COMMENTARY

A Model Protocol for Evaluating the Behavioral and Psychosocial Effects of BRCA1 Testing

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Breast cancer is the most common cancer in American women. A heritable component to breast cancer has been suspected for over a century because of the observation that a woman is at higher risk if she has had one or more first-degree relatives with breast cancer (1). Recent advances in molecular genetics have led to the isolation of a gene called BRCA1 on the long arm of chromosome 17. Mutations in this gene substantially increase the risk in women for breast and ovarian cancers (2,3). Cancer susceptibility conferred by BRCA1 mutations is inherited in an autosomal dominant fashion.

A study conducted by the Breast Cancer Linkage Consortium (BCLC) estimated that 45% of the families with a high risk of breast cancer alone and the large majority of breast cancer families who also have at least one individual with ovarian cancer are linked to the 17q site. In the analysis of 214 families collected worldwide through the BCLC, the cumulative risk for breast or ovarian cancer in mutation carriers was estimated to be 59% by age 50 years and 82% by age 70 years (4). Preliminary evidence suggests that there also may be an increased risk of prostate and colon cancers in BRCA1 mutation carriers (5). The penetrance of the gene for both breast and ovarian cancers may vary between families, perhaps due to different functional mutations within the BRCA1 gene (6). In families without a strong history of breast or ovarian cancer, cases are less likely to be associated with this gene. It has been estimated that approximately 5%-10% of the cases of breast cancer in the general population are associated with BRCA1 mutations (7). Germline BRCA1 mutations have been documented in approximately 10% of the women in the general population diagnosed with breast cancer before the age of 35 years (8) and in 13% of the women with breast cancer younger than age 30 years (9). Although the proportion of breast cancer cases associated with BRCA1 mutations is relatively low in the general population, the prevalence of these cancers means that a large number of cases per year are associated with this gene. To date, screening for BRCA1 mutations in the general population has been inhibited by the large number of mutations identified in this gene. However, the recent report of a single BRCA1 mutation in as many as 1% of Ashkenazi Jews raises the possibility of screening in this population in the near future (10). Germline BRCA1 mutations have been documented in eight (21%) of 39 Jewish women with breast cancer before the age of 40 years (9). Testing for mutations in the BRCA1 gene may be the first widespread use of presymptomatic genetic testing introduced into general medical practice (11).

Genetic testing for BRCA1 mutations will help at-risk women only if the risk information is beneficial psychologically or if it is translated into effective cancer prevention or surveillance behaviors. However, potential harm may result to those tested if they experience psychological distress, stigmatization, and/or discrimination on the basis of their genetic status (12-14). Previous studies (15-17) of cancer screening have provided evidence of adverse psychological reactions to risk information involving distress and impairment in daily functioning. This distress has important consequences for surveillance and prevention. Anxiety has been associated with a reduced likelihood of adherence to mammography, clinical breast examination, and breast self-examination in both normal and high-risk populations (18-20). Cases of genetic discrimination have also been cited (21). These risks are a particular concern, since the medical benefits of genetic testing for cancer susceptibility have yet to be demonstrated.

While this new genetic technology provides an unprecedented opportunity for targeted cancer prevention and surveillance efforts, our current knowledge of the behavioral, psychological, and social impacts of this information is too limited to enable the development of protocols that we know will be safe and ef-

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flective (22-23). Testing for BRCA1 mutations is now under way in several centers (11,24). Therefore, before testing for BRCA1 mutations becomes widespread, it is critical that we understand the psychological and behavioral consequences of genetic risk notification (25,26). The American Society of Human Genetics, the National Advisory Council for Human Genome Research, and the National Breast Cancer Coalition have called for a careful evaluation of BRCA1 testing before clinical testing or population screening is initiated (27,28).

To address these concerns, we have initiated a 4-year study of the behavioral and psychosocial effects of BRCA1 testing in a large Utah kindred (K2082). This kindred is the largest reported to date with an identified mutation at the BRCA1 locus (29). The members of K2082 are primarily Caucasian and of northern European descent. The majority of kindred members live in Utah and are members of the Church of Jesus Christ of Latter-day Saints (LDS or Mormons). The specific BRCA1 mutation in this kindred creates a stop codon at codon 1313 (2). The 2082 kindred has a high risk of ovarian cancer and a later age of onset for breast cancer compared with risk figures from the BCLC (3). The cumulative risk of breast or ovarian cancer to age 80 years in K2082 is approximately 90%. Our study is designed to provide genotype results and genetic counseling to women and men in K2082 and follow their responses to the information through detailed interviews and questionnaires over a 2-year period. The specific goals of the research are to 1) examine the impact of increased versus decreased risk information derived from genetic testing for a BRCA1 mutation on psychological distress; 2) examine the impact of genetic testing for a BRCA1 mutation on cancer-related attitudes and beliefs, including documentation of reasons why individuals choose or decline testing; 3) identify the use of health services and changes in health-related behavior by women and men who are carriers, noncarriers, and test decliners (of particular interest for female subjects are the use of mammography and vaginal ultrasound, the use of prophylactic mastectomy and oophorectomy, the use of breast self-examination, the use of psychiatric or psychological services, and the use of community support groups); and 4) identify changes in family and social environments that may result from an individual's knowledge of his or her genetic status. Familial and social consequences of primary concern are changes in family structure, family functioning, fertility intentions and behaviors, marital satisfaction/distress, employment, insurance status, and religious practices. This commentary will describe the study protocol and outline the preliminary results with respect to the interest in genetic testing in this family.

The protocol was developed with the assistance of a community advisory board that is composed of breast cancer survivors and advocates and with the assistance of the Genetic Science in Society Program of the University of Utah Center for Human Genome Research. The protocol and informed consent documents have been reviewed by two Institutional Review Boards at the University of Utah, as well as by representatives of the National Cancer Institute and the Ethical, Legal, and Social Implications Branch of the National Center for Human Genome Research.

**Study Protocol**

A flow diagram of the study protocol is provided in Fig. 1. In summary, kindred women and men are evaluated with detailed questionnaires before and at regular intervals after genetic testing or after recruitment for those who are not tested. There have been a number of guidelines (11,30-32) published since 1990 for presymptomatic genetic testing for cancer susceptibility and Huntington disease. Our protocol is consistent with these guidelines in several key respects. First, the potential power of this information is recognized. Subjects are fully informed of the risks and potential benefits of the study, and they have several opportunities to withdraw from the study prior to genetic testing. Two to eight weeks elapse between the initial consent and the provision of results. This time period permits subjects to reconsider their decision to proceed. All subjects receive genetic counseling before and after genetic testing. Psychiatric screening is performed before genetic testing and a family therapist is present during the results session. Subjects are encouraged to bring a support person who is not a kindred member to all sessions. Consultation from psychiatry, genetics, oncology, and surgery services is available to all participants and their immediate family members for the duration of the study. Second, strict confidentiality is maintained. All records are maintained in separate charts and computer files accessible by the investigators only. Third, DNA analysis is done with strict attention to accuracy in a Centers for Disease Control and Prevention-approved clinical diagnostic laboratory. Subjects are fully informed of the possibility of uninformative results and of inaccurate results.

**Identification and Contact of Study Population**

As noted, the 2082 kindred has been studied extensively by investigators at the University of Utah. However, the 2082 kindred is substantially larger than the number of individuals evaluated to date by these investigators. We estimate the portion of the kindred that is potentially at risk for the BRCA1 gene to be 700-800 adult individuals, none of whom had received genotype results prior to this research project. Members of the kindred who are excluded from the study include 1) individuals who are less than 18 years of age, 2) individuals who are not competent to consent to participation in the research study, 3) individuals who are unable to attend the two genetic counseling sessions at the University of Utah, and 4) previously untested members of the kindred who are not at risk for carrier status by virtue of the knowledge of the test results of their parents or grandparents. However, such individuals are provided genetic counseling at their request. All other members of the kindred are considered eligible for the study. This includes members of the kindred who have had breast or ovarian cancer, since individuals may develop these cancers despite being noncarriers for a BRCA1 mutation. In addition, women who are mutation carriers and who have experienced cancer may be unaware that they are at substantial risk for the development of a second primary cancer. Adult men are included to assess their psychological and behavioral responses to the genetic information, to inform them of the risk of passing the mutation to their children, and to inform them of the reported increase in risk for prostate
an colon cancers in mutation carriers. Approximately 100 spouses of married subjects are being recruited for interviews to assess the impact of genetic information on these individuals, their marital relationship, and the family. Prenatal testing for the BRCA1 mutation is not offered or provided through this study.

Prior to the base-line interview, a letter is sent to potential subjects that informs them of the availability of a test for the BRCA1 mutation and of the study of the effects of genetic information. Subjects are invited to return a stamped, self-addressed letter indicating whether they are interested in participating. Those who indicate that they are not interested are not contacted further. Those who indicate interest are contacted by phone by our project coordinator. Those who do not wish to participate in the entire study are invited to participate in the interviews. If the subject does not wish to participate at all, she or he is not contacted again. Those who agree to participate in the full study are sent an informed consent document to read, sign, and return. This consent form describes the overall project and documents consent for interviews but does not cover the necessary details for genetic testing. (Subjects sign a separate consent following counseling if they desire genetic testing.) Those who wish to participate only in the interviews are sent a consent document for that purpose only. Once the signed informed consent document has been received by the project office, an interviewer calls the subject to set up and conduct the base-line interview.

Our recruitment strategy is designed to limit the possibility of testing adult children prior to their at-risk parent. Detection of a BRCA1 mutation in a child would indicate that the parent from
the kindred is a mutation carrier as well. Testing of children first
would provide de facto testing of parents in this circumstance
without the benefit of informed consent and counseling for the
parent(s). Because of this concern, we stage recruitment in
nuclear families from the oldest generation to the youngest.
Progress through the protocol is also monitored for nuclear
families so that results are provided from the older generations
to the youngest as well. This strategy creates considerable logis-
tical problems with recruitment, for both the mailing of letters
and the scheduling of counseling sessions. In addition, this ap-
proach has decreased our recruitment, since many children
choose not to participate until their parent(s) has been tested
and, subsequently, children of mutation-negative parents often
choose not to participate in the project. To date, we have not
confronted the ethical dilemma of an adult child who requests
testing despite the refusal of testing by the kindred parent(s).
Should this situation arise, we will address the issue on a case-
by-case basis and encourage the family to resolve the dilemma
within the family, if possible.

The study is designed to follow individuals who decline
genetic testing using most of the same interview instruments
that are completed by subjects who pursue the full genetic test-
ing protocol. This will enable us to identify the personal factors
that may lead individuals to pursue or decline testing. In addi-
tion, negative psychosocial correlates of not participating have
been demonstrated in other studies of presymptomatic genetic
testing (33). Other than those who decline contact from the out-
set, we ask all subjects who withdraw from the testing protocol
prior to the time when results are provided to consent to the
base-line interview and the 1- and 2-year follow-up interviews.
Subjects who decline these interviews are not contacted further
by the investigators.

Counseling

After the base-line interview, all subjects requesting genetic
testing receive extensive pre- and post-test genetic counseling in
individual, in-person sessions. All sessions are audio recorded
(with the separate consent of the subject for this purpose only).
The pretest genetic counseling session includes a cancer family
history, a targeted medical and cancer screening history, presen-
tation of information about the BRCA1 gene and its mode of in-
eritance, cancer risks associated with mutations, the method
used for DNA analysis, and an overview of prevention and sur-
veillance options available for mutation carriers. The relative
lack of data on the efficacy of screening and prevention
strategies is emphasized. The risks, benefits, and limitations of
testing are reviewed, including psychological risks and the risk
to the subject’s employment and insurance status. As noted
above, a detailed consent form is signed at the completion of
counseling if the subject requests genetic testing.

Fostering an understanding of cancer risk is central to the
counseling dialogue. The concept of risk is discussed by ex-
plaining the general model of cancer development through the
accumulation of genetic mutations, whether somatic or germline
in origin. The relevance of subject genotype and age in this
process is explained. Visual aids are employed to model the cel-

ular accumulation of mutations and to illustrate the cumulative
risk for breast cancer, ovarian cancer, and both by decade for
mutation carriers in this kindred. Subjects are offered ample
time to explore questions and concerns. The pretest counseling
sessions average approximately 90 minutes.

All subjects are sent a letter after pretest counseling that
reviews the information in the session, including the concept of
cancer predisposition genes, dominant inheritance, the general
population risks and kindred-specific risks for breast, ovarian,
colon, and prostate cancers, the advantages and risks of genetic
testing, the plan for results, and a glossary of the medical and
genetic terms used. If the subject chooses not to have genetic
testing, the letter outlines the recommendations for individuals
at high risk.

Following pretest genetic counseling, a family therapist con-
ducts an assessment interview concerning the subject’s emotional
and psychological preparedness for testing and discusses possible psychological reactions to the genetic test results. (It
should be noted that involvement of a family therapist or a
similar professional is not a common feature of other BRCA1-
testing protocols and thus should not necessarily be considered a
standard of care.) Prior to conducting the assessment interview,
the family therapist reviews the participant’s responses from the
earlier base-line telephone interview that includes questions
concerning symptoms of depression and anxiety. (This portion
of the base-line interview is accessible to the family therapist
alone and not to the genetic counselors.) The family therapist,
in consultation with the psychiatrist, can defer subjects from
genetic testing if the subjects meet Diagnostic and Statistical
Manual (DSM) IV criteria (34) for major depression, general-
ized anxiety, or other serious psychological disturbances. Defer-
ing testing is appropriate only when the psychiatrist believes
the subject is incompetent to give a valid consent to the study or
when there is a strong suspicion that the information will cause
substantial harm to the individual. Deferred subjects may re-
enter the study if these concerns are resolved over time. This
option is consistent with recommendations by the National Cancer
Institute workshop on p53 predictive testing (32).

In the post-test counseling session, subjects are told their
results in a session with both the genetic counselor and family
therapist present. Risk information specific to BRCA1 mutation
carriers in the 2082 kindred is reviewed, again with the help of
graphic aids. Risk information is presented to subjects in a man-
ner appropriate to the subject’s age to emphasize the risks in dif-
f erent decades of life. Fig. 2, A-C, illustrates the risk of breast
cancer or ovarian cancer and the combined risk of either cancer
(in this kindred) to various ages on the basis of the current age
of the individual. For example, these figures illustrate that the
risk of breast cancer to age 60 years for a mutation carrier is
much greater for a woman of 30 years than for a woman of 50
years. Both mutation-positive and mutation-negative subjects
are provided guidelines for cancer prevention and screening (see
below). Altered risks to offspring are reviewed. Information is
provided about the consultations available through surgery, on-
cology, and psychiatry and on community resources for breast
care services.

Throughout the counseling session, psychological issues are
addressed as they arise. These may include issues such as fear of
cancer or medical procedures, past negative experiences with

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Commentary

A) Breast cancer risks (i.e., cumulative penetrance) by age in kindred 2082; B) ovarian cancer risks by age in kindred 2082; C) breast and ovarian cancer risks by age in kindred 2082.

Fig. 2. A) Breast cancer risks (i.e., cumulative penetrance) by age in kindred 2082; B) ovarian cancer risks by age in kindred 2082; C) breast and ovarian cancer risks by age in kindred 2082.

Surgical, Oncologic, and Psychiatric Consultation

All participants in the study are offered consultation services by members of oncology, surgery, and psychiatry departments following genetic testing. Medical, surgical, or extended psychiatric care are not provided by the study. All visits are documented in the research chart only. Study participants have no specific limits placed on the number of consultation visits available during the course of the study, although the individual consultants may limit the number of visits if no further benefits are anticipated or if referral or long-term therapy is appropriate. To date, few subjects have initiated visits with these specialists.

Subjects in the kindred may request that study information be shared with their personal physician. With written consent, all genetic information, test implications, and individual recommendations will be shared in written form with the personal physician. An assumption in these communications is that the majority of practicing physicians do not have a working knowledge of the relevant genetics. The study investigators are available to personal physicians to assist in the interpretation of the results and to explain the recommendations.

Counseling Content

Recommendations for risk reduction for breast and ovarian cancers are controversial for women in the general population, and there are few data available to justify any one set of recommendations for the high-risk women in this study. The recommendations outlined below were developed through a knowledge of the risk pattern in the kindred and were designed to be consistent with other guidelines published for this population (7,11). In general, we chose to recommend a relatively high level of cancer surveillance for mutation carriers, given the substantial risk for both breast and ovarian cancers in this kindred. A subcommittee of the Cancer Studies Consortium of the Ethical, Legal, and Social Implications Branch of the National Center for Human Genome Research currently is preparing recommendations for BRCA1, BRCA2, and hereditary nonpolyposis colon cancer mutation carriers (35). The recommendations provided to mutation carriers in our study are consistent with those developed by the Cancer Studies Consortium. Mutation-negative individuals in this kindred are at the same cancer risk as members of the general population. In the absence of professional consensus, we chose to offer American Cancer Society recommendations for this group, since these recommendations are widely published and familiar to many in the general population. In brief, these recommendations include monthly breast self-examination, professional breast examination every 3 years from ages 20-40 years and yearly thereafter, and regular mammography to include a base-line mammogram at 40 years of age, mammograms every 1-2 years between the ages of 40 and 50 years, and yearly mammography thereafter.

Counseling regarding breast cancer in women who are mutation carriers. Female carriers with a current age of 20 years in this kindred are expected to have a cumulative penetrance for breast cancer of 21% at age 50 years and 58% at age 70 years. (See Fig. 2, A-C. These figures are specific to this kindred only and are different from the aggregate figures in the BCLC study of 17q families.) The documented importance of
Breast self-examination on a monthly basis is recommended to the women, and they are encouraged to attend a training session in their community. Mutation carriers are advised to have a physical examination of the breast every 6 months beginning at age 20 years. Yearly mammograms are advised starting at an age of 25 years (2 years younger than the youngest age of onset in this kindred). After age 50 years, mammography is advised every 6 months. Women are also advised, however, that early and frequent radiation exposure through mammography could, theoretically, promote cancer development in BRCA1 mutation carriers. There are no data available on this concern. Women are advised about the availability of experimental breast cancer prevention trials at the University of Utah. Women are also made aware of the option of prophylactic mastectomy. The risks and potential benefits of this approach are explained, although counselors are nondirective with respect to this option. Consultation with our surgeon and/or oncologist is offered.

Counseling regarding breast cancer in women who are not mutation carriers. Women who are not mutation carriers are expected to have the same risk of breast cancer as the female population at large. Although they are not gene carriers, they will still be at risk for this common cancer and are cautioned about complacency. Women are informed of the American Cancer Society recommendations (see previous page).

Counseling regarding ovarian and colon cancer in women who are mutation carriers. Female mutation carriers with a current age of 20 years in this kindred are expected to have a cumulative incidence of ovarian cancer of 16% to age 50 years and 67% to age 70 years. No screening strategy has been proven to be of benefit in reducing mortality from ovarian cancer; therefore, recommendations to this group cannot be supported by data. We are suggesting that women obtain a pelvic examination every 6 months beginning at age 30 years (4 years younger than the youngest age of onset in this kindred). For women over 30 years of age, we also recommend that they have a yearly transvaginal ultrasound as well as testing to monitor the level of CA-125 (a 200-kd glycoprotein found on the surface of ovarian cancer cells) in the serum, even though we recognize that these tests have not been proven to reduce ovarian cancer mortality. The risks and benefits of prophylactic oophorectomy are discussed. Consistent with the National Cancer Institute Consensus Development Panel on Ovarian Cancer, we currently recommend oophorectomy at age 35 years or when childbearing is complete (36). The possibility of an increased risk of colon cancer is also discussed, and the recommendations of the American Cancer Society for colon cancer screening in the general population are offered.

Counseling regarding ovarian and colon cancer in women who are not mutation carriers. This group of women will have the same risk of developing ovarian cancer as the population at large. There are no screening tests of proven use in reducing ovarian cancer mortality, and these individuals are advised to have regular pelvic examinations and Pap smears as recommended by their private physicians. The recommendations of the American Cancer Society with respect to colon cancer are provided.

Counseling for men. Men who are mutation carriers are counseled that they have a 50% risk of transmitting the BRCA1 gene to each of their offspring. In addition, the preliminary evidence that mutation carriers may be at increased risk of developing prostate and colon cancers is discussed. Given the current uncertainty about risks for mutation carriers and the controversy over the risks and benefits of prostate and colon cancer screening, men are informed of the American Cancer Society recommendations for cancer screening for males in the general population. Men who are not mutation carriers are provided the current American Cancer Society recommendations for cancer screening in the general population.

Surgical consultation. Subjects with BRCA1 mutations who seek surgical counseling are advised with regard to the risks and potential benefits of bilateral mastectomy. The operation of total mastectomy is explained. Patients are informed that prophylactic surgical removal of breast tissue will not reduce their risk of contracting breast cancer to zero. There is a small chance that these patients will still develop breast cancer despite prophylactic total mastectomy (37). At the time of the consultation for the operative management of patients with the BRCA1 gene, prophylactic oophorectomy is discussed. Women are advised that there is a small residual chance of ovarian (epithelial) cancer, despite removal of the ovaries (38). The operation can be done laparoscopically or through a laparotomy. The risks and benefits associated with the laparotomy and laparoscopy are outlined for the women.

Data Collection

Interviews of subjects obtaining genetic test results are conducted at entrance to the study (base line) and at 1-2 weeks, 4 months, 1 year, and 2 years after the results were obtained. Those subjects who decline genetic testing are interviewed at base line and at 1 and 2 years after recruitment. All interviews are conducted using computer-assisted telephone interviewing techniques. The questionnaire is programmed and executed using a personal computer that monitors the flow of the interview. For example, the computer will not display questions about spouses or children if the respondent is single and childless. At the conclusion of each interview, the data have already been entered. With the consent of the subject, interviews are tape-recorded to allow later transcription of answers to open-ended questions.

Measures

The interviews contain questions that pertain to pretesting levels of emotional and psychological well-being of K2082 members, their spouses, and their families. In 1997, the National Health Interview Survey (NHIS) of over 40,000 households that will be conducted by the National Center for Health Statistics will include supplements assessing psychological distress. This presents an ideal opportunity to compare scores obtained from our study participants with a large national sample. To the extent possible, we have incorporated measures that also will be used in the NHIS. These measures have undergone extensive validity and reliability analyses, and additional field trials are under way. In addition, many have already been tested in the National Center for Health Statistics Cognitive Survey Methods
Laboratory. Given that study participants already may have somewhat elevated levels of distress (because of risk awareness arising from a family history of breast and/or ovarian cancer), the ability to compare scores on state-of-the-art measures with population data is a substantial advantage. Furthermore, the primary measures were designed specifically for telephone interviews with members of the general population.

Demographic Characteristics

Demographic measures are contained in the base-line questionnaire, including age, education, (un)employment history, health and life insurance coverage, income, and marital status. These characteristics may play a confounding role in affecting how individuals and their families respond to genetic test results, and they may be sensitive in and of themselves to information about genetic test results.

Age may play a role in affecting psychological distress following the receipt of test results, since younger women with positive results will be in a position to consider the prospects of cancer for a longer period of time. Moreover, concerns over body image may be greater for younger rather than older women. On the other hand, women in their middle reproductive years may be facing substantial risk of ovarian cancer but may not have achieved their ideal family size, while younger women have more opportunity to complete their families while their risks are still low. Women’s marital status, education level, family income level, and health insurance status may also affect how individuals respond to the test results, since these characteristics represent resources that women draw on as they consider what the test results mean to them.

For those of childbearing age, an important demographic characteristic is their fertility behavior and intention. Changes in fertility intentions may occur for both men and women with positive and negative test results as they examine whether they wish to pass on the risk of breast and ovarian cancers to future children. Accordingly, several questions are included that ask about the possibility of adopting children.

We also hypothesize that differences may appear between those who test negative and positive in terms of their socioeconomic status. Of particular interest is the possible change in job security and health/life insurance coverage before and after the test results are given. These issues are relevant because it has been generally assumed that as genetic diagnostic capabilities become increasingly powerful, those who undergo diagnosis may risk job or insurance loss if (positive) test results become known (39-41). We hope to provide some evidence with which to assess the appropriateness of contemporary proposals for legal protection against the employment and insurance risks of genetic diagnosis.

General Psychological Distress

The primary measure of distress for base-line and follow-up interviews is a new 10-item unpublished scale developed by Ronald Kessler and his research team at the University of Michigan. This scale is the product of their extensive work being conducted for the new core portion of the NHIS. Cronbach’s alpha coefficient of internal consistency for the scale is .96. The scale was developed from an initial item pool of more than 500 items from all of the widely used measures of distress (e.g., Symptom Check List-90 [SCL-90], General Well-being Scale, the State Anxiety Scale of the State-Trait Anxiety Inventory [STAI], and Center for Epidemiologic Studies [CES]-Depression Scale), using modern Item Response Theory methods. To allow comparisons between study findings and results, both from previous studies and similar studies under way in Europe, the STAI is also administered. For similar reasons, the Beck Depression Inventory is included in a packet mailed immediately prior to the 1-2-week and 4-month follow-up interviews.

Specific Distress Concerning BRCA1 Test Results

The Impact of Event Scale (IES) (42) is administered in the follow-up interviews. The IES measures event-related distress, and the frame of reference in this context is the notification of mutation carrier status. In addition to the IES total score, the measure yields a subscore for avoidance and a subscore for intrusive thoughts and feelings. We expect that the IES may be a more sensitive measure of the psychological distress following genetic testing than the more general distress scales.

Psychiatric Instruments

Two components of the forthcoming NHIS psychiatric supplement that were developed, pretested, and validated by group are used at base line and at follow-up questionnaires to identify individuals who meet DSM-IV criteria for major depressive episode or anxiety disorder. The development of the diagnostic screening scales was based on the National Comorbidity Survey, the first nationally representative survey of a U.S. sample to incorporate a structured psychiatric interview (43). This survey of more than 8000 respondents was administered in 1991.

Health Behaviors

Respondents are asked about specific health behaviors, including use of breast self-examination, clinical breast examination, mammography, transvaginal ultrasound, digital rectal examination, prostate-specific antigen screening (men only), sigmoidoscopy, participation in other research protocols (e.g., breast cancer chemoprevention involving use of tamoxifen), surgical procedures (including mastectomy and oophorectomy), and the use of medications for a variety of symptoms. Questions about the use of consultation services, including psychiatry/psychology, oncology, genetics, surgery, and lay support groups, are asked of all participants in the base-line and post-test surveys. Cancer-related health-behavior questions were adapted from two segments of a supplemental section in the NHIS, “General Cancer Knowledge and Attitudes” and “Cancer Screening Knowledge and Practice” (44). Since the kindred members are geographically dispersed, we did not consider it feasible to review medical records to validate self-reports of health behaviors. However, self-reports of breast cancer screening behaviors have been shown to be highly accurate (>95%) when validated against medical records (45).

Family Functioning

The internal dynamics of the family are measured at base line and follow-ups by the Family Adaptability and Cohesion
Evaluation Scale II (FACES II). FACES II is a scale that characterizes families along two critical dimensions identified within family sociology and systems theory: cohesion and adaptability. The combination of these two characteristics describes an individual’s family type within the Circumplex Model of Olson et al. (46). Families that have low values for both scales are more likely to experience adverse health when stressed, relative to families with higher levels of both adaptability and cohesion. FACES II and its variations have been used in more than 500 studies on family stress, including topics on divorce, sexual dysfunction, migration, cancer, drug abuse, and mental illness.

Fertility Behavior and Intentions

For those of childbearing age, an important demographic characteristic is their fertility intentions. Items on fertility behavior and attitudes from large, nationally representative surveys, such as the National Survey of Family Growth (47) and the National Survey of Families and Households (48), are included in the base-line questionnaire. Items used on these large surveys that are adapted for this study will be examined to compare our study sample with comparable subsamples from these national surveys.

Cancer, Genetic, and Health Knowledge and Attitudes

Questions about the participants’ knowledge, attitudes, and behaviors associated with genetics and cancer prevention are asked in all surveys. Additional questions are included that ask the respondents about their knowledge concerning the inheritance and risk related to BRCA1. These measures will allow us to assess whether individuals’ prior knowledge and perceived/real risks of breast cancer affects 1) whether or not they join the study, 2) whether or not they elect to receive the test results, 3) their psychosocial response to the test results, and 4) their attitudes/knowledge after receiving the test results. These questions have been supplemented with items developed by Lerman et al. (49,50) concerning cancer-related worry, perceived risk of carrying a cancer gene mutation, and perceived risk of contracting relevant types of cancer.

Social Stress

Participants and their families will receive their test results at varying points in their lives. Just as these results may alter the level of stress experienced by the participants and their families, other stressors are also likely to occur in the course of everyday living. Respondents are also asked about other chronic and eventful stressors on the basis of the Family Inventory of Life Events (FILE), a checklist of normative and non-normative life events and other stressors. FILE is used for the telephone interviews.

Family Structure

A full family census (number of family members living in the household and sex, age, and relationship of each member) is taken to characterize the family’s structure and life stages prior to the receipt of the test results and as an indicator of access to kin. These data are critical for examining the effects that family structure has on the participants’ response to the test results (51).

Social Support and Coping

The pretested base-line questionnaire includes an indicator of social support (52) and family coping/help-seeking (Family Crisis-Oriented Personal Evaluation Scales [F-COPES]). Social support is important to measure at base line, as it may buffer the possible adverse effects of the stress induced by the test results (53-56).

F-COPES is an instrument created to identify problem-solving and coping strategies used by families in difficult or problematic situations. F-COPES contains 30 coping-behavior items that focus on two levels of interaction: the way families handle problems within the family and outside the family. There are five subscales in F-COPES: church/religious resources, extended family, friends, neighbors, and community resources. A measure of individual coping strategies used in response to receiving test results is included in a mail-out questionnaire packet sent to mutation carriers that is completed prior to the first follow-up telephone questionnaire (57).

Couple Analysis

Information about an individual’s behaviors and attitudes during the course of this study are based primarily on self-reported data collected during telephone interviews. To examine the role that spouses play in affecting and being affected by the genetic test results received by their husbands and wives, we will interview 400 subjects (men and women) and 100 spouses. Couple-level models will be estimated similar to those described by Thompson (58), where an individual’s response to the genetic test results (i.e., the tested individual or the spouse of the tested individual) is affected by his/her base-line behavior and attitudes as well as his/her spouse’s base-line characteristics.

Genetic Counseling Processes

To examine how psychological processes related to the genetic counseling sessions might mediate the impact of test results, both the subject and the genetic counselor complete brief questionnaires. Subjects complete a short questionnaire immediately before the results session, while the genetic counselors complete one after both the initial genetic counseling session and the results session. The subject’s questionnaire focuses on expectations concerning the test result and the subject’s level of anxiety. The genetic counselor’s questionnaire includes ratings of perceived subject comprehension as well as a checklist to indicate the subjects’ primary areas of concern or confusion.

Preliminary Results

Recruitment to the study began in December 1994. As of March 4, 1996, 528 contact letters have been sent and 435 responses have been received. (Many of those who had not responded had only recently received their letters, so we anticipate a higher response rate than these figures suggest.) Of those 435 responses, 362 (83%) expressed interest in the project with the intent of proceeding to genetic testing. Of the 170 subjects who have participated to date in the first counseling ses-
sion, 156 (92%) have requested genetic testing. The primary reason for declining genetic testing following counseling is knowledge of a mutation-negative parent. Genetic tests have been performed on 156 individuals, and results have been provided to 125 subjects, including 35 women and 16 men who are mutation positive and 42 women and 32 men who are mutation negative. Two individuals have been deferred from testing by the investigators. Both individuals are women who have past histories of substance abuse and suicidal ideation, and both lacked good social supports. Both women agreed that deferral was reasonable and appropriate for them.

Limitations

The study sample for this project is not representative of the U.S. population in terms of religious affiliation, race, average family size, or in their experience with medical research. It is not known whether or how these differences might affect the study findings. This may limit the generalizability of findings on the basis of the entire sample. At the same time, the sample is not homogeneous. Important differences within the kindred occur in terms of religious affiliation, religiosity, and family size. This means that comparisons of study subgroups broken down by these variables can and will be conducted.

The issue of generalizability is addressed in part by our plan to measure many of the variables on which members of the LDS Church and their families may differ from non-LDS individuals and families. For example, social support and family coping style are measured for all study participants. Analyses will then compare average values of these variables by religion and religiosity. In this way, psychosocial characteristics of devout LDS and their families can be identified and compared with other families. These data will inform the interpretation and generalizability of overall study results.

Finally, some members of this kindred have been involved with research projects in the past that involved the isolation of the BRCA1 gene. Their familiarity with some of the issues in genetics and genetic testing may have influenced the knowledge base, base-line behavior, and psychological reactions measured in this project. The effects of prior knowledge and experience with genetic testing research projects on the receipt of genetic testing results will be examined empirically as part of this study.

As these data are analyzed and reported, the project investigators will be careful to note these limitations in the generalizability of the study’s findings. We believe that many of the psychosocial issues raised by genetic testing apply broadly to a wide range of religious and socioeconomic subgroups. Nevertheless, it is clear that many of the families studied in this project are somewhat larger in size and have more extensive social networks than the average U.S. family. By analyzing the different roles that process variables play in mediating the impact of genetic test results among different subgroups, we can provide some of the critical information necessary for an informed discussion of the broader implications of project results.

Conclusions

The goals of genetic testing for cancer susceptibility are a reduction in mortality and morbidity from cancer and/or a reduction in psychological distress through the provision of risk information. Unfortunately, there are many uncertainties involved in clinical testing for BRCA1 mutations. It remains unclear whether preventive or early detection methods for cancer are effective in BRCA1 mutation carriers. Further, it remains unclear whether the genetic testing will result in behavior that might prevent cancer or detect it in its early stages, even if current measures prove to be effective in this population. Finally, it remains uncertain whether genetic testing will enhance or impair an individual’s psychological well-being and family functioning in the high-risk family context. Our research and similar projects will be important in elucidating the behavioral and psychosocial responses to BRCA1 mutation testing that will be critical to developing safe and effective strategies for using this powerful technology.

References


Li FP, Garber JE. Gene for familial breast and ovarian cancer [see comment citations in Medline]. Lancet 1993;341:1060-1.


Donal CA, Ware JE. The measurement of social support. Res Community and Mental Health 1984:4:325-70.


Notes

1. See also the September 1995 position paper of The National Breast Cancer Coalition. Presymptomatic genetic testing for heritable breast cancer risk. Survey instruments are available on request.

2. Individuals who report their religious affiliation as members of the Church of Jesus Christ of Latter-day-Saints (LDS or Mormons) can be subdivided into two meaningfully different groups: devout, practicing members of the LDS church and individuals who describe themselves as LDS-affiliated but are not active members. Many of the characteristics commonly attributed to the former group do not apply to the latter. Therefore, the following summary compares characteristics of three groups: devout Mormons, nondevout Mormons, and non-Mormons. The_better_and most recent data concerning Mormon/non-Mormon differences in Utah come from an unpublished 1990 survey conducted by one of the authors (K. R. Smith). The sample contained devout (n = 801) and non-devout (n = 379) Mormons as well as non-Mormons (n = 501). When members of these three groups are compared, there are many similarities and some differences. With regard to family formation and dissolution, Mormons tend to remain together longer in their first marriage and to have more children. Because of the longer length of first marriage and higher fertility, devout Mormons tend to show a less diverse range of family structures than other groups. The three groups do not differ, however, on measures of marital quality, marital satisfaction, and marital communication. When compared with the other two groups, devout Mormons report more extensive social networks; they report more close friends and relatives that they talk to frequently. In addition, devout Mormons also report that they are more likely to be members of organizations, most notably the Parent-Teacher Association (PTA) and youth groups. This survey also gathered data regarding aspects of health and health behavior. Devout Mormons are more likely to have never smoked. Nondevout Mormons report slightly lower average health status than do others. When married respondents were asked for proxy reports concerning their spouses, the data revealed no significant differences between the three groups on global health status measures or amount of exercise. The 1990 survey is based on respondents in Utah, the religious center of the LDS church. Using other regional and national samples, several other studies of psychosocial differences between LDS and non-LDS persons have found some differences and many similarities between these groups. Mormons are relatively conservative in terms of premarital sexual behavior and are somewhat more likely to marry. Mormons do not score differently as a group on standardized measures of psychological adjustment (e.g., MMPI) relative to other religious groups and those who are not religious. The larger families of Mormons tend to be characterized by traditional beliefs concerning parental and sex roles. Some evidence suggests that Mormon mothers have a slightly greater risk of depression than non-Mormon mothers.

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The Radiation Biology Branch, National Cancer Institute (NCI), National Institutes of Health is accepting applications for a tenure track position involving preclinical and mechanistic studies evaluating the effects of oxidants, such as superoxide, hydrogen peroxide, nitric oxide, oxygen-related radicals, ionizing radiation, and redox-active chemotherapy drugs, on the modulation of tumor and normal tissue physiology and cytotoxicity. The emphasis of the position will be to develop approaches that could potentially lead to therapeutic gains in cancer treatment and an understanding of the mechanism(s) of action that oxidative stress can exert at the biochemical, cellular, and physiologic level. Candidates should have strong research credentials and should have a publication record in leading international journals in research areas related to oxidative stress, radiation biology, and/or cancer biology. Likewise, experience and/or a basic understanding of advanced analytical chemical and biochemical techniques, cell biology, radiation biology, and general concepts of molecular biology is desirable. The salary range for this position is $49,856 to $68,729 per annum which is equivalent to a GS-13 in the Civil Service. Applicants should send Curriculum Vitae, bibliography, selected publications, a brief statement of research interest, and have three letters of reference sent to: Marie Priest, Division of Clinical Sciences, National Cancer Institute, Building 31, Room 3A11, 31 CENTER DR MSC 2440, Bethesda, MD 20892-2440. This information must be received no later than August 30, 1996. The NCI is an Equal Opportunity Employer.