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13. ABSTRACT *(Maximum 200 Words)*

Three interrelated studies were conducted among urban African American women offered free genetic counseling and testing. Cross-sectional and longitudinal studies examined factors influencing interest in and readiness to undergo genetic testing, whether genetic counseling increased knowledge, and the psychosocial impact of DNA testing. 223 women signed the consent form for the study. Important observations resulting from this study that will impact on genetic counseling of women of African ancestry are: 1) The limited uptake of testing in this study despite continued educational interventions, including production of a study-specific videotape, support the importance of continuing to a) refine outreach and intervention efforts in order to increase awareness of BRCA counseling and testing among African American women and b) demonstrate sensitivity to concerns about stigmatization and family-related guilt that were noted in the first phase of the study. 2) Ethnicity and general distress remained more highly predictive of uptake of genetic testing than did education, supporting the importance of culturally specific beliefs and attitudes. 3) Finally, the outcome of genetic testing provided to those of African ancestry qualitatively approximated those of other ethnic groups, however, the greater incidence of missense variants of unknown origin in African Americans (first noted in this study) constitute a special challenge in counseling.

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Kenneth Hall 7/20/02

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Introduction

In the mid 1990's, molecular studies identified two large genes, BRCA1 on chromosome 17 and BRCA2 on chromosome 13; mutations in these genes were thought to be responsible for the majority of breast cancer cases in families with four or more affected relatives (Ford et al., 1995). Depending on the population studied, women with mutation in BRCA1/2 have 40% to 85% cumulative risk of developing breast cancer and 5% to 60% cumulative risk of developing ovarian cancer (Struewing et al., 1997; Whittemore et al., 1997; Schrag et al., 1997). There are several benefits associated with genetic testing for breast cancer susceptibility (Baum et al., 1997). For example, we have recently demonstrated that women found to be mutation carriers can increase the probability that breast cancer will be detected at early stage by increasing their breast cancer surveillance behavior (Scheuer et al., 2002) or seeking preventive surgery (Kauff et al., 2002) Women who learn that they do not carry a cancer-predisposition mutation may experience relief and improvements in quality of life (Baum et al., 1997). However, genetic testing can also have adverse psychological consequences including loss of insurance, stigmatization, and increased psychological distress (Croyle et al., 1997; Bankowski et al., 1991, Holtzman, 1989).

Most of the studies of the impact of counseling and genetic testing have predominantly focused on Caucasian women and have paid little attention to the role of ethnicity. Several lines of research suggest that minority women may have different attitudes toward genetic testing and that they may react differently to notification of test results. For example, African-American women have less knowledge about cancer (Michieuet et al., 1982), they utilize screening methods for breast cancer less often (Vernon et al., 1991; Powell et al., 1990) and they have higher levels of cancer anxiety (Miller et at al., 1994). Furthermore, African-American women believe that they have less control over their health (Miller & Hailey, 1994), and they have been found to have strong fatalistic attitudes toward cancer and cancer treatment (Bloom et al., 1987). These findings suggest that African-American women may also differ in their attitudes about genetic testing. In order for genetic testing to be successfully implemented in this population, it is important to: 1) identify factors that predict interest in testing; 2) examine the impact of genetic counseling on interest in genetic testing: and 3) measure the impact of risk notification on psychological adjustment and screening behaviors.

The present study examined these issues among urban women of African descent. The aims of the study were to: 1) identify factors that are associated with interest in genetic testing. 2) demonstrate the psychological effects of genetic counseling for women with family history of breast cancer; 3) measure the impact of risk notification based on genetic testing and its effects on psychological functioning and preventive and early detection behaviors. To achieve these aims, three interrelated studies were conducted. Study 1 was a cross-sectional study examining factors influencing interest in and readiness to undergo genetic testing. Study 2 was a

longitudinal investigation of whether genetic counseling increases knowledge and promotes readiness to undergo genetic testing. Study 3 consisted of pre- and post-notification evaluation of the psychosocial impact of DNA testing.

Body

Procedure:

Following a protocol approved by the Institutional Review Board (see Appendix), African-American women scheduled for an appointment at the Breast Examination Center of Harlem (BECH) were recruited. At the time of their visit the research assistant explained the study to eligible women and Survey 1 along with the consent form was mailed to interested women. All eligible women were offered genetic counseling free of charge and women whose family history indicated that the breast cancer in their family may be inherited were offered to undergo BRCA testing free of charge. Approximately 2 weeks after their genetic counseling session Survey 2 was mailed to the women.

Participants who had undergone BRCA testing and elected to receive their test results were informed about their results in accordance with IRB approved protocol (i.e., appropriate post-test counseling is provided). To assess acute distress and to monitor participants' well-being following notification, brief psychological measure was administered over the phone approximately 10 days after the notification session. Follow-up surveys were mailed to all women approximately 1, 6, and 12 months after their counseling/notification session.

Recruitment:

223 women signed the consent form and 164 returned Survey one while 73 women completed at least one of the follow-up assessments. As described in detail in previous progress reports we encountered several obstacles to recruitment during the study period, although the responses to questionnaires by those completing them was complete and fully analyzable. Below we will briefly summarize the challenges to recruitment as well as our efforts to overcome them: First, not until May 1997 were we able to recruit Ms. Chantal Duteau, one of relatively few genetic counselors of African-American background who completed training in recent years. As Ms. Duteau had no prior experience in cancer counseling she received extensive training in cancer genetic counseling at Memorial Sloan-Kettering before she was able to provide counseling to the women at BECH. During the course of this grant project, Ms. Duteau accumulated sufficient experience to become a superb educator and empathetic practitioner able to provide the full range of cancer genetic counseling services. Second, as the BECH does not offer free ovarian screening or peventive surgeries, recruitment was slowed down while we identified hospitals and clinics that provide ovarian screening as well as prophylactic surgeries (if requested) to those covered by Medicaid or those not having insurance. Institutions with support allowing care to these individuals were identified. A working collaboration with Dr. Giuseppe Del Priore, a

gynecologic surgeon at NYU/Bellevue Hospital was established to provide women participating in the study who had little or no insurance coverage the highest possible quality of preventive medical care, and special arrangements were made as well at MSKCC for selected patients. Third, the women at BECH were much less likely to be interested in participating in genetic studies than has been our experience at other MSKCC clinics. As this high refusal rate was, in part, due to low awareness of genetic testing for breast cancer, Ms. Duteau was encouraged and supported to develop an introductory video to increase their knowledge (see Appendix). The video was organized and produced and enacted by a genetic counselor (Ms. Duteau) and a study coordinator participating in the study. The video was played in the BECH waiting room area. Fourth, the women recruited from the BECH were much less likely to return mailed questionnaires than has been our experience at other MSKCC clinics. To address this problem we started to offer the women to complete the questionnaires with the research assistant either over the phone or in the clinic. Fifth, as we thought that it was important that we offered our women free testing for BRCA2 (cloned after the present study was funded), recruitment was stopped while we negotiated BRCA2 testing to be provided at no additional cost to the grant by Myriad Diagnostic Services. Finally, an unexpected research finding of the study was the high rate of genetic variants of unknown significance in the African-American population (see Results section) a finding that complicated the dissemination of genetic information throughout the families who had agreed to testing.

In our original Statement of Work we anticipated to be able to recruit 600 women but due to the above mentioned obstacles we modified our Statement of Work in 1999 to indicate that we anticipated to enroll 200 women with family histories of breast cancer. Although we were successful in that over 200 women consented to the study, only 164 returned the initial questionnaire. As will be documented, these data provided critical information on psychosocial predictors of those who declined genetic counseling . In addition the study was successful in meeting each of it's primary specific aims, and has generated preliminary data that will important in guiding further preventive and behavioral research involving cancer genetic testing in this community.

Results to Date: Preliminary results have been presented at the American Society of Human Genetics (1999, 2000), at the Era of Hope DOD (2000) and at the Society of Behavioral Medicine (2001). The results have also been accepted for publication, pending minor revisions, in Cancer Epidemiology Biomarkers & Prevention and subsets of the data were included in other publications in the year 2002 as well as in manuscripts under development. The results of this research have also resulted in the success of one of the investigators (H. Valdimarsdottir) in obtaining separate funding from the United States Army to further investigate the utilization of culturally-tailored counseling in BRCA decision making (see details in the Conclusion)

Result 1. Psychosocial predictors of BRCA counseling and testing decisions among urban African American women.

Presented at the Era of Hope DOD, 2000 and the Annual Meeting of Behavioral Medicine 2001.

Accepted for Publication in Cancer Epidemiology Biomarkers & Prevention (see Appendix).

Genetic counseling and testing for mutations in BRCA1/ 2 genes that increase breast cancer susceptibility potentially offer a number of benefits (e.g., more informed decision-making regarding breast cancer prevention options) but also raise potential problems (e.g., issues of discrimination). However, the literature suggests that African American women under-utilize genetics-related services. Therefore, the primary aim of the current study was to investigate predictors of the use of genetic counseling and testing for breast cancer susceptibility in this population. Participants were seventy-six African American at increased risk for breast cancer due to their family history of the disease. Participants were recruited from an urban cancer screening clinic and completed measures assessing sociodemographic information, breast cancer knowledge, breast-cancer specific emotional distress, and perceived benefits of and barriers to BRCA testing. Free BRCA counseling and testing was offered to all interested participants and measures were completed prior to counseling sessions. Based on their subsequent acceptance or refusal of these services, participants were described as having either: 1) declined BRCA-related genetic counseling (GC-); 2) participated in genetic counseling but refused genetic testing (GC+GT-); or 3) participated in both genetic counseling and testing (GC+GT+). Results revealed that participants who declined counseling had significantly less knowledge of breast cancer genetics than those who accepted both counseling and testing. No differences emerged between the three groups in terms of perceived benefits of testing. However, participants declining counseling demonstrated significantly higher perceived barriers scores compared those accepting counseling and testing. Specifically, those who did not participate in counseling reported greater anticipation of negative emotional responses to testing and more concern about stigmatization, while those who underwent both counseling and testing had significantly lower family-related guilt. Finally, cancer-specific distress was positively associated with participation in counseling, regardless of participation in testing. The current findings underscore the need for refinement of outreach and intervention efforts that both increase awareness of BRCA counseling and testing among African American women and provide information to those considering these options.

Result 2. Does Genetic Counseling for Breast Cancer Predisposition Increase Women's Knowledge?

Presented at the American Society of Human Genetics, 2000; (Brown et al. 2000)

An important goal of genetic counseling for cancer predisposition is to improve knowledge (or comprehension) about a range of topics, including principles of genetics and oncology, risks for cancer (family members' risks for cancer) and options for screening and primary prevention. However, (to date) there are little published data on knowledge and comprehension following genetic counseling for breast cancer. Therefore, the major aims of the present study were: 1) to examine the effectiveness of genetic counseling in improving general knowledge about breast cancer/genetics; and 2) to determine if the effectiveness of counseling is related to demographic and psychosocial factors. Participants were 107 women attending individual genetic counseling sessions for breast cancer susceptibility at Memorial-Sloan Kettering Cancer Center in New York and at the Breast Examination Center of Harlem. Approximately one week prior to their

counseling session the women completed measures of: 1) breast cancer knowledge (a 27-item questionnaire); 2) cancer specific distress (Impact of Events Scale); and 3) general distress (Profile of Mood States). Approximately one week following their counseling session, the women again completed the knowledge questionnaire. There was a significant increase in knowledge from before to after the counseling session (p=.0001). However, there was a wide variability among the women, with no improvement in knowledge among some women. The counseling was less effective for minority women (p=.007), less educated women (p=.05), and women with high levels of general distress (p=.003). When all of these variables were entered together into the equation, ethnicity and general distress remained significant while education was no longer significant. These findings suggest that some women may require different counseling protocols if genetic counseling is to be effective in educating them (about their risks and options).

Result 3. Social constraints and psychological adjustment following notification of uninformative BRCA1/2 test results.

Manuscript In Preparation

Genetic testing for breast cancer susceptibility is increasingly available to individuals with strong family histories of breast cancer. Although it has been suggested that genetic test results can have adverse psychological consequences relatively few studies have addressed this issue. The few existing studies have indicated that notification of negative test results improves psychological adjustment whereas no change is observed in psychological adjustment among individuals who receive positive test results. These studies did not examine the impact of receiving uninformative results (i.e., a deleterious mutation is not detected in the family despite strong family history of the disease) on psychological adjustment. As, these individuals continue to be at elevated risk of developing breast cancer BRCA testing may not alleviate their distress levels. In addition to date no study has examined the possibility that social support or lack thereof may moderate the impact of BRCA test results on emotional adjustment. Several studies have shown that individuals confronted with stressful life events, such as cancer, have better psychological adjustment if they are able to express their concerns about the stressful event. Therefore the major aims of the present study were to: 1) examine the impact of uninformative test results on cancer specific distress and depressive symptoms; 2) investigate whether individuals who perceive social barriers or social constraints to expressing their concerns about breast cancer have higher levels of cancer specific distress and depressive symptoms than individuals low on social constraints. Participants were 56 women who had received individual genetic counseling sessions for breast cancer susceptibility at Memorial-Sloan Kettering Cancer Center in New York or at the Breast Examination Center of Harlem. All of these women underwent BRCA testing and elected to learn their test results received inconclusive BRCA test results. Approximately one week prior to their counseling session the women completed measures of: 1) cancer specific distress (Impact of Events Scale); and 3) depressive symptoms (the Beck depression inventory). Approximately one month following their BRCA notification

session, the women completed the same questionnaires. The mean age was 51.3 (range 28 to 78), 16.3% were African American, and 74.5% had been diagnosed with breast cancer. To examine the impact of uninformative results on cancer specific distress and depressive symptoms a change score was calculated for each measure. A General Liner Model (GLM) was then computed entering baseline distress measures first into the equation. The demographic variables (i.e., ethnicity, age, breast cancer diagnosis) were unrelated to changes in cancer specific distress and depressive symptoms (p's > .20). Individuals who perceived constraints in expressing their concerns about breast cancer had significantly higher levels of depressive symptoms (F (4,65), p=.03). To examine this relationship further a median split was used to divide individuals into two groups, those above the median and those below the median on depressive symptoms. Depressive symptoms increased among individuals above the median on social constraints whereas depressive symptoms decreased among individuals below the median on social constraints (change scores -.28 and 1.64 respectively). Cancer specific distress decreased from before to one month following notification of results (changes score –2.3) and there was no relationship between social constrains and change in cancer specific distress. These results suggest that uninformative BRCA test results can result in increased depressive symptoms among individuals who perceive social barriers to expressing their concerns about breast cancer. Future studies should examine whether these women may benefit from psychosocial counseling or support groups.

Result 4. High frequency of sequence variants in women of African descent undergoing BRCA1 or BRCA2 testing.

American Journal of Human Genetics 1999 (Robson et al1999, and see Appenndix)

In this ongoing study with African American women, mutation data were presented from 57 individuals from 49 families who underwent BRCA1 and/or BRCA2 testing. Of the 53 individuals from 49 families who underwent BRCA1 coding sequence analysis, 5 individuals (9.4%) from 5 families (10.2%) were heterozygous for presumably deleterious BRCA1 mutations. An additional 21 BRCA1 sequence variants of uncertain significance were detected in 16 individuals (30.2%) from 16 families (32.7%). BRCA2 sequence analysis was performed on 33 individuals from 28 families (4 individuals tested only for previously identified mutations). Of the 29 individuals from 28 families undergoing complete BRCA2 coding sequence analysis, 2 (6.9%) were found to carry presumably deleterious mutations. An additional 17 individuals (58.6%) from 16 families (57.1%) were found to carry a total of 28 BRCA2 sequence variants of uncertain significance. Of 29 individuals (28 families) undergoing both BRCA1 and BRCA2 analysis, 21 persons (72.4%) from 20 families (71.4%) had at least one sequence variation of uncertain significance. More than one variant was noted in 17 individuals from 16 families. Several variants (3 BRCA1, 5 BRCA2) were observed in more than 1 family. These findings indicate that prevalence of genetic variants of uncertain significance must be taken into account when providing counseling regarding BRCA testing to individuals of African descent. Following presentation of these data, 10 additional cases from African American participants were ascertained on this research study, bringing the total to 67 women tested, with a similar rate of polymorphisms of unknown significance noted. Subsequently, these findings have been

confirmed in the laboratory of our colleague Dr. Funmi Olopade at the University of Chicago, who is undertaking a study of an endogenous Nigerian population to define the spectrum of polymorphisms encountered.

Result 5. Outcome of Screening and Surgery Following BRCA Testing

Kauf et al., New England Journal of Medicine, 2002 and Scheuer et al. Journal of Clinical Oncology, 2002.

Support for the current grant was acknowledged in both of these papers, which were among the first to prospectively establish detection of early-stage cancers, or prevention of breast and ovarian cancers in a large population of women. 5.4% of the 251 carriers of deleterious BRCA1 or BRCA2 mutations included in the screening study were of African American ancestry, and were participants in the current study There were no statistically significant differences in utilization of screening or prophylactic surgical options (mammography, ultrasound, mastectomy, oophorectomy) in African American compared to Caucasian kindreds. In one large kindred of African American ancestry (of Jamaican origin) there was the unusual presentation of a male affected by breast cancer. A disease-causing mutation was ultimately identified by genetic testing. The pedigree for this kindred is include in the Appendix. The participation and genetic testing of the proband's daughters was made possible by participation in this research study, and has been directly translated to the preventive cancer care of this family. From the psychosocial perspective, the instruments completed by the daughters did not indicate elevated levels of family related guilt or stigma, in distinction to the findings of part 2 of this study (discussed above), perhaps a testimony to the strong supportive role of the father (the proband) as well as the efforts of the genetic counselors. A case study of this family is being drafted for report in a genetics counseling journal.

Key Research Accomplishments and Further Research Stimulated By This Project

To date 223 women have signed the consent form, and 164 returned their baseline questionnaire. As detailed in our previous progress reports and summarized above we encountered several obstacles to ascertainment during the course of the study which prevented us for obtaining our initial recruitment goals. However, we were able to obtain important information bearing on all three study aims, and which will have impact on future counseling and outreach strategies.

Our first aim was to identify cognitive, emotional, and other factors that influence women's interest in genetic testing. Our results, which have been accepted for publication in a premier preventive oncology journal, indicate the following. First, women who declined counseling demonstrated significantly lower knowledge compared to those who accepted both counseling and testing. Interestingly, there were no significant differences across the three decision groups in terms of more general knowledge of breast cancer. Second, women who declined counseling were also more likely to anticipate stigmatization due to BRCA mutation carrier status compared to women who participated in counseling, regardless of testing decision. This is similar to other

reports that stigma, shame and secrecy surrounding breast cancer are barriers to breast cancer screening (e.g., mammography) in the African American community. Third, women who refused testing had significantly greater anticipated guilt regarding the carrier status of relatives than women who participated in testing. Such concern, specifically concern about feelings of guilt, may be due to the view that knowledge of one's BRCA test results and their ramifications in terms of disease risk, emotional and financial stability, represent a burden that is not carried by the patient alone, but by potentially many family members. Taken together these findings suggest that not only intervention content but also the stage at which specific content is presented is important considerations in the development of such interventions. For example, based on the current results, outreach into the African American community intended to educate individuals about initiating the genetic testing process may focus more on barriers to genetic counseling participation, specifically issues related to negative emotional reactivity and stigmatization. The findings also suggest that standard genetic counseling sessions may need to place greater emphasis on areas that are particularly salient for African American women, especially family-related guilt.

Our second aim was to examine the effectiveness of genetic counseling as a means of educating African- American women about genetic counseling/testing. Our result, described above, indicate that women with higher levels of distress are less likely to improve their knowledge of breast cancer/genetics than women with lower levels. This finding suggests that genetic counseling might be more effective if genetic counselors were to spend more time assessing and addressing women's emotional concerns. The African-American women were less likely to improve their knowledge about breast cancer/genetics than the Caucasian women. Although this finding needs to be replicated with a larger sample of minority women, it raises the possibility that genetic counselors may need to better address culturally specific beliefs and attitudes.

Our third aim was to examine the impact of genetic testing of psycho-behavioral outcomes. Comparing data from African American women to Caucasian women who had underwent BRCA testing, we have noted common outcomes in this aspect of the study. As only 6% of the women who underwent testing had informative results, that is, they either carried the mutation segregating in their family or they did not carry the mutation segregating in their family (i.e. true negative) we focused on the women receiving uninformative results. Our preliminary results indicate that one month following disclosure of the results depressive symptoms are increased both among African American women and Caucasian women who perceive constraints in expressing their concerns about breast cancer. These results suggest that there may be a subgroup of women who will benefit from psychological counseling or support groups following disclosure of BRCA test results. These finding are significant because if it is indeed the case that there is a greater likelihood of finding of missense mutations of unknown significance among those individuals of African ancestry, even though there may not be a difference in qualitative psychosocial response to such ambiguous test results, the quantitative risk for adverse outcome after testing may be greater in those of African-American ancestry simply because of the higher prevalence of these missense variants in this cohort.

These findings have therefore stimulated the recent research focus as well as future plans of this research group. In response to the findings of this study, one of the study investigators has focused on the impact of acculturation and the use of acculturation scales to account for health behaviors in the African-American population (see paper submitted to Cultural Diversity and Ethnic Minority Psychology in the Appendix). In addition Dr. Valdimarsdottir has recently received a research grant entitled "Impact of culturally tailored counseling on psychobehavioral outcomes and BRCA decision making among women with breast cancer" supported by the United States Army (as part of DAMD-17-01-1-0334). This project will further develop these acculturation scales for in cancer genetic counseling and prevention medicine. Another effort growing from the current study is the development of a protocol for a focus group organized by one of the study investigators (Dr. Offit with Dr. Valdimarsdottir) to further explore attitudes and beliefs about genetic testing.

Reportable Outcomes

Papers and Abstracts that acknowledge support of this grant

Kauff ND, Satagopan J, Robson M et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or a BRCA2 mutation. New England J Medicine 2002 346: 1609-1615

Robson M, Duteau-Buck C, Valdimirsdottir H, Guevara J, Baum RT, Hull J, McDermott D, Pinto M, Scheuer L, Offit K. High frequency of sequence variants in women of African descent undergoing BRCA1 or BRCA2 testing. American Society of Human Genetics annual meeting, abstract 105 (chosen for plenary presentation).

Scheuer L, Kauff N, Robson M et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J. Clin Oncol 2002; 20:1260-1268.

Brown K, Valdimarsdottir H, Erblich J, Amarel D, Scheuer L, Hull J, McDermott D, Bovbjerg D, Hurley K, Offit K. Does genetic counseling for breast cancer predisposition increase knowledge? American Society of Human Genetics. 2000 Annual Meeting. abstract 524.

Thompson HS, Valdimarsdottir HB, Duteau-Buck C, Guevarra J, Bovbjerg D, Richmond-Avellaneda C, Amarel D, Godfrey D, Brown K, Offit K. Psychosocial predictors of BRCA counseling and testing decisions among urban African American women. (in press, Cancer Epidemiology Biomarkers and Prevention).

Guevarra J, Tang TS, Valdimarsdottir HB, Freeman HP, Kwate N O A, Bovbjerg D, Ruttenberg Cancer Center. The African American acculturation scale and its relationship to smoking and breast self-examination frequency (submitted to Cultural Diversity and Ethnic Minority Psychology).

Video educational instrument

Genetic Testing for Breast Cancer Risk: Questions and Answers (included with Appendix materials)

Research Grants Awarded Based on Work Funded in this Grant

"Impact of culturally tailored counseling on psychobehavioral outcomes and BRCA decision making among women with breast cancer" supported by the United States Army Center Grant DAMD-17-01-1-0334, Bovberg, D, P.I. awarded in 2002.

Professional training afforded by this grant

Although this was not an educational training grant, an outcome of this project was the training of Chantal Duteau-Buck, M.S., a genetic counselor who happens to be of African-American ancestry, who acquired skills cancer genetic counseling of women at hereditary risk for breast cancer

Conclusions

In summary, the major observations resulting from this study (listed according to specific aim) that will impact on genetic counseling of women of African ancestry are: 1) There is a continued need for refinement of outreach and intervention efforts that both increase awareness of BRCA counseling and testing among African American women as well as greater sensitivity to concerns about *stigmatization* and *family-related* guilt, important psychosocial predictors of testing in this study population as documented in the first part of this project. 2) When multiple variables were compared, ethnicity and general distress remained highly predictive of uptake of genetic testing, while education was no longer significant, suggesting that culturally transmitted factors may outweigh educational interventions and that genetic counselors must address culturally specific beliefs and attitudes.3) Finally, the outcome of genetic testing provided to those of African ancestry qualitatively approximated those of other ethnic groups with respect to screening and preventive surgeries. However, the greater incidence of missense variants in those of African-American ancestry may lead to ambiguous results of testing which constitute an important challenge in this field.

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APPENDICES TABLE OF CONTENTS

Family Pedigree Chart

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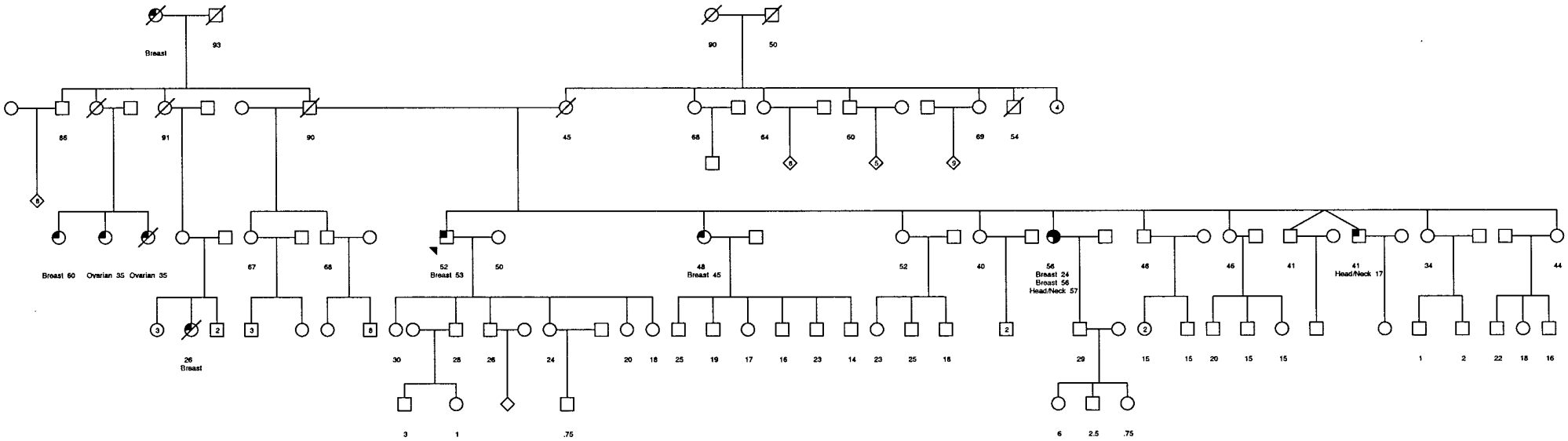
Protocol and Consent Form for Protocol # 95-011A(3) "Impact of Genetic Counseling and Testing for Breast Cancer

Video educational instrument: Genetic Testing For Breast Cancer: Questions and Answers.

Kindred 1635

(see discussion of this kindred on page 7 of the Final Report)



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Cancer-Specific Distress is Related to Women's Decisions to Undergo BRCA1 Testing

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Problem
To examine the role of demographic variables, objective risk, perceived risk and cancer-specific distress in women's decisions to undergo genetic testing

Methods
One-hundred and five women with family histories of breast cancer completed a baseline questionnaire after which they were invited to attend a genetic counseling session and provide a blood sample for BRCA1 testing

Results
Fifty-five percent of the participants provided blood samples. After controlling for age, objective risk and perceived risk, which were positively related to provision of blood sample, women with moderate levels of cancer-specific distress were more likely to provide a blood sample than women with high or low levels of cancer-specific distress.

Conclusions
Cancer-specific distress affects women's decisions to undergo genetic testing for BRCA1. Genetic counseling needs to address cancer-specific distress, since it may affect the probability that individuals are making an informed decision about undergoing genetic testing for breast-cancer susceptibility.

Keywords: BRCA1, Decision-making, Genetic testing, Distress

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INTRODUCTION

Consistent with risk estimates for most common cancers, women with histories of breast cancer in even one first-degree relative have been found in large epidemiological studies to be more than twice as likely to develop breast cancer themselves (1). A history of additional affected close relatives further increases the risk, as do other characteristics (e.g., bilateral disease, diagnosis at an early age) associated with a role for heredity in the etiology (2,3). Segregation analyses of families with multiple cases of breast and/or ovarian cancer suggest the existence of rare, autosomal dominant susceptibility genes (2,4). Linkage analyses has led to the identification and subsequent cloning of two large genes, BRCA1 on chromosome 17 and BRCA2 on chromosome 13; mutations in these genes are now thought to be responsible for the majority of breast cancer cases in families with four or more affected relatives (2). Depending on the population studied, women with mutation in BRCA1/2 have 40% to 85% cumulative risk of developing breast cancer and 5% to 60% cumulative risk of developing ovarian cancer (5–7).

For women with family histories, there are several benefits associated with genetic testing for breast cancer susceptibility (8). For example, women found to be mutation carriers can increase the probability that breast cancer will be detected at early stage by increasing their breast cancer surveillance behavior (e.g., mammography), or they can decrease the probability that breast cancer will develop by undergoing prophylactic mastectomy (9,10). In addition, women who learn that they do not carry a cancer-predisposition mutation may experience relief and improvements in quality of life (8). However, there are also several negative consequences associated with genetic testing (8). For example, women found to be mutation carriers may face uncertainty about their future, insurance discrimination, and worsened quality of life (11). Consequently, individuals considering genetic testing need to weigh the benefits against an array of possible costs of genetic testing. There are probably several factors that affect individuals' decisions to undergo genetic testing. Intentions to undergo genetic testing for cancer susceptibility have been found to be related to younger age (12), higher education (12), higher levels of perceived risk (13) and higher levels of cancer-specific distress, as assessed by the intrusion subscale of the Impact of Events Scale, IES (12,14). However, as intention to undergo genetic testing may not result in actual test (15) use, relatively little is known about predictors of actual test use. In two recent studies (16,17), variables found to be positively related to requests for BRCA1 test results included: being a female, younger age, more education, higher levels of objective risk, having health insurance, and higher levels of cancer-specific distress (IES). The participants in these studies were members of hereditary breast ovarian cancer (HBOC) families. They had provided blood samples several years earlier as part of studies conducted to localize the BRCA1 gene, and knew that a BRCA1 mutation had been identified in their family. Therefore, it is not clear if similar results would be obtained with individuals with less extensive family histories of breast cancer and no history of participation in genetic studies.

The possibility that cancer-specific distress may have a different impact on the decision to undergo genetic testing among women with less extensive family histories of cancer is raised by studies that have examined breast cancer screening behavior. These studies have found that high levels of psychological distress, assessed by a variety of measures, were related to reduced compliance with appropriate screening practices, including mammogprahy, clinical breast-examination, and breast self-examination (18–20). On the other hand, there have also been reports that high levels of distress about breast cancer facilitate appropriate screening practices (21,22). It has been suggested (23) that one of the reasons for these apparently contradictory findings is that the relation between distress and screening practices is curvilinear; too much or too little distress may inhibit screening while moderate levels of distress may facilitate screening.

The purpose of the present study was to examine the relation between demographic variables, objective risk, perceived risk, cancer specific-distress and decision making about BRCA1 testing among women

with family histories of breast cancer who had not previously received genetic counseling or participated in genetic studies. Based on the above reviewed literature we expected that education, objective risk, and perceived risk would be positively related to provision of a blood sample for BRCA1 testing. We also expected that women with moderate levels of cancer-specific distress would be more likely to provide a blood sample for BRCA1 testing than women with low or high levels of cancer-specific distress.

METHODS

Subjects

Participants were 105 women who were participating in an ongoing longitudinal study examining the psychological and behavioral impact of genetic counseling and testing for breast cancer susceptibility. The women were recruited from two clinics at Memorial Sloan-Kettering Cancer Center, the Special Surveillance Breast Program (SSBP N=62) and the Clinical Genetics Service (CGS, N= 43). To be eligible for the study the women had to: 1) be 18 years of age or older; 2) have at least one first-degree relative diagnosed with breast cancer; 3) have no personal history of cancer; 4) have never undergone genetic counseling for breast cancer; 5) be able to read and write English; and 6) willing to provide informed consent.

Procedure

Women who were scheduled for a routine mammography at a special surveillance breast clinic or self-referred for genetic counseling were contacted by telephone approximately one to two weeks prior to their scheduled appointment. The study was described as an investigation to learn more about women's attitudes and feelings about breast cancer and genetic testing for breast cancer susceptibility. Participants were told that they would be asked to complete questionnaires several times over the course of the study and that they would have the opportunity to undergo genetic testing, free of charge to determine whether or not they carry a mutation in the BRCA1 gene. It was emphasized to the women that they could: 1) refuse to participate; 2) discontinue their participation at any time; 3) fill out the questionnaires without going for genetic counseling or genetic testing; 4) attend the counseling session without undergoing genetic testing; and 5) decide not to learn their mutation status once their test results were available. It was also emphasized that the women could not undergo genetic testing unless they had attended the counseling session.

Women who met the study criteria and were interested in participating were mailed a consent form, the baseline questionnaire package, and a pre-stamped envelope. A few days later the women were contacted again by telephone to verify that they had received the questionnaire package, review the consent form, and answer any questions that they might have. The women then returned the signed consent form and the completed questionnaires prior to their genetic counseling visit (see below).

Women at relatively high risk (relative risk ≥ 2) for breast cancer who had signed the consent form and returned the completed questionnaires were invited to come in for individual genetic counseling. The counseling sessions were conducted by a genetic counselor and lasted one to two hours. After construction of the pedigree, the following issues were addressed: 1) possible reasons for familial clusterings of cancer; 2) the likelihood of the occurrence of cancer in the pedigree to be hereditary (i.e., conforming to the criteria for a hereditary cancer syndrome) or familial (i.e., not meeting those criteria); 3) limitations of pedigree analysis, including the inability to distinguish between a sporadic and inherited cancer; 4) the relative importance of various risk factors other than family history; 5) risk estimates for developing cancer based on family history and/or associated with BRCA mutations; 6) options for prevention and early detection, and their limitations 5) limitations and benefits of genetic testing for BRCA1; and 6) risks of receiving test results, including insurance discrimination and adverse psychological consequences.

After the genetic counseling, subjects were given the opportunity to provide a blood sample to be tested for mutation in BRCA1. For subjects who decided to undergo genetic testing, a separate informed consent for DNA testing was reviewed and participants were urged to consider the impact of negative, positive, and ambiguous results. It was also stressed that participants could decide not to learn their results once they became available.

Women at relatively low risk for breast cancer (relative risk < 2.0) followed the same procedure as the women at relatively high risk, except they were invited to attend a group genetic counseling session which addressed the same issues as the individual counseling.

Measures

Demographic questionnaires

Age, education, race/ethnicity and marital status were assessed using a standard self-report form (24).

Family history questionnaire

This questionnaire is designed to assess the occurrence of cancer in participants' biological first- and second-degree relatives. Participants are asked to supply detailed information about their family histories of cancer, e.g., ages of onset and occurrence of multiple cancers. The data from this questionnaire was used by one of us (KB), a genetic counselor kept blind to all other study data, to estimate lifetime objective breast cancer risk.

Perceived risk of breast cancer

Following previously published methods (24–26), subjects rated on a scale from 0% (not at all likely) to 100% (extremely likely) their perceived likelihood of developing breast cancer in their lifetime.

Impact of Event Scale (IES)

The intrusion subscale of the IES (27) was used to assess breast cancer-specific distress. This seven-item subscale assesses frequency of intrusive thoughts about a specific stressor, in this case, the threat of breast cancer. The coefficient alpha in the present sample was .88, consistent with values reported by Horowitz et al., (27). Subjects indicated how frequently each thought or behavior occurred "during the past week including today". This measure was selected as Lerman. Schwartz et al (17) found that intrusive thoughts about breast cancer were related to BRCA1 test use.

RESULTS

Characteristics of the study population.

The mean age of the sample was 45. 1 years (SD=9.3; range 21 – 72), The majority of the women were white (91%), well educated (75% had attended college) and married (61%). The mean perceived risk was 59.2% (SD=26.5; range 0–100) and the mean objective risk was 28.5% (SD=13.3; range 11%-50%). For the cancer-specific distress measure, the mean score on the IES intrusion subscale was 6.3 (SD=7.5; range 0–31). Fifty-five percent of the participants (N=58) provided a blood sample for genetic testing.

Are sociodemographic variables, objective risk and perceived risk related to who provides a blood sample for genetic testing?

To determine the bivariate correlates of blood provision we conducted a series of χ^2analyses. Specifically, we evaluated the associations of sociodemographics, objective risk, and perceived risk with blood provision. Because the distribution for both perceived risk and objective risk was skewed these variables were dichotomized based on a median split. Following the procedure by Lerman and colleagues, (17) age was dichotomized as < 50 vs. ≥ 50 years.

As shown in Table I, older women tended to be more likely to provide a blood sample for genetic testing, χ^2 (1, N=105)=3.4, p = .06, and women with higher levels of perceived and objective risk were significantly more likely to provide a blood sample for

genetic testing ($\chi^2(1,N=105)=4.2$, p= .04; $\chi^2(1,N=105)=8.0$, p= .005 respectively).

TABLE I Bivariate Associations With Provision of a Blood Sample for BRCA1 Testing

Variable	*Reference group*	*% providing blood*
Age	< 50	49^{+}
	≥ 50	69
Education	< College	57
	≥ College	55
Marital status	Married	59
	Unmarried	50
% objective risk	< 40	43**
	≥ 40	71
% perceived risk	< 70	48
	≥ 70	68*
Cancer-specific distress	Low distress	52**
	Moderate distress	77
	High distress	38

$^{+}$p < .10 *p < .05 **p < .01

Is cancer specific distress related to who provides a blood sample for genetic testing?

We also evaluated the bivariate association between cancer-specific distress, as measured by the IES intrusion subscale, and the provision of a blood sample for genetic testing. In order to examine the hypothesized curvilinear relationship between distress and provision of a blood sample, we categorized scores into low distress (IES 0–1, N=46), moderate distress (IES 2–9, N=30), and high distress (IES 10+, N=29), following the cutoff points established by Lerman and colleagues (17). As shown in Table I, women with moderate distress scores were more likely to provide a blood sample than women with low or high distress scores (χ^2 (1, N=105) = 9.25, p = .01).

Is cancer-specific distress related to who provides a blood sample after controlling for demographic and risk variables?

To determine whether cancer-specific distress predicted blood sample provision after controlling for potential confounders, we conducted a logistic regression analysis with hierarchical variable entry. On the first step we entered all of the variables with significant (p <. 10) associations with blood sample provision (age, perceived risk, objective risk). On the second step, we entered cancer-specific distress which was dummy coded with moderate distress serving as the reference cell. The results of this analysis are displayed in Table II.

TABLE II Hierarchical Logistic Regression Predicting Provision of a Blood Sample for BRCA1 Testing

	Step and variables	*Reference group*	χ^2	*Odds ratio*	*95% CI*
Step 1					
	Age	< 50 ≥ 50	14.9	2.4^{+}	6.1, 0.98
	objective risk	< 40 ≥ 40		3.1**	7.3, 1.32
	perceived risk	< 70 ≥ 70		2.1^{+}	5.2, 0.99
Step 2					
	Cancer-specific distress	Low distress High distress	13.3*	.24** .11*	0.54, 0.11 0.42, 0.03

Note CI=Confidence Interval
$^{+}$p < .10, *p < .01, **p < .001.

Age, perceived risk and objective risk, taken together, significantly predicted blood sample provision (χ^2 change (3, N=105) = 14.9, p = .002). Cancer-specific distress, entered on step 2, added significantly to the prediction of blood provision (χ^2 Change (2, N=105) = 13.32, p <.01). Inspection of the final odds ratios supported our prediction of a curvilinear relationship between distress and blood provision. Specifically, women with low levels of cancer-specific distress were less likely to provide a blood sample compared to women with moderate levels of cancer-specific distress (OR=.24, 95% CI=0.5, 0.1). Similarly, women with high levels of cancer-specific distress were less likely than those with moderate levels of distress to provide a blood sample (OR=.11, 95% CI=0.4, 0.03). In addition to cancer-specific distress, objective risk and perceived risk also were independently associated with blood provision (OR=4.4, 95% CI=18.5, 2,7; OR=2.5, 95% CI=6.7, 2.7 respectively). Specifically, women with higher levels of objective risk were about four times more likely to provide blood for genetic testing than women with lower levels of objective risk. In addition, there was a trend suggesting that women with higher levels of perceived risk were more likely to donate blood for genetic testing than women with lower levels of perceived risk.

DISCUSSION

The results of the present study indicate that cancer-specific distress is related to women's decisions to donate blood for BRCA1 testing. Women with moderate levels of cancer specific distress were more likely to donate blood than women with high or low levels of cancer specific distress. These results were obtained after controlling for age, objective risk and perceived risk, which were all positively related to provision of a blood sample for genetic testing.

The finding of a curvilinear relationship between cancer-specific distress and provision of a blood sample for BRCA1 testing is inconsistent with the finding reported by Lerman and colleagues (17) that individuals with high levels of cancer-specific distress were more likely to request BRCA1 test results than individuals with moderate or low levels of cancer-specific distress. There are at least three possible explanations for these discrepant findings. First, unlike the subjects in the present study, the participants in the study by Lerman et al. (17) included both affected and unaffected male and female members of previously studied HBOC families having extensive histories of breast cancer. Also, unlike participants in the present study who donated blood at the time of the study to learn their mutation status, the members of these HBOC families had donated blood several years earlier as a part of an investigation to localize the BRCA1 gene. Moreover, unlike participants in the present study, the members of the HBOC families were aware that a BRCA1 mutation had been found in their family. It is therefore possible that cancer-specific distress plays a different role in the decision to undergo genetic testing among members of these well-studied high risk families than among individuals in the present study who came from families with much less extensive family histories of breast cancer and who did not know if there was a BRCA1 mutation in their family. Second, cancer-specific distress may differentially affect the decision to provide a blood sample for genetic testing versus the decision to request test results. However, this is an unlikely explanation, as BRCA1 test results are now available for 34 of our participants, and none of them have declined to learn their mutation status. Third, the participants in these two studies could have had different levels of cancer-specific distress (IES). However, this is an unlikely explanation because the cancer-specific distress levels among participants in the present study showed a similar distribution (M=6.3, SD=7.5) to that reported by Lerman and colleagues (17) (M=6.2, SD=6.7). The finding in the present study that older women were more likely to provide a blood sample for genetic testing than younger women is also inconsistent with Lerman and colleagues (17) finding that younger women were more likely to request their BRCA1 test results. As with cancer-specific distress, these discrepant results may be due to the fact that the subjects in the present study differed on several variables from the participants in Lerman and colleagues

(17) study. Additional studies are needed to confirm the possibility that psychosocial variables (e.g., cancer-specific distress), as well as demographic variables (e.g., age), may differentially effect the decision to undergo genetic testing depending upon the population studied.

Whether the relationship between distress levels and the decision to undergo testing is linear or curvilinear, the results of the present study support an emerging consensus that distress may be an important variable to consider as we try to understand individuals' decisions to undergo testing. The data reported here revealed a significant relationship between cancer-specific distress levels and testing decisions even after controlling for other previously published predictors (e.g., age, objective risk, perceived risk). Cancer-specific distress has also been found to affect the effectiveness of genetic counseling. Lerman and colleagues (26) found that women who had high levels of cancer-specific distress were more likely to continue to overestimate their lifetime risk of developing breast cancer after the risk counseling than women with low levels of cancer-specific distress. Taken together, the results from these studies and the present study suggest that cancer-specific distress needs to be addressed in the context of genetic testing. Understanding the role of cancer specific-distress in genetic testing will assist in designing interventions which will increase the probability that individuals are making an informed decision about undergoing genetic testing for breast cancer susceptibility and minimize the possible negative psychological impact of genetic testing.

Consistent with previous studies which found that intentions to undergo genetic testing were related to high levels of perceived risk (13,14) the present study found that women with high levels of perceived risk were more likely to provide a blood sample for genetic testing. This finding further indicates the importance of addressing cancer-specific distress, as genetic counseling may not be effective in improving risk comprehension among women with high levels of cancer-specific distress (26).

The results of the present study should be interpreted cautiously for several reasons. First, as a majority of the women were White and well educated, we can not generalize our findings to individuals from other ethnic and sociodemographic backgrounds. Second, because of the small sample size we could not examine in the logistic regression analyses whether the relation between cancer-specific distress and provision of blood sample differed between women who were recruited from a special surveillance breast program and women who were self-referred for genetic counseling. However, the results form the bivariate analyses, computed separately for each recruitment site, indicated that, at both recruitment sites, women with moderate levels of cancer-specific distress were more likely to provide blood samples than women with low or high levels of cancer-specific distress. Third, the generalizability of these findings to BRCA2 test use needs to be examined as the BRCA2 gene had not been cloned when the present study started.

Despite these limitations, the results of the present study indicate the importance of understanding the role of cancer specific-distress in women's decisions to undergo genetic testing for breast cancer susceptibility.

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RISK-REDUCING SALPINGO-OOPHORECTOMY IN WOMEN WITH A *BRCA1* OR *BRCA2* MUTATION

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ABSTRACT

Background Risk-reducing salpingo-oophorectomy is often considered by carriers of *BRCA* mutations who have completed childbearing. However, there are limited data supporting the efficacy of this approach. We prospectively compared the effect of risk-reducing salpingo-oophorectomy with that of surveillance for ovarian cancer on the incidence of subsequent breast cancer and *BRCA*-related gynecologic cancers in women with *BRCA* mutations.

Methods All women with *BRCA1* or *BRCA2* mutations identified during a six-year period were offered enrollment in a prospective follow-up study. A total of 170 women 35 years of age or older who had not undergone bilateral oophorectomy chose to undergo either surveillance for ovarian cancer or risk-reducing salpingo-oophorectomy. Follow-up involved an annual questionnaire, telephone contact, and reviews of medical records. The time to cancer in the two groups was compared by Kaplan–Meier analysis and a Cox proportional-hazards model.

Results During a mean follow-up of 24.2 months, breast cancer was diagnosed in 3 of the 98 women who chose risk-reducing salpingo-oophorectomy and peritoneal cancer was diagnosed in 1 woman in this group. Among the 72 women who chose surveillance, breast cancer was diagnosed in 8, ovarian cancer in 4, and peritoneal cancer in 1. The time to breast cancer or *BRCA*-related gynecologic cancer was longer in the salpingo-oophorectomy group, with a hazard ratio for subsequent breast cancer or *BRCA*-related gynecologic cancer of 0.25 (95 percent confidence interval, 0.08 to 0.74).

Conclusions Salpingo-oophorectomy in carriers of *BRCA* mutations can decrease the risk of breast cancer and *BRCA*-related gynecologic cancer. (N Engl J Med 2002;346:1609-15.)

WOMEN with *BRCA1* or *BRCA2* mutations have a 60 to 85 percent cumulative lifetime risk (to 70 years of age) of invasive breast cancer and a 15 to 65 percent cumulative lifetime risk of invasive epithelial ovarian cancer.[1-3] Because of a paucity of prospective data regarding the efficacy of preventive approaches in carriers of *BRCA* mutations, counseling about screening, chemoprevention, and risk-reducing surgery has been based largely on expert opinion.[4] We have previously found that a combination of intense surveillance and risk-reducing surgery in carriers of *BRCA* mutations may allow the diagnosis of breast and ovarian cancers at an early stage.[5] Recent data also suggest that prophylactic mastectomy reduces the risk of breast cancer.[6]

Salpingo-oophorectomy for the prevention of ovarian and fallopian-tube cancers in carriers of *BRCA1* and *BRCA2* mutations is widely recommended,[4,7] but support for this approach comes from retrospective studies in which participants either were not genotyped[8] or were in some cases included in the analysis after self-selection for genetic testing years after the preventive surgery.[9] Reports of primary peritoneal cancer after oophorectomy in women at risk for hereditary ovarian cancer have called into question the ef-

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ficacy of this procedure for the prevention of *BRCA*-related gynecologic (ovarian, fallopian-tube, and primary peritoneal) cancers.[10-13] Retrospective series have also suggested that oophorectomy may protect against hereditary breast cancers.[14] We report a prospective evaluation of the role of salpingo-oophorectomy in reducing the risk of breast cancer and *BRCA*-related gynecologic cancers in carriers of *BRCA1* and *BRCA2* mutations.

METHODS

Study Subjects

All women evaluated for possible pathogenic *BRCA1* or *BRCA2* mutations in the context of genetic counseling at Memorial Sloan-Kettering Cancer Center in New York between June 1, 1995, and May 30, 2001, were offered enrollment in one of three follow-up studies that had been approved by the institutional review board. The study protocols and the results of a different analysis have been described in a previous report.[5] The current analysis contains additional follow-up and clinical information on 154 patients included in that report, as well as data on 23 carriers of *BRCA* mutations who were not included in that study. In the current study, we analyzed the prevention of cancer (the reduction in incidence) with surgery as compared with surveillance, whereas the previous study was limited to an analysis of the stage of the cancers that were detected.

Of 272 women found to carry a pathogenic *BRCA1* or *BRCA2* mutation, 265 elected to participate in follow-up studies. Of these 265 women, 63 who had undergone bilateral salpingo-oophorectomy before genetic testing were excluded from the analysis. An additional 25 women who were younger than 35 years of age at the time of testing were also excluded because, in our study, carriers of *BRCA* mutations were advised to initiate screening for ovarian cancer or consider risk-reducing oophorectomy after 35 years of age.

All remaining 177 women from 153 families were advised by physicians and staff of the Clinical Genetic Service of the hospital to begin surveillance for ovarian cancer with annual or twice-yearly gynecologic examinations, twice-yearly transvaginal ultrasonographic examinations, and twice-yearly determinations of the serum CA-125 concentration. For women whose childbearing was complete, consideration of salpingo-oophorectomy was recommended. All women with breast tissue at risk (i.e., who had not had bilateral mastectomies) were advised to undergo annual mammographic examinations, to have clinical breast examinations two to four times per year, and to perform breast self-examinations monthly. The option of risk-reducing mastectomy was also discussed. Patients chose their own screening and preventive interventions.

Follow-up through November 30, 2001, involved an annual questionnaire, telephone contact, and review of medical records. Pathology reports were obtained for all new cancers diagnosed during follow-up. Pathology reports were also obtained for 92 percent of risk-reducing surgical procedures. Four patients who were lost to follow-up before the first follow-up contact were excluded from the analysis. Three patients were found to have unsuspected early-stage gynecologic cancer (two had ovarian cancer, and one had fallopian-tube cancer) at the time of risk-reducing salpingo-oophorectomy and were excluded from the statistical analysis of cancer end points.

Statistical Analysis

The salpingo-oophorectomy group included all women who had a risk-reducing salpingo-oophorectomy with or without concomitant hysterectomy after the receipt of genetic-test results. The surveillance group included all women who did not elect to undergo risk-reducing salpingo-oophorectomy. Women who had a therapeutic oophorectomy because of abnormalities found through surveillance for ovarian cancer were included in the surveillance group, and their follow-up data were censored at the date of oophorectomy. For women in the surveillance group, the duration of follow-up was calculated from the date of receipt of genetic-test results to the date of diagnosis of new breast or *BRCA*-related gynecologic cancer, the date of last contact, or the date of death. For women in the salpingo-oophorectomy group, the duration of follow-up was calculated from the date of salpingo-oophorectomy to the date of diagnosis of new breast or *BRCA*-related gynecologic cancer, the date of last contact, or the date of death.

The demographic characteristics of the two groups were compared with the use of the independent-sample t-test for continuous variables and Fisher's exact test for discrete variables. Kaplan–Meier analysis and the log-rank test were used to compare the two groups in terms of the time to a subsequent diagnosis of cancer.

To calculate the hazard ratio for the combined incidence of breast cancer and *BRCA*-related gynecologic cancer after risk-reducing salpingo-oophorectomy, we used a Cox proportional-hazards model for multiple events.[15,16] This model allowed us to adjust for both differing frequency and differing timing of bilateral mastectomy between the two groups by censoring follow-up data related to breast cancer at the time of bilateral mastectomy. A Cox proportional-hazards model was also used to determine the separate hazard ratios for breast cancer after risk-reducing salpingo-oophorectomy and for *BRCA*-related gynecologic cancer after such surgery. Analyses were performed with the use of SPSS software (version 10.0, SPSS) and S-Plus software (version 6, Insightful). All reported P values are two-sided.

RESULTS

Of 170 women who met the criteria for entry, 98 elected to undergo risk-reducing salpingo-oophorectomy a median of 3.6 months after receiving the results of genetic testing, and 72 chose surveillance for ovarian cancer. There was no significant difference between the two groups in terms of mean age, percentage with *BRCA1* or *BRCA2* mutations, mean number of first- and second-degree relatives with breast, ovarian, fallopian-tube, or primary peritoneal cancer, and percentage with a history of breast cancer, systemic chemotherapy, or oral-contraceptive use. More women in the salpingo-oophorectomy group than in the surveillance group (29 of 98 women [30 percent] vs. 10 of 72 women [14 percent]) had undergone bilateral mastectomy before the start of follow-up ($P=0.02$). There was no significant difference in the number of women who underwent bilateral mastectomy during a mean of 24.2 months of follow-up. Complete demographic information for the two groups is summarized in Table 1.

Time to Cancer

Total follow-up was 191 woman-years in the salpingo-oophorectomy group and 152 woman-years in the surveillance group. When follow-up data were censored at the time of diagnosis of ovarian cancer or therapeutic oophorectomy, there were 139 woman-years of follow-up for the 72 women who elected surveillance for ovarian cancer. Ovarian cancer was diagnosed in four women and primary peritoneal cancer in one woman a mean of 17.0 months after the

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE WOMEN.

CHARACTERISTIC	SALPINGO-OOPHORECTOMY GROUP (N=98)	SURVEILLANCE GROUP (N=72)	P VALUE*
Age at the time of genetic test — yr			0.17
Mean	47.5	45.5	
Median	45.5	42.4	
Range	35.9–73.9	35.0–77.7	
Type of mutation — no. (%)			0.27
BRCA1	56 (57)	48 (67)	
BRCA2	42 (43)	24 (33)	
No. of first- or second-degree relatives with breast, ovarian, fallopian-tube, or primary peritoneal cancer			0.20
Mean	1.64	1.86	
Range	0–4	0–5	
Previous breast cancer — no. (%)	69 (70)	45 (62)	0.32
Age at the time of first breast cancer — yr			0.21
Mean	41.6	39.7	
Range	25–70	26–68	
Previous chemotherapy — no. (%)	60 (61)	39 (54)	0.43
Bilateral mastectomy — no. (%)			
Previous	29 (30)	10 (14)	0.02
During follow-up	9 (9)	6 (8)	1.00
Previous oral-contraceptive use — no./no. with data (%)	61/91 (67)	40/61 (66)	0.86
Duration of surveillance before risk-reducing salpingo-oophorectomy — mo			
Median	3.6	—	
Range	0.2–63.3	—	
Duration of follow-up after risk-reducing salpingo-oophorectomy or start of surveillance — mo			0.48
Mean	23.4	25.4	
Median	20.0	20.4	
Range	0.1–71.7	0.4–76.2	
No. of woman-years of follow-up	191	152	

*P values were calculated with the use of Fisher's exact test for discrete variables and the independent-sample t-test for continuous variables.

receipt of genetic-test results. All these cancers were diagnosed after suspicious or persistent abnormalities were noted either on transvaginal ultrasonography or in the serum CA-125 concentration. An additional seven women in the surveillance group had suspicious or persistent abnormalities that prompted surgical exploration a mean of 1.8 months after the receipt of genetic-test results. In all seven cases, the findings represented benign conditions. With a mean follow-up of 15.3 months after surgery, no new breast or gynecologic cancers had been diagnosed in these seven women.

During 191 woman-years of follow-up in the 98 women who chose to undergo salpingo-oophorectomy, primary peritoneal cancer was diagnosed in 1 woman 16.3 months after salpingo-oophorectomy. No other woman in this group underwent surgical exploration after salpingo-oophorectomy.

During 120 woman-years of follow-up in the 62 women with breast tissue in the surveillance group, breast cancer was diagnosed in 8 women a mean of 12.7 months after the receipt of genetic-test results. During 127 woman-years of follow-up in the 69 women with breast tissue in the salpingo-oophorectomy group, breast cancer was diagnosed in 3 women a mean of 10.3 months after risk-reducing salpingo-oophorectomy.

When the two types of cancer were analyzed together, breast cancer or *BRCA*-related gynecologic cancer was found to have been diagnosed in a total of four women in the salpingo-oophorectomy group during 186 woman-years of follow-up. In the surveillance group, 13 such cancers were diagnosed in 12 women during 135 woman-years of follow-up (Fig. 1). The estimated proportion free from breast cancer or *BRCA*-related gynecologic cancer at five years (according to the Kaplan–Meier analysis) was significantly greater in the salpingo-oophorectomy group (P=

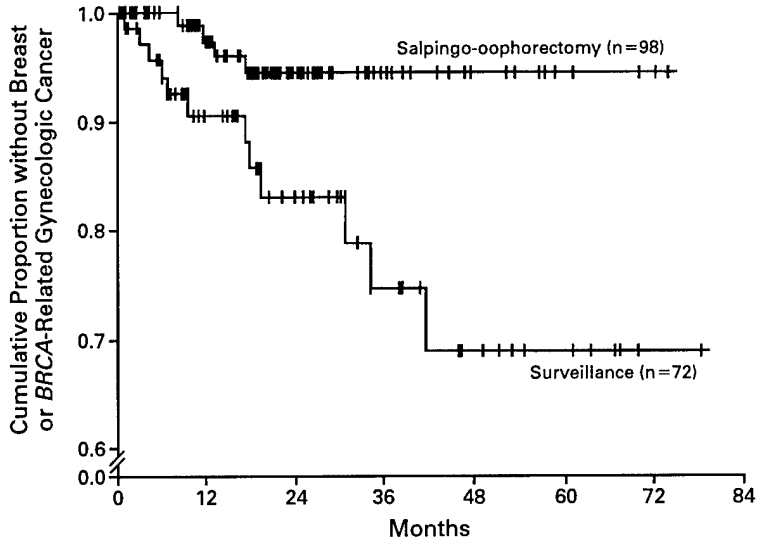
0.006) (Table 2). To take into account the different proportions of women in the two groups who had undergone bilateral mastectomy before study entry, a Cox proportional-hazards model for multiple events was used. This analysis revealed that the hazard ratio for the development of breast cancer or *BRCA*-related gynecologic cancer after risk-reducing salpingo-oophorectomy was 0.25 (95 percent confidence interval, 0.08 to 0.74) (Table 3). There was no significant effect of the type of mutation (*BRCA1* vs. *BRCA2*) on the time to breast or gynecologic cancer (P=0.31).

When the analysis was limited to new ovarian, fallopian-tube, and primary peritoneal cancers, the time to a diagnosis of cancer was longer in the salpingo-oophorectomy group than in the surveillance group (P=0.04) (Table 2). The hazard ratios for the development of *BRCA*-related gynecologic cancer or breast cancer after salpingo-oophorectomy are shown in Table 3.

Among the women in the surveillance group for whom detailed data were available, 51 of 63 (81 percent) indicated that they were undergoing ultrasonographic surveillance, CA-125–based surveillance, or both. Among patients undergoing such surveillance for ovarian cancer, a mean of 1.73 transvaginal ultrasonographic examinations (range, 1 to 4) and 1.68 determinations of the serum CA-125 concentration (range, 1 to 4) per year were reported. A total of 51 of 58 women with breast tissue in this group (88 percent) also underwent regular mammographic examination. In the salpingo-oophorectomy group, 63 of 65 women with breast tissue for whom data were available (97 percent) underwent regular mammographic examination. The risk of breast cancer or *BRCA*-related gynecologic cancer was significantly lower among the 98 women in the salpingo-oophorectomy group than among the 51 women who indicated that they were undergoing ultrasonographic surveillance, CA-125–based surveillance, or both (hazard ratio, 0.19; 95 percent confidence interval, 0.06 to 0.56).

Complications of Risk-Reducing Salpingo-oophorectomy

Complications were noted in 4 of the 80 women who underwent risk-reducing salpingo-oophorectomy



No. at Risk							
Salpingo-oophorectomy	98	69	36	17	11	4	0
Surveillance	72	44	28	16	9	5	1

Figure 1. Kaplan–Meier Estimates of the Time to Breast Cancer or *BRCA*-Related Gynecologic Cancer among Women Electing Risk-Reducing Salpingo-oophorectomy and Women Electing Surveillance for Ovarian Cancer.

P=0.006 by the log-rank test for the comparison between the actuarial mean times to cancer. A Cox proportional-hazards model for multiple end points, which took into account the different proportions of women in the two groups who had breast tissue at risk, yielded a hazard ratio for subsequent breast cancer or *BRCA*-related gynecologic cancer after risk-reducing salpingo-oophorectomy of 0.25 (95 percent confidence interval, 0.08 to 0.74).

TABLE 2. KAPLAN–MEIER ESTIMATES OF PROPORTIONS FREE FROM CANCER.

VARIABLE	SALPINGO-OOPHORECTOMY GROUP (N=98)	SURVEILLANCE GROUP (N=72)	P VALUE*
Ovarian, fallopian-tube, or primary peritoneal cancer			0.04
No.	1	5	
Projected proportion free from cancer at 5 yr (%)	98	83	
Breast cancer†			0.07
No.	3	8	
Projected proportion free from cancer at 5 yr (%)	94	79	
Breast cancer or *BRCA*-related gynecologic cancer			0.006
No.	4	12‡	
Projected proportion free from cancer at 5 yr (%)	94	69	

*P values were determined by the log-rank test.

†The Kaplan–Meier analysis was limited to the 131 women with breast tissue at the start of follow-up.

‡Metachronous breast and ovarian cancers were diagnosed in one patient in this group during follow-up.

TABLE 3. HAZARD OF BREAST CANCER OR *BRCA*-RELATED GYNECOLOGIC CANCER AFTER RISK-REDUCING SALPINGO-OOPHORECTOMY.*

VARIABLE	OVARIAN, FALLOPIAN-TUBE, OR PRIMARY PERITONEAL CANCER	BREAST CANCER	BREAST CANCER OR *BRCA*-RELATED GYNECOLOGIC CANCER
No. of patients included in analysis	170	131	170
Mean no. of months of follow-up	23.3	22.6	22.7
Hazard ratio (95% CI)	0.15 (0.02–1.31)	0.32 (0.08–1.20)	0.25 (0.08–0.74)

*Hazard ratios were calculated with the Cox proportional-hazards model for multiple events, and follow-up data related to breast cancer were censored at the time of bilateral mastectomy. CI denotes confidence interval.

without hysterectomy. In one woman, a laparoscopic salpingo-oophorectomy was converted to a laparotomy because there were multiple adhesions at the site of a previous repair of an umbilical hernia. Her postoperative course was complicated by an infection of the wound. In a second woman who underwent laparoscopic salpingo-oophorectomy, perforation of the bladder during the placement of a trocar necessitated drainage by a Foley catheter for five days. A third woman presented with a distal obstruction of the small bowel eight weeks after risk-reducing salpingo-oophorectomy. Operative findings were notable for adhesions between the distal ileum and staples on the right ovarian vessels, which caused a small-bowel obstruction at that point. The obstruction was relieved by lysis of the adhesions without need for bowel resection. In a fourth woman who underwent laparoscopic salpingo-oophorectomy, perforation of the uterus by a uterine manipulator necessitated laparoscopic suturing of the uterus and overnight observation. No complications were noted in 11 women who had a hysterectomy at the time of risk-reducing salpingo-oophorectomy or in 7 women whose uterine-surgery status at the time of risk-reducing salpingo-oophorectomy was not specified.

DISCUSSION

In this study, we prospectively evaluated 170 women with germ-line *BRCA* mutations who elected either risk-reducing salpingo-oophorectomy or surveillance for ovarian cancer. Survival free of breast cancer and *BRCA*-related gynecologic cancer was longer in the cohort that chose salpingo-oophorectomy: the projected proportion of women who will be free of breast cancer or *BRCA*-related gynecologic cancer five years from the time of salpingo-oophorectomy or the beginning of surveillance is 94 percent in the salpingo-oophorectomy group and 69 percent in the surveillance group. Three patients who were not included in the actuarial analysis were found to harbor an occult stage I gynecologic neoplasm at the time of what had been considered to be risk-reducing surgery. Taken together, these results provide strong support for including discussion of risk-reducing salpingo-oophorectomy as part of a preventive-oncology strat-

egy for women with a *BRCA1* or *BRCA2* mutation. Our findings recall those of Meijers-Heijboer et al.,[6] who showed in a similar prospective study that risk-reducing mastectomy decreased the risk of breast cancer in carriers of *BRCA* mutations.

The protective effect of salpingo-oophorectomy in this series was slightly lower than that found in a recent retrospective analysis.[9] The greater effect in that study may have reflected underascertainment of peritoneal cancers in carriers of *BRCA* mutations who had previously undergone oophorectomy. The trend toward a decreased risk of breast cancer after oophorectomy in our series is consistent with a previous retrospective case–control series[14] and with the finding that hormone deprivation has a beneficial effect on the risk of breast cancer.[17-20] The moderate reduction we found in the incidence of breast cancer must, however, be compared with the results recently documented by Meijers-Heijboer et al., in whose study no case of breast cancer occurred after prophylactic mastectomy in 76 women with *BRCA* mutations followed for the same length of time as in our series.[6]

The incidence of breast cancer and *BRCA*-related gynecologic cancer in our study of 53 cases per 1000 woman-years is somewhat higher than the 21 to 42 cases per 1000 woman-years that would be predicted on the basis of linkage studies.[21-23] This higher incidence may reflect the presence of preexisting cancers that were detected during the first year of follow-up. When the eight patients in whom cancer was diagnosed during the first year of follow-up are excluded from the analysis, the incidence of cancer in our cohort is 25 per 1000 woman-years, which falls within the range derived from linkage studies.

Only 4 of 98 risk-reducing salpingo-oophorectomy procedures (4 percent) in this series were associated with surgical complications. This rate is similar to those reported in other studies of laparoscopic gynecologic procedures[24,25] and lower than the complication rate of 8 to 17 percent associated with abdominal hysterectomy and concomitant bilateral salpingo-oophorectomy.[26,27] This rate contrasts with the complication rate of up to 30 percent that has been reported for risk-reducing mastectomy with reconstruction.[28]

Approximately 12 percent of the risk-reducing salpingo-oophorectomy procedures in our series included removal of the uterus. Although there is no proven increase in the risk of uterine cancer in carriers of *BRCA* mutations,[29] several authors have recommended concomitant hysterectomy because of the risk of cancer arising from the small amount of intramural fallopian-tube tissue that is left by salpingo-oophorectomy.[30,31] In a previous series, five cases of peritoneal carcinomatosis occurred after hysterectomy with bilateral oophorectomy in women with a hereditary predisposition to cancer.[11] Whether hysterectomy further reduces the risk of cancer is unknown, and prospective studies will be required in order to resolve this question.

Although the median time between genetic testing and risk-reducing salpingo-oophorectomy was only 3.6 months, a possible bias may have been introduced by beginning follow-up in the salpingo-oophorectomy group at the time of surgery. According to an analysis in which follow-up for all patients began at the time of notification of genetic-test results, however, salpingo-oophorectomy remained highly protective against breast cancer and *BRCA*-related gynecologic cancer (hazard ratio, 0.21; 95 percent confidence interval, 0.07 to 0.62). If the three cases of unsuspected gynecologic cancer detected at the time of risk-reducing surgery were included in this analysis, the hazard ratio for development of breast or *BRCA*-related gynecologic cancer would be 0.37 (95 percent confidence interval, 0.12 to 0.90). Another limitation of our study was the selection of time to cancer rather than overall survival as an end point. Salpingo-oophorectomy may have adverse effects on the lipid profile[32] and may increase the risks of cardiovascular disease[33] and osteoporosis.[34] There may also be psychosocial and sexual effects. A recent study demonstrated that women who underwent this type of surgery had more physical and emotional symptoms than those who underwent screening.[35]

Whether our results will translate into improved survival will depend, in large part, on the effectiveness of screening for ovarian cancer. We have found early-stage gynecologic cancers with ovarian ultrasonography and CA-125–based screening,[5] but these screening methods can fail to detect ovarian cancers at a curable stage.[36-39] Hormonal chemoprevention of breast cancer and ovarian cancer offers an additional potential strategy for some carriers of *BRCA* mutations.[40,41] In the absence of novel imaging techniques or new serum markers that can predictably identify early-stage ovarian and fallopian-tube neoplasms, risk-reducing salpingo-oophorectomy remains an important option for women at risk for hereditary breast or gynecologic cancer.

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High frequency of sequence variants in women of African descent undergoing *BRCA1* or *BRCA2* testing. *M. Robson*[1], *C. Duteau-Buck*[1], *H. Valdimirsdottir*[2], *J. Guevara*[1], *R. Baum*[1], *J. Hull*[1], *D. McDermott*[1], *M. Pinto*[1], *L. Scheuer*[1], *K. Offit*[1]. 1) Dept Human Genetics, Mem Sloan-Kettering Cancer Ctr, New York, NY; 2) Mt. Sinai School of Medicine, New York, NY.

Few studies have described the results of genetic testing for inherited breast and ovarian cancer susceptibility in individuals of African descent. Families in the present study were offered genetic testing after direct referral to a cancer risk counseling clinic or after recruitment from a screening population. Following pre-test counseling and informed consent, 57 individuals from 49 families underwent *BRCA1* and/or *BRCA2* testing. Of the 53 individuals from 49 families who underwent *BRCA1* coding sequence analysis, 5 individuals (9.4%) from 5 families (10.2%) were heterozygous for presumably deleterious *BRCA1* mutations. An additional 21 *BRCA1* sequence variants of uncertain significance were detected in 16 individuals (30.2%) from 16 families (32.7%). *BRCA2* sequence analysis was performed on 33 individuals from 28 families (4 individuals tested only for previously identified mutations). Of the 29 individuals from 28 families undergoing complete *BRCA2* coding sequence analysis, 2 (6.9%) were found to carry presumably deleterious mutations. An additional 17 individuals (58.6%) from 16 families (57.1%) were found to carry a total of 28 *BRCA2* sequence variants of uncertain significance. Of 29 individuals (28 families) undergoing both *BRCA1* and *BRCA2* analysis, 21 persons (72.4%) from 20 families (71.4%) had at least one sequence variation of uncertain significance. More than one variant was noted in 17 individuals from 16 families. Several variants (3 *BRCA1* , 5 *BRCA2*) were observed in more than 1 family. The high prevalence of genetic variants of uncertain significance must be taken into account when providing counseling regarding *BRCA* testing to individuals of African descent.

Outcome of Preventive Surgery and Screening for Breast and Ovarian Cancer in *BRCA* Mutation Carriers

By Lauren Scheuer, Noah Kauff, Mark Robson, Bridget Kelly, Richard Barakat, Jaya Satagopan, Nathan Ellis, Martee Hensley, Jeff Boyd, Patrick Borgen, Larry Norton, and Kenneth Offit

Purpose: **To prospectively determine the impact of genetic counseling and testing on risk-reduction strategies and cancer incidence in a cohort of individuals at hereditary risk for breast and ovarian cancer.**

Patients and Methods: **Two hundred fifty-one individuals with *BRCA* mutations were identified at a single comprehensive cancer center from May 1, 1995, through October 31, 2000. Uniform recommendations regarding screening and preventive surgery were provided in the context of genetic counseling. Patients were followed for a mean of 24.8 months (range, 1.6 to 66.0 months) using standardized questionnaires, chart reviews, and contact with primary physicians.**

Results: **Frequency of cancer surveillance by physical examinations and imaging studies increased after genetic counseling and testing. Twenty-one breast, ovarian, primary peritoneal, or fallopian tube cancers were detected after receipt of genetic test results. Among 29 individuals choosing risk-reducing mastectomy after testing, two were found to have occult intraductal breast cancers. Among 90 individuals who underwent risk-reducing salpingo-oophorectomy, one early-stage ovarian neoplasm and one early-stage fallopian tube neoplasm were found. Radiographic or tumor marker–based screening detected six breast cancers, five of which were stage 0/I, one early-stage primary peritoneal cancer, and three stage I or II ovarian cancers. Six additional breast cancers were detected by physical examination between radiographic screening intervals; four of these six tumors were stage I. No stage III or stage IV malignancies were detected after genetic testing.**

Conclusion: **This study provides prospective evidence that genetic counseling and testing increased surveillance and led to risk-reducing operations, which resulted in diagnosis of early-stage tumors in patients with *BRCA1* and *BRCA2* mutations.**

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GENETIC TESTING PROVIDES new opportunities for the prevention of hereditary cancers. Assuming a one in 345 frequency in the general population in the United States, and a one in 40 frequency in those of Ashkenazi Jewish background, up to 950,000 individuals in the United States carry mutations of the *BRCA1* and *BRCA2* tumor suppressor genes.[1,2] Approximately 100,000 breast cancer survivors are at risk for subsequent malignancies because of inherited *BRCA* mutations.[3,4] For *BRCA* mutation carriers, the risk for early-onset breast cancers is increased up to 20-fold,[5] and the lifetime risk for ovarian cancer is increased up to nine-fold.[6] Breast cancer risk is also increased in males with *BRCA* mutations.[7] Counseling of families at hereditary cancer risk has included discussion of the presumed but unproven benefit of radiographic, medical, and surgical options for screening and prevention.[8]

In this study, we provide prospective follow-up of both breast and ovarian cancer outcome in a large cohort of individuals with *BRCA* mutations who were counseled regarding available options for cancer screening and prevention. Using a multimodality approach of physician and self-examination, radiographic screening, and risk-reducing surgery, a high proportion of early-stage malignancies were detected. These results were achieved despite the limited sensitivity and specificity documented for the individual screening modalities used.

PATIENTS AND METHODS

Study Participants

Included in this report are 251 of 267 *BRCA1* or *BRCA2* mutation carriers identified from 1,865 patients who received genetic test results at Memorial Sloan-Kettering Cancer Center (MSKCC) from June 1, 1995, until October 31, 2000. Two hundred fifteen (86%) of 251 patients were involved at the outset in two institutional review board–approved protocols (one for those of Ashkenazi origin) that provided specific informed consent for prospective follow-up for 10 years. An additional 36 patients were enrolled on other protocols at a time when such specific consent was not deemed necessary for clinical follow-up; these patients have subsequently been approached for

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Table 1. Breast and Ovarian Cancer Surveillance and Risk-Reduction Recommendations for *BRCA1* and *BRCA2* Mutation Carriers

Modality	Frequency
Breast	
Screening*	
Mammography	Annually beginning at age 25
Clinical breast examination	Two to four times per year beginning at age 25
Self-breast examination	Monthly beginning at age 18
Chemoprevention	
Tamoxifen†	Consideration of use after age 35 and completion of childbearing
Risk-reducing surgery	
Risk-reducing mastectomy	Discussed as an option
Ovary	
Screening	
Transvaginal ultrasound	Two times per year beginning at age 35
Serum CA-125	Two times per year beginning at age 35
Chemoprevention	
Oral contraceptives	Consideration of use
Risk-reducing surgery	
Risk-reducing bilateral salpingo-oophorectomy	Discussed as an option after completion of childbearing

NOTE. Data adapted.[8-10]

*For male *BRCA2* mutation carriers identified in this study, recommendations included annual mammography (where possible), clinical breast examinations one to two times per year, and regular breast self-examination.

†Beginning in April 2000, postmenopausal women were offered participation in the randomized STAR (Study of Tamoxifen and Raloxifene) trial evaluating chemoprevention of breast cancer.

Table 2. Description of Study Cohort

	Female (n = 233)		Male (n = 18)	
	No.	%	No.	%
Age at test results, years				
Mean	46.8		60.0	
Range	24.1-79.0		28.2-74.0	
Follow-up, months				
Mean	25.0		22.0	
Range	1.6-66.0		2.7-56.1	
Mutation				
BRCA1	156	67.0	8	44.4
BRCA2	77	33.0	10	55.6
Personal history of breast cancer	143	61.4	6	33.3
Unilateral	118	50.7	6	33.3
Bilateral	25	10.7	0	0.0
Personal history of ovarian cancer	25	10.7	N/A	
Prior bilateral mastectomy	39	16.7	0	0.0
Therapeutic	19	8.2	0	0.0
Risk-reducing	20	8.6	0	0.0
Prior bilateral oophorectomy	54	23.2	N/A	
Ovarian cancer	25	10.7	N/A	
Risk-reducing	12	5.2	N/A	
Other indication	17	7.3	N/A	
No. of breast or ovarian cancers in first- or second-degree relatives				
Mean	2.18		2.83	
Range	0-9		0-6	

consent for continued follow-up. At the time of initial genetic counseling, all patients were asked to provide detailed information regarding personal and family history of cancer.

In accord with New York State law, all patients provided informed consent, including discussion of the risks and benefits, before genetic testing. Counseling also addressed medical and surgical options for screening and prevention. Individuals received recommendations for surveillance and descriptions of prevention options, including risk-reducing surgery.[8-10] Specific recommendations provided to carriers of *BRCA* mutations are summarized in Table 1. Of 251 patients shown to carry mutations of *BRCA1* or *BRCA2*, 222 (88%) were contacted by telephone by an MSKCC staff member at a median of 8.8 months after receiving genetic test results. Patients were asked to complete a structured phone questionnaire detailing present medical status, current cancer screening practices, and any risk-reducing operations they underwent. After this initial contact, patients were contacted annually by letter and asked to complete a questionnaire updating follow-up information. For 29 patients who did not respond to phone or mailing and who had provided specific informed consent, their primary physician was contacted and asked to provide follow-up information. Self-reported therapeutic and preventative surgical outcomes were confirmed by chart review and review of pathology reports, including all cases diagnosed with breast or ovarian cancer after genetic testing.

Of those tested, 267 individuals from 203 families were found to have presumed deleterious *BRCA1* or *BRCA2* mutations and received posttest counseling at MSKCC. Mutations were detected by full sequence or allele-specific analysis.[11,12] Individuals with missense variants of uncertain significance are not included in this report. Of the 267 individuals receiving posttest counseling at MSKCC, 251 (94%) are included in this report. Eight individuals declined participation or withdrew from the study and another eight individuals were lost to follow-up.

Statistical Analysis

Continuous variables were compared using the independent samples *t* test, and discrete variables compared using the Fisher's exact test. Age of testing refers to age at receipt of *BRCA* test results. The Wilcoxon signed-rank test was used to compare pre- and postcounseling screening frequency. In cases where multiple annual follow-up data were available, screening frequency at last follow-up was used in this analysis. The sign test was used to compare the proportion of patients participating in any screening before and after testing. Person-years of follow-up were calculated using the difference between date of last contact and date of results. Analysis was performed on SPSS software (Version 10.0; SPSS, Inc, Chicago, IL). Cancer incidence rates were calculated using the life-table method.[13] All reported *P* values are two sided.

RESULTS

The mean age at testing of the 251 individuals with *BRCA* mutations was 47.7 years (range, 24.1 to 79.0 years). Two thirds of individuals carried *BRCA1* mutations and one third

Table 3. Malignancies Diagnosed at Risk-Reducing Surgery

Patient ID No.	Mutation	Age at *BRCA* Testing (years)	Site of Cancer Diagnosis Before *BRCA* Testing	Age at Previous Cancer Diagnosis (years)	Site of Occult Cancer Diagnosis After *BRCA* Testing	Age at Diagnosis of Occult Cancer (years)	Type of Risk-Reducing Surgery (prior screening)
068	*BRCA2*, 6174delT	42	No prior cancer		Breast (DCIS)	42	RRM (negative MMG, 9 months prior; negative breast U/S, 1 month prior)
154	*BRCA1*, C61G	48	No prior cancer		Breast (DCIS)	50	RRM (negative MMG, 4 months prior)
035	*BRCA1*, 5382insC	51	Breast	46	Ovary (stage IC)	52	RRSO (negative TV U/S, < 1 month prior)
083	*BRCA1*, Q563X	46	No prior cancer		Fallopian tube (stage IA*)	47	RRSO (negative TV U/S and normal CA-125, 1 month prior)

Abbreviations: RRM, risk-reducing mastectomy; RRSO, risk reducing salpingo-oophorectomy; MMG, mammogram; TV U/S, transvaginal ultrasound.

*Tumor was limited to tubal mucosa without invasion of muscularis propria. No gross extrapelvic disease was noted, although comprehensive surgical staging was not performed.

carried *BRCA2* mutations. At time of testing, 59.4% of individuals had a personal history of breast cancer (Table 2). Additionally, 12 patients (4.8%) had a history of other malignancies, including uterine (three patients), oral cavity (two patients), vulvar, esophageal, papillary thyroid, renal, cervical, unknown primary, or leukemia. For those with a prior diagnosis of cancer, the median time between the prior cancer diagnosis and genetic testing was 4.8 months (range, 0.1 to 39 months).

After genetic testing, 14 breast and seven ovarian, primary peritoneal, or fallopian tube malignancies were detected over a mean follow-up of 24.8 months (range, 1.6 to 66 months). Of these, two breast cancers and two ovarian cancers were found at time of risk-reducing operations, six breast cancers and five ovarian cancers were detected by radiographic or tumor marker–based screening, and six breast cancers were found by physical examination between radiographic screening intervals. Of women who had not undergone prior bilateral mastectomy and therefore had breast tissue at risk, there were 344 woman-years (WY) of follow-up. There were 221 WY of follow-up for those who had not undergone prior bilateral oophorectomy. This corresponds to a breast cancer incidence rate of 41 per 1,000 WY (95% confidence interval [CI], 20 to 62) for women with breast tissue at risk. When women were stratified by history of breast cancer, four of 88 women without a prior history of breast cancer developed breast cancer during 158 WY of follow-up (25.3 per 1,000 WY; 95% CI, 0 to 51). Ten of 106 women with a prior history of breast cancer were diagnosed with a new primary breast cancer during 186 WY of follow-up (53.9 per 1,000 WY; 95% CI, 22 to 86). Nine of these 10 cancers were contralateral to the initial primary tumor. The histology of the single ipsilateral cancer was invasive ductal carcinoma associated with ductal carcinoma-in-situ (DCIS), suggesting that this was a new primary tumor. Incidence of ovarian and related müllerian malignancies was 32 per 1,000 WY (95% CI, nine to 55). Four of the seven ovarian cancers and five of 14 breast cancers were diagnosed within a year after testing.

Risk-Reducing Surgery

At the time of receiving genetic test results, 194 of 233 women had breast tissue at risk. Twenty (8.6%) of 233 had previously undergone risk-reducing mastectomies (RRM), and 19 of 233 had undergone bilateral mastectomies for breast cancer. Of the remaining 194 women, 29 (14.9%) underwent RRM at a median of 5.3 months (range, 0.1 to 34.8 months) after receiving results. Women electing RRM were younger than those not opting for surgery (mean, 43.0 *v* 46.8 years; $P = .015$), and had a greater number of breast and ovarian malignancies in first- and second-degree relatives (mean, 2.7 *v* 2.1 cancers; $P = .046$). They were not more likely to have had a personal history of breast cancer. Two women were found to have unsuspected DCIS in their RRM specimens (Table 3). In these two women, mammograms obtained within 9 months of surgery were not considered suspicious.

At the time of receiving genetic test results, 179 of 233 women had ovarian tissue at risk. Twenty-five (10.7%) of 233 had a personal history of ovarian cancer, and 29 had previously undergone bilateral oophorectomy for benign gynecologic indications or risk-reduction. Of the remaining 179 women, 90 (50.3%) underwent risk-reducing salpingo-oophorectomy (RRSO) at a median of 3.4 months (range, 0.1 to 49.7 months) after receiving results. Nineteen percent of RRSO included hysterectomies and 81% were bilateral salpingo-oophorectomies only. Women electing RRSO were older than those not opting for surgery (mean, 47.3 *v* 41.6 years; $P < .001$); 77 (64%) of 120 of women older than 40 elected RRSO compared with 13 (22%) of 59 younger than 40. Women electing RRSO were more likely to have had a prior breast cancer diagnosis (74.4% *v* 49.4%; $P =$

Table 4. Malignancies Diagnosed by Surveillance After Results Transmission

Patient ID No.	Mutation	Age at *BRCA* Testing (years)	Site of Cancer/Age of Diagnosis Before *BRCA* Testing (years)	Site of Cancer/Age of Diagnosis After *BRCA* Testing (years)	Method of Cancer Detection (prior screening, size of tumor)
025	*BRCA2*, 6174delT	77	No prior cancer	Breast (DCIS)/79	Abnormal MRI (MMG and breast U/S demonstrated no lesions)
027	BRCA1, 185delAG	49	Breast/42	Breast: contralateral T1cN0/51	Abnormal MMG (patient reports undergoing annual mammography, 1.3 cm)
139	*BRCA1*, 185delAG	35	Breast/34	Breast: contralateral T1bN0/57	Abnormal MMG (patient reports last MMG < 1 year prior, 0.8 cm)
145	BRCA1, Y978X	52	Breast/47	Breast: contralateral T1bN1a/56	Abnormal MMG (last normal MMG, 16 months prior, 0.7 cm)
208	*BRCA1*, 185delAG	43	Breast/41	Breast (DCIS): contralateral/45	Abnormal MMG (patient reports undergoing annual mammography)
228	*BRCA1*, 185delAG	68	Breast/42	Breast (DCIS): contralateral/70	Abnormal MMG (last normal MMG, 12 months prior)
011	*BRCA2*, 6174delT	67	Breast/61	Ovary (stage IIC)/67	Persistent complex adnexal mass on TV U/S, normal CA-125 (abnormality initially detected on first screening U/S 2 months prior)
021	*BRCA1*, 5382insC	48	No prior cancer	Primary peritoneal (stage IIC)/48	No prior TV U/S, preoperative CA-125: 60
038	*BRCA1*, 185delAG	44	Breast/43	Ovary (stage IC)/44	Complex adnexal mass and ascites on TV U/S, CA-125: 316 (first screening TV U/S 3 months prior showed multiple tiny focal calcifications; no prior CA-125)
127	*BRCA1*, Q563X	52	Adenocarcinoma unknown primary (presumed müllerian)/46	Ovary (stage IA)/55	Complex adnexal mass and ascites on TV U/S, CA-125: 59 (last normal TV U/S, 6 months prior; last normal CA-125, 2 months prior)
188	*BRCA1*, 185delAG	36	Breast/33 Breast (contralateral)/35	Ovary (unstaged)/38	Complex adnexal mass on TV U/S; preoperative CA-125, normal

Abbreviations: DCIS, ductal carcinoma-in-situ; MRI, magnetic resonance imaging; U/S, ultrasound; TV, transvaginal.

.001). Women undergoing RRSO did not have more family members affected with breast or ovarian cancer compared with those who did not have RRSO. Two women were found to have unsuspected stage I malignancies in their RRSO specimens (Table 3). In these two women, transvaginal sonograms obtained within 1 month of surgery were not considered suspicious. A preoperative CA-125 measurement was obtained in one case, and was also normal.

Outcome of Cancer Surveillance

Women not choosing to undergo RRM were advised to undergo clinical surveillance with monthly breast self-examination, clinical breast examination two to four times a year, and annual mammography. Some women, at the discretion of their physician, also received screening breast ultrasound or magnetic resonance imaging (MRI) examinations. With a mean follow-up of 24.1 months (range, 1.6 to 66.0 months), 12 (7.3%) of 165 women were diagnosed with a new primary breast cancer. In six women (five with *BRCA1* mutations, one with *BRCA2*), breast cancer was detected by radiographic surveillance at a mean of 20.2 months after *BRCA* results transmission (Table 4). Two noninvasive and three invasive cancers were detected by mammography. One case of DCIS was identified by MRI in a woman with an unremarkable mammogram and ultrasound examination. Of the three invasive cancers, all were less than 2 cm. A single lymph node metastasis was identified in a woman with a negative mammogram 16 months prior.

In six women (four with *BRCA1* mutations, two with *BRCA2* mutations), breast cancers were detected by physical examination in the interval between radiographic screening (Table 5). Interval cancers were detected at a mean of 10.1 months after receipt of genetic test results. Women with interval breast cancers were younger than those with screen-detected disease (41.3 *v* 56.7 years; $P = .048$). Palpable masses were detected by breast self-examination in five cases and by physician examination in one case. Mammograms had been obtained within 6 to 10 months in five cases, and were unremarkable. The remaining woman

Table 5. Malignancies Diagnosed Between Radiographic Screening Intervals

Patient ID No.	Mutation	Age at *BRCA* Testing (years)	Site of Cancer Diagnosis Before *BRCA* Testing	Age at First Cancer Diagnosis (years)	Site of Cancer Diagnosis After *BRCA* Testing/ Stage	Age at Follow-Up Cancer Diagnosis (years)	Method of Detection (timing of prior screening)	Imaging at Time of Follow-Up Diagnosis (size of tumor)
031	*BRCA2*, 6174delT	48	Breast	45	Breast (contralateral) T1bN1	49	Palpable mass on SBE (negative MMG 6 months prior and negative breast MRI 10 months prior)	No preoperative imaging (1.0 cm)
038	*BRCA1*, 185delAG	44	Breast	43	Breast (contralateral) T1cNO	44	Palpable mass on SBE (negative MMG 7 months prior)	Visible on MMG (1.8 cm)
061	*BRCA1*, 185delAG	37	Breast: left (DCIS)	29	Breast (contralateral to prior invasive cancer) T1cNX*	39	Palpable mass on SBE 3 months after delivery (patient did not obtain MMG in prior year secondary to pregnancy)	Visible on MMG (1.5 cm)
			Second primary Breast: right	34				
107	*BRCA1*, 185delAG	42	Breast	42	Breast (contralateral) T2N1	43	Palpable mass on CBE (negative MMG 9 months prior)	Visible on MMG and U/S (2.5 cm)
124	*BRCA1*, E1373X	35	No prior cancer		Breast T1bN0	35	Palpable mass on SBE (negative MMG 10 months prior)	Occult on MMG, visible on U/S (0.9 cm)
144	*BRCA2*, 6174delT	30	Breast	29	Breast (ipsilateral) T1bN0	34	Palpable mass on SBE (negative MMG and breast U/S 9 months prior)	No preoperative imaging (0.9 cm)

Abbreviations: SBE, breast self-examination; CBE, clinical breast examination.
*Ipsilateral axillary lymph node dissection performed at time of patient's prior lumpectomy.

had deferred mammography because of pregnancy, having last been screened 1.5 years before diagnosis. In four of six cases, presurgical imaging at the time of presentation with a palpable mass demonstrated radiographic abnormalities (mammogram in three, ultrasound alone in one). The remaining two women did not undergo imaging before excisional biopsy. Of the six cancers discovered between intervals of radiographic examination, five were less than 2 cm. Lymph node metastases were detected in one case.

Women not choosing to undergo RRSO were advised to undergo clinical surveillance with semiannual transvaginal ultrasonography and CA-125 measurement. At a mean of 17.0 months (range, 2.3 to 40.2 months) from testing, five (5.6%) of 89 women who retained their ovaries were found to have ovarian or primary peritoneal cancer in the course of surveillance (Table 4). No cases of ovarian or peritoneal malignancy were diagnosed in the intervals between radiographic screening. Surgical exploration was prompted by an abnormal transvaginal ultrasonogram in four of five cases. CA-125 levels were elevated in two of these cases, normal in one, and not measured in one. Two of the four cases were stage I, one was stage II, and one case was incompletely staged in the setting of unsuspected microscopic disease. In the fifth case, surgical exploration was prompted by the finding of an elevated CA-125 level in a woman with a family history of peritoneal carcinoma. Surgery revealed peritoneal cancer as a solitary implant on a fallopian tube; complete staging revealed no other site of disease. All women received adjuvant chemotherapy with no evidence of gynecologic cancer at a mean follow-up of 18.4 months (range, 0.2 to 38.9 months).

Of 89 patients with ovarian tissue at risk who did not undergo RRSO, ovarian screening data was available on 84. Of these, 62 (73.8%) received ovarian surveillance. Abnormal transvaginal ultrasonograms or CA-125 measurements were noted in 22 of 62 (35.5%) women. Five (22.7%) of 22 were found to have an ovarian or peritoneal malignancy (Table 4). Five patients with abnormal ultrasound and/or elevated CA-125 had surgery that revealed benign findings. In 12 cases, follow-up ultrasonograms (nine cases) or serial CA-125 determinations (three cases) normalized over time and no interventions were required. Including the two cases diagnosed at the time of RRSO in the setting of normal ultrasound and/or CA-125, the sensitivity of ovarian cancer

Table 6. Change in Screening Behaviors in Individuals Who Did Not Elect Risk-Reducing Operations

	N	Before Counseling		After Counseling		P
		No.	%	No.	%	
Breast tissue						
Any screening MMG	136	111	81.6	127	93.4	.001
Mean no. of mammograms per year		0.87		1.04		.001
Any screening CBE	117	113	96.6	114	97.4	.99
Mean no. of CBE per year		3.15		3.89		.001
Any BSE	114	88	77.2	95	83.3	.143
Mean no. of BSE per year		7.96		8.09		.842
Ovarian tissue						
Any screening TV U/S	70	25	35.7	51	72.9	< .001
Mean no. of TV U/S per year		0.51		1.31		< .001
Any screening CA-125	74	20	27.0	50	67.6	< .001
Mean no. of CA-125 per year		0.36		1.19		< .001

Abbreviations: N, patients with both pre- and posttest screening behavior reported; CBE, clinical breast examination (by a health care practitioner); BSE, breast self-examination.

screening by serial ultrasound and CA-125 determination was 71% (five of seven) and the specificity was 90.9% (50 of 55). There were six other cancers detected during follow-up, including melanoma (two patients), oral cavity, lung, pancreas, and metastatic neuroendocrine carcinoma.

Impact of Counseling and Testing on Screening Behavior

For women who did not undergo risk-reducing surgery before testing and who reported pre- and postcounseling screening frequency, there was an overall increase in mean number of mammograms, clinical breast examinations, ovarian ultrasonograms, and CA-125 determinations performed after genetic testing (Table 6). The effect of genetic testing on breast cancer screening was not statistically significant in the subset with prior breast cancer, attributable in part to a high incidence of baseline screening (data not shown). On average, 15 months after *BRCA* risk notification, 83% of patients were performing breast self-examination, compared with 77% at the time of initial visit (P = .14). Frequency of transvaginal ultrasound examination increased from one every 24 months to one every 9 months, and CA-125 determination frequency increased from once every 2.8 years to once every 10.1 months. Of 143 women with a history of breast cancer at the time of genetic testing, tamoxifen use was reported in 56 and raloxifene use was reported in 10 women. Of 90 women without a history of breast cancer, six initiated tamoxifen and three started raloxifene after counseling.

Ten men carried *BRCA2* mutations and eight carried *BRCA1* mutations. Six men had a prior history of breast cancer at a mean age of 58.3 years; all had *BRCA2* mutations. Five of the 10 *BRCA2* mutation carriers, all with a history of prior breast cancer, were participating in screening before counseling. After testing, eight of the 10 were participating in breast screening, including three by mammography. Five men reported tamoxifen use, all as part of breast cancer treatment.

DISCUSSION

The current screening and prevention options for individuals at highest hereditary risk for breast and ovarian cancer have presumed but unproven efficacy.[9,10] Retrospective studies have shown that mammography may detect some early-stage cancers in *BRCA* mutation carriers,[14] and that prophylactic mastectomy,[15] oophorectomy,[16] and/or hormonal chemoprevention[17,18] may be effective in reducing cancer risk. Recently, prospective reports have also compared the efficacy of radiographic screening and preventive surgery in women at hereditary risk for breast cancer.[19-21]

The observed 43% sensitivity of radiographic screening for breast cancer (six breast tumors detected radiographically, of 14 in total) is among the lowest reported in a series of women at increased familial risk.[14,19-21] Annual mammograms did not image breast malignancies in six cases, although in three of these the palpable lesions were able to be visualized on preoperative mammograms performed 3 to 9 months after the normal imaging study. The only node-positive tumor (patient no. 145) detected by mammography occurred in the setting of a 16-month interval from prior mammographic examination. Similarly, four of eight tumors detected in a recent trial combining mammography and MRI occurred between annual screening intervals.[19] Although the findings of this and the prior studies may be explained by varying quality of performance or interpretation of radiographic imaging, these interval cancers may represent "kinetic failures" of screening. Decreasing the

interval of radiographic screening (eg, to 6 months) may improve the ability to find early-stage tumors in *BRCA* mutation carriers. This prediction is also consistent with the higher mitotic rates and growth fraction in age-matched *BRCA1*-linked tumors.[22]

Participants with breast cancers detected by radiographic screening were older than those that presented with cancer between radiographic screening intervals. This supports the observation that mammography is less effective in younger women, whose breasts tend to be denser.[23] In one case where mammography failed to image a breast tumor, MRI succeeded, consistent with recent reports in the literature.[20,21,24] The least well documented of breast cancer screening modalities, breast self-examination, was practiced by greater than 75% of women at the time of genetic testing. The importance of this modality of cancer detection is supported by the observation that self-examination after testing led to the diagnosis of five interval cancers, with four of the five tumors lymph node–negative.

Pure intraductal carcinomas, previously reported to be rare in *BRCA* mutation carriers,[24] constituted half of radiographically detected breast cancers in this series. Two additional cases of DCIS were found in 29 RRM procedures, a rate for pure DCIS higher than reported in RRM specimens from women with familial breast cancer.[25] Although pure DCIS may be less frequent in *BRCA*-associated tumors, the existence of DCIS in association with invasive cancers is not uncommon in previously described cases.[24] Interestingly, no intraductal tumors were reported in 76 cases of prophylactic mastectomy or eight tumors detected by surveillance in a recent series.[19] In contrast, the finding of a noninvasive phase in a subset of *BRCA*-associated breast tumors in this and other recent series[20,21] further supports the rationale for screening approaches.

Prior studies have suggested superior sensitivity and specificity of ultrasound and CA-125 screening for ovarian cancer in high-risk compared with average-risk populations.[26] The reported specificity of ovarian cancer screening on the basis of a single abnormal ultrasound examination or CA-125 determination was only 22.7%; however, this improved to 90.9% if persistently abnormal tests were considered. The estimated 71% sensitivity of ovarian screening modalities is an overestimate, because it implies knowledge of the true-positive rate in this cohort. In contrast to the very poor sensitivity of annual ovarian screening reported recently,[27] the documentation of five early-stage ovarian or primary peritoneal cancers detected by semiannual ultrasound and CA-125 determinations supports the efficacy of this approach in genetically defined high-risk populations. In five cases, however, false-positive ultrasound examinations and/or CA-125 determinations resulted in unnecessary surgical explorations, confirming the limited specificity of these approaches.

The absence of ovarian cancers presenting between surveillance intervals in this series may have been because of the high uptake of risk-reducing oophorectomy in the cohort studied. The finding of two occult ovarian adenocarcinomas in 90 RRSO procedures performed after *BRCA* testing is somewhat lower than the incidence of two cancers in 50 operations reported in a previous series of women at hereditary risk for ovarian cancer.[28] The detection of early-stage ovarian malignancies in this series is consistent with recent reports of a preinvasive phase of *BRCA*-associated ovarian neoplasia.[29] Elective salpingo-oophorectomy may also result in a reduction of future incidence of ovarian[16] and breast cancer[30] in those at hereditary risk, although a small number of peritoneal cancers will continue to occur.[31]

This study constitutes the first prospective report of both breast and ovarian cancer screening and preventive surgery in a large cohort of individuals carrying *BRCA* mutations. The rate of müllerian cancers detected in this series, 32 per 1,000 WY, is higher than the ovarian cancer rate of five to 16 per 1,000 WY predicted for *BRCA* carriers from retrospective linkage consortium data.[32,33] Similarly, the 41 per 1,000 WY rate of breast cancer in this series is somewhat higher than the rate of 16 to 26 per 1,000 WY predicted from linkage studies.[33,34] However, the incidence rate for breast cancers observed for *BRCA* carriers in this series is similar to the rate of 33 per 1,000 WY documented in a smaller retrospective study.[14] One explanation for the higher rates observed in this series is the detection of prevalent early-stage cancers in the first year after testing.

Limitations of the study include the relatively short follow-up, the single-institution setting, and the highly motivated nature of the individuals seeking genetic testing services. It is possible that given the strong personal and/or family history of cancer in the study participants, genetic counseling rather than the specific results of genetic testing motivated the observed changes in screening and preventive practices. In addition, for those with a history of a prior cancer, physician recommendations may have motivated screening behavior. The documented increase in ovarian cancer surveillance, as well as the smaller but significant impact on breast cancer screening behavior, supports the rationale for cancer genetic counseling as one component of a preventive oncologic strategy.

Taking into account all modalities of radiographic screening, breast examination, and preventive surgery, 79% of breast cancers diagnosed after *BRCA* testing were stage I (or stage 0), 21% were stage II, and 0% were stage III/IV, compared with 37% of *BRCA*-associated breast cancer cases

presenting with stage 0/I disease, 51% with stage II disease, and 12% with stage III/IV disease in seven series of 279 *BRCA*-associated breast cancer cases.[34-40] The rate of lymph node–positive disease detected at screening in this series is identical to the rate of four (21%) of 19 combining two recent MRI screening trials involving 375 patients at hereditary risk for breast cancer.[20,21] Of the five ovarian or fallopian tube cancer cases staged in this series, none were stage III/IV, compared with 61% to 92% stage III/IV in the Surveillance, Epidemiology, and End-Results registry and in a series of consecutively ascertained *BRCA*-linked ovarian tumors, respectively.[41,42] The single case of primary peritoneal cancer in this series was stage IIC, the least common as well as earliest stage reported for this tumor type.[43]

The detection of early-stage tumors in this series was achieved despite a low sensitivity of radiographic breast cancer screening and a limited sensitivity and specificity of ovarian cancer surveillance in this high-risk cohort. More frequent mammographic examination, breast ultrasound, and MRI offer potential options to improve sensitivity of breast cancer screening in genetically predisposed individuals. In addition, our results indicate that both ovarian screening as well as risk-reducing salpingo-oophorectomy may lead to the diagnosis of early-stage ovarian cancers in genetically predisposed individuals. Larger prospective trials comparing frequency and modalities of cancer screening as well as the role of risk-reducing operations are necessary to determine optimal management of patients at hereditary risk for these malignancies.

APPENDIX

The appendix acknowledging special contributions is available online at www.jco.org.

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Psychosocial Predictors of BRCA Counseling and Testing Decisions Among Urban African American Women

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Cancer Epidemiology Biomarkers and Prevention

Abstract

Genetic counseling and testing for mutations in BRCA1/ 2 genes that increase breast cancer susceptibility potentially offer a number of benefits (e.g., more informed decision-making regarding breast cancer prevention options) but also raise potential problems (e.g., issues of discrimination). However, the literature suggests that African American women under-utilize genetics-related services. Therefore, the primary aim of the current study was to investigate predictors of the use of genetic counseling and testing for breast cancer susceptibility in this population. Participants were seventy-six African American at increased risk for breast cancer due to their family history of the disease. Participants were recruited from an urban cancer screening clinic and completed measures assessing sociodemographic information, breast cancer knowledge, breast-cancer specific emotional distress, and perceived benefits of and barriers to BRCA testing. Free BRCA counseling and testing was offered to all interested participants and measures were completed prior to counseling sessions. Based on their subsequent acceptance or refusal of these services, participants were described as having either: 1) declined BRCA-related genetic counseling (GC-); 2) participated in genetic counseling but refused genetic testing (GC+GT-); or 3) participated in both genetic counseling and testing (GC+GT+). Results revealed that participants who declined counseling had significantly less knowledge of breast cancer genetics than those who accepted both counseling and testing. No differences emerged between the three groups in terms of perceived benefits of testing. However, participants declining counseling demonstrated significantly higher perceived barriers scores compared those accepting counseling and testing. Specifically, those who did not participate in counseling reported greater anticipation of negative emotional responses to testing and more concern about stigmatization, while those who underwent both counseling and testing had significantly lower family-related guilt. Finally, cancer-specific distress was positively associated with participation in counseling, regardless of participation in testing. The current findings underscore the need for refinement of outreach and intervention efforts that both increase awareness of BRCA counseling and testing among African American women and provide information to those considering these options.

INTRODUCTION

One of the strongest predictors of a woman's lifetime risk of developing breast cancer is her family history of the disease. It is now estimated that between 5% and 10% of breast cancers are due to inherited mutations in one of two genes, BRCA1 and BRCA2 [1-3]. Research has shown considerable variability in cancer risk, reporting that individuals with mutations in BRCA1/2 have anywhere from 40% to 85% cumulative risk of developing breast cancer and a 5% to 60% cumulative risk of developing ovarian cancer [4;5]. Despite increasing recognition of the utility of genetic risk information, initial reports suggest that African American women may under-utilize genetic counseling and testing services [6]. Lerman and colleagues [7] reported that significantly fewer African American women provided a blood sample for analysis following pre-testing education and/or counseling compared to the White women in their sample. Similarly, a retrospective study by Hughes and colleagues [8] found that White women were significantly more likely to report use of genetic testing services in general than African American women. This is likely due, in part, to perceived testing benefits and barriers that are more salient in this ethnocultural group. Unfortunately, few studies have focused on the perceptions of African American women towards genetic testing.

The assessment of individual genetic risk for breast cancer has a number of potential benefits, including the facilitation of more informed decisions regarding breast cancer prevention (e.g., prophylactic mastectomy), the determination of family members' risks, and personal reassurance [9;10]. Agreement with such advantages of genetic testing has been shown to be fairly high among African American women [8;11 12]. A number of potential disadvantages to genetic testing also tend to be strongly endorsed by African American women. For example, studies have shown that African American women strongly endorse concerns about how BRCA testing might affect their family as well as the expectation that knowing that one carried a BRCA mutation would increase worry about their daughters and other family members [6;8;11 . Also, anticipation of difficulty in emotionally handling BRCA testing has been high, both in studies with African American women alone [6]and in comparison to White women[8;12]. Another potential barrier to BRCA testing may be concern about confidentiality of BRCA test results, as Donovan and colleagues reported that 72% of African American women in their sample reported concerns about confidentiality [12]. Finally, a variable that does not represent perceptions but appears to be an important barrier nonetheless is lack of knowledge about BRCA testing. Previous work has demonstrated that specific knowledge about breast cancer genetics is associated with stronger interest in BRCA testing among African American women [13].

The studies cited above have begun to establish trends in the endorsement of barriers to BRCA testing by African American women. However, further exploration is needed as regional and other sociodemographic differences may exist between study samples and studies are not consistent in terms of barriers assessed. Addressing group-salient barriers to BRCA testing may be an important strategy in increasing breast cancer prevention and control in a population that carries greater breast cancer burden in terms of higher mortality and lower survival when compared to all other ethnic groups [14]. In addressing these barriers, it is important to note that the studies cited above are limited. Specifically, these studies primarily explore factors that may predict BRCA testing, even though the process of genetic risk assessment includes an initial, separate decision regarding participation in pre-test counseling to discuss if genetic testing may or may not be helpful. It is important to isolate these two decisions because barriers to participation in genetic counseling may differ from barriers to genetic testing. Research designed to further investigate African American samples as well as acknowledge the separate components of the genetic testing process will provide critical information that may strengthen breast cancer prevention and control efforts. The results of such research may also guide the development of tailored interventions and outreach programs that are more sensitive to these distinctions. As a result, African American women

may make more informed decisions regarding their participation in these services and report greater satisfaction with the services they receive.

The present study is a prospective investigation of psychosocial predictors of genetic counseling and testing among African American women who were offered free BRCA-related services. The advantages of BRCA counseling and testing, as well as cognitive and emotional barriers, were assessed among African American women who either: 1) refused genetic counseling to discuss BRCA genes; 2) participated in genetic counseling but refused BRCA testing; or 3) participated in both genetic counseling and BRCA testing. Differences between the three groups in terms of perceived advantages and barriers were then examined.

METHODS

Participants

Participants were 76 African American women enrolled in a longitudinal study examining the psychological and behavioral impact of genetic counseling and testing for breast cancer susceptibility. The women were recruited from the Breast Examination Center of Harlem (BECH), a satellite community clinic affiliated with Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City. BECH provides comprehensive diagnostic breast and cervical screening services (e.g., mammogram, clinical breast exam, pap smear). BECH advertises its services widely in the Harlem community and provides services regardless of ability to pay. To be eligible for the study the women had to: 1) self-identify as African-American or Black; 2) be 18 years of age or older; 3) have at least one first-degree relative diagnosed with breast cancer; 4) report no previous breast cancer diagnosis; 5) report no previous genetic counseling for breast cancer risk; 6) be able to read and write English; and 7) provide informed consent.

Measures

Sociodemographic information. Basic sociodemographic information was obtained from each participant, including age, marital status, education, and income, using a standard self-report format.

Breast cancer knowledge. Twenty-two items (α = .76), currently being evaluated in a larger study, were developed by the research team to assess knowledge about risk factors for breast cancer using a "true or false"response format. Eight questions assessed knowledge about general risk factors for breast/ovarian cancer (e.g., "True or false: A woman is at a greater risk for developing breast cancer if she has: an early age of her childbirth; a late age of her first menstrual period"). Fourteen questions assessed knowledge about inheritance of breast/ovarian cancer disposition (e.g., "True or false: A woman who has a sister with an altered gene for breast cancer has a 50% chance (1 in 2) of also having an altered gene for breast cancer" " A woman is at a greater risk of developing breast cancer if she has a father with an altered gene for breast cancer").

Impact of Event Scale (IES [15]). The intrusive thoughts subscale of the IES was used to assess breast cancer-specific distress. This subscale includes 7-items that assess intrusive stress reactions to a specific stressor, in this case, the threat of breast cancer. Participants were asked to rate how frequently each thought or behavior occurred during the past week. The internal consistency of the measure in the present sample was high (α=.90).

Perceived benefits and barriers of BRCA testing: Twenty-one items, currently being evaluated in a larger study, were developed by the research team to assess participants' perceptions of the potential benefits (pros) and barriers (cons) of genetic testing for breast cancer susceptibility. These items were based on

our previous research [16] as well as that of others [8;10]. Participants indicated the extent to which they agreed or disagreed with each question using a Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). Seven questions (α = .66) assessed the potential pros of genetic testing (e.g., "Knowing that I carry the gene would help me decide whether to go for more frequent mammograms"). Fourteen questions (α = .76) were used to assess potential cons of testing. The con items included 5 subsets: anticipation of negative emotional reactions (e.g., "Knowing that I carry the gene would leave me in a state of hopelessness and despair"); confidentiality (e.g., "If I were found to carry the gene, I would worry that the results would not stay confidential"); stigma related to testing (e.g., "If I were found to have the gene, I would feel singled out"); family-related worry (e.g., "If I were found to carry the gene for breast cancer, I would worry about passing the gene to my children"): and family-related guilt (e.g., "I would feel guilty if one of my relatives had the gene and I did not"). The internal consistency of each of the five subsets of items in the current sample are as follows: negative emotional reactions, α=.46; confidentiality, α=.60; family-related worry, α=.63; family-related guilt, α=.60; and stigma, α=.70

Procedure

Study participants were enrolled through one of two strategies. In the first strategy, an African American research assistant briefly outlined the study and eligibility criteria to groups of women waiting for services in a public area at BECH. Interested women then approached the research assistant who verified eligibility criteria, briefly described the study and obtained contact information. The research assistant contacted the women later via telephone to describe the study in greater detail and, if women continued to express interest in the study, an informed consent form and assessment materials were mailed to them. Women were asked to return these forms via mail. In the second strategy, women who met the eligibility criteria were identified by nurse practitioners at BECH or the Clinical Genetics Service at MSKCC. Nurse practitioners did not recruit women but referred eligible women to the research assistant. Nurse practitioners described the study briefly as an investigation of attitudes and feelings about breast cancer and obtained contact information from women interested in learning more about the study. The research assistant then contacted these referred women, verified eligibility and described the study in detail. If women continued to express interest in the study, an informed consent form and the assessment were mailed to them and they were asked to return these forms via mail.

Recruitment and the presentation of information upon which participation interest and agreement was based was conducted by the research assistant, who informed women that they could: 1) refuse participation; 2) discontinue their participation at any time; 3) fill out the questionnaires without going for genetic counseling or testing; 4) attend the counseling session without undergoing genetic testing; and 5) decide not to learn their mutation status once their test results were available. It was also emphasized that the women could not undergo genetic testing unless they attended the counseling session. A few days later the women were contacted again by telephone to verify that they received assessment materials, to review the consent form, and to answer any questions that they might have. Counseling session appointments were confirmed for interested women. Those with appointments were asked to return the signed consent form and the assessment before their genetic counseling session. The total number of interested women who were mailed consent forms and assessment was 141. Only 54% of these women (N=76) returned these materials.

The counseling sessions were conducted by an African American master's level genetic counselor and lasted one to two hours. The counselor followed standard clinical practice [17]. Briefly, after construction of the pedigree, the following issues were addressed: 1) possible reasons for familial clusterings of cancer; 2) the likelihood of the occurrence of cancer in the pedigree to be "hereditary" (i.e., conforming to the criteria for a hereditary cancer syndrome) or "familial" (i.e., not meeting those criteria); 3) limitations of pedigree analysis, including the inability to distinguish between a sporadic and inherited cancer; 4) the relative importance of various risk factors other than family history; 5) risk estimates for developing

cancer based on family history and/or associated with BRCA mutations; 6) options for early detection and prevention, and the limitations of those options; 7) limitations and benefits of genetic testing for BRCA1/2; and 8) risks of receiving test results, including insurance discrimination and adverse psychological consequences.

At the end of the counseling session, women were asked if they wished to undergo genetic testing. A separate informed consent for DNA testing was reviewed for participants who decided to be tested. The women were urged to consider the impact of negative, positive, and ambiguous results and it was stressed they could choose not to learn their results once they became available.

RESULTS

Sample Characteristics

As shown in Table 1, the mean age of the sample was 43.4 years (SEM 1.1), 64% had less than $40,000 in annual income, 68% reported greater than a high school education (some college, bachelor's or graduate degree), and 41% were married or living with a partner. Seventeen women (22.4%) did not undergo genetic counseling (GC- group), 19 women (25.0%) underwent genetic counseling but declined BRCA testing (GC+GT- group), and 40 women (52.6%) underwent both genetic counseling and BRCA testing (GC+GT+group).

Insert Table 1 About Here

There were no significant differences between the groups based on any of the sociodemographic variables, but there was a trend for women in the GC+GT- to be younger than the women in the other two groups ($F(2,73)=2.64$, $p=.07$) and for the GC+CT+ to have higher income than women in the other two groups ($\chi^2(4, N=75)=8.6$, $p = .06$). Sixty-three percent of the women were referred to the research assistant by nurse practitioners. There were no significant differences between the groups in terms of being referred by a nurse practitioner versus having the research assistant be the only source of contact ($\chi^2(2, N=76)=2.6$ $p=.25$).

Breast cancer knowledge and genetic counseling /testing decisions. Scores summarizing participants' general breast cancer knowledge about genetics of cancer were computed by calculating the percent of correctly answered questions. On average, participants were correct on 42.5% (sd = 18.2) of the general breast cancer questions (score range: 12.5% - 87.5%). The average knowledge score for genetics of cancer was 45.4% (score range: 7.1% - 100%). As shown in Table 2, the results from analyses of variance (ANOVAs) showed that the groups did not differ on general knowledge about breast cancer ($F(2,71)=1.5$, $p=21$) but they were significantly different on knowledge about genetics of breast cancer ($F(2,73)=2.9$, $p < .05$). Planned comparisons revealed that the women in the GC- group had significantly less knowledge about genetics of breast cancer than women in the GC+GT+ group.

Insert Table 2 About Here

Perceived benefits and barriers of genetic testing. The most commonly perceived benefits and barriers were identified by tabulating the percentages of women who agreed or strongly agreed with each of the pros and cons items (See Table 3 and Table 4). Six of the seven benefits were endorsed by 70% or more of the women with the majority of the women indicating that the knowledge that they were mutation carriers would motivate them to perform breast self examination more frequently and help their daughters or sister to decide about

testing. Seven of the fourteen barriers were endorsed by more than 50% of the women with the most commonly cited barriers being worry about passing the gene to their children and worry about other family members who might be carriers.

Insert Tables 3 and 4 About Here

To examine if the three groups differed on perceived benefit and barriers of testing, the average score for the benefit questions and the barrier questions was computed. In addition, the average scores for the five subsets of the barrier questionnaire were computed. The results of ANOVAs indicated that the groups did not differ on perceived benefits of testing but there was a trend for the groups to differ on perceived barriers of testing. ($F(2,73)=2.79$, $p<.06$). The ANOVAs for the five barrier subsets indicated that the there was a significant difference between the groups on anticipated negative emotional reactions to test results ($F(2,73)=2.91$, $p<.05$), family-related guilt ($F(2,73)=2.97$, $p<.05$) and fear of stigmatization ($F(2,73)=6.48$, $p<.05$). As shown in Table 5, a planned comparison revealed that the women in the GC- group reported greater concerns about stigmatization than the women in the other two groups and they anticipated higher levels of negative emotional reactions to positive test results than the women in the GC+GT+ group. Lastly, the women in the GC- and the GC+GT- demonstrated stronger anticipation of guilt about family members if they were found to be mutation carriers than the women in the GC+GT+ group.

Insert Table 5 About Here

Breast cancer-specific distress. The mean score for IES intrusive thoughts subscale across the entire sample was 9.9 (SEM 1.0) with a score range from 0 to 35. This is consistent with other studies of women at increased risk for breast cancer that report mean intrusive thoughts scores ranging from 8.3 – 14.6 [18 19]. In the current sample, 14.5% of the women had scores higher than 19, the range of total IES scores that is reported as warranting clinical concern [20;21] and predictive of posttraumatic stress disorder [22]. Means for each decision group are presented in Table 5. Due to the skewed distribution a median split was used to classify individuals as below or above the median on intrusive thoughts. The chi square analysis revealed that 18% of the women in the GC- group were above the median in intrusive thoughts compared to 73% and 58% of the women in the GC+GT- and GC+GT+ groups respectively ($\chi^2(1,N=75)=11.2$, $p=.004$).

Relative contribution of demographic characteristics, knowledge, perceived barriers and intrusive thoughts to genetic counseling and testing. To determine the unique contribution of the variables found to be related to genetic counseling/testing in univariate analyses, a logistic regression was computed entering group membership as the dependent variable and income, age, knowledge about genetics, perceived barriers of testing and intrusive thoughts as independent variables. The results revealed a significant association between group membership and perceived barriers of testing ($p=.003$) and intrusive thoughts about breast cancer ($p=.05$). There was a trend for knowledge about genetics about breast cancer to be significantly related to group membership ($p=.09$), but age and income were not related to group membership (p's $> .20$).

DISCUSSION

The results of the current study indicate that African American women who differ in their BRCA counseling and testing decisions also differ across variables associated with these decisions. These findings are based upon a prospective investigation in which women completed and returned assessment

materials via mail prior to any genetic risk assessment services. First, it was reported that women in the three decision groups – those who refused counseling, those who accepted counseling but declined testing, and those who participated in both – differed significantly in their knowledge of breast cancer genetics. Specifically, those who declined counseling demonstrated significantly lower knowledge compared to those who accepted both counseling and testing. Interestingly, there were no significant differences across the three decision groups in terms of more general knowledge of breast cancer. Although previous work suggests that knowledge of genetic risk for breast cancer is associated with interest in testing [13], the current research is the first to find that such knowledge is associated with women's actual counseling and testing choices.

There were no differences observed in endorsement of genetic testing pros across groups. In fact, endorsement of all but one of the pros was equal or greater than 70%. This finding is consistent with previous studies in which African American ethnicity was associated with the high endorsement of the advantages of genetic testing [8;12]. However, the three decision groups did differ with regard to perceived disadvantages of genetic testing. As might be expected, women who declined both genetic counseling and testing endorsed significantly more barriers to genetic testing than women who accepted both counseling and testing. An investigation of subgroups of barrier items revealed further differences between all three groups. Women who declined counseling were more likely to anticipate negative emotional reactions to testing than women who accepted counseling whether they participated in testing or not. These results suggest that the expectation that one will experience distress may deter women from initiating the genetic risk assessment process. However, an opposite trend was observed in terms of intrusive thoughts about breast cancer, with women who accepted genetic counseling (regardless of testing decision) reporting more intrusive thoughts compared to women who declined counseling. These findings highlight the distinction between anticipated versus current distress as anticipated distress may lead one to avoid counseling while currently experienced distress may drive one to participate in counseling. The high prevalence of currently experienced distress is further evidenced by finding that 14.5% of the sample had intrusive thought scores in a range that may be interpreted as pathological [20;21 22]. It is possible that, in these cases, the engagement of genetic counseling and testing services was less about information seeking and actually represented an emotion management strategy.

The present research also found that women who declined counseling were also more likely to anticipate stigmatization due to BRCA mutation carrier status compared to women who participated in counseling, regardless of testing decision. This is similar to other reports that stigma, shame and secrecy surrounding breast cancer are barriers to breast cancer screening (e.g., mammography) in the African American community. It has been speculated that such stigma may be tied to one's religious or spiritual orientation, which may support the belief that cancer is God's will or God's punishment [23;24]. Other research has shown that African American women are more likely to endorse the belief that males respond unfavorably to breast cancer and that relationships with men would be affected by such information [25]. Anticipated negative effects on interactions with male partners and significant others may also contribute to stigma and shame related to breast cancer. It is plausible that these stigma-related beliefs may extend beyond breast cancer diagnosis and be applicable as barriers to BRCA counseling and testing, since the confirmation of mutation status may increase a woman's perceived (and actual) likelihood of eventually being diagnosed with breast cancer.

Interestingly, no differences in concern about the confidentiality of BRCA test results were observed between women in the three groups. There are two possible explanations for the failure to observe differences in this area. First, the confidentiality item employed in the current study may have lacked sensitivity to the context of confidentiality, which may include issues of disclosure to one's employer, insurance company, or family. One's concerns about confidentiality may vary considerably based on each of these contexts. Indeed, Durfy and associates [26] found that African American women reported stronger belief in the increased flow of information of test results to family members and physicians

compared to other groups. A second reason that differences in confidentiality concerns were not observed across groups may be the sample's overall high endorsement of worry about the confidentiality of genetic testing results. The strong endorsement of this concern across all participants may have decreased the likelihood that group differences would emerge.

There were also no group differences observed in family-related worries regarding genetic testing. However, women who refused testing had significantly greater anticipated guilt regarding the carrier status of relatives than women who participated in testing. Such concern, specifically concern about feelings of guilt, may be due to the view that knowledge of one's BRCA test results and their ramifications in terms of disease risk, emotional and financial stability, represent a burden that is not carried by the patient alone, but by potentially many family members. Such family concern may be a result of a collectivist or group-centered decision-making style that has previously been observed among African American women. Baldwin [27] asserts that decision-making practices among African American women are tied to daily living that centers on a core family or extended family group. She proposes that for African American women, decisions occur by mutual aid and cooperation among community members. Therefore, African American women may be less likely to pursue a health-related issue if it does not meet with the support of significant others or disrupts these relationships.

One of the limitations of the current study is that the pros and cons of BRCA testing were assessed but there was no separate examination of the pros and cons of BRCA counseling. It is possible that counseling attitudes represent a distinct set of attitudes across which the three decision groups may have differed significantly. Furthermore, in addition to the pros and cons assessed in the current study and others, there may be evaluations of the procedural aspects of genetic risk assessment that are associated with one's decision to participate in counseling and testing. For example, one may indicate that it is undesirable to disclose medical information to someone other than one's physician or have one's blood drawn. The exploration of BRCA counseling perceptions and procedural aspects of BRCA counseling and testing is an important focus of future research. Within the perceptions that were assessed, the internal consistency of the item subsets assessing disadvantages of testing is of concern. The alphas for most item subsets were marginal. The marginal reliability coefficients for item subsets is likely to due to the low number of items within each subset and small total sample size, which made it more difficult to demonstrate internal consistency. The future development of additional items for each subset and their evaluation in a larger sample is likely to result in greater reliability, especially given their substantial face validity. It is also important to note here that the study was not originally powered to address differences among decision groups. Post-hoc power analyses do show that the sample size of 76 achieved 84% power to detect significant group differences in stigma items and 80% power to detect significant group differences in breast cancer-specific distress. For the findings related to other item subsets, we cannot completely rule out Type II error.

Another limitation of the current study is a question of the generalizability of findings due to the low rate of informed consent forms returned by potential participants. Low rates of return of consent forms may have been due, in part, to low perceived urgency of participation in genetic risk assessment because participants did not have a breast cancer diagnosis. These low rates affect generalizabilty as women who ultimately did not provide informed consent and complete baseline measures may differ significantly from those who did participate in terms of demographic and psychological characteristics. However, the low rates of research participation, along with the observation that women who declined genetic counseling had less knowledge and reported more negative attitudes about genetic testing, underscores the need for outreach interventions designed to inform women of genetic counseling and testing options. The importance of outreach is supported by earlier work indicating that African American women may under-utilize genetic counseling and testing services [6].

Our findings further suggest that not only intervention content but also the stage at which specific content is presented is important considerations in the development of such interventions. For example, based on the current results, outreach into the African American community intended to educate individuals about initiating the genetic testing process may focus more on barriers to genetic counseling participation, specifically issues related to negative emotional reactivity and stigmatization. Current findings also suggest that standard genetic counseling sessions may need to place greater emphasis on areas that are particularly salient for African American women, especially family-related guilt.

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Table 1. Demographic Characteristics

Age	
mean (SEM)	43.4 (1.2)
range	21.6 - 68.5
Education N(%)	
high school graduate or less	24(31.6%)
partial collage	25(32.9%)
university graduate	20(26.3%)
graduate degree	7(09.2%)
Living arrangements	
N (%) living with partner	31(40.8%)
Income N (%)*	
less than $20,000	24(32.0%)
between $20,000 - $40,000	24(32.0%)
between $40,000 - $100,00	24(32.0%)
greater than $100,000	3(04.0%)

* missing information for one participant

Table 2. Breast cancer knowledge

Group Membership	General breast cancer knowledge	Knowledge about genetics of cancer
GC-	38.9(4.9) [a]	33.1(4.9) [a]
GC+GT-	41.5(4.6) [a]	43.6(4.7) [ab]
GC+GT+	41.3(3.2) [a]	47.4(3.2) [b]

Means (SEM) for percentages of correct answers.
Means within each column that do not have the same superscript letter are significantly different.

Table 3. Perceived Benefits of Testing

	Strongly Agree or Agree
Knowing that I carry the gene would motivate me to perform breast self-examination more frequently.	90%
If I were found to carry the gene, it would help my daughter(s) or sister(s) decide whether to undergo genetic testing.	89%
My concerns about developing (having a recurrence of) breast cancer would be reduced if I knew I did not carry the gene.	89%
Knowing that I carry the gene would help me decide whether to go for more frequent mammograms.	81%
Knowing whether or not I carry the gene would increase my sense of personal control.	74%
Knowing whether or not I carry the gene would help me make important life decisions (e.g., getting married, having children).	70%
Knowing that I carry the gene would help me to decide whether to undergo bilateral mastectomy (an operation to move both breasts) .	44%

Table 4. Perceived Barriers of Testing

	Strongly Agree or Agree
If I were found to carry the gene for breast cancer, I would worry about passing the gene to my children.	87%
Knowing that I carry the gene would cause me to worry more about other family members who could be carriers (e.g., mother, sisters, daughters).	79%
I would be ashamed if I were found to carry the gene.	78%
I would be frightened if I were found to have the gene.	73%
Being tested for the gene could jeopardize my insurance coverage.	58%
If I were found to carry the gene, I would worry that the results would not stay confidential.	56%
If I were found to carry the gene for breast cancer, I feel guilty if my daughter(s) developed breast cancer.	55%
I would be angry if I were found to carry the gene.	47%
I would feel guilty if one of my relatives had the gene and I did not.	25%
Knowing that I carry the gene would cause me to feel less healthy than other people.	22%
If I were found to carry the gene, it would cause others to view me negatively.	21%
If I were found to carry the gene, I would feel singled out.	19%
Knowing that I carry the gene would leave me in a state of hopelessness and despair.	18%
I would consider suicide if I were found to carry the gene for breast cancer.	3%

Table 5. Perceived barriers to genetic testing for breast cancer susceptibility

	Perceived barriers total score	Item subsets of the perceived barrier questionnaire					Breast cancer-specific distress
Group		Emotional Reactions	Confidentiality	Worry	Guilt	Stigma	
GC-	2.7(.16)[a]	2.6 (.18)[a]	2.8 (.29)[a]	3.5(.25)[a]	2.3(.26)[a]	2.3(.24)[a]	5.5 (2.2)[a]
GC+GT-	2.5(.16)[ab]	2.2 (.17)[ab]	2.8 (.28)[a]	3.6(.24)[a]	2.3(.24)[a]	1.6(.22)[b]	11.9 (2.0)[b]
GC+GT+	2.2(.11)[b]	2.1 (.12)[b]	2.5 (.19)[a]	3.6(.16)[a]	1.8(.17)[b]	1.3(.16)[b]	9.5 (1.5)[ab]

Means (SEM) for the perceived barrier scale and the five subsets. Means within each column that do not have the same superscript letter are significantly different.

Running Head: ACCULTURATION AND BSE FREQUENCY

The African American Acculturation Scale and its Relationship to Smoking and Breast Self-Examination Frequency

Submitted to Cultural Diversity and Ethnic Minority Psychology

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Abstract

The concept of acculturation is one factor that has been used to understand differences in health behaviors between and within a variety of racial and ethnic immigrant groups. Few studies, however, have examined the potential impact of acculturation on health behaviors among African-Americans. The present study had two goals: 1) to reconfirm relations between acculturation and cigarette smoking; 2) to investigate the impact of acculturation on another type of health behavior, cancer screening and specifically breast self-examination (BSE). African-American women (N=66) attending an inner-city cancer- screening clinic completed study questionnaires. Results reconfirmed psychometric properties of the AAAS; replicated the negative association between acculturation and smoking status; and found relations between African-American media preferences and women's adherence to BSE frequency guidelines. Findings from this study raise the possibility that specific aspects of acculturation may better explain specific health behaviors.

Further Psychometric Validation of the African American Acculturation Scale and its Relationship to Breast Self-Examination Frequency

The study of race as a factor in health and illness has a long-standing history in biomedical research. However, endeavors to explain differences in health and disease status on the basis of race as a biological indicator are no longer tenable as the scientific and medical community recognizes race to be a classification system constructed by society, not biology (Freeman, 1997). By conceptualizing race as a marker for other differences between groups (e.g., social circumstance, socioeconomic status (SES), cultural values and beliefs), we can obtain more meaningful information with implications for intervention and change. For example, some studies have found that after controlling for socioeconomic status, differences in health behaviors initially accounted for by race either diminish substantially or disappear completely (Breen & Keesler, 1994; Calle, Flanders, Thun, & Martin, 1993; Hiatt et al., 1996). Similar to SES, but less studied in the literature is acculturation, which may also better explain differences between groups as well as differences within groups.

Acculturation refers to the process in which an individual adopts or adheres to attitudes, beliefs, practices, or behaviors congruent with that of the dominant culture. Acculturation is a complex process involving multiple components (Berry, 1980), and the meaning of acculturation can vary depending on how it is measured. Efforts to operationalize acculturation have recognized the multi-dimensionality of the construct by incorporating factors such as traditional rituals and practices, food and activity preferences, ethnic composition of one's interpersonal relationships, values, and perceived self-identity. In addition, immigration status variables (e.g. place of birth, generational status in U.S., length of residency) have been used to calculate a person's level of acculturation. Earlier stages of acculturation measurement research produced

scales applicable to more inclusive ethnic and cultural groupings such as Asian Americans (Suinn, Richard-Figueroa, Lew, & Vigil, 1987), Hispanic Americans (Marin, Sabogal, Marin, & Otero-Sabogal, 1980), and Native Americans (Hoffman, Dana, & Bolton, 1985). More recently, acculturation scales have been designed to appreciate cultural distinctions within ethnic groups: Puerto Ricans (Tropp, Erkut, Coll, Alarcon, & Garcia, 1999), Greek-Americans (Harris & Verven, 1996), Taiwanese aboriginals (Cheng & Hsu, 1995), and Southeast Asians (Anderson et al., 1993).

Although acculturation is a concept that has attracted a great deal of attention in psychological research, it has received little research attention in the African-American community. According to Landrine and Klonoff (1994), the identification of African-Americans as a racial group, first, and an ethnic or cultural group, second, may explain the relative delay in exploring acculturation in this population. To date, only two scales have been developed to measure acculturation within the African-American population (Landrine & Klonoff, 1994; Snowden & Hines, 1999). Landrine and Klonoff's (1994) scale assesses several dimensions of African-American culture theoretically derived to reflect the degree of connection an individual has to African-American culture as opposed to the dominant culture (i.e., White American culture). Importantly, scores on the separate subscales of the AAAS have not been found to be associated with income, social class, or level of education (Landrine & Klonoff, 1994). This lack of confounding with other demographic variables suggests its potential to explore cultural constructs as they relate to other behaviors, performance, or functioning.

Acculturation has been examined increasingly as one of the factors accounting for variation in health behaviors among different cultural groups. For example, acculturation has

been found to be positively associated with ever having had a pap test among young Asian-American women (Tang, Solomon, Yeh, Worden, 1999), ever having had a mammography, first time and recent mammography or clinical breast exam among Hispanics (O'Malley, Kamer, Johnson, & Mandelblatt, 1999), illicit drug use among Mexican men and women (Vega, Alderete, Kolody, & Aguilar-Gaxiola, 1998) and greater alcohol consumption among Mexican American women (Alaniz, Treno, & Saltz, 1999). Among Korean Americans, high acculturation is related to higher body weight and light physical activity (Lee, Sobal, & Frongillo, 2000). In addition, smoking behavior has been linked to acculturation. Chen, Unger, Cruz, and Johnson (1999) found greater smoking behavior and earlier onset of smoking among more highly acculturated Asian-American youth, a relationship also documented in other Asian and Latino populations of varied ages (Ebin, et. al, 2001; Lee, Sobal & Frongillo, 2000; and Unger et. al, 2000).

Few studies have examined the relationship of acculturation and health behaviors among African-Americans. Landrine and Klonoff (1996) used the AAAS to examine the role of acculturation in cigarette smoking status, and a significant relationship was found. Specifically, African Americans who scored as less acculturated were more likely to be smokers. Klonoff and Landrine (1999) replicated this finding in a community sample. Here, they again found a significant association between the total acculturation score and smoking status, with less acculturated African-Americans being more likely to smoke. To our knowledge, there have been no studies using the AAAS to assess relations between acculturation and any health behavior other than smoking. The present study examined the role of acculturation in breast self-examination (BSE) frequency.

Although BSE has not been proven unequivocally to be effective in detecting breast cancer or reducing mortality related to the disease, it has been recommended consistently by national clinical societies (e.g. American Cancer Society, American Society of Clinical Oncology), as an important aspect of breast cancer surveillance, that has been shown to detect significant number of breast cancers (Porter, 1999). Among economically disadvantaged groups, cost can be a barrier to participating in clinical breast cancer screening (Rimer, 1992). Given that BSE is a cost-free screening procedure that is under a woman's personal control, examining BSE behavior among African American women is particularly relevant. Existing studies on BSE among African American women have yielded inconsistent results, with some indicating African American women tend to under-perform BSE (Underwood, 1999) and others indicating African American women tend to over perform BSE (Epstein et al., 1997). While BSE under-performance is well recognized to decrease the efficacy of this screening modality (Coleman, 1991), BSE over-performance is also thought to decrease the utility in women's ability to detect gradual changes in the breast (Haagensen, 1952).

As an example of a self-initiated health promoting behavior, it is important to understand factors that may encourage or deter BSE among African American women. The aims of the present study were to re-examine the relationship of acculturation and smoking status in an urban, inner city sample of African American women, and to examine the role of acculturation in another health behavior (BSE frequency). The AAAS has been recently revised to drop 26 items (Klonoff & Landrine, 2000), based on feedback from other investigators who reported that participants found many items objectionable. The present study, initiated before the scale revision, was completed without negative feedback by participants (see below).

Method

Data were gathered as part of a larger ongoing investigation of stress associated with having a family history of breast cancer. Results reported here are from women recruited from an inner city cancer screening clinic who self-identified as African American.

Setting. The Breast Examination Center of Harlem (BECH) provides advanced, comprehensive diagnostic screening services to members of the Harlem community. All services are provided at no out of pocket expense to the client. Ninety-seven percent of BECH's clientele is Black or Latina. At the time data was collected for this study, BECH's staff was 95% Black or Hispanic. Particularly relevant to this study, nurse practitioners at the BECH give clients instruction on how to properly perform BSE and frequency guidelines (i.e., once a month) are emphasized. Videotaped instructions on how to perform BSE also play repeatedly in the waiting area.

Procedure.

Participants were recruited from the BECH's waiting room on scheduled clinic days by an African American female researcher (JG). After agreeing to participate, all were given an appointment to meet with the researcher three to four weeks afterwards to complete study questionnaires. This schedule was to ensure that subjects would receive results of cancer screening prior to the interviews. None of the women received abnormal results. One subject who required a follow-up clinic visit due to unclear or suspicious results was excluded from the study. All women completed standardized measures (described in detail below) that assessed African American acculturation and breast self-examination behavior in addition to the measures used in the larger study. As noted by the developers of the AAAS (Landrine & Klonoff, 1996)

highly acculturated subjects may find the scale offensive, therefore, care was taken to explain the purpose of the measure to all participants. In our sample, only one woman refused to complete the measure, saying she did not see its relevance to her experience. Participants received $20 plus the cost of round trip public transportation for the visit.

Participants.

To be eligible participants had to be 25 or older, able to read/write English, and able to provide meaningful informed consent. The study excluded women who had a personal history of neoplasm or abnormal pathologic reports or were pregnant. The data of two women were deleted: the woman who did not complete the AAAS, and that of one woman with extreme missing data on the AAAS. As a result, 66 women completed all the measures.

Measures.

Demographic and Medical questionnaire. A standard questionnaire (Valdimarsdottir et al., 1995) was used to obtain information on age, education, and other demographic variables.

Age ranged between 26 -72 years, (M = 45.00, SD= 10.70). Eighty-five percent completed at least some high school. Income was trichotomized into < $10,000 (n=12); $10,000-$39,000 (n=40); and> $39,000 (n=14). Sixty- three percent were currently employed, and 30% were currently married. Forty-five percent were smokers as indicated by their responses to question taken from the National Health Interview Survey (Benson & Marano, 1995): "During your lifetime, have you smoked at least 100 cigarettes (5 packs)?" Smoking was unrelated to demographics in this data set. Forty-one percent had at least one first-degree relative (FDR) with breast cancer. It should also be noted that preliminary statistical analyses revealed no associations between FDR status and any other measure in the study.

Behavioral Measures

Assessment of breast self-examination. Two questions, based on published results and modified by the research team, assessed breast self-examination frequency. First, participants were asked: "How often do you perform breast self-examination? (1)*More than once a month;* (2) *Once a month;* (12 times a *year);* (3) *Every other month* (6 *times a year);* (4) *Four or five times a year*; (5)-*Two or three times a year;* (6) *Once a year;* (7) *Never.* Under-performance was operationally defined as those women who performed BSE less than once a month. Second, over-performance in the period following their clinical examination was evaluated with the question: "In the past three weeks, how many times did you perform breast self- examination? *(a) Never (b) Once (c)* 2-3 *times (d)* 4-5 *times (e) Six or more times."* Over-performance was operationally defined as performing BSE more than once during the prior three weeks. As would be expected, results on the two measures of BSE frequency were significantly related (chi-square $F=55.36$, $p < .001$).

Acculturation Measure.

African-American Acculturation Scale (Landrine & Klonoff, 1994). This 74- item measure assesses eight dimensions of African-American culture, which are: 1) Traditional African American Religious Beliefs and Practices (6 Items); 2) Traditional African American Family Structure and Practices (12 Items); 3) Traditional African American Socialization (11 Items); 4) Preparation and Consumption of Traditional Foods (10 Items); 5) Preference for African American Things (11 Items); 6) Interracial Attitudes (7 Items); 7) Superstitions (5 Items); and, 8) Traditional African American Health Beliefs and Practices (12 Items). Answers are reported in a Likert-style format, which range from (1) Strongly Disagree to (7) Strongly

Agree. A subject's score on a sub-scale is computed as the sum of the answers on that sub-scale, and a Total Summary Score is also computed. A higher score is thought to represent more traditionally African American views. Published reports by the scale's developers have demonstrated its psychometric properties (Landrine & Klonoff, 1994; Landrine & Klonoff, 1996).

With regard to missing data, only one participant omitted more than 6 items from the entire measure, and no participant missed more than 3 items from any one sub-scale, suggesting that missing items were randomly distributed. Following published procedures of the AAAS' s developers, we used mean substitution to replace missing items within sub-scales (Landrine & Klonoff, 1996).

Results

Phase 1 -In this phase of the study, we first examined the psychometric properties and concurrent validity of the AAAS using data from a sample of 35 women who completed the full questionnaire. More critically, we examined relations between AAAS scores and a health behavior (e.g., smoking) previously reported to be associated with those scores (Klonoff & Landrine, 1996). Having confirmed previous findings with the AAAS, we then examined the relations between scores on that measure and BSE. Consistent with previously published results (Landrine & Klonoff, 1994), data from this sample demonstrated a wide range of scores (e.g., a range of over 250 points on the total AAAS score and a range of more than 200 points on the total AAAS score found in previously published results). Also consistent with published findings (Landrine & Klonoff, 1994), in this data set the AAAS was not significantly related to demographic variables.

We next examined concurrent validity of the AAAS by following the previously published approach of the scale's developers. They argued that persons of an ethnic group who live in an ethnic-minority neighborhood are likely to be the more traditional members of their culture (because of constant exposure to the culture), whereas those who live in predominately White or integrated neighborhoods are likely to be more acculturated (Landrine & Klonoff, 1994). Thus, we examined the scores of the answers to the question "I currently live in a Black neighborhood" and divided the subjects into two extreme groups: 1) The "Other residence" group consisted of the women in this sample who circled "This is absolutely not true of me" (n=5); and 2) the "Black neighborhood residence" group who circled "This is absolutely true of me" (n=20). MANOVA analyses revealed that the Black neighborhood group scored significantly higher (i.e., more traditionally African American) than the other residence group (i.e., more acculturated) across the eight AAAS sub-scales ($F= 2.86$, $p < .05$). Next we examined the relations between acculturation and smoking. MANOVA analyses revealed that smokers (n=16) scored higher than non-smokers (n=19) across the eight sub-scales ($F = 2.50$, $p < .05$). Upon closer examination of the data (Table 1), we found significant differences between the smokers and non-smokers on the Family Practices ($F = 5.14$, $p < .05$) and Interracial Attitudes ($F = 4.71$, $p < .05$) sub-scales, as well as on the Total Summary Score ($F = 5.79$, $p < .05$).

Finally, we examined the AAAS scores in relation to BSE frequency (Table 2). ANOVA results revealed that the mean for BSE "Under-performers" (n= 17) differed from "Others" (n= 18) on the Preference for African American Things sub-scale, the Socialization summary score and on the Total Summary Score. Women who under-performed BSE (i.e., less than once a month), scored lower on these sub-scales (i.e., more acculturated). The difference on the

Preference sub-scale remained significant after Bonferroni correction to reduce possible Type I error associated with assessment of multiple outcomes (i.e., $p < .05$ divided by 9). Consistent with these results, analysis of BSE over performance indicated that "Over-Performers" (n=21) also differed from "Others" (n= 14) on the Preference for African American Things and Socialization sub-scales, as well as on the Total Summary Score. We found that women who over-performed BSE scored significantly higher on the Preference sub-scale of the AAAS (i.e., higher scores indicate greater preference) even after Bonferroni correction.

Phase 2 – In this phase of the study, an additional 31 women completed only the Preference for African American Things sub-scale (12 items) in addition to the other study measures, to provide additional data on the relationship between this sub-scale and BSE frequency. The focus on that sub-scale served to reduce participant burden, while providing additional data on the one AAAS sub-scale that indicated a significant relation to BSE frequency in Phase 1. Confirming what was found in Phase 1, women who under performed BSE scored significantly lower on the Preference for African American Things sub-scale ($F = 6.42$, $p \leq .01$); the mean score for "Under-performers" (N=31; mean 45.48, S.D. 13.82) versus "Others" (N=35; mean 53.53, S.D. 11.98). For over-performance the pattern was again similar to that in Phase 1; the mean Preference scores of "Over-Performers" (N=23; mean 56.23 S.D. 9.42) was significantly higher than for "Others" (N=43; mean 46.28, S.D. 14.01) ($F = 9.29$, $p < .01$).

Given the findings relating Preference scores and BSE frequency, it was of interest to examine the individual items on that sub-scale as a first step in considering potential explanations for the relations (Table 3). For BSE under-performance, only questions #18 *(i.e., I read, or used to read, Essence magazine)* and #23, *(i.e, I read, or used to read, Jet magazine)*

reached significance. The mean score of women who under-performed BSE was significantly lower on those questions (F=10.72 and F=10.26, respectively; $p < .01$ for both questions). For BSE over-performance, only question #16 *(i.e., I listen to Black radio stations)* reached significance, with significantly higher scores for women who over- performed BSE (F=10.58; $p < .01$).

Discussion

The objectives of this study were to re-confirm the psychometric properties and validity of the original African American Acculturation Scale (AAAS) (Landrine & Klonoff, 1994) in an independent sample of urban, inner city African American women, to re-examine the relationship between acculturation and smoking status, and to investigate the role of acculturation in breast self-examination (BSE). Descriptive statistics of scores on the AAAS in our sample were similar to those found in reports by the scale's developers (Landrine & Klonoff, 1994). That is, we found similar ranges in variability for total acculturation and dimension scores, and also found that women who lived in a African American community scored higher on the AAAS (i.e., less acculturated) compared to women who lived in a integrated community. Also consistent with initial reports by the scale's developers, we did not find responses on the AAAS to be associated with income, social class, or level of education. These results provide further corroboration for the validity of the AAAS as a measure of the acculturation construct. We also replicated the relationship between acculturation and smoking status reported in previous studies (Landrine & Klonoff, 1996; Klonoff & Landrine, 1999). Consistent with those studies, we found a negative association between acculturation and smoking, with less acculturated African American women more likely to be smokers. Findings across studies of African Americans are in contrast to

research with Latino and Asian American populations. Future research should investigate the mechanisms that underlie this difference. It may be a reflection of the fact that acculturation for Latinos and Asian Americans has been based on integration into North American culture following recent immigration. For African Americans, deeper integration into "mainstream" culture does not necessarily imply the loss of tightly anchored, historical cultural traditions.

Interestingly, the acculturation dimension that predicted smoking status in the present study, as well as those conducted by the scale developers, was Family Structure and Practices. This dimension reflects the extent to which one's immediate and extended family adheres to practices, customs, and values (e.g., informal adoption) specific to African American culture (Landrine & Klonoff, 1994). It is unclear why smoking was linked to family practices in this sample. The literature has found parental smoking behavior and other family environmental factors to be significantly associated with children's current and future smoking behavior (Jackson, Henriksen, Dickinson, Levine, 1997, Jackson, Henriksen, Dickinson, Messer, Robertson, 1998; Bailey, Ennett, Ringwalt, 1993). Yet, research shows that African American parents are more likely to employ proactive anti-smoking socialization with their children than European American parents (Clark, Scarisbrick-Hauser, Gautam, & Wirk, 1999; Gittelsohn, Roche, Alexander, & Tassler, 2001), and the literature shows that African American youth smoke less and start later than their European American peers (Bobo & Husten, 2000; Ellickson, McGuigan, & Klein, 2001; Harrell, Bangdiwala, Deng, Webb, & Bradley, 1998; Vega, Gil, & Zimmerman, 1993).

The final aim of this study was to explore the role of acculturation in BSE under-performance and over-performance. Performance of breast self-exam has been reported to be

related to earlier pathological stage of cancer diagnosis and symptom presentation, smaller tumor size, and less axillary lymph node involvement (Foster & Costanza, 1984; Hugley & Brown, 1981; Philip, Harris, Flaherty, & Josline, 1986). In addition, Porter et al. (1999) found that 66% of tumors detected between mammography screening intervals were discovered via breast self-examination. Tumors detected during screening intervals were larger in size, more severe in disease stage, and more prevalent in younger women. Thus, BSE may be particularly beneficial as a method of detection for younger women whose disease progression is faster and more aggressive (Porter et al., 1999). Given the available evidence, BSE continues to be recommended strongly as a good health behavior and important breast cancer screening modality by the American Cancer Society (ACS, 1999) and the American Society of Clinical Oncology (Smith et al., 1999), respectively. With regard to rates of BSE performance, fifty-one percent of the women in this study reported performing BSE at least once a month. This rate is consistent with the rate (49.7%) reported in a random sample of low income, African American women ages 40 and over living in a Florida city (Mickey, Durski, Worden, & Danigelis, 1995) and also fell into the range (41 % to 67%) reported by other populations of women 50 and older in the U.S. (NCI Breast Cancer Screening Consortium, 1990).

While under-performing BSE has obvious implications for the utility of this screening modality, less appreciated are the potential drawbacks to over-performing BSE. It has long been recognized that over-performing BSE may decrease a woman's ability to detect gradual changes in the breast as well as induce cancer anxiety (Haagensen, 1952). Excessive BSE performance may also increase the likelihood of false positive findings, which, in turn, may result in increased anxiety (Lennan, Kash, & Stefanek, 1994; Haefner, Becker, & Janz, 1989). Women may also use

their over-reliance on BSE as a screening modality as a reason for opting out of or not adhering to other screening modalities such as mammography (Epstein & Lerman, 1997). Both under- and over-performance of BSE may then lead to diminished utility of this screening modality.

Results of the present study revealed significant associations between acculturation and BSE frequency. BSE under-performers were more acculturated, and BSE over-performers were less acculturated. In addition to identifying a relationship between global acculturation and BSE frequency, we found that Preference for African American Things was also significantly correlated. This subscale reflects the extent to which an individual has a preference for African American newspapers, periodicals, music, activities, arts, and people (Landrine & Klonoff, 1994). Close inspection of this dimension with item analyses revealed that items related to Black print media were significantly associated with BSE under-performance, where under-performers were less likely to read these magazines.

BSE over-performance was significantly associated with one item: I) "I listen to Black radio stations", where over-performers were more likely to listen to these stations. Taken together, these findings highlight the importance of mass media in publicizing breast cancer as a major health concern. Turnbull (1978) found that a significant proportion of women increased their BSE performance from no performance/under performance to once a month or more as a result of the mass media surrounding Betty Ford's mastectomy. Additionally, women cited television/radio and periodicals/books as their number one and two sources of information, respectively (Turnbull, 1978). Among Latina women, Richardson et al. (1987) also found those reported reading or hearing about (via television) the importance of performing BSE were more likely to perform BSE more frequently. Based on these studies, it would appear that mass media

is influential in breast cancer screening among ethnic minority women and women in general. That an association was suggested between exposure to African American mass media and BSE frequency among African American women in the present study is consistent with past research.

We do not know whether women who did not read Black magazines simply read other periodicals, or whether they were not exposed to print media at all. This knowledge would be important in determining an appropriate means by which to effectively reach this population through the press. This issue is particularly important given that African American women have the highest rate of breast cancer mortality among women in the U.S (ACS, 1999). This differential impact may well be reflected and underscored in African American media sources as compared to the general mass media. Future research should compare breast cancer coverage between difference media sources examining both the frequency of breast cancer articles appearing in issues as well as accuracy and clarity of information presented in articles.

These findings suggest the importance of identifying specific acculturation mechanisms that may influence the behavior of interest. Different health behaviors are likely to be associated with different acculturation dimensions. For example, Tang et al., (1999) found that among Asian American women, modesty was related to BSE, but not other aspects of culture. And, the present study found the Family Structure and Practice dimension to be significantly associated with smoking status, as did Landrine and Klonoff, 1996, and Klonoff and Landrine, 1998. Increasing the specificity with regard to the role of acculturation in health behaviors may thus assist us in targeting specific barriers for intervention. Results from the present study thus have several clinical implications. Because the medical community has been focused predominantly

on promoting breast cancer screening behavior, the problem of over-utilization or over-performance of screening has perhaps received less attention.

Limitations to this study should be noted. Because the sample size was relatively small and women were recruited specifically from a low-income, inner city breast cancer-screening center, our results cannot be generalized to all African American women. It is likely that the prevalence of BSE under-performance and/or over-performance may be higher among women who do not receive BSE education and training as those in our sample did. In this initial study, we deliberately selected women who were instructed by African American health care providers in proper BSE technique in order to hold BSE training, knowledge of BSE guidelines, and ethnic background of health care providers constant.

The study of African American acculturation is an emerging area of research. Initial results on the relationship between acculturation and smoking status and BSE frequency suggest that this concept has some utility in understanding some of the variability among African-American women in health behaviors. Future studies should examine acculturation in relation to breast cancer screening modalities other than BSE. Given that African American women have the highest mortality rate for breast cancer and routine mammography has been shown in some studies to be effective in reducing breast cancer mortality by as much as 40% (Frisell, Lidbrink, Hellstrom, & Rutqvist, 1997), it would be important to investigate possible cultural variables as one of the factors that may be predictive of mammography utilization. In terms of assessment with the AAAS, Klonoff and Landrine (2000) recommend that researchers use the shortened revised version. Although our sample did not have negative feedback regarding the scale, a

shorter version at the very least reduces participant burden. It will be useful to examine whether the items remaining in the revised version continue to predict health variables such as BSE.

Future research should also explore the role of the mass media in publicizing breast cancer screening information among African American women as well as other ethnic groups. While breast cancer impacts differently women of various ethnic backgrounds, how this information is presented and explained in the media may well influence women's screening behaviors. As a construct, acculturation may provide useful information for enhancing our understanding of differences between and within groups that racial distinctions cannot, although other variables (e.g. socioeconomic status) must also be investigated. Clearly, the value of the concept of acculturation in clinical research depends on how it is operationalized and utilized in understanding and predicting other health behaviors. For African Americans, acculturation may perhaps be better defined as participation in and facility negotiating the dominant culture, rather than preferences for African American things. By identifying specific acculturation components that facilitate or deter health behaviors, we may be better able to implement interventions to improve health status among different ethnic and cultural communities.

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Table 1

AAAS scores for women with or without history of smoking

AAAS	Smokers (n=16)	Non Smokers (n=19)	F	p
Preferences	56.03	45.92	3.58	.067
Family Practices	61.02	51.56	5.14	.030
Health Beliefs	54.43	50.68	0.60	.445
Socialization	53.75	49.56	0.73	.397
Foods	44.95	37.34	2.90	.098
Religion	32.69	36.87	2.11	.155
Interracial Attitudes	34.33	26.54	4.71	.037
Superstitions	25.31	21.4	2.80	.104
Summary Score	366.71	315.62	5.79	.021

Table 2

Women who Under Perform BSE Scored Lower than Women who Over Perform BSE

AAAS Scale	Under Performance Assessment Past year				Over Performance Assessment Past 3 weeks			
	Under Performers (n=17)	Others (n=18)			Under Performers (n=17)	Others (n=18)		
	Mean (S.D.)	Mean (S.D.)	F	Sig.	Mean (S.D.)	Mean (S.D.)	F	Sig.
Preferences	**42.13 (16.11)**	**58.48 (12.32)**	**11.46**	**.001**	**59.88 (8.05)**	**44.31 (17.60)**	**9.55**	**.004**
Family Practices	54.55 (14.45)	57.05 (12.11)	0.31	.581	58.71(12.18)	53.92(13.72)	1.12	.298
Health Beliefs	49.66 (14.14)	54.97 (14.18)	1.23	.275	55.03(14.38)	50.63(14.17)	0.8	.376
Socialization	45.79 (15.27)	56.84 (11.35)	5.94	.020	58.54(9.12)	46.54(15.22)	7.36	.010
Foods	38.01(12.47)	43.47(14.28)	1.45	.237	45.28(13.66)	37.84(12.90)	2.66	.112
Religion	32.12 (10.41)	36.94(5.85)	2.88	.098	38.00(4.15)	32.34(10.07)	3.94	.055
Interracial Attitudes	28.53(10.25)	31.58(11.79)	0.65	.426	31.45(12.24)	29.20(10.54)	0.34	.566
Superstitions	21.56(7.58)	24.72(6.37)	1.78	.191	25.71(6.50)	21.50(7.06)	3.16	.084
Summary Score	312.39(70.38)	364.09(53.79)	6.00	.010	372.96(41.84)	316.32(71.45)	7.12	.011

*Bolded numbers indicate Bonferoni corrected significance was reached ($p < .05$ divided by 9 = .005).

Note: Re-analyses excluding women whose responses revealed long-term under performance and short-term over performance (n=4) yielded an identical pattern of results.

Institutional Review Board

TO: Dr. Kenneth Offit

FROM: Dr. Roger S. Wilson
Chairman, Institutional Review Board

DATE: August 26, 1998

RE: Protocol and Consent Form Amendments for Protocol # 95-011A(3)

Your protocol and consent form amendments for Protocol # 95-011A(3) "Impact of Genetic Counseling and Testing for Breast Cancer", as outlined in your attached memo, were reviewed at the August 25, 1998 Institutional Review Board meeting and were approved.

RSW:mi
Enclosure

Memorial Sloan-Kettering Cancer Center
1275 York Avenue. New York. New York 10021
Telephone 212.639.7592

NCI-designated Comprehensive Cancer Center

Read 8/14/98 RW

RECEIVED
AUG 14 1998
MSKCC
IRB

Date: August 21, 1998

To: Dr. Roger S. Wilson
Chairman, IRB
Box 56

From: Dr. Heiddis Valdimarsdottir HV
Clinical Assistant Attending

Re: IRB protocol #95-11A(2)

As I'll be leaving Memorial to take a faculty position at Mt. Sinai School of Medicine on August 21, 1998, I would like to modify this protocol.

1. As indicated on the MSKCC IRB title page, Dr. Kenneth Offit in the Department of Human Genetics will now be the principal investigator and Dr. Valdimarsdottir will serve as a consultant on the project. Two new research assistants, Daniella Scott and David Amarel, have been added as participating and consulting investigators. Dr. Jamie Ostroff in the Department of Psychiatry and Behavioral Sciences has been added as a participating investigator.

2. Dr Valdimarsdottir's name has been removed form the consent forms.

cc:

Dr. Jimmie Holland
Dr. jamie Ostroff

IMPACT OF GENETIC COUNSELING AND TESTING FOR BREAST CANCER

Principal Investigator:

Kenneth Offit, M.D., M.P.H.*	Department of Human Genetics, MSKCC

Responsible Investigators:

Chantal Duteau-Buck, M.S.*	Department of Human Genetics, MSKCC
Charlene Schulz, M.S.*	
Alice Schluger M.A.*	
Michael Kramer, M.A.*	
Daniella Scott, B.A.*	
David Amarell, B.A*	
Suresh Jhanwar Ph.D.	
Jimmie Holland, M.D. *	Department of Psychiatry and Behavioral Sciences, MSKCC
Mary Jane Massie, M.D.*	
Patrick Borgen, M.D.	Department of Surgery/Breast Service, MSKCC
Alexandra Heerdt, M.D.	
Kimberly Van Zee, M.D.	
Ann Zauber, Ph.D.	Department of Biostatistics/Epidemiology, MSKCC
Diana Godfrey, M.A.*	Breast Examination Center of Harlem, MSKCC
Harold Freeman, M.D.*	

Consultant:

Heiddis Valdimarsdottir, Ph.D.	Mount Sinai School of Medicine

*Consenting Researcher

Contents:

TITLE: **Impact of Genetic Counseling and Testing for Breast Cancer**

1. SPECIFIC AIMS:

The overall aim of this proposal is to demonstrate the psychological effects of genetic counseling for family history of breast cancer, and the additional psychological impact of genetic testing as it is introduced into clinical counseling approaches.

1. Objectives:

1.1 To identify women most likely to benefit from genetic testing for heritable breast cancer risk.

1.2 By means of a cross-sectional analysis, to identify cognitive, emotional, and other factors that influence interest in and readiness to donate a DNA sample for BRCA testing.

1.3 To examine the effectiveness of genetic counseling as a means of educating women who are considering having genetic testing.

1.4 To measure the impact of risk notification based on genetic testing and its effects on psychological functioning and preventive and early detection behaviors.

2. PLAN:

Three interrelated studies of genetic testing for BRCA are proposed. Study 1 will examine interest in and readiness to donate a DNA sample for BRCA testing among women of varying risk for breast cancer (Survey 1).

Study 2 will evaluate the impact of genetic counseling for women who are at high genetic risk for breast cancer (Study 2a) and low genetic risk for breast cancer (Study 2b). Women who have completed Study 1 and have also completed screening questionnaires used to determine genetic risk will be eligible to participate. For women at relative risk ≥ 2.0 (high genetic risk), counseling will consist of individual sessions with a genetic counselor. For women at relative risk < 2.0 (low genetic risk), counseling will consist of an educational slide show followed by a discussion led by a genetic counselor. The impact of these interventions on distress, knowledge, interest in, and readiness to undergo genetic testing will be evaluated using a quasi-experimental research design. Specifically, we will compare the responses of women who receive these interventions with those of women of comparable risk, who choose not to undergo genetic counseling, using data collected at Surveys 1 and 2. In addition, we will examine the relation of counseling to participants' decision to donate a DNA sample for genetic testing.

Study 3 will examine the psychological and behavioral impact of testing for BRCA mutations. Women who had participated in Studies 1 and 2 will be eligible to participate. Women who wish to receive the results of testing will be assessed before notification (Survey 2) and after notification (Surveys 3a, 3b, 3c). Women who do not undergo genetic testing will receive these surveys at comparable timepoints. The principal analyses will compare the impact of receiving positive vs. negative genetic test results on psychological functioning as well as prevention and early detection behaviors.

In order to explain the research design and methods, the three studies are described separately. For each study,

we present an overview and description of procedures, subjects, research design, and analytic strategy.

3. EXPERIMENTAL DESIGN AND METHODS:

3.1 Study 1

Overview. Study 1 is a cross-sectional study of women at varying risk for breast cancer. Four issues are addressed in Study 1. First, we will measure levels of interest in and readiness to undergo genetic testing for BRCA mutations among women at varying risks for breast cancer. As part of this analysis, we will also examine background variables (sociodemographic, medical, and family history) as they relate to interest in and readiness to undergo testing. Second, we will examine the utility of the Decisional Balance Model (Janis and Mann, 1977) for understanding women's readiness to be tested for BRCA. Third, we will examine how interest in and readiness to undergo testing is influenced by perceived risk of developing cancer and emotional distress (general and cancer-specific). Fourth, we will examine the relative importance of background factors, decisional balance, perceived risk, and emotional distress in understanding interest in and readiness to undergo genetic testing.

Procedures. Women seen at the SSBP and the BECH will be invited to join the study at the time of their appointment. Women seen by the Clinical Genetics Service will be recruited by telephone prior to their scheduled counseling visit. The women who agree to participate will be mailed (confidential labeling will be placed on the envelopes) a packet of materials prior to their genetic counseling appointment. Enclosed in the packet will be a formal invitation to participate in Study 1, an informed consent form, and a copy of Survey 1. On or about the date the packet arrives via mail, potential participants will also be contacted by telephone to verify that the study packet was received, to answer questions regarding study participation, and to secure informed consent. Individuals who consent will then be instructed to return the completed questionnaire in a postage paid pre-addressed envelope. Women will also have the option of filling out the questionnaires in the clinic where a research assistant will be available to assist them and answer any questions. The study coordinator will go over the questionnaires and ensure that the consent form has been signed and all questionnaires completed. At the time of their scheduled appointment subjects will be asked to read and sign a consent for follow-up assessments (Surveys 2 and 3) to be conducted over the following twelve months time. Although these surveys address research questions relating to Studies 2 and 3, obtaining consent at this time is necessary since many participants may have no further direct contact with study staff (see below).

Subjects. To be eligible participants must be: age 18 or older, able to read/write English, and be able to provide meaningful informed consent. Approximately 24 women are newly enrolled into the SSBP each month. About 64 are enrolled into the Clinical Genetics Service per month. Nearly all new enrollees (>98%) would meet eligibility criteria and, based on previous experience, we anticipate that 90% would provide informed consent. We anticipate the SSBP and the Clinical Genetic Service's populations to reflect Memorial Hospital's patient population which is over 92% Caucasian. To increase the number of minorities enrolled in the study, we will also recruit subjects from the Breast Examination Center of Harlem. Over 97% of its patient population is minority. Based on these projections, we anticipate that approximately 600 women would be accrued during the study.

Research Questions and Statistical Analysis

Question 1. What is the level of interest in and readiness to donate a DNA sample for BRCA testing among women at varying genetic risk for breast cancer.

Background. To date, interest in BRCA1 testing has been examined in first-degree relatives of women diagnosed

with ovarian cancer (Lerman et al, 1994) and in family members participating in genetic linkage studies (Lynch et al, 1993). Interest among women participating in special surveillance breast programs has yet to be determined even though these women may be among the first individuals to be offered testing for BRCA1 (King et al, 1993). In order to plan for future genetic testing, it is essential to accurately determine the level of interest and the readiness to undergo testing among women at varying genetic risk and to describe the sociodemographic and medical characteristics of women who are likely to seek and not seek testing.

Approach and Analysis. Participants will complete a self-report questionnaire prior to their genetic counseling visit. With regard to Question 1, participants will read a brief description of hereditary breast and ovarian cancer and the potential for identifying a gene associated with hereditary risk. Participants will then be asked about their interest in and readiness to donate a DNA sample for BRCA testing (see Measures).

Data will be analyzed for the sample as a whole and for subgroups that vary in terms of major sociodemographic, medical, and family background factors. Sociodemographic variables include: age, ethnic/minority group membership, education, marital status and income. Medical factors include: previous history of breast biopsy, presence of nonmalignant breast disease, and previous history of other cancers. Family background factors include: reported family history of breast or ovarian cancer (number of first-and second-degree relatives affected, age at diagnosis), degree of personal experience with friends/relatives affected by breast or ovarian cancer, and level of genetic breast cancer risk as determined by a review of the screening questionnaires (see Measures). These variables were selected for study based on reviews of research into genetic testing for Huntington's disease (e.g., Markel et al, 1987) and previous research on interest in genetic testing for breast/ovarian cancer (Lerman et al, 1994).

The major dependent variable in these analyses will be participants' self reported level of readiness to undergo gene testing which is measured as an ordered categorical variable. Since readiness is a newly created index, we must first assess its overall distribution. Readiness will be related to other variables to assess if the face validity of ordered categories is preserved. If so, the multiple regression analyses will be used to examine the relation of background factors to level of readiness.

The other major dependent variable is interest in genetic testing. Since three levels of interest are likely to be reported (interested, uninterested, undecided), polychotomous logistic regression analysis will be used to examine the relation of background factors to interest in genetic testing.

Question 2. Does the Decisional Balance Model explain women's interest in and readiness to donate a DNA sample for BRCA testing?

Background. As summarized recently by Prochaska and colleagues (1994), the Decisional Balance Model has been used successfully to predict readiness to engage in numerous health-related behaviors including stopping smoking and undergoing regular mammography. The key tenet of the model is that readiness is a function of the balance between the perceived "pros" and "cons" of engaging in the behavior. When cons outweigh pros, individuals are unlikely to adopt the target behavior within the next six months. When pros equal cons, individuals are likely to be contemplating adoption of the target behavior, and when pros outweigh cons individuals are likely to have adopted the target behavior (Prochaska et al, 1994). In this study, we hypothesize that, if perceived pros of undergoing genetic testing outweigh perceived cons, individuals are likely to be interested in and ready to undergo genetic testing; if cons outweigh pros, individuals are likely to be less interested and less ready to undergo testing.

Approach and Analysis. As part of Survey 1, perceived pros and cons of genetic testing for BRCA will be

assessed using the Modified Decisional Balance Scale and interest in and readiness to undergo testing will be assessed using face-valid self-report rating scales (see Measures). In order to test the hypothesis that the balance between pros and cons will be associated with readiness to undergo testing, we will use the same approach as Rakowski et al (1993) used to relate decisional balance to adoption of routine mammography. Specifically, scores on the final versions of the Pros and Cons Scales (to be determined via item analysis) will be converted to standardized T scores, from which we will derive a summary decisional balance measure by subtracting the Con T score from the Pro T score.

As stated above (see Question 1), the data analytic strategy to be used will depend on the observed distribution of readiness scores. If readiness is a continuum, then multiple regression analysis will be used to examine the relation of decisional balance to level of readiness. Alternatively if the distribution seems to be bimodal (low vs. high readiness), then logistic regression will be the major analytic strategy. Polychotomous logistic regression may also be used if 3 or more distinct levels of readiness emerge. Should background variables (sociodemographic, medical or family) be found to be significantly associated with readiness to undergo testing (see Question 1), these variables will be entered into the regression analyses before examining the relation between decisional balance and level of readiness.

The other major dependent variable is interest in genetic testing. Since three levels of interest are likely to be reported (interested, uninterested, undecided), polychotomous logistic regression analysis will be used to examine the relation of decisional balance to interest in genetic testing. Since interest and readiness are likely to be positively related (a point we will test empirically through classification analysis), similar relations with decisional balance are expected. That is, women who view the pros as outweighing the cons are likely to be interested in genetic testing whereas women who view the cons as outweighing the pros are likely to be uninterested. Women who view the pros and cons as balanced are likely to be undecided about testing.

In addition to conducting these statistical analyses, we will examine the decisional balance items most frequently endorsed by women at lower levels of readiness. These data will serve to identify the beliefs and concerns of women about the potential impact of receiving results of BRCA testing.

Question 3. Do perceived risk of breast cancer, psychological distress (general and cancer-specific) and cognitive representations explain women's interest in and readiness to donate a DNA sample for BRCA testing?

Background. According to the Health Belief Model (Becker, 1974), higher perceptions of personal risk increase the likelihood that individuals will engage in precautionary health behavior. Although genetic testing for BRCA is not itself a precautionary behavior, the results of testing are likely to affect the decision to undertake precautionary actions (e.g., prophylactic surgery). Along these lines, preliminary data indicate that interest in genetic testing for colon cancer is positively related to perceived risk of colon cancer (Croyle and Lerman, 1993). The decisions to undergo genetic testing and undertake precautionary behavior are also likely to be affected by psychological distress, as predicted by the Decisional Balance Model (Janis & Mann, 1977). According to this model, psychological distress influence the cognitive processes that are essential for arriving at stable decisions. We will also examine if cognitive processes are related to women's decisions to undergo genetic testing. According to the Dual Process Model, both cognitive and emotional processes play a key role in an individual's response to health threats (Leventhal et al., 1970;1983). The cognitive processes serve a function in this model similar to that found in the rational belief models (e.g., the Health Belief Model); that is these processes generate a cognitive representation of the health threat (breast cancer) and generate rational plans of action (e.g., increased participation in cancer screening).

Approach and Analysis. As part of Survey 1, we will assess perceived risk of developing breast cancer, cognitive representations, as well as general and cancer-specific emotional distress. A statistical approach similar to that described in Question 2 (multiple and logistic regression analyses) will be used to evaluate the relation of perceived vulnerability and psychological distress with interest in and readiness to undergo genetic testing as well as intention to adopt various precautionary behaviors. Should background variables be significantly associated with interest and readiness to undergo testing (see Question 1), these variables will be entered into the model first to determine if the relation of perceived vulnerability and psychological distress to readiness and interest is moderated by demographic, medical, or family history variables.

Question 4. What are the relative contributions of background factors, decisional balance, perceived vulnerability, cognitive representations and psychological distress to interest in and readiness to undergo testing for BRCA?

Background. Patient decision-making about medical treatments is likely to be influenced by both cognitive and emotional factors (e.g., Redeimeier et al, 1993). In the case of genetic testing for BRCA, it is quite possible that decisional balance (a cognitive perspective) will be influenced by both perceived vulnerability and psychological distress (an emotional perspective) and vice versa. Moreover, demographic factors (e.g., age), medical history (e.g., previous breast biopsies), and family history (e.g., personal experience with breast cancer) are likely to influence both cognitive and emotional perspectives on the issue of genetic testing for BRCA.

Approach and Analysis. Data collected in Study 1 will be used to conduct hierarchical regression analyses designed to examine the interrelations among the various sets of predictor variables (background factors, decisional balance, perceived vulnerability and psychological distress) and to examine the effects of each variable set on readiness or interest, adjusting for the effects of the other sets of predictor variables. Using hierarchical regression, we will test the hypothesis that the relation of background variables to interest and readiness is mediated by decisional balance, perceived vulnerability, and psychological distress. For example, we anticipate that the relation of family history to interest is mediated by levels of cancer-specific psychological distress. A second hypothesis to be tested is that decisional balance is influenced by perceived risk and vice versa. For example, women higher in perceived risk of breast cancer are expected to view the pros of being tested as outweighing the cons.

3.2 Study 2

Overview. Study 2 is a longitudinal evaluation of genetic counseling for women at high genetic risk and low genetic risk of breast cancer. For women who are at high genetic risk (relative risk ≥ 2.0) we will examine the effects of individual genetic counseling on psychological distress, knowledge, and interest in and readiness to donate a DNA sample for BRCA testing (Study 2a). For women who are at low familial risk (relative risk < 2.0), we will examine the effects of an educational slide show and counselor-led discussion of breast cancer, genetic testing and surveillance options on the same outcome measures (Study 2b).

The algorithm for genetic risk assessment that will be used was developed as a means of standardizing criteria for referral to the Clinical Genetics Service at MSKCC based on family history. An optical scannable form was developed and printed by National Computer Systems, Inc. (NCS). This form, called a Family History Questionnaire (FHQ), elicits family history information for first-, second-, and some third-degree relatives. The FHQ is completed by the patients and then scanned by an NCS (TM) OPSCAN @ 5 optical scanner and the data are transferred and then stored through the use of MSKCC's clinical research data base (CRDB). By exporting data to the Cyrillic pedigree-drawing software, a family tree is generated using the data gathered from the FHQ. Standardized algorithms were developed to identify family histories which are diagnostic of, or suggestive of,

the major cancer predisposition syndromes. In addition, published epidemiologic empiric risk estimates were used to identify individuals with a relative risk>2.0 (based on family history and/or age of onset) for developing breast, ovarian, colon, prostate, thyroid or melanoma cancers. To facilitate mass screening, these algorithms were converted into a computer program so that each FHQ could be quickly assessed for major cancer syndromes. The computer generates a report which accompanies the pedigree in the patient's medical record. It provides a risk assessment and recommends genetic counseling and/or individualized screening for the cancers for which the individual is (or other family members are) at risk.

Due to ethical considerations, it is not possible to randomly assign women to either intervention or control (i.e., no counseling) conditions. Instead, the services that women will receive as part of Study 2 will be determined by: 1) the participant's genetic risk for breast cancer (low vs. high) as determined by review of screening questionnaires; and 2) the participant's response to an invitation to receive genetic counseling. Women who receive genetic counseling will be compared to women of comparable risk who choose not to receive counseling but who are assessed on the same outcome measures at the same timepoints. These procedures were designed to build upon current clinical practice in the MSKCC Clinical Genetics Program and to serve as a foundation for future experimental research on psychosocial aspects of genetic counseling and testing.

Procedures. Once each participant has completed Study 1, she will become eligible for Study 2. A key distinction will be made on the basis of participants' relative risk of developing breast cancer.

Study 2a. Participants who complete Study 1 and are at high risk (relative risk ≥ 2) for cancer will be invited to receive genetic counseling at MSKCC or at the BECH. Counseling will be conducted by a genetic counselor and will consist of a single 90 minute session (described below). Prior to the counseling session, probands are asked to complete a detailed family history form, from which a pedigree is constructed utilizing the pedigree drawing program, Cyrillic.

The counselor will review the pedigree with the proband for accuracy and completeness, and this naturally leads to a discussion of general approaches to risk assessment. The possible reasons for familial clusterings of cancer are noted and the occurrence of cancer in the pedigree is categorized as most likely to be hereditary (i.e. conforming to the criteria for a hereditary cancer syndrome) or familial (i.e. not meeting those criteria). The limitations of pedigree analysis are pointed out, including the inability to distinguish between a sporadic and inherited cancer. The relative importance of various risk factors other than family history is explained. Probands also receive a grounding in basic principles of cancer biology and genetics, as appropriate.

Once the proband has been educated in the above-mentioned issues, risk data are presented. Whether familial or hereditary risk is involved, it is useful to compare the proband's risk to that of the general population. The concept of "using up" risk as one ages free of disease is also explained.

In families with a syndromic diagnosis such as hereditary breast or breast/ovarian cancer syndrome or Li-Fraumeni syndrome, Mendelian (dominant) risks are applied. Autosomal dominant inheritance is explained in detail. In addition, the counseling includes a description of the spectrum and natural history of the syndrome. Other family members at 50% risk of having inherited a major susceptibility gene are identified and assistance in notifying them is provided if requested (i.e., an informational letter is made available for the proband to mail to relatives).

General options for screening, risk-reducing surgery, and participation in Phase I and III clinical prevention trials at MSKCC are explained. Specific recommendations for frequency of screening are offered; the approach to surgical interventions and clinical trials, however, attempts to be nondirective. The current status of genetic

testing for the relevant disease is described. Referrals are provided as necessary.

Women who are recruited from the Clinical Genetics Service who express an interest in genetic testing will be offered commercial testing. For those women at high genetic risk recruited from the SSBP or BECH, costs of BRCA1 testing will be paid for by funded grants. Testing for mutations in BRCA2 will also be offered; however, these costs must be borne by the patient unless funding for BRCA2 testing becomes available. All testing will be completed according to procedures described in IRB-approved protocol, #96-51A(1), which is used for studying individuals with family histories of breast or ovarian cancer. The informed consent is reviewed and risks, benefits, and limitations are explained. In making the decision about whether to be tested, patients are urged to consider the impact of negative, positive, and ambiguous results. The protocol also provides participants with the option to give a sample and not learn the results. Individual questions and concerns will be addressed as they arise in the course of the counseling session.

Participants at high risk who decide not to receive genetic counseling will be mailed a copy of Survey 2 (to be returned in a pre-paid mailer) to complete at timepoints comparable to individuals at high risk who undergo genetic counseling.

Study 2b. Participants who complete Study 1 and are at low risk for cancer (relative risk < 2.0) will be invited to participate in a professionally-led group discussion of breast cancer, genetic testing, and surveillance options. Each group will be limited to 10 individuals. The material presented will be standardized; however, in keeping with a group format, participants will be encouraged to ask questions and share their concerns after the presentation is finished. Occasionally, owing to scheduling constraints, a low risk individual may receive individual counseling.

The group will begin with an introduction to the basics of genetics. Key words and principles such as chromosomes, genes, and autosomal dominant inheritance will be defined. Next, hereditary and familial cancer will be defined and several pedigrees of each type will be displayed. The possible reasons for familial clustering of cancer (other than heredity) as well as the limitations of pedigree analysis (i.e. the inability to distinguish between a sporadic and inherited cancer) will be explained. The presentation will emphasize how most cancers are not hereditary. It will further be explained that it is reasonable to expect from current studies that few individuals in this low risk group are likely to test positive for an inherited mutation.

Participants who nonetheless elect to have genetic testing will be offered commercial testing and will enroll in the IRB-approved protocol 96-51A(1) described above. As with the high risk probands, the informed consent is reviewed and risks, benefits, and limitations of the genetic testing are explained. In deciding whether to be tested, patients are encouraged to imagine the impact of negative, positive and ambiguous results. The protocols offer the option to give a sample and not learn the results. Questions and concerns will be addressed as they arise.

Participants at low genetic risk who decline the invitation to receive genetic counseling will be mailed a copy of Survey 2 (to be returned in a pre-paid mailer) to complete at timepoints comparable to individuals at low risk who undergo genetic counseling.

Subjects. To be eligible for Study 2, participants must have met eligibility criteria for and complete Study 1. It is estimated that, over the course of the study, 350 participants who complete Study 1 will be at high genetic risk and thus will be eligible for Study 2a. Based on current experience, we anticipate that 70% of high risk women will agree to undergo counseling (n =245). Assuming a 10% rate of failure to complete Survey 2, approximately 315 will provide data for analysis in Study 2a.

Similarly, we anticipate that, over the course of the study, 250 participants who complete Study 1 will be at low genetic risk and thus will be eligible for Study 2b. We anticipate that 40% of low risk women will agree to undergo counseling in a group format (n = 100). Assuming a 10% rate of failure to complete Survey 2, approximately 225 low risk women will provide data for analysis in Study 2b.

Research Questions and Statistical Analysis

Question 5. Does genetic counseling benefit women at high genetic risk for breast cancer (Study 2a).

Background. For women at high genetic risk for breast cancer, genetic testing has the potential to provide informative results. Positive test results would indicate a lifetime risk for developing breast cancer of up to 80-90% and a lifetime risk for developing ovarian cancer of up to 25-85% and is likely to aid decision-making about increased surveillance and/or preventive surgery. Through the process of genetic counseling, women at high genetic risk can be educated about the role that BRCA testing could play in subsequent medical treatment planning. Moreover, genetic counseling may be an effective means of bringing perceived risk estimates in line with empirically based estimates. Previous research (see Background) suggests that women at both high and low genetic risk attending the SSBP are likely to overestimate their risk and to be experiencing heightened emotional distress (general and cancer-specific).

Approach and Analysis. Participants who completed Study 1 and are at high genetic risk (relative risk ≥ 2.0) will be invited to receive individual genetic counseling. Approximately one week after the completion of counseling, participants will be mailed and asked to complete Survey 2 (to be returned in a prepaid mailer). High risk individuals who completed Study 1, but who choose not to receive genetic counseling, will be mailed Survey 2 at equivalent intervals since completion of Survey 1. Specifically, we will seek to match each woman completing counseling with one or more women who declined counseling and mail them all Survey 2 on the same date.

The psychosocial and medical characteristics of counseled and non-counseled women will be compared to determine if any characteristics discriminate between those selecting and rejecting counseling.

Repeated measures analysis of variance will be used to assess whether knowledge, distress, perceived risk and readiness have changed from pre-counseling (Survey 1) to post-counseling (Survey 2) for those having genetic counseling. We will also assess whether there was a change in these measures for those not electing counseling. We might anticipate that the counseled women would change in their attitudes but those with no counseling would not. However because the genetic counseling option was selected or rejected by the women rather than randomly assigned, the interpretation of an effect by genetic counseling must be balanced by an understanding of potential differences in patients selecting or refusing counseling. The data from this quasi-experimental design (Campbell and Stanley, 1963) will require additional analysis to assess potential factors associated with changes in counseled and non-counseled women other than that due to having had counseling.

The results of these analyses will indicate: 1) whether certain demographic, medical, genetic background, or psychosocial variables are associated with the decision of high risk women to participate in genetic counseling, 2) whether genetic counseling for high risk women has a beneficial impact, and 3) whether the beneficial impact is associated with or is independent of factors found to be related to the decision to participate in genetic counseling.

Question 6. Does genetic counseling benefit women at low genetic risk for breast cancer (Study 2b).

Background. It is unclear to what extent genetic testing for BRCA will be informative for women at low genetic

risk for breast cancer. Nevertheless, interest in genetic testing is likely to be high in this group due to heightened perceptions of breast cancer risk and/or limited understanding of the genetics of breast cancer. The goals of the professionally-led discussions to be conducted with low risk women will be to increase participants' level of knowledge about breast cancer genetics and to bring perceived risk estimates in line with empirically based estimates.

Approach and Analysis. Participants who complete Study 1 and are at low genetic risk (relative risk < 2.0) will be invited to attend a professional-led discussion of breast cancer risk, genetic testing, and surveillance behaviors. Approximately one week after the session, participants will be mailed Survey 2 and asked to complete and return it in a pre-paid mailer. Low risk individuals who complete Study 1 but who decline the invitation to receive genetic counseling will be surveyed at a similar timepoint. Data analyses similar to those described in Question 5 for high risk women will be conducted.

Question 7. What background and psychosocial factors influence the decision to donate a DNA sample for genetic testing?

Background. Whether the counseled women elect to give blood for genetic testing will be a major outcome in the present study. We hypothesize, as in Questions 2 and 3, that the decision to donate a blood sample for DNA testing will be influenced by both cognitive and emotional factors.

Approach and Analysis. The opportunity to give a blood sample for future genetic testing will occur only after participants complete genetic counseling (individual or group) and Survey 2. Background data, as well as psychosocial data from Surveys 1 and 2, will be examined for their relation to whether or not participants provide blood samples for banking. Logistic regression analysis will be used to identify predictors of blood banking (see Study 1). Interaction effects will be included in the model to determine whether there are differences in predictors based on whether women are from the low risk (group counseling) or high risk (individual counseling) subgroups.

3.3 Study 3

Overview. Study 3 is a longitudinal study of the psychosocial and behavioral impact of notification of genetic test results for BRCA mutations. As part of Study 3, the women will be assessed at multiple timepoints before and after notification. Women who receive negative results will be compared to women who receive positive results in terms of their psychological functioning as well as their subsequent patterns of prevention and early detection behaviors. We will also examine if women who elect not to go for testing differ form those who elected to be tested.

Procedures. Subjects who elect to receive their test results will be informed in accordance with IRB protocol #93-102 or #96-51 (i.e., appropriate post-test counseling will be provided). To assess acute distress and to monitor participants' well-being following notification, subjects will be administered brief psychological measures (see Measures) immediately after their notification session and again 10 days later. Follow up surveys (see Measures) will be mailed to all subjects approximately 1 (Survey 3a), 6 (Survey 3b) and 12 (Survey 3c) months after their notification session. Patients who desire their results but do not wish to continue their participation in the psychosocial aspect of the study will receive their results and genetic counseling in accordance with IRB protocol #93-102 or #96-51. Genetic counselors will remain available to study participants for continued consultation and support.

Dr. Mary Jane Massie, one of the co-investigators on the protocol, is a psychiatrist with extensive experience in

counseling women at increased risk for breast cancer as well as women considering preventive mastectomy. She will be available as needed to evaluate study participants identified by the genetic counselor as requiring psychiatric assessment. Dr. Massie will also provide psychotherapy or make a referral within the community for any woman requiring ongoing supportive counseling after notification of results.

Subjects. To be eligible for Study 3, women must have completed Study 1 and Study 2. As described above (see Study 2), we anticipate that approximately 345 women (245 high risk and 100 low risk) will accept genetic counseling as part of Study 2. We anticipate that 70% of high risk women (n=172) and 20% of low risk women (n=20) will eventually undergo genetic testing and thus will be eligible to participate in Study 3.

Research Questions and Statistical Analysis

Question 8. What is the psychological impact of notification of BRCA test results?

Background. Notification of BRCA test results has the potential to affect both general as well as cancer-specific psychological distress. Based on preliminary research on families involved in linkage studies (Lynch et al, 1993), it can be hypothesized that notification of negative results will be followed by reductions in psychological distress whereas notification of positive results will be followed by increases in psychological distress.

Approach and Analysis. In order to assess the psychological impact of notification, scores on general and cancer-specific distress measures will be entered into separate BRCA status (BRCA-, BRCA+) x Time repeated measures ANOVA designs. Since all participants will have also completed Studies 1 and 2, a wealth of pre-notification data will be available for inclusion in the analyses. A Group x Time interaction effect would demonstrate the expected differential effect of receiving negative vs. positive results on psychological functioning. Additional simple effects analyses will be conducted to identify whether increases in post-notification distress are short- or long-lived.

In addition, we will conduct multiple regression analyses to explore the possible impact of demographic, medical, family background, social support, cognitive and emotional variables on psychological reactions to BRCA notification. Results of these analyses will allow us to determine whether background variables (demographic, medical, or familial) and/or cognitive and emotional variables moderate and/or mediate the psychological impact of being informed of BRCA carrier status. For example, it is possible that women of younger age, who have had close family members die from breast cancer, and who rate the perceived threat of breast cancer as high may experience the greatest psychological distress upon being notified that they are BRCA carriers.

An important factor that may affect post-notification levels of distress is the process of notifying other relatives of their own potential cancer risks. As part of the genetic counseling, carriers of BRCA will be encouraged to share this information with appropriate relatives so these individuals may become aware of their own potential risk. As part of the surveys, we will monitor participants' intentions and actions about informing relatives and examine whether informing others has a positive or negative relation with levels of psychological distress.

Question 9. What is the impact of notification of BRCA results on subsequent prevention and early detection behaviors?

Background. Notification of BRCA carrier status has the potential to aid women in their decision-making about subsequent early detection and prevention activities. Preliminary research derived from linkage testing (Lynch et al, 1993) suggests that women may be more likely to elect preventive surgery if notified that they have tested positive for BRCA1 mutations. It is also possible that women notified of negative BRCA status may

subsequently underestimate their breast cancer risk and be nonadherent with early detection recommendations (Lerman et al, 1993). We will seek to address these issues by reviewing follow-up self-report data as well as data routinely recorded for all participants in the SSBP and BECH.

Approach and Analysis. Self-reports and medical records from follow-up visits to the SSBP and BECH will be used to monitor subsequent early detection and prevention behaviors among women who have been notified of their BRCA status. Of particular interest is the relation of BRCA notification to decision-making about preventive surgery. Logistic regression analysis will be used to determine whether there are differences in rates of preventive surgical procedures (mastectomy, oophorectomy) among women who test positive vs. negative for BRCA mutations. Among women who do not undergo preventive surgery, we will examine whether adherence to surveillance recommendations for early detection of breast and/or ovarian cancer differs based on notification of negative vs. positive BRCA carrier status.

4. PSYCHOBEHAVIORAL MEASURES FOR STUDIES 1, 2, and 3

Participants will complete three rounds of psychosocial measures: Survey 1 (e.g., at recruitment); Survey 2 (e.g., following their genetic counseling); Survey 3 (e.g., 1 month, 6 months, and 12 months after notification of results. In addition, subjects who receive genetic test results will be contacted by phone (or in person by the research assistant) on the day of notification (Phone Survey 1a) and 10 days after notification of results (Phone Survey 1b), patient availability permitting.

BACKGROUND MEASURES (Modifying variables)

The Sociodemographic/Medical Questionnaire is currently in use in the SSBP to record basic sociodemographic and medical data upon initial visit. As part of this questionnaire, respondents are asked for detailed information about their family history of cancer with special reference to breast and ovarian cancer. These data will be used to arrive at an initial estimate of participant's genetic risk for breast cancer (i.e., relative risk $< \text{or} \geq 2.0$). This questionnaire will be administered to each participant once during the study as these variables are not expected to change during the course of the study.

Perceived Risk of Cancer will be assessed using face-valid questions which measure subjective vulnerability to cancer. To assess if perceived vulnerability is specific for breast cancer, perceived vulnerability for other types of cancers as well as other life-threatening diseases will be assessed. Questions assessing participants' expectations about their BRCA1 status and who they would inform if they were found to be a carrier are also included. Perception of cancer risk has been found to be positively correlated with both interest in genetic testing (Croyle & Lerman, 1993) and cancer-specific distress (Valdimarsdottir et al, 1994) and negatively correlated with health behaviors (Kash et al, 1992). This scale will be included in Surveys 1, 2 and 3.

The Interpersonal Support Evaluation List (ISEL: Cohen et al., 1985) assesses three categories of support: "tangible support" (perceived availability of material resources); "appraisal support" (perceived availability of someone to talk with about problems); and "belonging support" (perceived availability of people to do things with) and has been found to be valid an reliable (alphas .77 to .87). This scale has been used extensively in studies of psychological factors that may "buffer" the effects of stress on psychological adjustment. The ISEL will be administered to each participant once, as participants' perceptions of social support networks are not expected to change over the course of the study.

The Social Constraint Scale (SCS) (Lepore et al., 1996) assesses the degree to which participants feel that they need to inhibit their thoughts and feelings about breast cancer to others. The scale has been found to be both

valid and reliable (alphas ranging form .77 to .81). The SCS has been found to be related to intrusive thoughts and depression in studies of bereaved mothers and cancer patients (Lepore et al., 1996). This scale will be included in Surveys 1, 2, and 3.

Illness Perception Questionnaire (IPQ). The IPQ (Weinman et al., 1996) examines the characteristics of patients' cognitive representation of an illness (e.g., breast cancer) and its treatment, which has been shown to affect levels of distress. The IPQ has demonstrated high internal consistency (coefficient=.88). This scale will be included in Surveys 1, 2 and 3(a and c).

Family Environment Scale (FES). The FES (Moos and Moos 1994) assesses the social environment of families. The FES, composed of 10 subscales that measures the actual, preferred and expected social environment of families, has been found to be valid and reliable (alphas ranging from .78 to .61). In order to reduce participant's burden, only 3 subscales (cohesion, expressiveness and conflict) of the FES will be used to examine how family relations may affect women's decisions to undergo genetic testing and the impact of risk notification on family relationships. The FES will be included in Surveys 1 and 3(c).

DISTRESS AND QUALITY OF LIFE MEASURES

The Brief Symptom Inventory (BSI) will be used to assess general psychological distress (Derogatis and Spencer, 1982). It assesses nine separate symptom dimensions (somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and provides three global indices of distress. Our previous work has shown that women with family histories of breast cancer report greater distress on the BSI than women without family histories of breast cancer. In order to reduce participants' burden, only the anxiety and depression subscales will be included in the present study. The BSI will be included in Surveys 1, 2, 3 to measure distress in the past 14 days.

The Profile of Mood States-Short Form (POMS-SF) (Shacham et al., 1983) will be used to assess current psychological distress. This short form will be included to measure acute distress which may not be captured by the 14-day time frame of the BSI. The POMS will be included in all Surveys as well as in the 2 Phone Surveys.

The Impact of Event Scale (IES) (Horowitz et al, 1979) will be used to assess cancer-specific psychological distress. The IES assesses intrusive and avoidance thoughts about a specific stressor. In the present study, items will be anchored to the threat of breast cancer. Our previous work has shown that women with family histories of breast cancer report significantly more intrusive and avoidant thoughts about breast cancer than women without family histories of breast cancer. The IES will be included in all Surveys 1, 2, 3 to measures cancer-specific distress in the past 14 days. In addition the IES will be included in Phone Survey 2 to assess cancer-specific distress in the past 7 days.

The Beck depression Inventory (BDI) (Beck et al., 1974) will be used to assess participants' general levels of depression. The BDI is a classic 21-item scale that measures severity of depression symptomatology, specifically the presence and intensity of emotional, cognitive, and somatic aspects of depression. Internal consistency and validity of the scale are well documented (Beck et al., 1974). The BDI will be included in Surveys 1, 2, and 3.

Medical Outcome Study 36-item short-Form Health Survey (MOS-36). The MOS (Stewart et al., 1988) is a brief quality of life questionnaire that assesses physical, social and role functioning, mental health, general health perceptions, bodily pain, and vitality. It has been extensively tested for reliability and validity and shown to have

adequate psychometric properties. This scale will be included in Surveys 1 and 3.

GENETIC TESTING MEASURES

Readiness to Donate a Blood Sample for Future BRCA Testing will be assessed using a face-valid forced-choice self-report format developed by the research team. Specifically, respondents will be asked to choice one of the following: 1) I have already donated a blood sample for genetic testing.; 2) I plan to take the test as soon as possible (within the next 30 days); 3) I plan to take the test sometime in the near future (within the next 6 months); 4) I do not plan to take the test in the near future (not within the next 6 months); 5) I do not plan to take the test at all. In addition, interest in BRCA testing will be assessed using the same forced-choice self-report format (yes, no, don't know) used by Croyle and Lerman (1993) to assess interest in genetic testing for colon cancer susceptibility. This measure will be included in Surveys 1, 2 and 3.

Perceived Pros and Cons of BRCA1 Testing will be assessed using a self-report measure developed by the research team (Modified Decisional Balance Scale). This questionnaire is modeled after a similar measure developed by Rakowski and colleagues (1993) to relate decisional balance to adoption of routine mammography. Items were derived based on a review of the literature on genetic testing for inherited diseases and on interviews conducted with women at increased genetic risk for breast cancer. Scores on the final versions of the Pros and Cons Scales (to be determined via item analysis) will be converted to standardized T scores, from which we will derive a summary decisional balance measure by subtracting the Con T score from the Pro T score. This measure will be included in Surveys 1, and 2. An identical questionnaire, with modified wording will be included in Surveys 3.

The Genetic Knowledge Questionnaire is a face-valid measure developed by the research team which assesses participants' understanding of key genetic terms and principles (e.g., chromosomes, genes, autosomal dominance) as well as the principles underlying genetic testing for inherited diseases. This questionnaire will be included in Surveys 1, 2 and 3.

Intentions to Inform Others About Genetic Testing will be assesses by a self-report measures developed by the research team.

GENETIC COUNSELING MEASURES

Readiness to Undergo Genetic Counseling will be assessed using a face-valid forced-choice self-report format developed by the research team. Specifically, respondents will be asked to choice one of the following: 1) I have made an appointment for genetic counseling.; 2) I plan to go for genetic counseling as soon as possible (within the next 30 days); 3) I plan to go for genetic counseling sometime in the near future (within the next 6 months); 4) I do not plan to go for genetic counseling (not within the next 6 months); 5) I do not plan to go for genetic counseling at all. This measure will be included in Surveys 1 and 2.

Perceived Pros and Cons of Genetic Counseling will be assessed using a self-report measure developed by the research team (Modified Decisional Balance Scale). This questionnaire is modeled after a similar measure developed by Rakowski and colleagues (1993) to relate decisional balance to adoption of routine mammography. Scores on the final versions of the Pros and Cons Scales (to be determined via item analysis) will be converted to standardized T scores, from which we will derive a summary decisional balance measure by subtracting the Con T score from the Pro T score. This measure will be included in Surveys 1. An identical questionnaire, with modified wording will be included in Survey 2.

MEASURES OF BREAST CANCER SCREENING AND PREVENTION BEHAVIORS

The Early Detection Behavior/Medical Decision Checklist has been developed by the research team to assess participants' adherence to early detection recommendations (e.g., breast self exam, clinical breast exam, routine mammography) and their medical decision following notification of test results (e.g., prophylactic mastectomy). The self-report information obtained will be verified against SSBP records whenever possible. The checklist will be included in Surveys 1, 2, and 3.

5. POWER ANALYSES FOR STUDIES 1, 2, and 3

Study 1: We anticipate 600 women to be enrolled into Study 1. With this large number of women, the study can detect a correlation of readiness with a factor such as SES or health belief models of 0.11 or greater with a power of 0.80 at the .05 (2-sided) level of significance. For univariate analyses, small effects can be detected as to the impact of the decisional balance model or health belief model on readiness. However, the main focus of Study 1 is on the relations among the independent variables and how these variables interwind to predict readiness for gene testing. We would anticipate that each of the 3 sets of variables discussed above would require at least 3 variables per set to summarize the components of that group. Consequently, we would anticipate at least 3*3 + 1(overall effect) = 10 or more independent variables or covariables in assessing readiness. We recognize that these power estimates are based on the dependent and independent variables are normally distributed when we are likely to have ordinal relationships both for the dependent and independent variables. However, the focus of this analysis is on the interrelationships among the predictors and their impact on readiness. These estimates of variation explained over and above the effect of other variables is consistent with that purpose.

Study 2: Separate analyses are performed within Study 2 for high risk and low risk women because of differences in the content and format of genetic counseling. We will consider a combined analysis if warranted but power is derived for separate analyses. Among high risk women, 245 are expected to undergo counseling and 105 are not; for the low risk women, 100 will be counseled and 150 will not. In the statistical design, pre- and post-counseling is a within group factor and counseled/noncounseled is a between group factor. Of interest is whether there is a different degree of change for the counseled than the non-counseled women (i.e., the size of the interaction effect of time and counseling status). For the high risk women, a time by counseling effect with a partial R^2=0.04 is detectable with a power of 0.80 at the 0.05 (2-sided) level of significance. For the low risk women, a time by counseling effect with a partial R^2=0.02 is detectable with a power of 0.80 at the 0.05 (2-sided) level of significance. Other factors (e.g. baseline sociodemographic and medical characteristics related to the decision to seek or not seek counseling) could be related to change over time. The detectable partial R^2 is not changed markedly even when we allow for estimation of the effect of 10 other variables.

Study 3: We estimate that 192 women (172 high risk and 20 low risk) will be notified of BRCA1 status. BRCA1 positive status could range from 20% to 50% of these women. Psychosocial measures of distress (i.e., BSI) are obtained at 3 points before notification and 2 points following notification. The major between group effect is positive or negative BRCA1 status and the within group effect is the multiple time points. For the purposes of a conservative estimate of effect size, we will consider just two points in time (average pre-notification distress and average post-notification distress). The actual analysis will incorporate all time points. For two periods, the study can detect a time by gene status effect accounting for a partial R^2=0.08 with a power of 0.80 at the.05 (2-sided) level of significance. We recognize that only moderate size differences are detectable by Study 3. However, moderately large differences in reactions would be anticipated for notification of positive gene carrier status.

6. HUMAN SUBJECTS:

6.1 Subjects: Potential subjects in this study will be drawn from the patient population of the Special Surveillance Breast Program (SSBP) at Memorial Sloan-Kettering Cancer Center (MSKCC), patients referred to the Clinical Genetics Service at MSKCC and their family members, and the patient population of the Breast Examination Center of Harlem. The SSBP was established in 1982 to provide comprehensive breast services, such as breast cancer screening, nutritional guidance, genetic counseling and psychological support, for women at increased risk of breast cancer due to a history of at least one first-degree relative treated for breast cancer or a history of a breast biopsy found to contain atypical or hyperplastic cells. Relatives of MSKCC breast cancer patients who express concern about their own increased risk of disease are referred to the SSBP. In addition, women with surgically treated atypical or hyperplastic benign conditions are encouraged to receive the enhanced surveillance available through the SSBP. The MSKCC Clinical Genetics Service offers genetic counseling and education regarding cancer risk to individuals and their family members. Overall, this service enables individuals to take advantage of the latest advances in the understanding of the genetic aspects of cancer and their relationship to environmental factors.

Established in 1979, the MSKCC Breast Examination Center of Harlem provides to the Harlem community with the most advanced, comprehensive diagnostic screening services for patients with breast and/or cervical cancer or those at high risk for the disease(s). Ninety-seven percent of the BECH's population are minority women.

To be eligible participants will be: age 18 or older, able to read/write English, and able to provide meaningful informed consent. Approximately 24 women are newly enrolled into the SSBP each month. About 64 women are newly enrolled into the Clinical Genetics Service each month. Nearly all new enrollees (>98%) would meet eligibility criteria and, based on previous experience, we anticipate that 90% would provide informed consent. Minority subjects from the SSBP and Clinical Genetics Service will be included as represented in the population of Memorial Hospital, which is 92% Caucasian, 5% African American, 2% Hispanic and 1% other ethnic/racial groups. To increase the number of women of color enrolled in the study, additional minority women will be recruited from the BECH.

Based on these projections, we anticipate that approximately 600 women would be accrued during the study.

6.2 Potential Risk: Psychological risks include increased stress related to risk notification of carrier status. Other psychological risks include anger, depression, "survivor guilt" and altered family relations. There is the risk that those who test negative but are carriers of other predisposition genes will not comply with appropriate screening guidelines. There is also a potential risk due to "genetic discrimination" by insurance carriers, which is addressed in the informed consent.

6.3 Risk Minimization: A psychiatrist with extensive experience in counseling women at increased risk for breast cancer will be available as needed to evaluate study participants identified by the genetic counselor as requiring psychiatric assessment. The genetic counselors will be available to subjects throughout the study for questions and support. Referrals to specialists in detection of breast and ovarian cancer will also be provided. Extensive efforts will be made to coordinate and integrate aspects of the medical care of individuals participating in the study. Post-notification follow-ups will be conducted to monitor participants' well-being approximately 0 and 10 days after risk notification.

6.4 Benefits of the Study: Benefits of the study include a potential reduction of uncertainty about hereditary risk and the potential benefit of early detection of malignancy in those who increase surveillance on the basis of risk notification. For those found not to be carriers, a potential exists for avoidance of prophylactic surgical procedures which might otherwise be contemplated. For all participants, there will be the benefit of

genetic counseling as well as referral and information on cancer prevention and early detection options.

6.5 Confidentiality: Basic rules of confidentiality of research and medical ethics will be closely adhered to in the study. Data will be kept in a confidential research file, with identification numbers used instead of names wherever possible. Access to the research data bases will be limited, and all mechanical data (files, records) will be kept in a secured location. No information from this study will be entered into the patients' medical record.

6.6 Procedure for obtaining informed consent: Informed consent will be obtained in two stages. For Study 1 consent will be obtained prior to subjects' genetic counseling appointment. Consent for Studies 2 and 3 is obtained at the time of subjects' counseling session. (See section 3.1 above.) The key elements of the informed consent which will be explained to subjects are: 1) the research status of the study; 2) the prospect of physical and psychological risk and the provisions for it; 3) the lack of guarantee of benefit from participation; 4) the confidentiality of the subjects' responses to all study measures; 5) the voluntary nature of the study; 6) the lack of consequence to care associated with consent or refusal to participate; 7) the freedom to withdraw from the study or to refuse to answer specific questions at any time; and 8) the willingness and availability of the investigators to provide help with any problems that may arise as a result of the study questionnaire.

Subject who decide to undergo genetic testing will enroll in IRB protocol #93-102 or #96-51.

7. BACKGROUND:

7.1 Breast cancer genetic counseling based on population-derived data: Counseling of individuals based on epidemiologic data has been performed and reported from a freestanding referral center (Kelly, 1991) and from the Royal Free Hospital in London, England (Houlston et al 1992). While a high level of compliance with mammography screening was demonstrated (Houlston et al 1992), issues of psychological counseling for women considering prophylactic surgery and the impact of counseling on other emotional and cognitive functions were not addressed in this study.

An extensive epidemiologic literature has documented family history of breast cancer as a significant risk factor for this disease (summarized in Offit and Brown, 1994). These data provide relative risk estimates for individuals with first-, second-, or third-degree relatives affected, and further characterize risk based on age of onset and whether disease was bilateral (Macklin, 1959; Anderson, 1971; 1974; 1976; Brinton et al, 1979; 1982; Sattin et al, 1985; Ottman et al, 1986; Tulinius et al, 1992; Houlston et al, 1992; Slattery et al, 1993; Carter et al, 1989; Colditz et al, 1993). While population-derived data are fully appropriate for risk counseling for polygenic disorders, it has been recognized that such counseling will underestimate the risk in hereditary syndromes, and overestimate the risk in "sporadic" cases (Knell, 1993). This has led to the development of multidisciplinary genetic counseling approaches for common adult malignancies which integrate empiric, Mendelian, and Bayesian methods of risk estimation (Offit and Brown, 1994).

In order to facilitate clinical counseling, population-derived data have been reanalyzed to provide actuarial age-specific risks. Anderson and colleagues analyzed 556 carefully verified pedigrees with unilateral or bilateral breast cancer in the probands and derived tabular absolute risk data readily applicable to counseling of women with at least one sister affected by breast cancer (Anderson et al, 1985). Analysis of 2,852 cases and 3,146 matched controls in the Breast Cancer Detection and Demonstration Project (BCDDP) (Gail et al, 1989; 1992) provided the basis for the model of Gail and colleagues. In this proportional hazards model, five variables were utilized to derive risk ratios (Gail et al, 1989; 1992). The five variables utilized in the model are: current age, age at first live birth, age at menarche, number of first-degree relatives with breast cancer, and number of prior biopsies. The third large data set available for counseling is that derived from 4,730 breast cancer cases ages 20

through 54 and 4,688 controls in the Cancer and Steroid Hormone study (Wingo et al, 1988; Claus et al, 1990;1994). These tabular risk data can be readily applied to most commonly encountered counseling scenarios. Another data set reporting risk to women with a family history of breast cancer was derived from a prospective study of 117,998 registered nurses followed since 1976 (Claus et al, 1994). Baseline history of breast cancer was assessed for mothers and sisters, with development of breast cancer updated for mothers, but not for sisters, in 1982. *In situ* lesions, noted to be more common in the cohort with a family history of breast cancer, were excluded from the analysis. Despite these methodological limitations, the absence of a potential for recall bias in this study establishes it as a valuable source of cumulative risk data for use in clinical counseling.

7.2 Breast cancer genetic counseling based on BRCA1 carrier status: The cloning of the BRCA1 gene has the potential to provide refined assessments of hereditary breast cancer risk for individuals demonstrated to carry mutations of this gene. It has been estimated that up to 40% of breast cancers presenting before the age of 30 and most instances of breast/ovarian cancer syndrome, are associated with abnormalities of the *BRCA1* gene (Hall et al, 1990; Biesecker et al, 1993; Easton et al, 1993; King et al, 1993; Ford et al, 1994; Claus et al, 1991). The lifetime risk for developing breast cancer for gene carriers was 86% with a 59% risk by age 50 (King et al, 1993). The lifetime risk for developing ovarian cancer for gene carriers was estimated at 25 to 85% (King et al, 1993). In a study of 33 families with evidence of linkage to BRCA1, the risk for ovarian cancer in *BRCA1* carriers already affected by breast cancer was estimated to be 29% by age 50 and 44% by age 70 (Ford et al, 1994). There was also a fourfold increased risk of colon cancer for both men and women and a threefold increase in prostate cancer in male *BRCA1* carriers (Ford et al, 1994). Genetic counseling, based on this information (with the exception of the risks for colon and prostate cancer), has been performed for individuals of large families utilizing linkage studies (Biesecker et al, 1993; Breo, 1993; Lynch et al, 1993).

Because of its large size (>100 kb, 21 coding exons), and because of the heterogeneity of mutations detected (including regulatory mutations) (Miki et al, 1994), it is unlikely that rapid screening tests for BRCA1 mutations will be made available until the later period of this proposal. During this period, sequence analysis will be required for affected individuals within families in order to understand the spectrum of mutations and their penetrance characteristics. The translation of BRCA1 mutation testing to population-based screening, suggested by some (Biesecker et al, 1993), will be significantly affected by the sensitivity and specificity of screening methodologies employed. For example, given an 85% detection rate for tests for the cystic fibrosis carrier state, most physicians were opposed to widespread testing for this common recessive disease, although this attitude changed dramatically as the rate approached 100% (Faden et al, 1994). Guidelines developed to guide the clinical implementation of p53 carrier testing for a dominant cancer predisposition syndrome (Li et al, 1992), recommended that risk notification in these settings be restricted to individuals carrying mutations confirmed to be present in at least one affected family member. To be most effective, BRCA1 testing in its initial implementation should be directed to populations most likely to derive meaningful results (King et al, 1993).

While genetic counseling in the setting of linkage studies has been highly individualized, and aided by the requirement for family participation, the availability of mutation tests will require broadly based counseling techniques. Such techniques have been demonstrated for common genetic diseases; for example, videotapes have been integrated into group counseling for hemoglobinopathies (Loder et al, 1991) but have not been evaluated for cancer genetic counseling.

7.3 Psychological effects of genetic counseling: Genetic counseling for breast cancer has largely been directed at subsets of strictly hereditary cases participating in linkage studies for BRCA1 (Biesecker et al, 1993; Lynch et al, 1993). Psychometric studies in this setting have been preliminary. There was no serious adverse psychologic impact of risk notification to 32 individuals based on linkage studies of one large Utah family, however, there were no formal psychological tests or psychiatric interviews as part of this study (Lynch et al,

1993). Possible effects of risk notification based on DNA testing include psychological distress, stigmatization, and genetic discrimination (Bankowski et al, 1991; Beckwith, 1991; Holtzman, 1989). These effects are of critical significance in cancer risk notification for breast cancer, because increased anxiety has been correlated with a reduced likelihood of adherence to such measures as mammography, breast self-examination, and clinical breast exam (Lerman et al, 1994; Kash et al, 1992; Alagna et al, 1987). Studies of cancer screening by mammography have documented impairments in mood and function in the setting of abnormal results (Lerman et al, 1991). Studies examining levels of distress in the setting of DNA-based risk notification for life-threatening, adult onset genetic diseases have largely been restricted to Huntington disease (Wiggins et al, 1992). Interestingly, differences in distress in carriers and non-carriers were negligible by 12 months post test notification, although levels remained high in those who opted not to have testing, and in those for whom the test was not informative (Wiggins et al, 1992). This latter finding is relevant to BRCA1 testing; population- based implementation of BRCA1 linkage testing for families of average size is likely to result in a high proportion of individuals with noninformative linkage results (Offit and Brown, 1994, National Advisory Council, 1994, Lerman, 1994). Because of the important differences between the clinical features, diagnosis, and prognosis of breast cancer and Huntington disease, the psychological factors associated with readiness for and response to DNA testing can be expected to differ significantly.

Psychological models which integrate risk perception and precautionary health behavior have been developed and applied to other adult onset chronic diseases for which preventive options exist. According to the Health Belief Model (Becker, 1974), higher perceptions of personal risk increase the likelihood that individuals will engage in precautionary health behavior. This model has not been applied to genetic testing for hereditary breast cancer, although interest in and readiness to undergo genetic testing for BRCA1 is likely to be greater in women who report higher perceived risk of developing breast cancer and greater anxiety about developing cancer (Lerman et al, 1994). Preliminary data indicate that interest in genetic testing for colon cancer is positively related to perceived risk of colon cancer (Croyle and Lerman, 1993). Although psychological models (e.g., Decisional Balance Theory) have been developed to predict readiness to engage in preventive behaviors (Janis & Mann, 1977; Prochaska et al, 1994), these models have not been formally tested in the setting of genetic testing for cancer predisposition.

8. SIGNIFICANCE:

To date, the psychological impact of genetic counseling and DNA testing has not been demonstrated for cohorts of women at increased risk for breast cancer. By utilizing a "high risk" setting (a special surveillance program) this study will directly test the clinical efficacy and applicability of genetic counseling and testing for a population of women most likely to desire this information and most likely to benefit. Specifically, this study will seek to address the following: namely, to identify individuals who are most likely to benefit from genetic testing for heritable breast cancer, to develop educational strategies for individuals considering genetic testing, to assess individual readiness for genetic testing, to determine factors that influence the decision to be tested, and to examine the psychosocial impact of learning test results.

As described above, this study will test, in a prospective study design, the impact of multidisciplinary genetic counseling for breast cancer utilizing empiric, Mendelian, Bayesian, and other statistical methods to estimate cancer risk based on family history and compare this to the additive impact of DNA testing as it is introduced. The study will develop a strategy for educating "high-risk" individuals, in which there is a higher likelihood of clinically meaningful results, as well as "lower-risk" cohorts, for whom a positive test is less likely, about the potential usefulness of genetic testing for breast cancer. If successful, this strategy may provide a model for the integration of the direct BRCA1 test on a wider level. In addressing counseling of the low risk cohort (i.e. relative risk of the proband < 1.5), this study will pilot novel strategies, including group educational sessions employing

audiovisual teaching aids.

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MEMORIAL SLOAN-KETTERING CANCER CENTER
1275 YORK AVENUE
NEW YORK, NY 10021

INFORMED CONSENT FOR CLINICAL RESEARCH

You are being asked to participate in a clinical research study. The doctors at Memorial Hospital study the nature of disease and attempt to develop improved methods of diagnosis and treatment. This is called clinical research. In order to decide whether or not you should agree to be part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent.

This consent form gives detailed information about the research study which the interviewer will discuss with you. Once you understand the study, you will be asked to sign this form if you wish to participate. You will have a copy to keep as a record.

The research study being proposed to you is: "IMPACT OF GENETIC COUNSELING AND TESTING FOR BREAST CANCER - STUDY 1."

PURPOSE OF THE RESEARCH

The purpose of this research is to learn more about women's attitudes about genetic counseling and testing for breast cancer susceptibility as well as their interest in providing blood samples for genetic testing.

DESCRIPTION OF THE RESEARCH PROCEDURES

Should you decide to participate in this study, you will be asked to complete a questionnaire at home or at your convenience. This questionnaire asks about your attitudes toward and interest in genetic testing for cancer susceptibility as well as your concerns about cancer. This questionnaire should require no more than 60minutes to complete.

SIDE EFFECTS

There are no physical risks associated with study participation. It is possible that you may become upset in the process of completing questionnaires that request information about your mood and emotions, your concerns about breast cancer and genetic testing, and your family relations.

If you are injured as a result of your participation in this research study, emergency care, hospitalization and outpatient care will be made available by the hospital and billed to you as part of your medical expenses. No money will be provided by the hospital as compensation for a research-related injury.

You will be informed of the progress of the research study. During the time you are part of it, you will be informed of any new findings which might affect your willingness to continue.

BENEFITS

There is no direct benefit to you from participation in this study. However, your participation may help other patients because physicians will have an opportunity to learn more about women's attitudes toward genetic testing for breast cancer.

FINANCIAL COST

Participation in this study will not involve any additional financial cost to you.

PRIVACY

Your research and hospital records are confidential. Your name or any other personally identifying information will not be used in reports or publications resulting from the study. The Food and Drug Administration or other authorized agencies may inspect your records.

RIGHT TO REFUSE OR WITHDRAW

The choice to enter, or not to enter, this study is yours. You are in a position to make a decision if you understand what the doctor has explained and what you have read about the research study and other possible forms of care. If you decide not to participate, the other choices are available to you without prejudice. If you begin the study, you still have the right to withdraw at any time. If you should withdraw, there will be no penalty or loss of benefits to which you are entitled.

Memorial Sloan-Kettering Cancer Center's Institutional Review Board is legally responsible for making sure that research with patients is appropriate and that the patient's rights and welfare are protected. It has reviewed this research study.

The investigator in charge of this research study is Dr. Kenneth Offit (212-639-6760). If you need more information about this study before you decide to join, or at any other time, you may wish to contact him. In the event that you do decide to participate, they should also be called if there are side effects from the research study. A non-physician whom you may call for information about the consent process, research patient's rights or research-related injury is Ms. Janice Levy (212-639-5804).

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

Title: IMPACT OF GENETIC COUNSELING AND TESTING FOR BREAST CANCER - STUDY 1

Purpose: 1) To learn more about women's attitudes about genetic testing for breast cancer susceptibility;

2) To assess women's interest in providing blood samples for genetic testing.

STATEMENT OF INVESTIGATOR OBTAINING INFORMED CONSENT

I have fully explained this research study to the patient or guardian _____. In my judgment, and the patient's, there was sufficient access to information, including risks and benefits, to make an informed decision.

Date:_____ Investigator's Signature _____

Investigator's Name (print) _____

PATIENT'S (OR GUARDIAN'S) STATEMENT

I have read the description of the clinical research study or have had it translated into a language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my/the patient's participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want (the patient) to take part in it.

Date:_____ Patient's Signature _____

Patient's Name (print) _____

MEMORIAL SLOAN-KETTERING CANCER CENTER
1275 YORK AVENUE
NEW YORK, NY 10021

INFORMED CONSENT FOR CLINICAL RESEARCH

You are being asked to participate in a clinical research study. The doctors at Memorial Hospital study the nature of disease and attempt to develop improved methods of diagnosis and treatment. This is called clinical research. In order to decide whether or not you should agree to be part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent.

This consent form gives detailed information about the research study which the interviewer will discuss with you. Once you understand the study, you will be asked to sign this form if you wish to participate. You will have a copy to keep as a record.

The research study being proposed to you is: "IMPACT OF GENETIC COUNSELING AND TESTING FOR BREAST CANCER - STUDY 2 and STUDY 3."

PURPOSE OF THE RESEARCH

The purpose of this research is to learn more about women's attitudes about genetic counseling and testing for breast cancer susceptibility as well as their interest in providing blood samples for genetic testing. We are also interested in learning more about the psychological and behavioral impact of genetic counseling and notification of gene test results.

DESCRIPTION OF THE RESEARCH PROCEDURES

You will be offered an appointment for genetic counseling, which will include a discussion of breast cancer, your family history of cancer as well as the potential risks, benefits, and limitations of genetic testing for breast cancer. *If,* after the counseling, you decide that want to donate a blood sample for genetic testing you will be invited to participate in a separate ongoing research study, which looks at genetic causes of cancer. If you decide to participate in that study, you will be asked to donate a blood sample for genetic testing, and you will have the opportunity to learn or not to learn your test results once they are available. If you choose to obtain your test results, you will receive post-test counseling during which your test results and their meaning will be explained.

Independent of your decision to undergo genetic counseling and/or gene testing, you will be asked to complete questionnaires at home or at your convenience at three different points in time. The questionnaires ask about your attitudes toward and interest in genetic counseling and testing for cancer susceptibility, your mood and emotions, and your concerns about cancer. The questionnaires will be mailed to you in approximately 3 months, 6 months, and 12 months. Each questionnaire should require no more than 60 minutes to complete.

Should you decide to receive your test results, you will also be contacted approximately 1 day and 1 week after receiving your test results and asked to complete a phone interview about your mood and emotions. The phone interview should require no more than 10 minutes of your time. If you choose so, you can receive your test results without completing the questionnaires.

SIDE EFFECTS

There are no physical risks associated with study participation. It is possible that you will experience emotional distress if you choose to undergo genetic counseling and/or be informed about the results of your gene testing. It is also possible that you may become upset in the process of completing questionnaires that request information about your emotions and mood as well as your concerns about breast cancer. For this and other reasons, access to genetic and psychological counseling will be made available to you.

If you are injured as a result of your participation in this research study, emergency care, hospitalization and outpatient care will be made available by the hospital and billed to you as part of your medical expenses. No money will be provided by the hospital as compensation for a research-related injury.

You will be informed of the progress of the research study. During the time you are part of it, you will be informed of any new findings which might affect your willingness to continue.

BENEFITS

There is no direct benefit to you from participation in this study. However, your participation may help other patients because physicians will have an opportunity to learn more about the psychological and behavioral impact of genetic counseling and testing for breast cancer.

FINANCIAL COST

If you decide that you want to undergo commercial genetic testing for breast cancer susceptibility, you will be responsible for these costs.

PRIVACY

Your research and hospital records are confidential. Your name or any other personally identifying information will not be used in reports or publications resulting from the study. The Food and Drug Administration or other authorized agencies may inspect your records.

RIGHT TO REFUSE OR WITHDRAW

The choice to enter, or not to enter, this study is yours. You are in a position to make a decision if you understand what the doctor has explained and what you have read about the research study and other possible forms of care. If you decide not to participate, the other choices are available to you without prejudice. If you begin the study, you still have the right to withdraw at any time. If you should withdraw, there will be no penalty or loss of benefits to which you are entitled.

Memorial Sloan-Kettering Cancer Center's Institutional Review Board is legally responsible for making sure that research with patients is appropriate and that the patient's rights and welfare are protected. It has reviewed this research study.

The investigator in charge of this research study is Dr. Kenneth Offit (212-639-6760). If you need more information about this study before you decide to join, or at any other time, you may wish to contact him. In the event that you do decide to participate, they should also be called if there are side effects from the research study. A non-physician whom you may call for information about the consent process, research patient's rights or research-related injury is Ms. Janice Levy (212-639-5804).

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

Title: IMPACT OF GENETIC COUNSELING AND TESTING FOR BREAST CANCER - STUDY 2 and STUDY 3

Purpose: 1) To learn more about women's attitudes about genetic testing for breast cancer susceptibility.

2) To assess women's interest in providing blood samples for genetic testing.

3) To learn about the impact of counseling for breast cancer susceptibility on women's perceived risk of developing cancer and their attitudes about genetic testing.

4) To learn about the psychological and behavioral impact of notifying women of their DNA tests results.

STATEMENT OF INVESTIGATOR OBTAINING INFORMED CONSENT

I have fully explained this research study to the patient or guardian _____. In my judgment, and the patient's, there was sufficient access to information, including risks and benefits, to make an informed decision.

Date:_____ Investigator's Signature _____

Investigator's Name (print) _____

PATIENT'S (OR GUARDIAN'S) STATEMENT

I have read the description of the clinical research study or have had it translated into a language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my/the patient's participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want (the patient) to take part in it.

Date:_____ Patient's Signature _____

Patient's Name (print) _____

VOLUNTEER ID NUMBER __ __ __ __ __ __

Date Completed: __ __/__ __/__ __
(month) (day) (year)

PERSONAL DATA

Background Measures

1. Today's date: ___ ___/ ___ ___/ ___ ___ (m/d/y)

2. Birth date: ___ ___/ ___ ___/ ___ ___ (m/d/y)

3. Height: _____ (ft) _____ (in)

4. Weight: _____ (pounds)

5. Ethnic group (circle one number):

   1 White (non-Hispanic) 2 Black (non-Hispanic)

   3 Hispanic 4 Asian/Pacific Islander

   5 American Indian or Alaskan Native 6 Asian/Indian

   7 Other (specify _____)

6. Marital status (circle one number):

   1 Never married 2 Currently married

   3 Separated 4 Divorced

   5 Widowed

7. Current living arrangement (circle one number):

   1 Live alone 2 Live with roommate who is not partner

   3 Live with spouse or partner 4 Live with parents

   5 Other (specify _____)

8. How long in current living arrangement (circle one number):

   1 Less than 1 month 2 One to 6 months

   3 Seven months to 2 years 4 Two to 5 years

   5 More than 5 years

9. Level of school completed (circle one number):

   1 Less than 7th grade 2 Junior High School (9th grade)

   3 Partial high school (10th or 11th grade) 4 High School graduate

   5 Partial college or specialized training 6 Standard college or university graduate

   7 Graduate professional training (graduate degree)

10. Current employment situation (circle one number):

A. WORKING

1 Full time at job
2 Part time at job

B. ON LEAVE

3 On leave with pay
4 On leave without pay

C. NOT EMPLOYED

5 Seeking work
6 Not seeking work
7 Receiving disability
8 Not self-supporting
9 Homemaker
0 Retired

D. STUDENT

1 Full time
2 Part time

11. Which category best describes your occupation? If you are not currently employed, which best describes your **LAST** job? If you are a homemaker, which best describes your spouse's usual occupation? (circle one number)

1. Professional, Technical, & Related Occupations (as teachers/professors, nurses, lawyers, physicians, & engineers)
2. Manager, Administrator, or Proprietor (as sales managers, real estate agents, or postmasters)
3. Clerical & Related Occupations (as secretaries, clerks or mail carriers)
4. Sales Occupations (as sales persons, demonstrators, agents & brokers)
5. Service Occupations (as police, cooks, or hairdressers)
6. Skilled Crafts, Repairer, & Related Occupations (as carpenters, repairers, or telephone line workers)
7. Equipment or Vehicle Operator & Related Occupations (as drivers, railroad brakemen or sewer workers)
8. Laborer (as helpers, longshoreman, or warehouse workers)
9. Farmer (owners, managers, operators or tenants)
10. Member of the military
11. Other (please describe) _____

12. Approximate annual gross income for your household: (circle one number)

1 Less than $ 10,000
2 $10,000 - $19,999
3 $20,000 - $ 39,999
4 $40,000 - $59,999
5 $60,000 - $100,000
6 Greater than $100,000

(Remember, all information will be used for statistical purposes only)

PERCEIVED VULNERABILITY

We would like to get your opinion on how likely you think it is that you will **develop** the cancers listed below. If you have had any of these cancers please indicate how likely you think it is that you will have a **recurrence.**

1. On a scale from 0% (not at all likely) to 100% (definitely), how likely do you think it is that you will develop (have a recurrence of) breast cancer in your lifetime? _____%

2. On a scale from 0% (not at all likely) to 100% (definitely), how likely do you think it is that you will develop (have a recurrence of) colon cancer in your lifetime? _____%

3. On a scale from 0% (not at all likely) to 100% (definitely), how likely do you think it is that you will develop (have a recurrence of) ovarian cancer in your lifetime? _____%

4. On a scale from 0% (not at all likely) to 100% (definitely), how likely do you think it is that you carry a gene for breast cancer? _____%

5. If you had to think of the possibility that you might someday get breast cancer (have a recurrence), how would you rate your chances compared to other individuals your age, with a similar family history of cancer: (Circle one)

A. Much higher B. A little higher C. About the same D. A little lower E. Much lower

During the past **two weeks...**

6. How often have you worried about the possibility of getting (having a recurrence of) breast cancer?

_____None of the time _____Occasionally _____Often _____All the time

7. How often has your mood been affected by your concern that you might get (have a recurrence of) breast cancer some day?

_____None of the time _____Occasionally _____Often _____All the time

8. How emotionally upset or distressed have you been about the possibility of getting (having a recurrence of) breast cancer?

_____None of the time _____Occasionally _____Often _____All the time

9. How often have thoughts about getting (having a recurrence of) breast cancer affected your abilitiy to perform your daily activities?

_____None of the time _____Occasionally _____Often _____All the time

10. How often have you worried about the possibility of getting (having a recurrence of) ovarian cancer?

_____None of the time _____Occasionally _____Often _____All the time

11. How often has your mood been affected by your concern that you might get (have a recurrence of) ovarian cancer some day?

_____None of the time _____Occasionally _____Often _____All the time

12. How emotionally upset or distressed have you been about the possibility of getting (having a recurrence of) ovarian cancer?

_____None of the time _____Occasionally _____Often _____All the time

13. How often have thoughts about getting (having a recurrence of) ovarian cancer affected your abilitiy to perform your daily activities?

_____None of the time _____Occasionally _____Often _____All the time

14. Has your doctor (nurse) spoken to you about your family history of cancer?

_____Not at All _____A little bit _____Quite a bit

15. Has your doctor (nurse) spoken to you about your risk of developing (having recurrence of) breast cancer?

_____Not at All _____A little bit _____Quite a bit

Family Environment Scale

The following questionnaire consists of statements about family relations. Please circle T or F for each statement as it applies to your family.

	True	False
1.	Family members really help and support one another.	T F
2.	Family members often keep their feelings to themselves.	T F
3.	We fight a lot in our family.	T F
4.	We often seem to be killing time at home.	T F
5.	We say anything we want to around our home.	T F
6.	Family members rarely become openly angry.	T F
7.	We put a lot of energy into what we do at home.	T F
8.	It's hard to "blow off steam" at home without upsetting somebody.	T F
9.	Family members sometimes get so angry they throw things.	T F
10.	There is a feeling of togetherness in our family.	T F
11.	We tell each other about our personal problems.	T F
12.	Family members hardly ever lose their tempers.	T F
13.	We rarely volunteer when something has to be done at home.	T F
14.	If we feel like doing something on the spur of the moment we often just pick up and go.	T F
15.	Family members often criticize each other.	T F
16.	Family members really back each other up.	T F
17.	Someone usually gets upset if you complain in our family.	T F
18.	Family members sometimes hit one another.	T F
19.	There is very little group spirit in our family.	T F
20.	Money and paying bills is openly talked about in our family.	T F
21.	If there's a disagreement in our family, we try hard to smooth things over and keep the peace.	T F
22.	We really get along well with each other.	T F
23.	We are usually careful about what we say to each other.	T F
24.	Family members often try to one-up or out-do each other.	T F
25.	There is plenty of time and attention for everyone in our family.	T F
26.	There are a lot of spontaneous discussions in our family.	T F
27.	In our family, we believe you don't ever get anywhere by raising your voice.	T F

Many people have different beliefs with regard to what can be done to prevent breast cancer from developing or recurring if they have had breast cancer. Please indicate how much you agree with the following statements.

I do the following to reduce my risk of developing (having a recurrence) breast cancer:

		Strongly Agree		NEITHER Agree nor Disagree		Strongly Disagree
1.	I avoid food with additives	1	2	3	4	5
2.	I eat bran or other high-fiber food	1	2	3	4	5
3.	I avoid harmful health habits like smoking and excess drinking	1	2	3	4	5
4.	I get enough sleep	1	2	3	4	5
5.	I avoid salt and heavily salted food	1	2	3	4	5
6.	I have regular medical check-ups	1	2	3	4	5
7.	I do regular aerobic or strenuous exercise	1	2	3	4	5
8.	I avoid too much physical exertion	1	2	3	4	5
9.	I try to breath clean air and drink pure water	1	2	3	4	5
10.	I take vitamins	1	2	3	4	5
11.	I try to find out what others do to prevent breast cancer	1	2	3	4	5
12.	I try to get medical information and understand the causes of breast cancer	1	2	3	4	5
13.	I use drug-store remedies	1	2	3	4	5
14.	I eat a balanced diet	1	2	3	4	5
15.	I go for regular mammograms	1	2	3	4	5
16	I perform breast self-exams	1	2	3	4	5
17.	I eat vegetables	1	2	3	4	5
18.	I eat fruits	1	2	3	4	5
19.	I avoid too much emotional distress	1	2	3	4	5
20.	I have friends and maintain a good family life	1	2	3	4	5
21.	I avoid feelings like anger, anxiety, and depression	1	2	3	4	5
22.	I think positively	1	2	3	4	5
23.	I take things as they come and don't struggle	1	2	3	4	5
24.	I stay mentally alert and active	1	2	3	4	5

SOCIAL CONSTRAINT

Sometimes, even when people have good intentions, they may say or do things that upset you. Think about the PAST TWO weeks and indicate how often your spouse/partner, friend or family member did the following things.

Thinking about your **SPOUSE/PARTNER** in the past TWO weeks ....
(if you don't have a partner go to question # 8)

	Never	Rarely	Some-Times	Always
1. How often did you feel as though you had to keep your feelings about breast cancer to your self because they made your partner uncomfortable?	1	2	3	4
2. How often did you feel that you could discuss your feelings about breast cancer with your partner when you wanted to?	1	2	3	4
3. When you talked about breast cancer, how often did your partner give you the idea that s/he did not want to hear about breast cancer?	1	2	3	4
4. How often did you feel that your partner let you down by not showing you as much love and concern as you would have liked?	1	2	3	4
5. How often has your partner really got on your nerves?	1	2	3	4
6. How often did your partner change the subject when you tried to talk about breast cancer?	1	2	3	4
7. How often did your partner tell you not to worry so much about your health?	1	2	3	4

Thinking about your **FRIEND/FAMILY MEMBER** in the past TWO WEEKS.....

	Never	Rarely	Some-Times	Always
8. How often did you feel as though you had to keep your feelings about breast cancer to your self because they made your friend/family member uncomfortable?	1	2	3	4
9. How often did you feel that you could discuss your feelings about breast cancer with your friend/family member when you wanted to?	1	2	3	4
10. When you talked about breast cancer, how often did your friend/family member give you the idea that s/he did not want to hear about breast cancer?	1	2	3	4
11. How often did you feel that your friend/family member let you down by not showing you as much love and concern as you would have liked?	1	2	3	4
12. How often has your friend/family member really got on your nerves?	1	2	3	4
13. How often did your friend/family member change the subject when you tried to talk about breast cancer?	1	2	3	4
14. How often did your friend/family member tell you not to worry so much about your health?	1	2	3	4

Please indicate whether you were rating your friend or family member: ____Friend ____Family member

<u>During the past two weeks how often did you talk:</u>	Not at All	Rarely	Some-Times	Quite-a bit	A great deal
to your spouse/partner about your breast cancer concerns?	1	2	3	4	5
to your friend about your breast cancer concerns?	1	2	3	4	5
to your family member about your breast cancer concerns?	1	2	3	4	5
<u>During the past two weeks how often did you want to talk more to:</u>					
your spouse/partner about your breast cancer concerns?	1	2	3	4	5
your friend about your breast cancer concerns?	1	2	3	4	5
your family member about your breast cancer concerns?	1	2	3	4	5

ISEL

This scale is made up of a list of statements each of which may or may not be true about you. **For each item statement we would like you to circle probably TRUE (T) if the statement is true about you or probably FALSE (F) if the statement is not true about you.**

You may find that many of the statements are neither clearly true nor clearly false. In these cases, try to decide quickly whether probably TRUE (T) or probably FALSE (F) is most descriptive of you. Although some questions will be difficult to answer, it is important that you pick one alternative for each statement.

Please read each item quickly but carefully before responding. Remember that this is not a test and there are no right or wrong answers.

1. There is at least one person I know whose advice I really trust . . . . . T F
2. If I decide on a Friday afternoon that I would like to go to a movie that evening, I would find someone to go with me. . . . . T F
3. If for some reason I were put in jail, there is someone I could call who would bail me out . . . . . T F
4. In general people don't have much confidence in me . . . . . T F
5. No one I know would throw a birthday party for me. . . . . T F
6. If I had to go out of town for a few weeks, someone I know would look after my home (plants, pets, yard, etc.) . . . . . T F
7. There is really no one I can trust to give me good financial advice . . . . . T F
8. I have someone who takes pride in my accomplishments . . . . . T F
9. Most of my friends are more successful at making changes in their lives than I am. . . . . T F
10. If I were sick and needed someone to drive me to the doctor, I would be in trouble finding someone . . . . . T F
11. There is really no one who can give me objective feedback about how I'm handling my problems. . . . . T F
12. There are several different people with whom I enjoy spending time . . . . . T F
13. I don't often get invited to do things with others. . . . . T F
14. There is no one I could call on if I needed to borrow a car for a few hours. . . . . T F
15. When I need suggestions for how to deal with a personal problem I know there is someone I can turn to. . . . . T F
16. Most people I know think highly of me. . . . . T F
17. If I needed a quick emergency loan of $100, there is someone I can get it from. . . . . T F

18. There is someone who I feel comfortable going to for advice about sexual problems. . . . . T F

19. If I wanted to have lunch with someone, I could easily find someone to join in with me. . . . . T F

20. Most of my friends are more interesting than I am. . . . . T F

21. There is someone I can turn to for advice about handling hassles over household responsibilities. . . . . T F

22. I am more satisfied with my life than most people are with theirs. . . . . T F

23. If I needed some help in moving to a new home, I would have a hard time finding someone to help me . . . . . T F

24. Most people I know don't enjoy the same things that I do. . . . . T F

25. I feel that there is no one with whom I can share my most private worries and fears. . . . . T F

26. When I feel lonely, there are several people I could call and talk to. . . . . T F

27. If I were sick, there would be almost no one I could find to help me with my daily chores. . . . . T F

28. I have a hard time keeping pace with my friends. . . . . T F

29. I think that my friends feel that I'm not very good at helping them solve problems . . . . . T F

30. If I got stranded 10 miles out of town, there is someone I could call to come get me . . . . . T F

31. I regularly meet or talk with members of my family or friends. . . . . T F

32. If a family crisis arose few of my friends would be able to give me good advice about handling it. . . . . T F

33. I am closer to my friends than most other people. . . . . T F

34. There are very few people I trust to help solve my problems. . . . . T F

35. I feel that I'm on the fringe in my circle of friends. . . . . T F

36. If I had to mail an important letter at the post office by 5:00 and couldn't make it, there is someone who could do it for me. . . . . T F

37. If I needed a ride to the airport very early in the morning, I would have a hard time finding anyone to take me. . . . . T F

38. There is someone I could turn to for advice about changing my job or finding a new one. . . . . T F

39. If I wanted to go out of town (e.g., to the coast) for the day I would have a hard time finding someone to go with me. . . . . T F

40. I am able to do things as well as most other people. . . . . T F

IPQ

Please read each statement carefully. For each statement, circle the responses that best represents your opinion, using the key below.

		Strongly Disagree	Disagree	Neither agree/ Disagree	Agree	Strongly Agree
1.	If you have breast cancer, the illness will last for a long time	1	2	3	4	5
2.	What I do can cause breast cancer	1	2	3	4	5
3.	The symptoms of breast cancer are distressing	1	2	3	4	5
4.	Not letting my emotions out can cause breast cancer	1	2	3	4	5
5.	Breast cancer is due to a blow to the breast	1	2	3	4	5
6.	Changing your diet will help to control breast cancer	1	2	3	4	5
7.	Breast cancer is disabling	1	2	3	4	5
8.	The symptoms of breast cancer become worse over time.	1	2	3	4	5
9.	Breast cancer has become easier to live with	1	2	3	4	5
10.	Feeling depressed causes breast cancer.	1	2	3	4	5
11.	The symptoms of breast cancer are constant	1	2	3	4	5
12.	Radiotherapy/Chemotherapy will control breast cancer	1	2	3	4	5
13.	Breast cancer has serious financial considerations	1	2	3	4	5
14.	The symptoms of breast cancer affect many parts of the body	1	2	3	4	5
15.	Stress is a major factor in causing breast cancer	1	2	3	4	5
16.	People are aware of the symptoms of breast cancer all the time.	1	2	3	4	5
17.	You can control breast cancer	1	2	3	4	5
18.	The symptoms of breast cancer are embarrassing	1	2	3	4	5
19.	Breast cancer is caused by deficiencies in the immune system.	1	2	3	4	5
20.	No one is responsible for the onset of breast cancer	1	2	3	4	5
21.	Feeling run-down or overworked causes breast cancer	1	2	3	4	5
22.	Cancer is controlled by reducing stress.	1	2	3	4	5
23.	There is little that can be done to improve breast cancer	1	2	3	4	5
24.	There is a lot that you can do to control the symptoms of breast cancer.	1	2	3	4	5
25.	Environmental poisons cause breast cancer	1	2	3	4	5
26.	Having breast cancer strongly affects the way you see yourself as a person	1	2	3	4	5
27.	When you have breast cancer, you are aware of your illness all the time	1	2	3	4	5
28.	Breast cancer does not have too much of an effect on your life	1	2	3	4	5
29.	Radiotherapy/ Chemotherapy will be effective in curing breast cancer	1	2	3	4	5
30.	Breast cancer is caused by another illness	1	2	3	4	5
31.	Whether breast cancer gets better or worse depends on the skill of the medical/ health professional	1	2	3	4	5
32.	Breast cancer will subside for a period and then recur	1	2	3	4	5
33.	The course of breast cancer is largely dependent on fate or chance	1	2	3	4	5
34.	What people do determines whether the breast cancer gets better or worse	1	2	3	4	5
35.	Breast cancer improves with time	1	2	3	4	5

		Strongly Disagree	Disagree	Neither Agree/ Disagree	Agree	Strongly Agree
36.	Breast cancer is directly due to your own behavior	1	2	3	4	5
37.	Breast cancer is terminal	1	2	3	4	5
38.	Pollution of the environment causes breast cancer	1	2	3	4	5
39.	Diet plays a major part in causing breast cancer	1	2	3	4	5
40.	Breast cancer is genetic	1	2	3	4	5
41.	Other people play a large role in causing breast cancer	1	2	3	4	5
42.	It is just by chance if you develop breast cancer	1	2	3	4	5
43.	Having breast cancer strongly affects the way other people see you	1	2	3	4	5
44.	If you have breast cancer, the illness will last for a long time	1	2	3	4	5
45.	I would be angry if I were found to have breast cancer	1	2	3	4	5
46.	I would be ashamed if I were found to have (recurrence of) breast cancer	1	2	3	4	5
47.	I would be frightened if I were found to have (recurrence of) breast cancer	1	2	3	4	5
48.	Breast self-examination greatly improves the chance of successful treatment and cure for women who develop breast cancer.	1	2	3	4	5
49.	Mammography greatly improves the chance of successful treatment and cure for women who develop breast cancer.	1	2	3	4	5

CECS

Below are listed some of the reactions people have to certain feelings or emotions. Read each one and indicate to what extent it describes the way you generally react. Indicate your answer by circling the appropriate number on the scale. Please work quickly.

	Almost never	Some-times	Often	Almost always
When I feel angry or very annoyed:				
I keep quiet	1	2	3	4
I refuse to argue or say anything	1	2	3	4
I bottle it up	1	2	3	4
I say what I feel	1	2	3	4
I avoid making a scene	1	2	3	4
I smother my feelings	1	2	3	4
I hide my annoyance	1	2	3	4
When I feel afraid or worried:				
I refuse to say anything about it	1	2	3	4
I hide my unhappiness	1	2	3	4
I put on a bold face	1	2	3	4
I keep quiet	1	2	3	4
I let others see how I feel	1	2	3	4
I smother my feelings	1	2	3	4
I bottle it up	1	2	3	4
When I feel unhappy or miserable:				
I let others see how I feel	1	2	3	4
I keep quiet	1	2	3	4
I refuse to say anything about it	1	2	3	4
I tell others about it	1	2	3	4
I say what I feel	1	2	3	4
I bottle it up	1	2	3	4
I smother my feelings	1	2	3	4
When I feel distressed or worried about breast cancer:				
I let others see how I feel	1	2	3	4
I keep quiet	1	2	3	4
I refuse to say anything about it	1	2	3	4
I tell others about it	1	2	3	4
I say what I feel	1	2	3	4
I bottle it up	1	2	3	4
I smother my feelings	1	2	3	4

Distress and Quality of Life Measures

POMS - Short Version

Below is a list of words that describe feelings people have. Please read each one carefully. Then CIRCLE ONE number which best describes HOW YOU HAVE BEEN FEELING **TODAY.**

The numbers refer to these phrases:

0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

1	Friendly	0	1	2	3	4	36 Miserable	0	1	2	3	4
2	Tense	0	1	2	3	4	38 Cheerful	0	1	2	3	4
3	Angry	0	1	2	3	4	39 Bitter	0	1	2	3	4
4	Worn out	0	1	2	3	4	40 Exhausted	0	1	2	3	4
5	Unhappy	0	1	2	3	4	41 Anxious	0	1	2	3	4
7	Lively	0	1	2	3	4	43 Good-natured	0	1	2	3	4
8	Confused	0	1	2	3	4	48 Helpless	0	1	2	3	4
12	Peeved	0	1	2	3	4	49 Weary	0	1	2	3	4
13	Considerate	0	1	2	3	4	50 Bewildered	0	1	2	3	4
14	Sad	0	1	2	3	4	51 Alert	0	1	2	3	4
15	Active	0	1	2	3	4	52 Deceived	0	1	2	3	4
16	On edge	0	1	2	3	4	53 Furious	0	1	2	3	4
17	Grouchy	0	1	2	3	4	55 Trusting	0	1	2	3	4
18	Blue	0	1	2	3	4	56 Full of pep	0	1	2	3	4
19	Energetic	0	1	2	3	4	58 Worthless	0	1	2	3	4
20	Panicky	0	1	2	3	4	59 Forgetful	0	1	2	3	4
21	Hopeless	0	1	2	3	4	60 Carefree	0	1	2	3	4
26	Uneasy	0	1	2	3	4	61 Terrified	0	1	2	3	4
27	Restless	0	1	2	3	4	63 Vigorous	0	1	2	3	4
28	Unable to concentrate	0	1	2	3	4	64 Uncertain about things	0	1	2	3	4
29	Fatigued	0	1	2	3	4	65 Bushed	0	1	2	3	4
30	Helpful	0	1	2	3	4						
31	Annoyed	0	1	2	3	4						
32	Discouraged	0	1	2	3	4						
33	Resentful	0	1	2	3	4						
34	Nervous	0	1	2	3	4						

IES

Below is a list of comments made by people about stressful events. **IN THE LAST TWO WEEKS INCLUDING TODAY, PLEASE INDICATE HOW FREQUENTLY THESE COMMENTS WERE TRUE FOR YOU ABOUT BREAST CANCER.** If the item did not occur, please mark the "not at all" column.

The numbers refer to these phrases:

0= Not at all
1= Rarely
3= Sometimes
5= Often

		Not at	Rarely	Some-times	Often
1.	Thought about it when I didn't mean to	0	1	3	5
2.	I avoided letting myself get upset when I thought about it or was reminded of it	0	1	3	5
3.	I tried to remove it from memory	0	1	3	5
4.	I had trouble falling asleep or staying asleep, because of pictures or thoughts about it that came into my mind	0	1	3	5
5.	I had waves of strong feelings about it	0	1	3	5
6.	I had dreams about it	0	1	3	5
7.	I stayed away from reminders of it	0	1	3	5
8.	I felt as if it was unreal	0	1	3	5
9.	I tried not to talk about it	0	1	3	5
10.	Pictures about it popped into my mind	0	1	3	5
11.	Other things kept making me think about it	0	1	3	5
12.	I was aware that I had a lot of feelings about it, but I didn't deal with them	0	1	3	5
13.	I tried not to think about it	0	1	3	5
14.	Any reminder brought back feelings about it	0	1	3	5
15.	My feelings about it were kind of numb	0	1	3	5
**	Have these experiences (#1-15, above) interfered with your daily activities?	0	1	3	5

BDI

On this questionnaire are groups of statements. Please read each group of statements carefully. Then pick out the one statement in each group which best describes the way you have been feeling for the **PAST TWO WEEKS, INCLUDING TODAY**. Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

A)
0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

B)
0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and things cannot improve.

C)
0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

D)
0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything any more.
3 I am dissatisfied or bored with everything.

E)
0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty most of the time.

F)
0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

G)
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

H)
0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults
3 I blame myself for everything bad that happens.

I)
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

J)
0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry all the time now.
3 I used to be able to cry but now I can't even though I want to.

K)
0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

L)
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

M)
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty making decisions than I used to.
3 I can't make decisions at all any more.

N)
0 I can work as well as before.
1 It takes extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do work at all.

O) 0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive.
3 I believe I look ugly.

P) 0 I can sleep as well as I used to.
1 I don't sleep as well as I used to.
2 I wake up earlier than I used to and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

Q) 0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

R) 0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all any more.

S) 0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.
(On a diet: NO___; YES___)

T) 0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains, upset stomach, and constipation.
2 I am very worried about physical problems and it is hard to think about much else.
3 I am so worried about my physical problems, I cannot think about anything else.

U) 0 I have not noticed any recent changes in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex than I used to be.
3 I have lost interest in sex completely.

BSI

Below is a list of problems and complaints that people sometimes have. Read each one carefully, and select one of the numbered descriptors that best describe **HOW MUCH DISCOMFORT THAT PROBLEM HAS CAUSED YOU IN THE LAST 2 WEEKS.** Please circle the number to the right of the problem. Do not skip any items. If you change your mind, erase your first answer completely.

		Not at All	Slightly	Mod-erately	Extremely
1.	Nervousness or shakiness inside	1	2	3	4
2	Thoughts of ending your life	1	2	3	4
3.	Suddenly scared for no reason	1	2	3	4
4.	Feeling lonely	1	2	3	4
5.	Feeling fearful	1	2	3	4
6.	Feeling blue	1	2	3	4
7.	Feeling not interested in things	1	2	3	4
8.	Feeling tense or keyed up	1	2	3	4
9.	Spells of terror or panic	1	2	3	4
10.	Feeling hopeless about the future	1	2	3	4
11.	Feeling so restless you couldn't sit still	1	2	3	4
12.	Feeling of worthlessness	1	2	3	4

1. In general, would you say your health is (check one):

   Poor ___ Fair ___ Good ___ Very good ___ Excellent ___

2. *Compared to one year ago*, how would you rate your health in general now? (check one)

Much better now than one year ago	___
Somewhat better now than one year ago	___
About the same now as one year ago	___
Somewhat worse now than one year ago	___
Much worse now than one year ago	___

3. The following items are about activities you might do during a typical day. *Does your health now limit you* in these activities? If so, how much? (check appropriate answer)

	Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	___	___	___
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	___	___	___
Lifting or carrying groceries	___	___	___
Climbing *several* flights of stairs	___	___	___
Climbing *one* flight of stairs	___	___	___
Bending, kneeling or stooping	___	___	___
Walking *more than a mile*	___	___	___
Walking *several blocks*	___	___	___
Walking *one block*	___	___	___
Bathing or dressing yourself	___	___	___

4. During the *past 2 weeks, including today,* have you had any of the following problems with your work or other regular daily activities *as a result of your physical health*? (check yes or no for each)

	Yes	**No**
Cut down the *amount of time* you spent on work or other activities	___	___
Accomplished less than you would like	___	___
Were limited in the *kind* of work or other activities	___	___
Had *difficulty* performing the work or other activities (for example, it took extra effort)	___	___

5. During the *past 2 weeks, including today,* have you had any of the following problems with your work or other regular daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)? (check yes or no for each)

	Yes	No
Cut down the *amount of time* you spent on work or other activities	___	___
Accomplished less than you would like	___	___
Didn't do work or other activities as *carefully* as usual	___	___

6. During the *past 2 weeks, including today,* to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (check one)

Not at all ___
Slightly ___
Moderately ___
Quite a bit ___
Extremely ___

6.5. How much *bodily discomfort* have you had during the *past 2 weeks, including today*? (check one)

None ___
Very mild ___
Mild ___
Moderate ___
Severe ___
Very severe ___

7. How much *bodily pain* have you had during the *past 2 weeks, including today*? (check one)

None ___
Very mild ___
Mild ___
Moderate ___
Severe ___
Very severe ___

8. During the *past 2 weeks, including today,* how much did *pain* interfere with your normal work (including both work outside the home and housework)? (check one)

Not at all ___
A little bit ___
Moderately ___
Quite a bit ___
Extremely ___

9. These questions are about how you feel and how things have been with you *during the past 2 weeks, including today*. For each question, please give the one answer that comes closest to the way you have been feeling (check appropriate answer).

During the past 2 weeks, including today:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Did you feel full of pep?	___	___	___	___	___	___
Have you been a very nervous person?	___	___	___	___	___	___
Have you felt so down in the dumps that nothing could cheer you up?	___	___	___	___	___	___
Have you felt calm and peaceful?	___	___	___	___	___	___
Did you have a lot of energy?	___	___	___	___	___	___
Have you felt downhearted and blue?	___	___	___	___	___	___
Did you feel worn out?	___	___	___	___	___	___
Have you been a happy person?	___	___	___	___	___	___
Did you feel tired?	___	___	___	___	___	___

10. During the *past 2 weeks, including today*, how much of the time has your *physical health or emotional problems* interfered with your social activities (like visiting with friends, relatives, etc.)? (check one)

All of the time ___
Most of the time ___
Some of the time ___
A little of the time ___
None of the time ___

11. How **TRUE** or **FALSE** is *each* of the following statements for you? (check appropriate answer)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
I seem to get sick a little easier than other people	___	___	___	___	___
I am as healthy as anybody I know	___	___	___	___	___
I expect my health to get worse	___	___	___	___	___
My health is excellent	___	___	___	___	___

Genetic Testing Measures

GENETIC TESTING

In a small number of families, several family members develop breast cancer, often at younger ages. Scientists believe that, in some of these families, women who develop breast cancer have inherited a particular gene that makes them susceptible to cancer. This gene is passed down from generation to generation in these families. Some family members will inherit the gene and others will not.

It is now possible to perform a blood test to determine which members of these families have this breast cancer gene. A woman who has the gene would have an increased risk of developing breast cancer in her lifetime. A woman who didn't have the gene would have the same risk of developing breast cancer as a woman with no family history of breast cancer.

Now that such a blood test is currently available, which of the following best describes what your intentions are? Please check one

_____ I have already donated a blood sample for genetic testing.

_____ I plan to take the test as soon as possible (within the next 30 days).

_____ I plan to take the test sometime in the near future (within the next 6 months).

_____ I do not plan to take the test in the near future (not within the next 6 months).

_____ I do not plan to take the test at all.

The following is a list of issues a woman might consider in deciding whether or not to take the blood test described above. Please indicate the degree to which you agree or disagree with each of the following by circling the appropriate number on the right side of the page. Please circle NA for those questions that are not relevant for you.

		Strongly Agree		Neither Agree nor Disagree		Strongly Disagree	
1.	My concerns about developing (having a recurrence of) breast cancer would be reduced if I knew that I did not carry the gene.	1	2	3	4	5	
2.	I feel I already know my chances of getting breast cancer, (Having a recurrence) so I wouldn't learn anything more from genetic testing.	1	2	3	4	5	
3.	Knowing that I carry the gene would help me decide whether to go for more frequent mammograms.	1	2	3	4	5	
4.	Knowing that I carry the gene would leave me in a state of hopelessness and despair.	1	2	3	4	5	
5.	If I were found to carry the gene, it could jeopardize my insurance coverage.	1	2	3	4	5	
6.	If I were found to carry the gene, it would help my daughter(s) or sister(s) decide whether to undergo genetic testing.	1	2	3	4	5	NA
7.	Genetic testing is not worthwhile because it could lead to family problems.	1	2	3	4	5	

		Strongly Agree		Neither Agree nor Disagree		Strongly Disagree	
8.	Knowing that I carry the gene would worsen my quality of life.	1	2	3	4	5	
9.	Knowing that I carry the gene would motivate me to perform breast self-examination more frequently.	1	2	3	4	5	
10.	If I were found to carry the gene for breast cancer I would worry about passing the gene to my children.	1	2	3	4	5	NA
11.	Knowing that I do not carry the gene would not be helpful since I could still develop (have a recurrence of) breast cancer.	1	2	3	4	5	
12.	Knowing that I carry the gene would help me decide whether to undergo bilateral oophorectomy (an operation to remove the ovaries) .	1	2	3	4	5	NA
13.	Knowing whether or not I carry the gene would increase my sense of personal control.	1	2	3	4	5	
14.	Knowing that I carry the gene would cause me to worry more about other family members who could be carriers (e.g., mother, sisters, daughters).	1	2	3	4	5	
15.	If I were found to carry the gene, I would worry that the results may not stay confidential.	1	2	3	4	5	
16.	I would be angry if I were found to carry the gene.	1	2	3	4	5	
17.	Knowing that I carry the gene would help me to decide whether to undergo bilateral mastectomy (an operation to move both breasts) .	1	2	3	4	5	NA
18.	I would be ashamed if I were found to have the gene.	1	2	3	4	5	
19.	I do not feel comfortable speaking to family members about genetic testing.	1	2	3	4	5	
20.	Knowing that I carry the gene would help me decide whether to take tamoxifen (a drug that may prevent breast cancer).	1	2	3	4	5	NA
21.	I would consider suicide if I were found to carry the gene for breast cancer.	1	2	3	4	5	
22.	I would feel guilty if one of my relatives had the gene and I did not.	1	2	3	4	5	
23.	If I were found to carry the gene for breast cancer, I would feel guilty if my daughter(s) developed breast cancer.	1	2	3	4	5	NA
24	Knowing whether or not I carry the gene would help me make important life decisions (e.g., getting married, having children).	1	2	3	4	5	NA
25.	If I were found to carry the gene it could lead to problems with my employers.	1	2	3	4	5	NA
26.	I would be frightened if I were found to have the gene.	1	2	3	4	5	
27.	If I were found to carry the gene, it could lead to marital problems.	1	2	3	4	5	NA

		Strongly Agree		Neither Agree nor Disagree		Strongly Disagree	
28.	Knowing that I do not carry the gene would not be helpful since I might have another gene not yet identified.	1	2	3	4	5	
29.	Other family members have encouraged me to undergo genetic testing.	1	2	3	4	5	
30.	My spouse/partner has encouraged me to undergo genetic testing.	1	2	3	4	5	NA
31.	I plan to have a genetic test for breast cancer, only if my health insurance covers the cost.	1	2	3	4	5	
32.	I plan to have a genetic test for breast cancer, even if I have to pay for it myself.	1	2	3	4	5	

33. For a genetic test for breast cancer, I would be willing to pay (check one):

_____ $25 _____ $50 _____ $100 _____ $200 _____ $500 _____ $1,000 _____ over $2,000

KNOWLEDGE ABOUT BREAST CANCER AND GENETICS

The following questions are to find out how much you already know about cancer and genetics. Please indicate you answer in the space provided. This is NOT a test. Your answers to these questions will help us evaluate our counseling program.

			Don't know
1.	What is the lifetime risk of developing breast cancer for the average woman in the United States 0% - 100%?	_____%	_____
2.	If a genetic test were to indicate that a woman inherited a susceptibility to breast cancer, then on a scale from 0% (not at all likely) to 100% (definitely), how likely do you think she is to develop breast cancer before the age of 80 ?	_____%	_____
3.	If a genetic test were to indicate that a woman did not inherit a susceptibility to breast cancer, then on a scale from 0% (not at all likely) to 100% (definitely), how likely to you think that she is to develop breast cancer before the age of 80 ?	_____%	_____

4. If a genetic test was to indicate that a woman inherited a susceptibility to breast cancer, then:

	True	False	Don't know
a. Nothing can be done to prevent breast cancer from developing.	1	2	9
b. The faulty gene could be replaced with a correctly functioning gene.	1	2	9
c. More aggressive recommendations for screening and prevention should be followed.	1	2	9
d. Nothing can be done to prevent ovarian cancer from developing.	1	2	9

5. A woman is at a greater risk for developing breast cancer if she has:

a. several close relatives with breast cancer	1	2	9
b. a history of fibrocystic disease	1	2	9
c. a late age of her first menstrual period	1	2	9
d. an early age of her first childbirth	1	2	9
e. a father with a breast cancer gene	1	2	9

6. A woman is at a greater risk for developing ovarian cancer if she:

a. has several close relatives with ovarian cancer	1	2	9
b. has a prior history of breast cancer	1	2	9
c. uses oral contraceptives	1	2	9
d. has a history of multiple full term pregnancies	1	2	9

7.	A woman whose mother has had a breast cancer should never take female hormones (estrogen).	1	2	9

		True	False	Don't Know
8.	If a genetic test were to indicate that a woman has inherited a susceptibility to breast cancer, she will very likely develop:			
	a. Breast cancer	1	2	9
	b. Ovarian cancer	1	2	9
	c. Lung cancer	1	2	9
	d. Colon cancer	1	2	9
9.	If a woman who already has had breast cancer was found to have inherited a susceptibility to breast cancer, she is at risk for developing:			
	a. Breast cancer in her other breast	1	2	9
	b. Ovarian cancer	1	2	9
	c. Lung cancer	1	2	9
	d. Colon cancer	1	2	9
10.	Early onset breast cancer (before 50) is less likely to be associated with an altered gene than is late onset breast cancer.	1	2	9
11.	A woman who has a sister with an altered gene for breast cancer has a 50% chance (1 in 2) of also having an altered gene for breast cancer.	1	2	9
12.	A woman who doesn't have an altered gene can still get breast cancer.	1	2	9
13.	Men can carry a gene for breast cancer.	1	2	9
14.	There is more than one gene that can cause breast cancer.	1	2	9
15.	Having one's ovaries removed will definitely prevent ovarian cancer	1	2	9
16.	A woman who has her breast removed will definitely not get breast cancer.	1	2	9
17.	Using a scale from 0 (not at all curable) to 100 (completely curable), how curable do you think breast cancer is?	_____		
18.	Using a scale from 0 (not at all preventable) to 100 (completely preventable), how preventable do you think breast cancer is?	_____		

AWARENESS OF GENETIC TESTING

We would like to know how much you have heard about genetic testing and different cancers. Please circle one number on each line.

		Almost Nothing	Relatively Little	A Fair Amount	A lot
1.	How much have you heard or read about genetic testing for inherited disease?	1	2	3	4
2.	How much have you heard or read about genetic testing for cancer?	1	2	3	4
3.	How much have you heard or read about genetic testing for breast cancer?	1	2	3	4
4.	How much have you heard or read about genetic testing for colon cancer?	1	2	3	4

BELIEFS ABOUT ACCESS TO TESTING

Many people have different beliefs with regard to access to genetic testing. Please indicate how much you agree with the following statements.

		Strongly Disagree	Somewhat Disagree	Somewhat Agree	Strongly Agree
1.	Once genetic testing for cancer is available, it should be offered to everyone.	1	2	3	4
2.	Genetic testing for cancer should only be offered to people if their doctor thinks that they may have an altered gene.	1	2	3	4
3.	Women who carry the gene for breast cancer should be able to test their unborn child.	1	2	3	4
4.	If I were found to have the gene for breast cancer, I would want to have my children tested at the earliest possible age.	1	2	3	4
5.	If a child is tested for the BRCA the parents should have the right to know the results.	1	2	3	4
6.	If a genetic test is not going to have a medical impact on a child, it should not be done simply to reassure the parents.	1	2	3	4

If you were to undergo genetic testing for breast cancer susceptibility, would to tell any of the following people about your decision?

	Yes	No	Not appli-cable	Don't know	I have already spoken to them
My husband	1	2	3	4	5
My mother	1	2	3	4	5
My father	1	2	3	4	5
My daughter(s)	1	2	3	4	5
My son(s)	1	2	3	4	5
My sister(s)	1	2	3	4	5
My brother(s)	1	2	3	4	5
My grandmother (on your mother's side)	1	2	3	4	5
My grandfather (on your mother's side)	1	2	3	4	5
My grandmother (on your father's side)	1	2	3	4	5
My grandfather (on your father's side)	1	2	3	4	5
My general practitioner	1	2	3	4	5
My gynecologist	1	2	3	4	5
My friend(s)	1	2	3	4	5
Others- if yes whom would you tell?	1	2	3	4	5
_____	1	2	3	4	5
_____	1	2	3	4	5
_____	1	2	3	4	5

Genetic Counseling Measures

GENETIC COUNSELING

Genetic counseling examines the hereditary basis of cancer and offers support and guidance. Please indicate below your willingness to make an appointment.

_____ I have already made an appointment

_____ I plan to make an appointment as soon as possible (within the next 30 days).

_____ I plan to make an appointment sometime in the near future (within the next 6 months).

_____ I do not plan to make an appointment in the near future (not within the next 6 months).

The following is a list of reasons why some women might or might not decide to undergo genetic counseling. Please indicate the degree to which you agree or disagree with each of the following by circling the appropriate number on the right side of the page.

		Strongly Agree				Strongly Disagree
1.	Genetic counseling would reduce my fear and concerns about developing breast cancer.	1	2	3	4	5
2.	I feel I already know my chances of getting breast cancer, so I wouldn't learn anything more from genetic counseling.	1	2	3	4	5
3.	Genetic counseling would help me decide whether I should undergo genetic testing for breast cancer	1	2	3	4	5
4.	I need to get more information about what genetic counseling has to offer.	1	2	3	4	5
5.	Genetic counseling would help me initiate discussions about cancer risk with my family.	1	2	3	4	5
6.	Genetic counseling would help me make important life decisions (e.g., having children).	1	2	3	4	5
7.	Genetic counseling would help me better understand cancer risks of other family members.	1	2	3	4	5
8.	It would be distressing for me to talk to a genetic counselor	1	2	3	4	5
9.	Genetic counseling would help me decide whether to undergo preventive surgery.	1	2	3	4	5
10.	Undergoing genetic counseling could jeopardize my health insurance	1	2	3	4	5
11.	Genetic counseling would make me worry about the breast cancer risk of other family members (e.g., mother, daughters).	1	2	3	4	5
12.	To benefit from genetic counseling I would need to have a better background (more schooling) in science.	1	2	3	4	5
13.	Genetic counseling would not help me deal with my fears and uncertainty about developing breast cancer.	1	2	3	4	5
14.	Genetic counseling would not provide me with any means of preventing breast cancer.	1	2	3	4	5
15.	My doctor (nurse) has spoken with me about my risk of breast cancer, so I wouldn't learn anything new from genetic counseling	1	2	3	4	5
16.	I am interested in genetic counseling, but I don't have the time.	1	2	3	4	5
17.	I am interested in genetic counseling, but I live to far away	1	2	3	4	5

Breast Cancer Screening and Preventive Behavior Measures

BREAST SELF-EXAMINATION

Instructions: *If you have had bilateral mastectomy please skip the following questions and go to next page.*

How often do you perform breast self-examination?

1. More than once a month
2. Once a month
3. Every other month
4. Four or five times a year
5. Two or three times a year
6. Once a year
7. Never

Please indicate how much you agree or disagree with each statement.

1. How confident are you in your ability to do breast self-examination?

Not at all confident 1 2 3 4 5 6 7 Extremely Confident

2. I feel relieved after doing a breast self-exam.

Disagree strongly 1 2 3 4 5 6 7 Agree strongly

3. I get anxious every time I think about breast self examination.

Disagree strongly 1 2 3 4 5 6 7 Agree strongly

CLINICAL BREAST EXAM

During a clinical breast exam, a health care provider checks the breasts for lumps.

When was your last clinical breast exam? (circle one)

1. Within the past year
2. Between 1 and 2 years ago
3. Between 2 and 3 years ago
4. Over 3 years ago
5. Never had a clinical breast exam

MAMMOGRAPHY

How many mammograms have you had?

_____ None _____One _____ Two _____ Three _____ Four _____ Five or more

Date of last mammogram:_____

Please indicate how much you agree or disagree with each statement.

1. How confident are you in mammography?

Not at all confident 1 2 3 4 5 6 7 Extremely confident

2. I feel relieved after having a mammogram.

Disagree strongly 1 2 3 4 5 6 7 Agree strongly

3. I get anxious every time I think about having a mammogram.

Disagree strongly 1 2 3 4 5 6 7 Agree strongly