Report: Year 3

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Introduction:

It is clear from epidemiological studies that environmental factors are largely responsible for differences in breast cancer rates across populations and changes in U.S. rates over time. Dietary factors and those related to physical activity may have powerful influences on adult weight gain and several physiologic processes that could lead to cancer. However, obtaining unbiased self-reports of these behaviors is difficult, in part because they are subject to systematic reporting errors, such as recall and social desirability biases. This case-control study is measuring diet, adult weight history, and physical activity in women undergoing a diagnostic evaluation for potential breast cancer, but prior to diagnosis. The focus will be on two main suspects in breast cancer: consumption of fat as a factor that could be associated with increased risk; and certain fruits, vegetables, and grains containing high concentrations of functional constituents (phytoestrogens, antioxidants, protease inhibitors, indole glucosinolates) that may be protective. High levels of adult weight gain and physical inactivity, both of which may be related to increased risk, will be examined both as potential confounders to the diet exposures as well as independent predictors of breast cancer risk. The unique design of this case-control study provides a way to measure diet and other self-report measures before they can be affected by a woman's knowledge of whether or not she has breast cancer. We expect that a total of about 13,000 women will receive routine mammography for the first time in the Breast Care Center at the Palmetto Richland Memorial Hospital Campus of the Palmetto Health Alliance/South Carolina Cancer Center (BCC) over the 48-month recruitment period. Of these, about 5,400 will have confirmation by advanced diagnostic techniques, and about 20% of these will have histologically confirmed breast cancer. We project that 60% of women coming in for advanced diagnostic techniques (N=3,240 women [20-80 yrs]), will be willing to participate, of whom one-fifth (n=648) will have primary breast cancer. Age-, clinical system (i.e., Richland vs. Baptist)-, and time-matched controls will be obtained from the remaining disease-free women who visit the respective clinical sites within 3 weeks of the time that her matched case (i.e., women with breast cancer) enters the clinical system. Results from this investigation will add to our body of knowledge of the modifiable behaviors that are associated with incident breast cancer.

Specific Aims:

Using information from recently completed studies on sources of bias in assessment of dietary intake, this study will attempt to reconcile discrepancies between results of laboratory animal studies and cross-national comparisons strongly implicating diet as a cause of breast cancer and those from conventional epidemiologic studies that are much more equivocal on this topic. It will account for a number of covariates, especially physical activity and adult weight gain. The purpose of the proposed research is to test whether a dietary pattern associated with high-fat (generally salty or sweet) foods increases risk whereas a pattern emphasizing whole grain and vegetable intake decreases risk. This study is designed with full recognition that dietary variables are collected using assessment methods that are seen by subjects as "tests" and, therefore, are susceptible to psychological factors that are known to affect individuals in test-taking situations. Because secondary prevention will remain an important issue for the foreseeable future, it is also important that assessed populations be accessible and amenable to follow up to determine which, if any, dietary factors may be predictive of prognosis among those diagnosed with breast cancer and to increase disease risk among those found to be free of disease at baseline. The faculty and staff of the Breast Clinic, from which all cases and the clinic-based controls will be obtained, have a keen interest in the research potential of the clinic. Given high rates and thoroughness of patient follow-up, the clinic also presents excellent opportunities to investigate the natural history of breast cancer prognoses and to follow up breast cancer patients.

The primary goal of the proposed research is to investigate the role of diet and adult weight gain, with historical levels of activity being obtained to "characterize prior activity" to use as an adjustment for confounding in the etiology of breast cancer. The secondary goal of the research

will be to assemble cohorts of disease-free, high-risk women and breast cancer patients to: 1. Establish breast cancer risk factors in women at high risk because of either a family history of the disease or presence of a precancerous lesion (i.e., women determined not to have breast cancer at the time of enrollment); and 2. delineate lifestyle, psychosocial and/or treatment factors that might affect prognosis in women with a histologically confirmed cancer of the breast, as done previously [1, 2].

Work Accomplished:

The approved Statement of Work (see Appendix 1) categorized the work objectives for the project into 4 discrete tasks, each with indications for the months from the study timeline in which these tasks will be accomplished. Due to unforeseen delays in getting Human Subjects approval from the Institutional Review Boards of the three bodies governing this research [(i.e., U.S. Army, University of South Carolina, and the Palmetto Health Alliance (now Palmetto Health)], the original study timeline was revised. The original timeline started in July 2000 (month 1) and participant recruitment was scheduled to begin in January 2001 (month 7). Final approval from all three institutions was not obtained until late February 2001, with recruitment beginning at Palmetto Baptist in the spring of 2001 and at the Richland Hospital campus of Palmetto Health in the spring of 2002. Full-scale recruitment at Richland began with the post-vacation flow of work in September 2002.

With improvements in diagnostic procedures and concomitant reductions in the interval between first contact with the clinical system and diagnosis, we have had to modify our study design as described below. The recruitment is now proceeding well. As a consequence of the design change, we have taken the opportunity to begin looking at the existence of bias in reporting health-related behaviors and will use these data in formal testing of study hypotheses, as we have done in previous work in BrCA studies. Differences in BMI (kg/m^2) of enrollees vs. screenees (but not cases vs. controls) indicate selection bias in overall enrollment into the study. Although it is too early to make strong inferences based on data collected, we have observed results confirmatory of other studies (i.e., higher breast cancer rates in the more educated and in Whites). Higher likelihood of BrCA in widowed women and lower likelihood in divorced and separated women are intriguing. Results indicating protection with more vigorous physical activity outside of the home and with more household activity are also consistent with those observed in other studies. There appear to be some differences emerging in terms of intakes of specific food groups, which will need to be monitored. Initial results on the DNA from buccal cells indicates sample adequacy.

In the following sections, each individual sub-task outlined in the Statement of Work (Appendix 1) is indicated in bold text and by a an alphabetic indicator (e.g., a, b, c,...). Our work to accomplish these sub-tasks follows in bulleted form. Where applicable, problems encountered in completing tasks are described and our plans for overcoming these barriers are outlined.

Task 1: Run-in Phase, Months 1-6 (July-December 2000):

a) Review baseline lifestyle and demographic questionnaire for completeness and for content validity.

- An initial Baseline questionnaire was complied (Appendix 2) and included the following sections
  - Demographics
  - Food Frequency Questionnaire
  - Physical Activity Assessment (Lifetime, Past-Year)
  - Medical/Family History
  - Personal Reaction Inventory (also known as the Marlowe Crowne Social Desirability Scale)
  - Martin-Larsen Approval Motivation scale (to measure social approval)
  - SF-36 Quality of Life

b) Revise baseline questionnaire as necessary.

- During questionnaire development phase, considerable refinement was made to several aspects of the baseline questionnaire in order to meet the objectives of this investigation and provide additional information about modifiable risk factors for breast cancer not specifically outlined in the original application (as secondary analyses)
  - The scope of the original FFQ was expanded to more effectively measure vegetable and fruit consumption in enough detail to evaluate specific dietary hypotheses
  - Two Physical Activity Assessments were adapted for self-administration
  - Sections on medical and family history were lengthened to support further research into the impact of sleep patterns, non-steroidal anti-inflammatory drugs, and various lifestyle factors on breast cancer development
- Ten clinic nurses pilot tested the baseline questionnaire in order to check for readability and relevance, as well as to assess the feasibility of administering a lengthy instrument to study participants.
- Pilot questionnaire data were also used to test questionnaire scanning software and SAS programming files. Data quality also was assessed from these pilot data.

c) Hire and train the Research Assistant.

- We currently employ four part time graduate assistants (2 PhD and 2 Masters candidates) and 2 assistants to recruit, collect data in the field and for data management tasks.
- A Data Manager is currently overseeing all aspects of data processing.

d) Develop a Manual of Operations (MOP), a detailed document describing data management systems.

- The MOP has been completed: and revisions were made as needed. (None required during this reporting period)

- The MOP's content is based on our successful experience with other large-scale epidemiologic studies, and describes how SAS, Teleform (optical scanning software), Excel, EpiInfo and other data management/tracking software are effectively integrated to manage and analyze the data.
- A Coding Manual was compiled and checked for accuracy.
- Standard Operating Procedures were developed to ensure that; participants are effectively and ethically recruited; high quality data are collected during the patient visits, and that data are efficiently and accurately entered for analysis.
- Security measures have been implemented to protect all participant information.

e) Develop and pilot test the participant tracking database, as well as all measurements and documenting procedures.

- A participant-tracking database has been constructed and is functioning in support of our recruitment and monitoring efforts.

f) Train staff in all data-related and clinic-based procedures.

- Staff is retrained on a regular basis to ensure quality data management and optimal procedures for participant recruitment, clinical measurements, and security.

Task 2: Recruitment, Months 7-48:

a) Of the 5,400 women visiting the Breast Care Center at the Palmetto Richland Memorial Hospital Campus of the Palmetto Health Alliance/South Carolina Cancer Center (BCC) for an advanced diagnostic work-up to rule in or rule out breast cancer, enroll 60% (3,240 women) as participants for the study.

As noted in the introduction, due to changes in regulations and the clinical system, it has been necessary to modify the recruitment strategy over time. We currently have settled on Strategy #3 as the final one that will be used for the duration of the study. We provide the three options considered as a permanent note for the record.

Strategy #1
Patients entering the clinical system for a screening mammogram were asked to complete a consent for telephone contact. Approximately 20% of the women were asked to return to the clinic for a diagnostic work-up for positive radiographical findings. Those patients who had agreed to contact upon screening were contacted and asked to participate.
Problems: Only 1/3 of patients who were scheduled for diagnostic work-up were referred from screening. The other 2/3 were patients referred by family physicians or Ob/Gyn physicians for suspicious symptoms (i.e. palpable mass). These patients did not have the opportunity to sign the consent for contact.
Strategy #2
Instead of telephone contact, we recruited participants as they waited for their diagnostic appointment in the clinic. No consent would be needed to talk with patients about their participation.

Problems: Although the response was positive, we were dependent upon the waiting time at the clinic. For instance, if the schedule was heavily booked, wait times were increased and participation increased. With less waiting time, patients were less inclined to participate. Other patients indicated that they would like to participate, but could not make a decision at that time because of anxiety associated with a diagnostic work-up. We also discovered that case recruitment did not meet expectations based upon clinic statistics. Thus providing further evidence that the anxiety associated with the appointment was preventing study participation.

Strategy #3

With improvements in diagnostic procedures and concomitant decreases in waiting time, most patients were completing the survey aware of their breast cancer status. Thus, the recall bias that we had hoped to avoid with the original study design was not possible. This necessitated the latest change in which cases and controls would be recruited via different clinical routes. Because of these changes in practice patterns, it was determined that we could go somewhat farther "downstream" to the oncology practice. Virtually all oncologists in the Midlands (the catchment area for the three tertiary care facilities serving the central portion of the state) practice out of South Carolina Oncology Associates (SCOA). Currently, SCOA has offices in each of the hospitals. At the end of 2003, they will be moving to a single practice site, which is centrally located in relation to the hospitals. Patients will receive all outpatient treatment at this site.

Cases: are now recruited after diagnosis and prior to chemotherapy administration. Places of contact for recruitment of breast cancer cases are the hospital tumor registry, oncologist office, breast health nurse, surgical service, and radiation oncology.

Controls: Because recruitment at the diagnostic appointment was not proving to be the optimal time to approach patients for participation, we will recruit controls via telephone recruitment after a screening or diagnostic appointment. Both mammography clinics will obtain consent for contact from all patients coming to the clinic for either a screening mammogram or diagnostic work-up. Those consenting to contact are placed in a database for telephone contact. Controls will be matched to cases on the hospital/clinic at which they were originally seen.

b) Using instruments described in section 4.2., collect data on: diet, physical activity, and other aspects of lifestyle; demographic variables; family and personal health-related history; and social desirability and social approval.

- Of the 990 participants agreeing to participate and to whom questionnaires were provided, 451 participants have returned the questionnaires. A protocol is in place to follow up with participants who have not returned questionnaires.

c) Collect and bank pre-diagnostic blood, urine, and buccal and breast tissue samples among a subset for future molecular epidemiologic analyses and biochemical validation of dietary assessment procedures, to be funded by future ancillary projects.

- Isolation and purification of genomic DNA from buccal cells was carried out on samples of seven patients, which were randomly chosen.

- The technique used was the phenol-chloroform extraction method for purification of DNA. Polymerase chain reaction (PCR) was used to amplify genomic DNA and agarose gel electrophoresis performed. The gel showed the presence of DNA, but since we were not specifically looking for any nucleic acid sequences the PCR technique was used just to confirm the presence of DNA in the samples.

- The collection method of DNA was found to be effective in getting substantial amount of DNA after PCR. The samples were stored in 70% ethanol. Changes in storage procedures like change in storage vials, processing with EDTA and then storing for future use in 70% ethanol is recommended, for efficient processing and isolation of DNA.

d) Take anthropometric measurements, as described in section 4.3.

- 87% of participants recruited have had anthropometric measurements taken.

e) Abstract medical records for relevant health history and pathology data.

- As part of the new recruitment procedures, we obtain monthly downloads from the Cancer Data Management department (Tumor Registry) that includes the pathology section of the medical record, patient identifiers (for linkage), and other relevant data.

Task 3: Data Entry, Verification, and Interim Analyses, Months 7-48:

a) Flag all outlier and illogical responses.

- Most of the questions in the PWHS questionnaire require that the study participant fill in the bubbles with pencil. There are a few questions, which require them to write numbers (for recalled previous weight, height, etc). Once the questionnaires are received from the study participants the study staff look for any stray pencil marks that may cause incorrect values to be output when they are scanned. After this check and making corrections if any, the questionnaires are scanned using the Teleform software. A verification process is built into the software that allows the study staff to verify the scanned data with the actual questionnaire. After the verification process is completed the software outputs the data into a 'Comma Separated Value' (CSV) file.

- Towards the process of creating an analytic dataset SAS programs have been written to read these CSV files and to look for errors in the data. Multiple programs have been written to check individual sections of the questionnaire. The program written to read in the measurements collected in the clinic checks for extreme values of height, weights, and other body measurements. If any extreme values are detected the study staff check the actual clinic form to verify and correct the information if there is an error. Once the clinic data has been checked and any errors corrected the data is output into an analytic dataset. As participants are enrolled into the study the same process is followed and the data is appended to the original dataset.

- SAS programs have also been written to check for consistency of the physical activity data collected in the questionnaires. These programs calculate the number of hours a participant has spent in a certain category of activity per day. Similarly programs have been written to identify outliers in the Food Frequency Questionnaire (FFQ). The program calculates the number of servings of the different food groups (based on USDA recommendations) and looks for outliers in these data.

- We send the participants a report with results based on their clinic measurements and on the physical activity data.

b) Verify all outlier and illogical responses, re-contacting participants, if necessary.

- Up until this point we have not encountered any critical errors that has required us to re-contact the participants.

c) Conduct simple descriptive analyses (e.g., cross-tabulations and univariate statistics).

- An interim analysis has been completed as of July 31, 2003. See appendix.

d) At months 13, 25, and 37 conduct multivariable analyses, as described in section 4.8. of the proposal.

- All previous sections (a, b, c) have been implemented in order to prepare for this task.
- As above, we are too early in the recruitment process for this task to be completed, at least in terms of formal hypothesis testing. However, as noted we have conducted descriptive interim analyses as of July 31, 2003.

Key Research Accomplishments:

Currently, we have been collaborating with Palmetto Health on the design and implementation of a research database and utilizing their cancer data management system to its fullest potential. As the result of recent HIPAA guidelines, we have developed and implemented a research database that will greatly benefit this study as well as future studies. In this process, we have developed an optically scannable pre consent form, which greatly decreases staff effort on data entry and increase data accuracy.

Reportable Outcomes:

Study products: There have been a considerable number of data collection instruments and recruitment and informational materials that have been produced in the first year of the study (see appendices). As no such study has been attempted in South Carolina previously, the existence of these instruments and materials has far-reaching implications. Additionally, each patient is given a report of her anthropometric, physical activity, and dietary data along with an explanation of what these values mean. We also are planning to write a paper with the Cancer Data Management department team on recruitment of cases through their rapid ascertainment system.

Funding applied for and received based on this award:

Our Clinical Sciences Studies Liaison, Swann Adams (Doctoral Candidate) was recently funded for her grant entitled "Physical Activity and Hormone Receptor-Defined Breast Cancer" by the American Colleges Sports Medicine Paffenbarger Grant.

A Co-Principal Investigator, Dr. Joan Cunningham, was awarded a grant by the South Carolina Research Initiative entitled "Cancer Prevention Drug Discovery for Breast and Colon Cancer".

Training opportunities: there currently are two graduate assistants (1 doctoral and 1 masters student in the Department of Epidemiology and Biostatistics at the Arnold School of Public Health) who are working on various aspects of this study.

Planned applications?
1) Follow-up QOL and body composition outcomes at 12- and 24-months, post-diagnosis
2) Follow-up recurrence?
3) Physical Activity and Hormone Receptor-Defined Breast Cancer

References:

1. Hebert JR, Hurley TG, Ma Y. The effect of dietary exposures on recurrence and mortality in early stage breast cancer. Breast Cancer Res Treat 1998;51:17-28.
2. Hebert JR, Augustine A, Barone J, Kabat GC, Kinne DW, Wynder EL. Weight, height and body mass index in the prognosis of breast cancer: early results of a prospective study. Int J Cancer 1988;42:315-318.

Appendices:

A.1. Approved Statement of Work
A.2. Interim Analysis
A.3. Revised Palmetto Women's Health Study Participant Report Summary and thank you letter
A.4. Pre-Consent Form – Teleform
A.5. Approved Institutional Review Board Consent Form
A.6. Letter to Tumor Registry recruits
A.7. Phone Script for recruitment
A.8. HIPAA Waiver – Palmetto Health Alliance
A.9. Letter from South Carolina Oncologists Associates Physicians

On file:

Compiled Baseline Questionnaire
Compiled Coding Manual
Standard Operating Procedures
Biosketch of Project Manager
Era of Hope Poster Presentation

Appendices

A.1. **Approved Statement of Work**
A.2. **Interim Analysis**
A.3. **Revised Palmetto Women's Health Study Participant Report Summary and thank you letter**
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A.7. **Phone Script for recruitment**
A.8. **HIPAA Waiver – Palmetto Health Alliance**
A.9. **Letter from South Carolina Oncologists Associates Physicians**

Appendix A.1.

Approved Statement of Work

PI: James R. Hebert, ScD.

STATEMENT OF WORK

Quasi-Prospective Study of Breast Cancer and Diet
(Note that the SOW listed above is the one now in effect)

Task 1: Run-in Phase, Months 1-6:

a) Review baseline lifestyle and demographic questionnaire for completeness and for content validity.
b) Revise baseline questionnaire as necessary.
c) Hire and train the Research Assistant.
d) Develop a Manual of Operations (MOP), a detailed document describing data management systems. The MOP content is based on our successful experience with other large-scale epidemiologic studies, and will describe how SAS, Teleform (optical scanning software), Excel, EpiInfo and other data management/tracking software will be completely integrated to manage and analyze the data.
e) Develop and pilot test the participant tracking database, as well as all measurements and documenting procedures.
f) Train staff in all data-related and clinic-based procedures.

Task 2: Recruitment, Months 7-48:

a) Of the 5,400 women visiting the Breast Care Center at the Palmetto Richland Memorial Hospital Campus of the Palmetto Health Alliance/South Carolina Cancer Center (BCC) for an advanced diagnostic work-up to rule in or rule out breast cancer, enroll 60% (3,240 women) as participants for the study.
b) Using instruments described in section 4.2., collect data on: diet, physical activity, and other aspects of lifestyle; demographic variables; family and personal health-related history; and social desirability and social approval
c) Collect and bank pre-diagnostic blood, urine, and buccal and breast tissue samples among a subset for future molecular epidemiological analyses and biochemical validation of dietary assessment procedures, to be funded by future ancillary projects.
d) Take anthropometric measurements, as described in section 4.3.
e) Abstract medical records for relevant health history and pathology data.

Task 3: Data Entry, Verification and Interim Analyses, Months 7-48:

a) Flag all outlier and illogical responses.
b) Verify all outlier and illogical responses, recontacting participants, if necessary.
c) Conduct simple descriptive analyses (e.g., cross-tabulations and univariate statistics).
d) At months 13, 25, and 37 conduct multivariable analyses, as described in section 4.8. of the proposal.

Task 4: Final Data Analyses, months 49-60:

a) Perform all exploratory analyses to test for adherence to model assumptions.
b) Test study hypotheses.
c) Conduct post-hoc analyses of study data.

d) Prepare manuscripts.
e) Archive datasets for future analyses and future patient follow-up.
f) Plan future studies.

Appendix A.2.

Interim Analysis

Table 1. Participant demographic characteristics of the Palmetto Women's Health Study

Variable	Case % (n=46)	Control % (n=382)	p-value
Education			
≤ Highschool	13.0	18.8	0.66
Some college	41.3	33.5	
College Completed	19.6	26.2	
More than College	26.1	21.5	
Employment Status			
Full-time	56.5	59.5	0.61
Part-time	8.7	12.0	
Unemployed	34.8	28.5	
Paternal Race			
White	82.6	83.8	0.49
African American	13.0	14.6	
Hispanic	0	0.5	
Native American	2.2	0.5	
Other	2.2	0.5	
Maternal Race			
White	83.0	82.7	0.52
African American	14.9	14.6	
Hispanic	0	1.0	
Native American	0	0.8	
Other	2.1	0.8	
Menopausal Status			
Pre Menopausal	30.0	39.8	0.25
Post Menopausal	70.0	60.2	
1st Degree Relative with Breast Cancer			
Yes	12.5	9.3	0.56
No	87.5	90.7	
Ever Pregnant			
Yes	89.7	86.8	0.62
No	10.3	13.2	

Table 2. Participant reproductive and anthropometric characteristics of the Palmetto Women's Health Study

Variable	Case Mean (SD) n=46	Control Mean (SD) n=382	p-value
Age	56.6 (11.5)	50.4 (12.6)	0.00
Age at 1st Menses	12.3 (2.1)	12.3 (2.1)	0.98
Age at 1st Pregnancy	22.4 (4.8)	22.3 (5.7)	0.43
Number of Pregnancies	2.1 (1.5)	2.6 (1.7)	0.43
Height (cm)	160.8 (6.7)	162.1 (6.1)	0.85
Weight (kg)	65.5 (13.8)	69.4 (16.7)	0.59
Body Mass Index	24.6 (5.2)	26.3 (6.3)	0.48
Waist to Hip Ratio	0.76 (0.07)	0.77 (0.08)	0.85
Percent Body Fat	30.1 (14.2)	34.7 (7.6)	0.71

Table 3. Diet and physical activity characteristics of participants in the Palmetto Women's Health Study.

Variable	Case Mean (SD) n=46	Control Mean (SD) n=382	p-value
Food Group (servings/day)			
Alcohol	0.1 (0.4)	0.2 (0.4)	0.03
Fruit	2.1 (1.9)	2.1 (2.1)	0.83
Vegetable	2.9 (1.9)	3.2 (3.3)	0.25
Bread, Cereals, Pasta	2.8 (2.9)	3.0 (3.3)	0.56
Beans	0.2 (0.1)	0.3(0.5)	<0.001
Fish	0.2 (0.2)	0.3 (0.7)	0.04
Meat, Poultry, Egg	2.0 (2.7)	1.7 (2.1)	0.57
Milk, Yogurt, & Cheese	1.5 (1.3)	1.5 (1.6)	0.73
Type of Physical Activity (hours/week)			
Recreational	1.9 (2.5)	2.3 (3.2)	0.45
Occupational/Volunteer	5.0 (12.4)	9.2 (11.2)	0.96
Household	11.0 (6.2)	9.5 (3.2)	0.18
Lawn & Garden	0.9 (1.6)	1.2 (2.8)	0.31

Table 4. Multivariate Modeling of Breast Cancer Risk- Palmetto Women's Health Study

Variable*	Odds Ratio	Confidence Interval
Nut Consumption	0.96	0.42 - 2.16
Alcohol Consumption	0.61	0.15- 2.47
Bean Consumption	0.29	0.05 - 1.82
Bread, Cereal, & Pasta Consumption	1.08	0.90 - 1.29
Fish Consumption	0.41	0.08 -2.10
Fruit Consumption	0.99	0.84 - 1.15
Meat Consumption	1.24	0.99 - 1.57
Milk, Cheese, & Yogurt Consumption	1.08	0.79 - 1.46
Vegetable Consumption	0.98	0.84 - 1.15
Household Activity	1.00	0.97 - 1.05
Lawn & Garden Activity	0.94	0.78 - 1.14
Recreational Activity	0.94	0.82 - 1.08
Occupational/Volunteer Activity	0.99	0.96 - 1.02
Body Mass Index	0.95	0.88 - 1.02
Percent Body Fat	0.97	0.94 - 1.01

* All models were adjusted for menopausal status and 1st degree relative with breast cancer

Appendix A.3.

Revised Palmetto Women's Health Study Participant Report Summary and thank you letter

«FN» «LN»

August 15, 2003

«FN» «LN»
«Address»
«City», «State» «Zip»

Dear Ms. «LN»,

Thank you very much for completing our questionnaire and participating in the Palmetto Women's Health Study. This study was designed to learn more about how women's lifestyle choices, such as nutritional intake and physical activity patterns, may affect their breast health. Studies of this nature would not be possible without your efforts and willingness to participate in research.

As a small token of appreciation for taking time out of your busy schedule to participate in the study, we have enclosed an analysis of the body measurements taken during your recent clinic visit. Also included is an initial report that assesses your physical activity patterns during the past year. In the future, we will also be sending you additional reports assessing your nutritional intake. We also will make general reports of study findings available to you as they emerge.

If you have any questions about your results please contact Wendy McKenzie at (803) 434-1628 or wendy.mckenzie@sc.edu. We appreciate you taking the time to participate in this study and doing your part in moving research forward in this important area. Thank you once again for sharing your valuable experiences to help in the fight against breast cancer.

Sincerely,

James R. Hebert, MSPH, Sc.D.
Principal Investigator
Department of Epidemiology and Biostatistics
Norman J. Arnold School of Public Health
University of South Carolina
Columbia, SC 29208

Palmetto Women's Health Study Participant Report Summary

As a part of the Palmetto Women's Health Study, we took several different body measurements and we asked you to complete a questionnaire that evaluated your physical activity habits. We would like to take this opportunity to provide an explanation and summary of your results from the body measurements and the physical activity questionnaire. A missing value in any category indicates that the information was not reported.

Your body measurements were:

Height (inches): **«height»**
Weight (pounds): **«weight»**
Body mass index (BMI): **«bmi»**

Body mass index (BMI) is an indicator of body fatness and was calculated by dividing your body weight (in kilograms [kg]) by your height (in meters squared [m^2]). One kilogram equals 2.2 pounds and one meter equals 39.37 inches. The most recently published national data (1988-94) reported the average American woman to be 63.7 inches tall (5′ ¾ in); to weight 152 lbs; and to have a BMI of 26.4 kg/m^2.

During the past decade, Americans have gained an average of ten pounds and this remarkable change in the population has been termed an "obesity epidemic". Higher BMI levels are associated with increased risk for heart disease, diabetes, hypertension, colon cancer, and breast cancer among post-menopausal women. Current public health recommendations for BMI suggest that adults achieve and maintain a BMI of 25 kg/m^2 or less for optimal health.

The circumference measurements we obtained were to examine your body fat distribution. It has been shown that individuals with bodies that are apple shaped (fat primarily in the abdominal section) have a higher risk for certain diseases than individuals with bodies that are pear shaped (fat located primarily in the hip and buttocks area). One way to determine if you are at a higher risk is to calculate your waist- to- hip ratio by diving your waist circumference by your hip circumference. Waist- to- hip ratios of less than 1.0 are associated with better health.

Your waist-to-hip ratio was: **«whr»**.

The final body measurement we obtained came from the bioelectrical impedance machine from which we determined the percentage of your total weight that came from fat-free and fat weight. Fat-free weight includes the weight of your bones, internal organs, muscles, and body water. Fat-free weight is important because it gives us an indication of your muscle mass, which represents the metabolically active tissue in your body.

	% Body Weight	Weight (pounds)
Fat-free tissue:		**«PctFatFrTis»**
Fat tissue:	**«PctBodyFat»**	**«FatMass»**

Currently, there are no formal guidelines for "normal" or healthy values of percent body fat or percent fat-free tissue as they relate to specific diseases, like heart disease or diabetes. Current public health recommendations use BMI and waist circumference as indicators of disease risk. If you have any questions or concerns about the measurements above, please don't hesitate to give us a call or ask your physician.

Physical Activity

Past Year Physical Activity Recall. The information you provided in the questionnaire provided a wealth of information about your physical activity patterns. Selected information from your *Past Year* Physical Activity Recall is provided below. Based on your report, we counted up the number of hours spent in different types and levels of physical activity. Here are your results:

	Household activity		**Lawn and Garden**		
Light	«chlt_d»	(hrs/wk)	Moderate	«lgmod_d»	(hrs/wk)
Moderate	«chmod_d»	(hrs/wk)	Vigorous	«lgvig_d»	(hrs/wk)
Total	«totch_d»	(hrs/wk)	Total	«totlg_d»	(hrs/wk)

	Occupational activity		**Exercise/recreations/sports**		
Light	«ovlt_d»	(hrs/wk)	Moderate	«tmodrec»	(hrs/wk)
Moderate	«ovmod_d»	(hrs/wk)	Vigorous	«totvigrec»	(hrs/wk)
Vigorous	«ovvig_d»	(hrs/wk)	Total	«totrec»	(hrs/wk)
Total	«totocc_d»	(hrs/wk)			

Current public health recommendations suggest that, for physically inactive individuals (about 60-70% of the US population!), participating in moderate intensity activities at least five days each week for 30 minutes each day (or 2½ hours/week) can improve your health. Moderate activities include brisk walking, raking leaves, or riding a bicycle. Participating in vigorous activities at least three times each week for 20 minutes each time (or 1 hour/week) provides similar benefits. Vigorous activities include jogging, aerobics, or lap swimming. Meeting these goals could help you reduce your risk of heart disease, diabetes, hypertension, obesity, osteoporosis, and certain forms of cancer (colon and breast cancer).

We hope that you have found the information we have provided to be helpful and informative. If you have any questions about your results, please don't hesitate to call us with your questions (803.434.1635).

Thank you again for your participation in the study. The information you provided will help us to better understand the way in which a woman's lifestyle choices affect her breast health.

Appendix A.4.

Pre-Consent Form – Teleform

«FN» «LN»

32512

PALMETTO HEALTH

We are here to serve you better

Help us to improve our service...

The South Carolina Comprehensive Breast Center has many programs and projects available to all women

If you qualify for one of these studies, may we contact you with more information?

If you do not wish to be contacted, please indicate 'No' and complete the information below. This is our only to way to be sure that we have the most accurate and up-to-date information on you.

Please indicate if you would like more information.

After completing this form, please return it to the staff.

Thank you for taking time to help!

☐ **Yes, I would like more information** ☐ **No**

_____ ☐☐ / ☐☐ / ☐☐

Signature **Date**

First Name

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Last Name

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Date of Birth (for identification purposes only)

☐☐ / ☐☐ / ☐☐

Social Security Number (last 4 digits)

(for identification purposes only) ☐☐☐☐

If you checked "yes ":

Phone Number

☐☐☐ - ☐☐☐ - ☐☐☐☐

Best Time to Call

☐ **Morning**
☐ **Afternoon**
☐ **Evening**

M

If you have any questions, or if returning form by mail, please contact/send to:
Wendy McKenzie, Project Coordinator, 15 Medical Park, Suite 301, Columbia, SC, 29203;
Phone: 803-434-1628

R

32512

Commonly Asked Questions:

1. What is the purpose of signing this?

The South Carolina Comprehensive Breast Center and South Carolina Cancer Center are working to promote programs and projects about how to improve important women's health issues. The purpose of this form is to obtain your permission for us to contact you by phone, and tell you about current programs or projects for which you may qualify. We cannot contact you without your consent.

2. Who will receive permission to contact me and where will they get my information?

If you check "yes", the South Carolina Comprehensive Breast Center and South Carolina Cancer Center will receive your name, date of birth, and phone number from the completed form. The release of the your name and other information to the South Carolina Comprehensive Breast Center and South Carolina Cancer Center is strictly confidential- no one else will receive your information.

If you check "no", we will not call you.

3. Am I obligated to participate in a program if I check 'yes' on the form?

Checking "yes'" on the form does not obligate you to participate in any program or project. Your possible participation will be discussed only after you have been contacted by phone and the details of a particular program or project have been fully explained to you. If the you decide later that you no longer want to be contacted at all, your name will be removed from our list.

4. How often will I be called?

You will be contacted if it appears that you may qualify for a program or project. We estimate that you might receive 1 to 2 calls per year.

5. I live out of town. Is it okay if my number is long distance?

We are interested in talking with all patients who would like to be contacted, regardless of whether they live in the Columbia area or out of town.

6. What do the programs or projects involve and what will I be asked to do?

Most of the programs or projects involve a questionnaire that you can complete at your own convenience. Some studies may also involve a clinic visit where, for example, your body measurements might be taken or you might be asked to give a urine sample. An estimate of the amount of time it takes to participate in a particular study will be provided when you are contacted by phone.

Appendix A.5.

Approved Institutional Review Board Consent Form

PALMETTO HEALTH ALLIANCE

IRB #2000-69
(No samples required)

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

TITLE: QUASI-PROSPECTIVE STUDY OF BREAST CANCER AND DIET

PRINCIPAL INVESTIGATOR: James R. Hebert, Sc.D.

ADDRESS: Department of Epidemiology and Biostatistics
University of South Carolina
School of Public Health
Columbia, SC 29208
Phone: 803.777.7666

SUBJECT'S NAME: _____ **DATE:** _____

SPONSOR: United States Department of Defense

INVITATION TO TAKE PART AND INTRODUCTION:

You are invited to volunteer for a research study. This form is designed to provide you with information about the study and to answer any questions that you may have. You have been asked to be in this study because you have recently been scheduled for a visit for diagnostic services at one of the hospitals within the Palmetto Health Alliance (Columbia, S.C.).

PURPOSE OF THE RESEARCH:

The main purpose of this study is to investigate the relationship between diet and physical activity levels and breast cancer risk. While much has been written about diet and breast cancer, results of research studies have produced inconsistent results in relating health related behaviors to breast cancer.

YOUR RIGHTS: It is important for you to know that:

- **YOUR PARTICIPATION IS ENTIRELY VOLUNTARY.**
- **YOU MAY DECIDE NOT TO TAKE PART OR DECIDE TO QUIT THE STUDY AT ANY TIME.**
- **YOU WILL BE TOLD ABOUT ANY NEW INFORMATION OR CHANGES IN THE STUDY THAT MIGHT AFFECT YOUR PARTICIPATION.**
- **THE QUALITY OF CARE YOU RECEIVE AT THE HEALTH CENTER WILL NOT BE AFFECTED IN ANY WAY IF YOU DECIDE NOT TO PARTICIPATE, OR IF YOU WITHDRAW FROM THE STUDY.**

PROCEDURES:

We will be asking you to complete a questionnaire packet that contains questions about several topics such as your education, job, date of birth, and the age(s) of your children, if any.

IRB APPROVAL

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Subject's Initials_____

Additionally, we will ask you to indicate the types and amounts of foods you typically eat, as well as your body weight and physical activity levels throughout your life. This questionnaire packet will require up to 2 hours to complete. It consists of six different questionnaires ranging from 1 to 19 pages. We have selected questionnaires that have been used in other national studies and found to be acceptable to a wide range of individuals. Despite this, you are not required to answer questions that you do not feel comfortable answering.

In addition to completing the questionnaire packet, we will ask you to visit our offices located in or near the breast clinic for about 30 minutes in order to complete additional measurements. For most people, they will prefer to do this while they wait for their clinic appointment; however, it can be scheduled on another day more convenient to you. If we do not complete your measurements before you are called to your breast clinic appointment, you may stop by the office after your appointment to complete the appointment.

During this visit, we will measure your weight, height, the circumference of your hips and waist (with a tape measure), and your body composition (using bioelectrical impedance). For the bioelectrical impedance measurements, we will ask you to lie down for about 5 minutes. Research personnel will place two electrodes on your hand and two on your feet. There is no risk of electrical shock and you will not feel the measurement being made. If, **as a part of your routine medical care**, you are scheduled for or have had a diagnostic breast biopsy, we will obtain a small portion of the biopsy tissue for this research study. No extra breast tissue will be taken during the biopsy for the purposes of this research study, and the small amount donated for this research will not interfere in any way with your medical care. **This only allows us to utilize breast tissue that your doctor will take or has already taken as a part of his/her normal care for you-a breast biopsy will not be done just for this study.** The biopsy material obtained for this research study may be used to determine enzyme levels that are important in regulating levels of female hormones (estrogens).

ALTERNATIVES:

You may choose to not take part in this study. If so, you would not have to do any of the things listed above that pertain to this research study. As a part of your medical care, you may still be asked to undergo a breast biopsy. Your decision not to take part in this study will not affect your medical care in any way.

RISKS AND INCONVENIENCES:

There is minimal risk or discomfort when we measure your weight, height, arm skin thickness, waist and hip circumferences, or body composition using bioelectrical impedance. There is minimal risk in answering any of the study questions.

All results obtained as part of this research will remain confidential. When we do the statistical analyses for the entire study we will not reveal your identity or the identity of anyone else in the study.

Subject's Initials_____

COMPENSATION IN CASE OF INJURY:

All forms of medical diagnosis, treatment and research, whether routine or experimental, involve some risk of injury. In spite of all precautions, you might develop complications from participation in this study. In the event of any injury resulting directly from the research procedures, neither the study personnel, the University of South Carolina, nor the Palmetto Health Alliance have made any provision for the payment of any financial compensation to you or to provide any financial assistance for medical or other costs.

This study is being funded by the Department of Defense and conducted by the United States Army in conjunction with the University of South Carolina. Army regulations provide that, as a volunteer in a study conducted by the United States Army, you are authorized all necessary medical care for any injury or disease that is a direct result of your participation in the research. The Principal Investigator or his designee will assist you in obtaining appropriate medical treatment under this provision, if it is required. If you have any questions concerning your eligibility for Army-funded medical treatment you should discuss this issue thoroughly with the Principal Investigator or his designee before you enroll in this study. This is not a waiver or release of your legal rights.

BENEFITS:

This study may be of no direct benefit to you. However, we will make study results available to you when it is feasible for us to do so. At the end of the study, you may request a summary of all of your own results with a brief description of what they mean. As results from the entire study are published, we will advise you and you may request copies of these as well. Additionally, the knowledge gained from your participation in this research may help further our understanding of how to prevent or treat breast cancer.

COSTS:

There will be no direct cost to you for participating in the study.

REMOVAL FROM STUDY:

You may be taken out of the research study if it appears that you are unable to keep your appointment, provide cheek or urine samples, or do not provide valid answers on the questionnaires. If this occurs, you will be given a full explanation for your removal.

CONFIDENTIALITY:

Your research records will be confidential to the extent possible by law. In all records of the study a code number will identify you and only the researchers will know your name. Your name will not be used in any reports or publications of this study. Your discussions with anyone who works on this study will be kept confidential, with two exceptions. We are compelled by law to inform an appropriate other person if: (1) we hear and believe that you are in danger of hurting

Subject's Initials_____

yourself or someone else, or (2) if there is reasonable suspicion that a child, elder, or dependent adult has been abused.

FUTURE CONTACT:

Cancer research proceeds in stages, and questions may develop that are presently unknown to us. We may want to ask you to participate in a follow-up breast cancer study at some point in the future. If this occurs, the reasons for your eligibility and the purposes of the follow-up study will be clearly described to you. You have a right to accept or decline participation in future studies should we contact you.

PATIENT PROTECTION:

Further information on the research to be performed, or regarding the risks and benefits of participation, or alternative treatments may be obtained from James R. Hebert at 803-434-6009. This study has been approved by the committee to protect human rights for the Palmetto Health Alliance. Information concerning your rights as a research subject can be obtained by contacting the Office of Corporate Counsel at (803) 296-2124.

Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. This will entail billing your insurance provider. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

Subject's Initials_____

PALMETTO HEALTH ALLIANCE

IRB #2000-69
(No samples required)

Title: QUASI-PROSPECTIVE STUDY OF BREAST CANCER AND DIET
P. I. Name: James R. Hebert, Sc.D.

I have read the informed consent to participate in a research study or it was read to me by: _____. Anything I did not understand was explained to me by: _____, and any questions I had were answered by: _____.

I certify that I am / am not [circle one] participating in another research project at this time, and have discussed the implications of such activity with the project director(s) of this project and/or my physician.
During this study, I have been asked to answer questions about my diet, weight history, and physical activity, and to donate a portion of my breast biopsy for breast cancer research (only if applicable). In addition, I have been asked to allow body composition measures to be made (height, weight, circumference measures, and bioelectrical impedance measures). There is a chance that the information and biological samples donated to this study may be used in other research studies and may have some commercial value. No commercial value is anticipated at this time. Should donated sample(s) lead to the development of a commercial product, the University of South Carolina will own it and may take action to patent and license the product. The University of South Carolina does not intend to provide any compensation for participation in this study nor for any future value that the sample(s) that I have provided may be found to have. I may not receive notice of future uses of my sample(s).

"The purpose and procedures of this research project and the predictable discomfort, risks, and benefits that might result have been explained to me. I have been told that unforeseen events may occur. I have had an opportunity to discuss this with an investigator, and all of my questions have been answered. I agree to participate as a volunteer in this research project being conducted through the Palmetto Health Alliance. I understand that I may end my participation at any time. I understand that there is a possibility that the information I provided, and the tissue samples, which I also provided to this study, may be used in other research studies and could potentially have some commercial applicability. I have been given a copy of this consent form."

IRB APPROVAL

03-26-2003 - 03-25-2004

Subject's Initials_____

PALMETTO HEALTH ALLIANCE

IRB #2000-69
(No samples required)

Print Name of Participant	Date	Signature of Participant	Date
Print Name of Person Obtaining Consent	Date	Signature of Person Obtaining Consent	Date
Print Name of Witness	Date	Signature of Witness	Date

Participant's permanent address and telephone number:

_____

_____

IRB APPROVAL

03-26-2003 - 03-25-2004

Subject's Initials_____

Appendix A.6.

Letter to Tumor Registry recruits

«FN» «LN»

Palmetto Women's Health Study
South Carolina Cancer Center
15 Richland Medical Park, Suite 301
Columbia, SC 29203

Dear Patient,

With the permission of your physician, we are contacting you regarding the Palmetto Women's Health Study. This project is designed to investigate possible causes of breast cancer. With this study, we may find ways that women will be able to prevent breast cancer. We have enclosed a brochure about the project. In the next few days, someone from our project will be contacting you to give you more information and to discuss your possible participation. If you do not wish to be contacted, please call me at (803) 434-1628. On behalf of thousands of women affected by breast cancer, we thank you for your help!

With regards,

Wendy McKenzie
Project Coordinator

Enclosure

«FN» «LN»

Appendix A.7.

Phone Script for recruitment

«FN» «LN»

Case Recruitment Script

Hello, this is (your name)_____ with the South Carolina Cancer Center. Is (potential participant's name) available?

If No:

Do you know when might be a better time to contact (name)? *(Record in tracking database)* Thank you for your time.

If Yes:

The South Carolina Cancer Center has approved a project to study breast cancer risk for women. Would you have a few minutes that I might be able to give you more information?

If no: Would you like for me to call you another time?

If no: *Thank you for your time.*

If yes: *When might be a better time? (Record information in tracking database and arrange for contact)*

If yes:

The study is called the Palmetto Women's Health Study and is designed to investigate how women's lifestyle choices such as their diet or physical activity influence their risk for breast cancer. All women aged 20 to 80 years who have not been diagnosed with breast cancer previous to the current diagnosis are eligible for the study. All that is involved with the study is to complete a brief, 20-minute clinic appointment and a questionnaire. The clinic appointment can be done at any time at your convenience. We will take your body measurements like your height, weight, the size of your stomach and hips, as well as your percent body fat. The questionnaire will be given to you to take home and complete. It usually takes about 2 to 3 hours to finish and will ask you questions about the foods you normally eat and the types of activities that you do. We encourage participants to work on the questionnaire in sections so that it is not too burdensome. The questionnaire can be done at your leisure; however, it must be completed before you start any chemotherapy or radiation. These treatments can change your tastes for some foods and or your energy level, so we want to be sure that you have already done the questionnaire before your treatment starts. As a token of our appreciation, we will provide you with a $20 gift certificate to a local grocery store or a free registration for the Breast Cancer Walk for Life upon completion of the questionnaire and the clinic appointment. Once we receive your questionnaire, we will provide

to you a report of your diet, activities, and body measurements based upon your answers to the survey. Does this study sound like something that you would be interested in doing?

If no: Thank you for your time.

If yes: We have offices at both Palmetto Richland and Palmetto Baptist. When would be a good time for you to come to our offices for the clinic appointment? (record appointment) Which office would you prefer to visit? (record place)

Provide directions to office

If the scheduling of the appointment is greater than a week away, arrange to send the questionnaire to the participant.

If necessary, explain to the participant again what procedures will be done at the clinic appointment (consent form and measurements).

On behalf of thousands of breast cancer survivors, we thank you for your help. If you have any questions before your appointment, please call 434-1628. We will call you the day before your clinic visit to remind you of your appointment. Have a good day.

Script for Control Recruitment

Hi, could I please speak to ___Subject name_____.

If "No": This is ___Your name___ with the University of South Carolina, we were just calling to provide some information on our programs available through the South Carolina Comprehensive Breast Center. We will try contacting Ms.____Subject last name_____ at a later time. Thank you for your time.

If "Yes":

My name is ___Your name___ , with the South Carolina Comprehensive Breast Center. At your last mammogram, you had indicated that you would like more information on our research studies. Do you have a few minutes for me to tell you about a project we have available to our patients?

[If **yes**, proceed with description of study]

[If **No**, continue:] Is there a better time to discuss this project with you further?

[If **yes**, schedule second recruitment call]

[If **No**, end the call by saying:] Thank you for your time and have a nice day.

Description of Study:

This project, called the Palmetto Women's Health Study, is looking at how diet and physical activity are related to women's breast health. All that is involved with the study is to complete a brief, 20-minute clinic appointment and a questionnaire. The clinic appointment can be done at any time at your convenience once we have received your questionnaire. We will take your body measurements like your height, weight, the size of your stomach and hips, as well as your percent body fat. We will mail the questionnaire for you to complete at home. It usually takes about 2 to 3 hours to finish and will ask you questions about the foods you normally eat and the types of activities that you do. We encourage participants to work on the questionnaire in sections so that it is not too burdensome. The questionnaire can be done at your leisure, but we would like for you to complete it before your clinic appointment. As a token of our appreciation, we will provide you with a $20 gift certificate to a local grocery store or a free registration for the Breast Cancer Walk for Life upon completion of the questionnaire and the clinic appointment. In addition, we will provide to you a report of your diet, activities, and body measurements based upon your answers to the survey. Does this study sound like something that you would be interested in doing?

[If **yes**, proceed with eligibility.]

[If **No**, end the call by saying:] Thank you for your time and have a nice day.

Eligibility:

I first need to check and make sure that you are eligible for the study.

Are you between the ages of 20 and 80?

(If **no)** "Unfortunately, you are not eligible for this particular study; however, we will contact you if there are any studies in the future for which you may qualify. Thank you for your time."

(If **yes**) Proceed to next question.

Have you ever been diagnosed with breast cancer?

(If **no,** subject is eligible) "It appears that you do qualify for the study, we can go ahead and schedule your appointment". (Proceed to appointment scheduling)

(If **yes**) "How recently were you diagnosed?"

(If within the last 6 months, the subject is eligible.) "It appears that you do qualify for the study, we can go ahead and schedule your appointment". (Proceed to appointment scheduling)

(If more than 6 months, the subject is not eligible.) "Unfortunately, you are not eligible for this particular study; however, we have another study for which you may qualify. May another staff member call you to give you more information?" (If **yes**, e-mail subject information to Wendy) "Thank you for taking time to talk with me."

Appointment scheduling:

The clinic appointment can be done on either the Palmetto Health Richland or the Palmetto Health Baptist campus. We usually schedule the appointment in 2 to 3 weeks to allow people ample time to complete the questionnaire. When would it be convenient for you to come in for the clinic appointment? Which campus would you like to come to?

Record the appointment time and place in the PWHS_Tracking database.

Do you need directions to the clinic?

If yes:

Baptist: The appointment will take place in the mammography center located across the street from Palmetto Health Baptist at ???? Sumter Street. You may park in the parking garage above the mammography center.

Richland: The appointment will take place at 15 Richland Medical Park. This building is located on the corner of Harden Street Extension and Bull street, right next door to the CVS drugstore. The building has "15 Medical Park" on a sign near the roof of the building. The actual address of the building is 3555 Harden Street Extension. Our offices are located on the 3rd floor in suite 301, which is to the right upon exiting the elevators.

A staff member will meet you in the lobby.

In order for us to send you your questionnaire, I will need your address. (Record in PWHS_Tracking database)

ONLY ASK THIS QUESTION IF THE PINK CONSENT WAS NOT OBTAINED AT ONE OF THE MAMMOGRAPHY CLINICS.

I also need to know if you are currently having regular mammograms.

(If **yes**) Where do you usually go to get your mammogram done? (This will determine what ID number is assigned- be sure to record in database if location is not Baptist or Richland).

Do you have any questions at this time?

On behalf of the entire Palmetto Women's Health Study research staff I would like to thank you for participating in this study. Have a nice afternoon/evening.

Appendix A.8.

HIPAA Waiver – Palmetto Health Alliance

Pursuant to section 164.512(i)(2)(ii) of the December 2000 Privacy Rule of the Health Insurance and Portability Act, a waiver of authorization to release protected health information is requested for PH IRB # 2000-69, "A Quasi-Prospective Study of Diet and Breast Cancer". Patient information contained within the Tumor Registry of Palmetto Health is requested for recruitment purposes. This information includes patient name, address, phone number and diagnosis for all newly diagnosed breast cancer patients. According to the revised ruling, a waiver may be granted under the following conditions.

(1) "The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:"

(a) "An adequate plan to protect the identifiers from improper use and disclosure;"

Standard operating procedures for PH IRB#2000-69 and all study personnel require that all computers with access to protected patient information are password protected (See Appendix I). Personnel are required to memorize this password and are not permitted to display this word. The database in which identifying patient information will be stored will also be password protected and subject to the same discretion used for computer passwords. Additionally, personnel are required to log off of or shut down computers upon leaving the office. Doors are required to be locked upon exit of the office. All doors to the building of 15 Medical Park are locked during evenings and weekends.

Personnel violations of any of the above protections will result in a verbal reprimand with the first count, a letter of reprimand on the second count and immediate dismissal with the third count. Surveillance and enforcement of these regulations will be the responsibility of the study coordinator.

All research data is stored on a single network server. The server data is automatically backed up on a daily basis using a mix of incremental and full dumps with weekly and monthly archives to maintain the highest levels of data security. Access to the server is restricted to on-site staff that enters the main USC network system through a login and password system. Once in the main network environment, staff can link to the server PC using another login and password. Only specific staff, which has previously been given permission by the system administrator, can link to the server using the second level login/password.

As required by PH IRB and USC SPAR, all personnel have completed training in the Protection of Human Subjects, which includes training in the protection of patient confidentiality. All personnel are trained in study procedures and regulations upon initiation of employment. In addition, continuing education on study procedures and regulations is conducted every 6 months during project meetings.

All personnel have read and signed a confidentiality agreement for PH IRB# 2000-69 (See Appendix II). All new personnel will be required to sign the agreement upon initiation of employment.

(b) "An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and"

All information received from the Palmetto Health Tumor Registry will be used for recruitment purposes only. Names will be received electronically from tumor registry personnel to study. Unless otherwise specified, receipt of this electronic information will be the responsibility of Swann Adams. As a former employee of Palmetto Health, Ms. Adams has maintained her Palmetto Health GroupWise e-mail account since her office resides upon Palmetto Health property at 15 Medical

Park. Consequently, electronic patient information will be protected by provisions established by Palmetto Health for its electronic messaging system. All information received will then be entered into an Access database in order to facilitate call assignments to multiple personnel. Once the patient information is saved in the database, the electronic mail message will be deleted from the mailbox and purged from the trash within 24 hours.

All patients will be contacted and given detailed information regarding study procedures, risks, and benefits. For those denying participation in the research study, identifying information will be deleted from the database within 2 weeks of contact. For those interested in participation, an appointment will be made with the patient to obtain informed consent and conduct study procedures. For those who initially agree to participation, but subsequently decline, identifying information will be deleted within 2 weeks of the decline of participation.

(c) "Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;"

Per the above regulation, all information received from the Palmetto Health Tumor registry will not be reused or disclosed except as required or permitted by law.

(2) "The research could not practically be conducted without the waiver or alteration; and"

In an effort to confirm to HIPAA guidelines, previous recruitment efforts have required the cooperation of clinic staff at each mammography clinic. A consent for contact (See Appendix IV) was created for this use. Clinic personnel were asked to request that all patients complete this consent for contact. Patients who did not wish to be contacted were asked to indicate "No" on the contact form and sign their name so that research personnel could be sure that all patients were informed of this research opportunity. Research staff worked with clinic personnel to ensure that the form could be easily administered. From this collaboration, the back of the form was created which listed answers to commonly asked questions. On Oct 8th for Baptist and Oct 25th 2002 for Richland, research administration met with all clinic staff during regularly scheduled staff meetings to discuss the purpose of research and the consent for contact. Staff appeared to be enthusiastic about the process and understood its importance to Palmetto Health's research efforts. Research personnel have since monitored these efforts and have documented the percentage of patients who received and signed a form (regardless whether consent for contact was given). Appendix IV details the daily percentages with an overall average for each clinic. Statistics have been divided into regular screening mammograms and diagnostic work-up. Presumably, our highest yield of breast cancer cases will arise from the diagnostic work-up patients. As evidenced by Appendix IV, Richland mammography clinic has on average requested that 41% of screening patients and 2% of diagnostic patients complete the consent for contact. It should be noted that this statistic is simply a count of those patients administered the consent and is not a count of the number of patients who responded "Yes" on the consent for contact. The Baptist mammography clinic averaged 37% for screening patients and 23% for diagnostic patients. As evidenced by the minimum statistics, there are days during which not a single patient is administered the consent for contact. We have met with the Baptist staff to discuss these numbers and have been told that there is often not enough time for the consent to be administered. To date, we have received consent for contact on 6, 682 women of which only 5 persons have been diagnosed with breast cancer per Tumor Registry records.

We have also proposed hiring an employee to staff each mammography clinic and administering the consent for contact to all patients. We have figured that such an action would require an additional, $57,000 per year

to staff both clinics during hours of operation (50 hours/week). Unfortunately, there are not ample funds either with this grant or other resources to allow this type of employment.

Consequently, there is ample evidence to assert that we cannot practically conduct this research without a waiver.

(3) "The research could not practicably be conducted without access to and use of the protected health information. "

Prior to formal initiation of the consent for contact, research personnel were stationed at each clinic to recruit women into the study face-to-face. Only those women who were attending the clinic for a diagnostic work-up were approached. Baptist was staffed from November 2001 until July of 2002 and Richland was staffed from April 2002 until July 2002. The project was able to recruit 741 women of which only 22 went on to be diagnosed with breast cancer. Comments that we heard from women were: "I am too worried about this appointment to think about this right now", "I would like to talk to you later, but not right now", and "I have to leave right after my appointment and cannot stay to talk to you". From research staff, we were told that many patients agreed to participate, but did not have enough to time to complete all the study procedures. There were some concerns expressed by clinic staff that we were delaying their schedule, although it should be noted that our research staff detained no patient once they were called for their appointment. We simply requested that the patient return after their mammography appointment was concluded. Too often, patients left the clinic without returning.

This type of recruitment proved to be ineffective both financially and in terms of numbers of cases recruited. Due to clinic logistics, personnel were required to work in pairs to recruit participants; thus 4 people per shift were required between both Richland's and Baptist's mammography clinic. While this expense would have been acceptable if recruitment yield had been high, as stated previously we only recruited 22 cases in the 10-month recruitment period. The grant could not support such expenditure and still not meet it's recruitment deadline of August 2004.

With information received from the Palmetto Health tumor registry, women recently diagnosed with breast cancer can be contacted directly, greatly enhancing our recruitment efforts. Thus, this research could not practically be conducted without access to and use of the protected information.

Appendix A.9.

Letter from South Carolina Oncologists Associates Physicians

Dear Patient,

South Carolina Oncology Associates in conjunction with the University of South Carolina Arnold School of Public Health is conducting a project called the Palmetto Women's Health Study. Its purpose is to investigate possible causes for breast cancer. With this important study, we may find ways that women will be able to decrease their risk for development of breast cancer. I have attached a brochure about this project to this letter. In the next few days someone with the study will be contacting you to give you more information and to discuss your possible participation. If you do not wish to be contacted about this study, please indicate this on the attached form and return it. I believe this is an important study and your participation will be a valuable contribution to our understanding of breast cancer. On behalf of thousands of women affected by breast cancer, I wish to thank you for your help with this project.

Sincerely,

SC Oncology Physician

«FN» «LN»