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14. ABSTRACT 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.

BODY

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.

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.

The study database was completed during Year 1, tested in Years 1 and 2, and became fully operational during Year 2. We are now using the database for all data entry and participant tracking. During Year 4 we will make slight modifications to the database to accommodate accrual of comparison participants.

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).

Participant accrual is ongoing. To date, we completed 370 interviews with former CARE participants. Thus far, just over 70% of eligible women have completed an interview. In addition to the 370 interviews that have been completed, we currently have 24 interviews scheduled and in September will contact a new group of at least 150 CARE participants. Thus, during our no-cost extension year, we expect to reach a total of at least 500 completed cohort interviews.

During Year 4, we also continued comparison group accrual. We will continue to focus on comparison group accrual during the no-cost extension year. To date we have completed or scheduled 151 comparison group interviews. We expect to complete our comparison group enrollment during the no-cost extension year.

With the no-cost extension, we expect to reach our projected sample sizes. With nearly 400 completed and scheduled cohort interviews, we are close to reaching our proposed cohort sample of 500.

Tasks 3 and 4. Preliminary Data Analyses and manuscript preparation (months 24-48)

We had originally proposed to begin preliminary data analyses at the start of Year 3. However, due to initial delays in approval of the protocol, we have had to delay preliminary analysis of data. Preliminary data analysis has begun on two research questions. First, we examined the communication of genetic test results among individuals who underwent BRCA1/2 testing. Specifically, analyzed the association between communication with family members and long-term quality of life outcomes. We have submitted a manuscript based upon these results (Tercyak, K.P., Graves, K.D., Peshkin, B.N., Schwartz, M.D. Long-term follow-up of women's decisions to share BRCA1/2 test results with first-degree relatives. Under Review). We are also in the process of writing a manuscript based upon our data related to menopausal symptoms among women who underwent BRCA1/2 testing. We expect this manuscript to be submitted in the Fall of 2007. During the no-cost extension year we will conduct additional analyses related to our key study outcomes – and expect to publish at least three additional manuscripts

KEY RESEARCH ACCOMPLISHMENTS

Our accomplishments to date include:

- enrolling and completing interviews with over 400 participants
- submitting our first manuscript based upon data from this project

REPORTABLE OUTCOMES

To date we have submitted one manuscript focused on familial communication of genetic test results. This manuscript was submitted to *Psychoonology*.

Data for this manuscript were based on 274 women who had completed an interview by the time of data analysis for this paper. Demographic characteristics of the women who participated are as follows: *M (SD)* age = 54.1 (9.6) years, 91.1% Caucasian, 96.4% college-educated, and 70.2% lived in households with a family income $\geq$ \$75k. The *M (SD)* calendar time that had elapsed since testing averaged 5.3 (1.2) years.

Table 1. Family Structure and Closeness Ratings			
Relative Category	N	%	M (SD) closeness
Parents	158	57.7	
Mothers	126	46.0	3.8 (0.5)
Fathers	116	42.3	3.6 (0.8)
Siblings	238	86.9	
Sisters	173	63.1	3.7 (0.7)
Brothers	139	50.7	3.4 (0.9)
Spouses	214	78.1	3.9 (0.5)
Children	185	68.9	
≤ 18	55	29.7	3.8 (0.3)
< 18	130	70.3	3.9 (0.5)

Data regarding women's family structure are presented in Table 1. As shown, more than one-half of women were able to report on family communication to parents, over three-quarters reported on communication to siblings and spouses, and slightly more than two-thirds reported on communication to children.

When family communication was analyzed via disclosure (Yes/No) to relatives, rates of communication to adult relatives was consistently high: 94.4% reported disclosing their BRCA1/2 test results to their mothers, 87.1% to their fathers, 96.5% to their sisters, 84.2% to their brothers, 98.1% to

their spouses, and 95.3% to their children over the age of 18; disclosure was less common to children under the age of 18 (53.6%).

To examine the potential impact of test results (i.e., carriers vs. uninformatives) on disclosure patterns to relatives, the association between these variables was tested via Chi-square statistics. There were no significant differences in rates of disclosure between carriers and uninformatives to all relatives except for brothers; carriers were more likely to disclose their test results to their brothers than were uninformatives, $X^2(1) = 8.14, p = .004$.

Table 2. Association of closeness with disclosure		
Relatives	r_{pb}	$s_{ry(1.2)}$
Mothers	.25*	.25*
Fathers	.28*	.30*
Sisters	.16*	.16*
Brothers	.40*	.39*
Spouses	.20*	.21*
Children ≥ 18	.25*	.25*
Children < 18	-.09	-.10
Note. r_{pb} denotes point-biserial correlation between closeness and disclosure; $s_{ry(1.2)}$ denotes semi-partial correlation between closeness and disclosure, controlling for test results.		

Finally, the potential association between kinship and disclosure was examined via point-biserial correlations, with and without the potential impact of test results partialled out. These results, shown in Table 2, consistently indicate that women who reported stronger kinship ties and closer relationships with their adult relatives during the time they underwent *BRCA1/2* testing were more likely to inform those relatives of their results. The strength of these associations remained largely unchanged when genetic test results were accounted for. For children under the age of 18 years, closeness was not associated with disclosure.

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

APPENDIX A: Current Salaried Study Personnel

Marc D. Schwartz, Ph.D.	Principal Investigator
Beth N. Peshkin, M.S.	Co-Investigator
Kathryn L. Taylor, Ph.D.	Co-Investigator
Claudine Isaacs, M.D.	Co-Investigator
Kristi Graves, Ph.D.	Project Director
Christy Gell, M.S.	Data Specialist
Sharon Hecker	Research Assistant