Award Number: DAMD17-03-1-0553

TITLE: Long Term Outcomes of BRCA1/BRCA2 Mutation Testing

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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.
This project aims to gain a better understanding of the implications of genetic testing for breast-ovarian cancer susceptibility. The primary goal is to evaluate the impact of BRCA1/BRCA2 mutation testing on long-term psychosocial (quality of life, distress, social functioning) and prevention/surveillance (mammography, CA125, transvaginal ultrasound, prophylactic mastectomy, prophylactic oophorectomy, and chemoprevention) outcomes. To accomplish this, we will measure outcomes within a group of women who received BRCA1/BRCA2 test results at least four years ago. We will divide our sample based upon their personal cancer history—evaluating cancer survivors with different measures compared to unaffected individuals. For both survivors and unaffected individuals, we will recruit separate comparison samples of women who have never received BRCA1/BRCA2 testing. During this past year, we received final approval from the DOD to begin accrual. We have initiated accrual and to date have completed follow-up interviews with xxx women. During the upcoming year, we will continue accrual of our genetic testing cohort and will initiate accrual of our comparison groups.
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INTRODUCTION

Genetic testing for breast-ovarian cancer susceptibility has the potential to reduce breast and ovarian cancer mortality among high risk women. However, there has been ongoing concern regarding the quality of life implications of learning one's mutation status. To date, there have been no studies to evaluate the long-term psychosocial and behavioral impact of receiving clinical BRCA1/2 test results. Several studies have examined these outcomes in the short-term. Although preliminary evidence suggests that the receipt of a positive BRCA1/2 test result does not lead to increased short-term distress, it is clear that women who receive positive test results do report more distress than those who receive negative test results. It is not clear, however, whether this distress has long-term implications. It is possible that distress could decline over time as the individual adapts to her positive test result and ongoing risk. Alternatively, the modestly elevated distress reported in the short-term could be evidence of chronic stress. Ongoing stress has been shown to adversely impact health behaviors and health outcomes. Given the risk status of this population, it is particularly important to better understand the long-term distress levels and the role of distress in adoption of recommended breast and ovarian cancer risk reduction and early detection behavior. To date, there have been no studies to examine these issues.

One of the main potential benefits of BRCA1/BRCA2 testing is to motivate carriers to take behavioral action to reduce their risk of breast and ovarian cancer mortality. However, we do not yet know whether carriers actually engage in such actions. Preliminary evidence suggests that a relatively small proportion of carriers obtain prophylactic surgery in the year following testing. The proportion of carriers who utilize chemopreventive agents such as tamoxifen remains unknown. The few studies to examine screening utilization in the year following disclosure found sub-optimal rates of screening among positives. In fact, rates of mammography have not been found to increase following a positive mutation test. Although mutation carriers did report higher rates of mammography, this difference was due to appropriate decreases in screening among younger noncarriers. In terms of ovarian cancer screening, rates of CA-125 and transvaginal ultrasound do increase among carriers in the year following testing. However, overall ovarian cancer screening rates remain below 30%. To date, there have been no studies to evaluate the long-term cancer prevention and screening behaviors of this population. If genetic testing is to fulfill its promise of reducing mortality among individuals from hereditary cancer families, behavioral change must follow the receipt of a positive test result. The first step to addressing this question is to evaluate the behavior of individuals in the years following testing. If individuals remain non-adherent to prevention and screening guidelines, it is particularly important to understand why and to identify early predictors of behavioral non-adherence in this vulnerable population. We will evaluate the role of distress/quality of life as a potential predictor of adverse behavioral outcomes.

The primary goal of this project is to evaluate long term psychosocial (quality of life, distress, social functioning) and prevention/surveillance (mammography, CA125, transvaginal ultrasound, prophylactic mastectomy, prophylactic oophorectomy and chemoprevention) outcomes. To accomplish this we will measure outcomes within a group of women who received BRCA1/BRCA2 test results at least four years ago. We will divide our sample based upon their personal cancer history – evaluating cancer survivors with different measures compared to unaffected individuals. For both survivors and unaffected individuals we will recruit separate comparison samples of women who have never received BRCA1/BRCA2 testing.

Until we better understand the long-term outcomes of BRCA1/2 testing, it is unlikely that such testing will fulfill its promise to reduce breast and ovarian cancer mortality. By evaluating the impact of
testing, appropriate intervention strategies can be developed so that individuals at-risk for distress or non-adherence could be targeted for early intervention and/or ongoing support. This research could provide information necessary to make decisions about how and where to allocate scarce counseling resources and to tailor health promotion efforts to individual needs. Genetic testing for breast-ovarian cancer susceptibility is becoming more widely available to the general population. Prior to its routine use, we should make sure that we fully understand its long-term implications.
We have listed each of the tasks from our Statement of Work, and the associated accomplishments.

**Task 1.** Finalize accrual procedures and measures to be included (months 1-6).

a. Meet with CARE program staff to confirm the procedures for patient recontact.

We completed this task during year 1 and have generated a list of CARE participants who are eligible for recontact for this study.

b. Finalize recruitment letters for each of the study cohorts.

These letters were completed during year 1 and were included with the Year 1 Annual Report.

c. Finalize the telephone questionnaires to be administered to each cohort.

These interviews were completed during Year 1, were approved by the DOD IRB, and were included in the Year 1 Annual Report.

d. Develop interview database.

We have completed the study database, beta tested the database and have begun using the database for participant tracking and data entry.

e. Develop subject tracking system using Access database.

The tracking system has been developed and is currently being utilized for participant tracking.

f. Review computer databases of each cohort to determine procedures for participants recruitment and eligibility.

Done.

**Task 2.** Conduct participant accrual (months 4-48).

Due to the delay in approval by the Department of Defense IRB (see Year 1 Annual Report), the initiation of participant accrual was delayed. However, upon receipt of final DOD approval, we did initiate accrual of our CARE cohorts. To date, we have mailed initial contact letters to 327 former CARE participants. Of these, 33 (10%) have been returned due to incorrect addresses (we are currently attempting to update these addresses) and 3 (1%) were ineligible for participation. Thus, at the present time we have contacted 291 eligible women for participation. Of the 291 eligible women contacted to date, 59 (20%) have declined participation. We have completed 91 (31%) follow-up interviews and we have 56 (19%) interviews that are scheduled. The remaining 85 (29%) participants have agreed to participate and are currently pending follow-up interviews. We are in the process of scheduling these interviews and anticipate an ongoing high completion rate (at least 80%) of the pending interviews. Thus, from our first mailing, we anticipate completing at least 215 interviews by Oct 1, 2005 – for an anticipated completion rate of 74%. We will send out our second cohort mailing in October. We expect to have comparable participation rates with this upcoming mailing. Thus, by
the conclusion of Year 3 of this award, we expect to have approximately 400 cohort interviews completed. In the upcoming 12-months, we will also initiate comparison group accrual. Since comparison group participants must be matched to cohort participants, we have had to delay our comparison group accrual while awaiting enrollment of sufficient cohort group participants. In the interim, we have prepared patient contact lists and obtained all needed physician approvals to begin contacting comparison group participants. We anticipate that accrual and interviewing of comparison participants will begin by 11/1/05. We expect to enroll 100-125 comparison participants in Year 3.

Despite the initial accrual delay of over a year while awaiting DOD IRB approval, we will be able to attain our projected sample sizes for each of our study groups. However, in order to achieve our projected sample sizes we will require a no-cost extension following the final year of the award. This will allow us to continue participant accrual throughout the final year of the award.

Task 3. Preliminary Data Analyses (months 24-33)

We had originally proposed to begin preliminary data analyses at the start of Year 3. However, we now anticipate that data analysis will begin between month 6 and month 9 of Year 3.

Task 4. Final analysis and manuscript preparation (months 34-48).

Our final analyses will be delayed by approximately six months and will begin in month 40. Manuscript preparation will now begin in month 44 and continue into our anticipated no-cost extension.

KEY RESEARCH ACCOMPLISHMENTS

Our accomplishments to date include the initiation of our telephone interviewing and the completion of over 70 interviews. We expect that the pace of interviewing will increase considerably over the next year.

REPORTABLE OUTCOMES

To date we have no reportable outcomes.

CONCLUSIONS

This project seeks to gain a better understanding of the long-term psychosocial and behavioral implications of undergoing genetic counseling and testing for breast-ovarian cancer susceptibility. Since the start of the study, we have prepared all of our data collection and data management tools, hired our study staff, begun regular meetings, and compiled lists of participants to be contacted for participation. However, due to delays on the part of the Department of Defense Human Subjects review, we have been unable to commence study accrual and interviewing. After receiving final DOD approval, we initiated accrual and have been completing interviews at the expected pace.

REFERENCES

None
APPENDICES

A. Study Personnel Listing...p. X
## APPENDIX A: Current Salaried Study Personnel

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Marc D. Schwartz, Ph.D.</td>
<td>Principal Investigator</td>
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<td>Beth N. Peshkin, M.S.</td>
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<td>Kathryn L. Taylor, Ph.D.</td>
<td>Co-Investigator</td>
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<tr>
<td>Claudine Isaacs, M.D.</td>
<td>Co-Investigator</td>
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<tr>
<td>Kristi Graves, Ph.D.</td>
<td>Project Director</td>
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<td>Clinton Finch, B.S.</td>
<td>Data Manager/Programmer</td>
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<tr>
<td>Lauren DeEcheandia, M.S.</td>
<td>Data Specialist</td>
</tr>
<tr>
<td>Shibao Feng, Ph.D.</td>
<td>Biostatistician</td>
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