

# Fertility Intentions Following Testing for a *BRCA1* Gene Mutation

Ken R. Smith,<sup>1</sup> Lee Ellington,<sup>1</sup> Anna Y. Chan,<sup>2</sup> Robert T. Croyle,<sup>3</sup> and Jeffrey R. Botkin<sup>1</sup>

<sup>1</sup>University of Utah, Salt Lake City, Utah; <sup>2</sup>U.S. Bureau of the Census, Washington, District of Columbia; and <sup>3</sup>National Cancer Institute, Bethesda, Maryland

## Abstract

**Objective:** To test whether fertility intentions differed among persons who tested positive, tested negative, or did not know their genetic status for a mutation of the *BRCA1* gene. **Method:** Participants were members of a large Utah-based kindred with an identified mutation at the *BRCA1* locus. Participants received genetic counseling prior to testing and were interviewed at baseline before testing and at three points after receiving test results from a genetic counselor. The sample included men and women who completed all interviews, were between ages 18 and 45, and were fertile, resulting in a sample of 101 respondents. The primary dependent variable measured whether a subject indicated that they were moderately or very sure at all three post-testing interviews that they intended to have additional children. Effects of *BRCA1* mutation status on fertility intentions were estimated using multivariate logistic regressions where we controlled

for gender, age, marital status, and baseline fertility intentions. **Results:** Female carriers were less likely to want additional children in relation to female non-carriers (odds ratio 0.12, 95% confidence interval 0.01–1.23;  $P = 0.074$ ). No differences were found among men. There was a significant difference in the effect of mutation status on fertility intentions between males and females (Gender  $\times$  Carrier status interaction;  $P = 0.009$ ). Persons who did not know their mutation status were less likely to want more children than noncarriers (odds ratio 0.09, 95% confidence interval 0.01–0.75;  $P = 0.027$ ). **Conclusion:** Predictive genetic testing for late-onset cancer susceptibility affects family planning decision-making. Persons contemplating predictive testing should be informed about possible effects such testing may have on their plans for future fertility. (Cancer Epidemiol Biomarkers Prev 2004; 13(5):733–40)

## Introduction

Psychosocial studies on the effects of predictive testing for cancer and other adult-onset diseases have largely focused on their psychological impact (*e.g.*, depression or distress) and on insurance issues (1–9). No systematic investigation has examined how childbearing intentions may differ between reproductive-aged individuals who have or do not have a genetic mutation that confers a greater susceptibility to common diseases such as breast cancer.

In the present study, we examined fertility intentions reported by adults of reproductive age after they received genetic test results for a mutation of the *BRCA1* gene. It is estimated that ~5–10% of breast cancer cases in the general population are associated with heritable mutations (10). Women who carry mutations in the *BRCA1/BRCA2* genes have a substantially increased risk of developing breast cancer and ovarian cancer. In 1994, *BRCA1* was the first major mutation associated with breast cancer to be identified and fully sequenced (11).

Data derived from the Breast Cancer Linkage Consortium indicated that the breast cancer risk in *BRCA1* mutation carriers is ~85% by age 70 and the ovarian cancer risk is 63% by age 70. Among recruited families with multiple members affected with cancer, the lifetime risks of breast cancer and ovarian cancer for female *BRCA1* carriers is 85% and 65%, respectively (12); however, for mutation carriers from a population from families not selected for cancer family history, the risk is lower (13, 14). In families that have not been selected based on family cancer history, *BRCA1* mutation carriers have average cumulative risks by age 70 of 65% for breast cancer and 39% for ovarian cancer (15). There is also evidence of an increased risk of prostate cancer in *BRCA1* mutation carriers (16). Therefore, genetic testing for *BRCA1* mutations is relevant to men as well due to an increased risk of cancer and because men can transmit the mutation to their offspring. *BRCA1* mutation carriers are also at excess risk for cancers of the pancreas, uterine body, and cervix (16). Although female carriers are at increased risk for cancer, both male and female carriers have a 50% chance of transmitting the altered gene to each offspring.

With an increased risk of cancer among mutation carriers, particularly mothers, parents and prospective parents may be concerned about the mother's health and mortality during the child rearing years. Additionally, parents may be concerned about transmitting the increased risk to their children. In general, we hypothesized

Received 6/24/03; revised 1/5/04; accepted 1/16/04.

**Grant support:** National Cancer Institute grant CA63681, National Human Genome Research Institute grant HG00199, and National Center for Research Resources grant M01-RR00064.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

**Requests for reprints:** Ken R. Smith, 225 S. 1400 East, University of Utah, Salt Lake, UT. E-mail: Ken.smith@fcs.utah.edu

that mutation carriers would be less likely than non-carriers to report a desire for additional children, and this effect would be stronger for women than men.

A small literature exists that has examined how predictive testing for noncancer disease susceptibility affects family planning among tested persons. The findings are limited and inconsistent given the small sample sizes and the fact that fertility questions are secondary to the specific aims of the studies (17). A few studies have considered actual fertility changes based on genetic counseling (18) or perceived or known genetic risks to adults, generally for extremely rare diseases [e.g., spinocerebellar ataxia (19), amyotrophic lateral sclerosis (20), and Huntington's disease (21, 22)]. In a study of persons who have been tested for *BRCA1/BRCA2* gene mutations, Lodder *et al.* (23) asked individuals 6 months after receiving their test results whether they would consider terminating a pregnancy if the fetus was a carrier. The authors reported that no carriers felt that ending a pregnancy was acceptable, while a small percentage (10–14%) of noncarriers did.

The purpose of this article was to examine fertility intentions reported by adults of reproductive age after they received genetic test results for a mutation of the *BRCA1* gene. To date, no study of genetic testing for breast cancer and ovarian cancer susceptibility has systematically examined the effects of genetic testing on fertility intentions.

## Materials and Methods

Data for this analysis were based on a large longitudinal study on the psychosocial and behavioral consequences of *BRCA1* mutation testing. The methods of recruitment, eligibility criteria, and protocol for this study were described in detail elsewhere (24) but summarized here. Study participants were members of a large Utah-based kindred of northern European descent (K2082) with an identified mutation at the *BRCA1* locus (25). All subjects in the study are descendants of a founding couple (four to five generations earlier) known to be *BRCA1* mutation carriers. The full sample comprises 111 distinct nuclear families.

Members were first contacted by letter and invited to participate in a prospective study that offered in-person genetic/family counseling prior to being offered mutation testing. Individual genetic counseling was also provided during a session when test results were provided to subjects. Invitation letters were sent to members of the oldest generation within a pedigree followed by letters inviting their adult descendants. To protect the privacy of parents' genetic information, adult offspring of parents who declined to participate were not themselves contacted unless the parents first provided written consent. Only 13% of these parents comprising the older generation ( $n = 152$ ) declined to participate themselves and less than half of those precluded the involvement of their adult children. Kindred members who expressed interest were contacted by phone and provided with more information, sent a consent form, and then completed a baseline interview.

Participating kindred members met individually with a genetic counselor to discuss whether they were in-

terested in being tested. The session included discussions about family cancer history, medical and cancer screening history, educational information about the *BRCA1* mutation, and associated cancer risks. Genetic counselors also explored the risks, benefits, and limitations of testing. Further details of the counseling issues associated with this study were described elsewhere (26). If, after counseling, the individual wished to be tested, a blood sample was drawn and the test was conducted. The individuals then returned for an in-person genetic counseling session to discuss their individual results.

Participants who received their test results were contacted for the first telephone follow-up interview 1–2 weeks after the receipt of their test results. Subsequent telephone interviews were conducted 4 months, 1 year, and 2 years after the receipt of test results.

Contact letters and response forms were mailed to 759 potential subjects. Five hundred of these individuals received full information about the project by telephone. Subjects who did not receive full project information ( $n = 259$ ) did so because they refused to participate in the study at the time of the initial invitation to the study ( $n = 124$ ) or project staff were unable to reach them (after repeated attempts) after the initial contact letter had been sent ( $n = 135$  of uncertain eligibility). Of the 759 subjects, 408 completed the baseline questionnaire for a response rate (type 1, which assumes all of 135 uncertain eligibility subjects were indeed eligible; <http://www.aapor.org>) of 53.8%. For the 500 subjects who received complete information about the study, 408 completed the baseline interview for a cooperation rate of 81.6%. Unfortunately, for many of these subjects, we could not confidently measure their ages because they were not subjects in the study. This means we could not know how many potential subjects were in our target age group of 18–45.

Of these 408 subjects, we first restricted the sample to those who were of childbearing age (between ages 18 and 45,  $n = 163$ ). We further limited this subsample to respondents who were still able to have children ( $n = 124$ ) to generate a pool of eligible persons for this analysis. In an effort to understand how fertility intentions changed over the 2-year period following the receipt of mutation status information, we also required that the respondent complete the 4-month, 1-year, and 2-year interviews. Twenty-three persons of the 124 initially eligible subjects dropped out of the study by the 2-year interview, leaving 101 subjects that are the basis for this analysis. Accordingly, the sample comprises 81.5% (101 of 124) of the eligible subjects identified at the time of the baseline interview.

## Measures

*Fertility Intentions/Behaviors.* Participants were asked two questions about their intentions to have more children at baseline and again at the 4-month, 1-year, and 2-year follow-up interviews. The two responses at each time point were coded and combined to create a single dummy variable representing the participants' certainty about their fertility intentions. The first question was answered in a yes (1) or no (0) response: "Looking to the future, do you (and your wife/husband) intend to have a(nother) child sometime?" The second question was in a three-point Likert format: "How sure are you

that you will have (more) children? Are you very sure, moderately sure, or not at all sure?" At each post-test interview, these two variables were combined to create a single dichotomy where individuals who were moderately or very sure they wanted a(nother) child were coded 1 and all others were coded 0. Hereafter, these are called time-specific measures of fertility intentions. For 18 husbands of tested wives and 14 wives of tested husbands from the sample of 101 subjects, we asked the same two fertility intention questions as was asked of the tested individuals at ~1-year post-test. A similar dichotomous fertility intention variable was then constructed for these spouses.

A composite dependent variable was also constructed based on a summary of each subject's responses at the three measurement points post-testing. Individuals who indicated that they were moderately or very sure at all three time points that they intended to have additional children were coded 1 and all others were coded 0.

From the 2-year interview, we asked subjects explicitly about their connection between their genetic status and their family planning decisions based on the following question: "Have you changed your plans about how many children to have because you know your genetic status?" Subjects answering "yes" were coded 1 and all others were coded 0.

**Social and Demographic Variables.** Gender, number of existing biological children, education (years), marital status, and age (years) were measured during the baseline interview.

**Cancer History.** All participants were asked if they had ever been diagnosed with cancer (breast, ovarian, prostate, and lung) or had cancer-related surgery (oophorectomy, hysterectomy, and mastectomy). Additionally, all subjects were asked about the number of first-degree and second-degree female relatives who had been diagnosed by a physician as having breast cancer and/or ovarian cancer.

**Test-Related Distress.** The Revised Impact of Event Scale (IES; 27, 28) was administered to participants who had blood drawn to determine their carrier status. The IES is a 15-item scale that measures event-related distress and was modified for this study to assess distress related to participants' receipt of their genetic test result. Internal consistency of the IES in this sample was high (Cronbach's  $\alpha = 0.90$ ). The measure used in this analysis was taken at the 4 months post-test interview.

**Perceived Risk of Breast Cancer.** At baseline, women were asked about their perceived risk of developing breast cancer based on the following question: "On a scale from 0 to 100, where 0 is no chance at all and 100 is absolutely certain, what do you think are the chances that you will get breast cancer sometime during your lifetime?" A similar question was asked of women regarding perceived ovarian cancer risk. The two perceived risk measures were highly correlated ( $r = 0.58$ ,  $P < 0.001$ ) and had similar effects on fertility intentions. Only the breast cancer risk measure was considered in the analysis.

**BRCA1 Mutation Status.** Subjects who chose to be tested were identified as carriers or noncarriers based on blood drawn for a DNA test. The *BRCA1* mutation in this

kindred created a stop codon at codon 1313 on chromosome 17q. The DNA test was a direct PCR test for this specific *BRCA1* mutation performed by the University of Utah's DNA Diagnostic Laboratory. For some participants whose parents or grandparents tested negative, they may have learned that they were noncarriers because individuals with noncarrier ancestors are also noncarriers. Some participants chose to participate in the study but chose not to learn their carrier status. The final sample included carriers ( $n = 25$ ), noncarriers ( $n = 62$ ), and those with unknown mutation status (UMS;  $n = 14$ ).

**Statistical Methods.** We estimated the association between the receipt of *BRCA1* mutation status and the intentions to have additional children by multiple logistic regressions. The primary dependent variable of interest was whether a respondent stated that they were moderately or very sure that they wanted to have additional children at all three interviews (fertility composite variable). In an attempt to illustrate the pattern of responses over time, we estimated separate logistic regressions for fertility intentions at each of the three time-specific interviews. In these analyses, the dependent variable is coded 1 if subjects were moderately or very sure that they want additional children as determined at the time of that particular interview. All other respondents were coded 0.

All models included information on *BRCA1* mutation status as measured by two dummy variables: carrier versus noncarrier and UMS versus noncarrier. Other covariates included in the model were age, gender, and whether respondents were moderately or very sure that they wanted more children.

We also examined the effects of personal and family cancer history, education, number of biological children, and, for the female subsample, perceived risk of breast cancer. In addition, we explored whether test-related distress, as measured by the IES, might act as a mediator between receipt of mutation testing and fertility intentions. None of these characteristics were found to be associated with fertility intentions and their inclusion did not alter in any substantive way the effects of mutation status on fertility intentions.

Our analyses are based on models that included the baseline measure of fertility intentions but not the number of children the participants already had. These two measures are highly correlated ( $r = -0.57$ ; those with more children are less likely to want additional children) and including both measures in the model led to imprecise estimates of both of their regression parameters. For this reason, and given that we were using fertility intentions as our dependent variable and we sought to control for such intentions at baseline, our final models controlled for baseline fertility intentions but not number of children. When we included number of children but excluded baseline fertility intentions, the effects of *BRCA1* mutation status on post-test fertility intentions were not substantively altered.

There were many instances where two or more family members were represented in the sample, suggesting that their fertility intentions were correlated. Generalized estimating equations were estimated using SAS PROC MIXED to assess whether accounting for correlated responses affected the results (29). In general, the

simpler regression models that assumed independent observations yielded results that were practically identical to those using generalized estimating equation. Accordingly, results using standard logistic regressions are reported here.

## Results

Demographic data are presented in Table 1. The sample of 101 included 67 females and 34 males. Eighteen husbands of tested wives and 14 wives of tested husbands were studied as a complement to the larger analysis of the full sample.

The proportion of subjects who reported being moderately or very sure that they wanted additional children is 59.4%, 47.5%, and 41.6% at the 4-month, 1-year, and 2-year interviews, respectively. Nearly 40% (39 of 101 or 38.6%) reported wanting additional children at all three of the post-test interviews of the sample. Of the remaining 62 subjects, 60% (37 of 62) reported that they were certain that they did not want additional children in each of the three post-testing interviews. Another 22.5% (14 of 62) of this subset of respondents indicated during the 4-month interview that they wanted more children but then reported that they were sure that they had completed their childbearing at both 1-year and 2-year post-test interviews.

The majority of participants (61.4%, 62 of 101) learned that they did not carry the *BRCA1* gene mutation, 24.7% (25 of 102) learned that they were carriers, and 13.9% (14 of 101) chose not to learn their carrier status (the UMS group). The covariates that we examined did not differ between these three groups with two exceptions. Carriers were more likely to have a mother with breast cancer or ovarian cancer (60%) followed by noncarriers (47%) and by the UMS group (21%;  $\chi^2 = 5.37$ ,  $df = 2$ ;  $P = 0.068$ ). This pattern was largely due to differences observed among women ( $\chi^2 = 9.5$ ,  $df = 2$ ;  $P = 0.009$ ). Among carriers and noncarriers, mean IES scores at the 4-month interview were higher for carriers ( $M = 12.24$  compared with  $M = 6.74$  for noncarriers;  $P = 0.019$ ), a pattern consistent with previous studies on genetically tested women using these data (3).

In Table 2, we report the results of a set of time-specific logistic regressions. Each model assessed whether *BRCA1* mutation status affects fertility intentions for a given post-test interview. For reasons of parsimony and given the relatively small sample size, all models initially included education level, personal cancer history, family cancer history, perceived cancer risk at baseline, and IES score. Given their weak association with fertility intentions, these variables were excluded from the models. Only those key variables that exhibited a significant relationship to fertility intentions (carrier status, age, gender, marital status, and baseline fertility intentions)

**Table 1. Descriptive statistics for the total sample and for *BRCA1* mutation carriers, noncarriers, and UMS**

| Label  | Total    |              |       | Carriers |              |      | Noncarriers |              |      | Unknown  |              |       |
|--|----------|--------------|-------|----------|--------------|------|-------------|--------------|------|----------|--------------|-------|
|  | <i>n</i> | Prop or mean | SD    | <i>n</i> | Prop or mean | SD   | <i>n</i>    | Prop or mean | SD   | <i>n</i> | Prop or mean | SD    |
| <i>BRCA1</i> mutation carrier (=1)                   | 101      | 0.248        | 0.434 | 25       | 1            | 0    | 62          | 0            | 0    | 14       | 0            | 0     |
| UMS (=1)   | 101      | 0.139        | 0.347 | 25       | 0            | 0    | 62          | 0            | 0    | 14       | 1            | 0     |
| No. biological children baseline                     | 101      | 1.782        | 1.616 | 25       | 1.92         | 1.63 | 62          | 1.806        | 1.73 | 14       | 1.429        | 1.016 |
| Certain want more children baseline (=1)             | 101      | 0.584        | 0.495 | 25       | 0.44         | 0.51 | 62          | 0.613        | 0.49 | 14       | 0.714        | 0.469 |
| Certain want more children 4 months (=1)             | 101      | 0.594        | 0.494 | 25       | 0.44         | 0.51 | 62          | 0.613        | 0.49 | 14       | 0.786        | 0.426 |
| Certain want more children 1 year (=1)               | 101      | 0.475        | 0.502 | 25       | 0.4          | 0.5  | 62          | 0.5          | 0.5  | 14       | 0.5          | 0.519 |
| Certain want more children 2 years (=1)              | 101      | 0.416        | 0.495 | 25       | 0.4          | 0.5  | 62          | 0.435        | 0.5  | 14       | 0.357        | 0.497 |
| Want more children all times dichotomy (=1)          | 101      | 0.386        | 0.489 | 25       | 0.32         | 0.48 | 62          | 0.419        | 0.5  | 14       | 0.357        | 0.497 |
| Alter fertility plans after test result 2 years (=1) | 101      | 0.069        | 0.255 | 25       | 0.16         | 0.37 | 62          | 0.032        | 0.18 | 14       | 0.071        | 0.267 |
| Whether had a personal history of cancer (=1)        | 101      | 0.03         | 0.171 | 25       | 0            | 0    | 62          | 0.048        | 0.22 | 14       | 0            | 0     |
| No. first/second-degree female relatives with BC/OC  | 101      | 1.564        | 1.337 | 25       | 1.64         | 1.15 | 62          | 1.677        | 1.44 | 14       | 0.929        | 1.072 |
| No. first-degree female relatives with BC/OC         | 101      | 0.634        | 0.902 | 25       | 0.72         | 0.74 | 62          | 0.694        | 1.02 | 14       | 0.214        | 0.426 |
| Whether mother had BC/OC (=1)                        | 101      | 0.465        | 0.501 | 25       | 0.6          | 0.5  | 62          | 0.468        | 0.5  | 14       | 0.214        | 0.426 |
| No. sisters had BC/OC                                | 101      | 0.149        | 0.555 | 25       | 0.12         | 0.44 | 62          | 0.194        | 0.65 | 14       | 0            | 0     |
| Age (years)  | 101      | 31.604       | 6.359 | 25       | 31.84        | 5.96 | 62          | 31.839       | 6.72 | 14       | 30.143       | 5.586 |
| Female (=1)  | 101      | 0.663        | 0.475 | 25       | 0.72         | 0.46 | 62          | 0.645        | 0.48 | 14       | 0.643        | 0.497 |
| Education (years)                                    | 101      | 14           | 1.817 | 25       | 13.52        | 1.69 | 62          | 14.258       | 1.9  | 14       | 13.714       | 1.541 |
| Perceived breast cancer risk baseline                | 67       | 48.94        | 23.23 | 18       | 48.333       | 30.4 | 40          | 50.975       | 20.3 | 9        | 41.111       | 19.49 |
| IES 4 months   | 87       | 8.226        | 9.934 | 25       | 12.237       | 12.1 | 62          | 6.742        | 8.58 |          |              |       |
| Married (=1)   | 101      | 0.822        | 0.385 | 25       | 0.76         | 0.44 | 62          | 0.806        | 0.4  | 14       | 1            | 0     |

Note: (=1), the variable is a dummy variable; BC/OC, breast cancer or ovarian cancer.

**Table 2. Effects of *BRCA1* mutation status on fertility intentions at 4 months, 1 year, and 2 years post-test based on multiple logistic regressions**

| Variable                                   | Main effects |           |         |        | Main effects + interaction |         |           |         |        |       |
|--|--------------|-----------|---------|--------|----------------------------|---------|-----------|---------|--------|-------|
|  | Estimate     | P         | OR      | 95% CI | Estimate                   | P       | OR        | 95% CI  |        |       |
| <b>4 months</b>                            |              |           |         |        |                            |         |           |         |        |       |
| Intercept                                  | 7.41         | 0.0275    |         |        | 8.76                       | 0.0182  |           |         |        |       |
| UMS (=1)                                   | 0.49         | 0.687     | 1.64    | 0.15   | 18.11                      | 0.44    | 0.7198    | 1.56    | 0.14   | 17.38 |
| <i>BRCA1</i> mutation carrier (=1)         | -0.79        | 0.3558    | 0.45    | 0.09   | 2.43                       | -0.32   | 0.7282    | 0.73    | 0.12   | 4.38  |
| Age baseline                               | -0.28        | 0.0037    | 0.75    | 0.62   | 0.91                       | -0.32   | 0.0032    | 0.72    | 0.58   | 0.90  |
| Wants additional children baseline (=1)    | 2.49         | 0.0017    | 12.03   | 2.55   | 56.70                      | 2.52    | 0.0023    | 12.42   | 2.45   | 62.93 |
| Married (=1)                               | 1.12         | 0.2764    | 3.06    | 0.41   | 22.93                      | 1.26    | 0.2819    | 3.53    | 0.36   | 35.11 |
| Female(=1)                                 | -0.40        | 0.6107    | 0.67    | 0.14   | 3.15                       | -0.83   | 0.3211    | 0.43    | 0.08   | 2.26  |
| Female × <i>BRCA1</i> mutation interaction |              |           |         |        |                            | -4.80   | 0.0253    | 0.01    | <0.001 | 0.55  |
| Model likelihood ratio ( <i>df</i> ) P     |              | 82.04 (6) | <0.0001 |        |                            |         | 87.58 (7) | <0.0001 |        |       |
| <b>1 year</b>                              |              |           |         |        |                            |         |           |         |        |       |
| Intercept                                  | 6.1305       | 0.0308    |         |        | 6.8841                     | 0.0218  |           |         |        |       |
| UMS (=1)                                   | -1.2619      | 0.1338    | 0.283   | 0.054  | 1.474                      | -1.3361 | 0.1223    | 0.263   | 0.048  | 1.432 |
| <i>BRCA1</i> mutation carrier (=1)         | -0.0558      | 0.9426    | 0.946   | 0.207  | 4.318                      | 0.312   | 0.7137    | 1.366   | 0.258  | 7.232 |
| Age baseline                               | -0.2945      | 0.0008    | 0.745   | 0.627  | 0.886                      | -0.3206 | 0.0008    | 0.726   | 0.602  | 0.876 |
| Wants additional children baseline (=1)    | 1.601        | 0.0485    | 4.958   | 1.011  | 24.32                      | 1.5519  | 0.0668    | 4.72    | 0.898  | 24.81 |
| Married (=1)                               | 2.2135       | 0.03      | 9.147   | 1.239  | 67.54                      | 2.4667  | 0.0277    | 11.78   | 1.311  | 105.9 |
| Female(=1)                                 | -0.8507      | 0.1871    | 0.427   | 0.121  | 1.512                      | -1.3145 | 0.0738    | 0.269   | 0.064  | 1.135 |
| Female × <i>BRCA1</i> mutation interaction |              |           |         |        |                            | -3.9485 | 0.0365    | 0.019   | <0.001 | 0.78  |
| Model likelihood ratio ( <i>df</i> ) P     |              | 67.07 (6) | <0.0001 |        |                            |         | 72.06 (7) | <0.0001 |        |       |
| <b>2 years</b>                             |              |           |         |        |                            |         |           |         |        |       |
| Intercept                                  | 13.343       | 0.001     |         |        | 14.274                     | 0.0008  |           |         |        |       |
| UMS (=1)                                   | -2.1534      | 0.0259    | 0.116   | 0.017  | 0.772                      | -2.26   | 0.0245    | 0.104   | 0.015  | 0.748 |
| <i>BRCA1</i> mutation carrier (=1)         | 0.4885       | 0.5977    | 1.63    | 0.266  | 10                         | 1.0347  | 0.3153    | 2.814   | 0.373  | 21.21 |
| Age baseline                               | -0.533       | <0.0001   | 0.587   | 0.453  | 0.76                       | -0.5666 | <0.0001   | 0.567   | 0.431  | 0.748 |
| Wants additional children baseline (=1)    | 0.5333       | 0.5807    | 1.705   | 0.257  | 11.31                      | 0.5826  | 0.5697    | 1.791   | 0.24   | 13.35 |
| Married (=1)                               | 2.4821       | 0.0574    | 11.97   | 0.925  | 154.8                      | 2.7519  | 0.0491    | 15.67   | 1.01   | 243.1 |
| Female(=1)                                 | -2.0219      | 0.0128    | 0.132   | 0.027  | 0.651                      | -2.7123 | 0.0051    | 0.066   | 0.01   | 0.443 |
| Female × <i>BRCA1</i> mutation interaction |              |           |         |        |                            | -4.3056 | 0.0573    | 0.013   | <0.001 | 1.144 |
| Model likelihood ratio ( <i>df</i> ) P     |              | 80.67 (6) | <0.0001 |        |                            |         | 84.76 (7) | <0.0001 |        |       |

Note: (=1), the variable is a dummy variable.

were used as covariates in the final models. Finally, we report results that included an interaction between gender and *BRCA1* mutation status. *BRCA1* mutation status is represented by two dummy variables: carrier *versus* noncarrier and UMS *versus* noncarrier. This interaction is restricted to the interaction between gender and the dummy variable "carrier *versus* noncarrier." No interaction is included between gender and "UMS *versus* noncarrier" due the small number of subjects in the UMS group.

Table 2 shows a clear pattern of association between mutation status and fertility intentions over time. First, the main effect of being a mutation carrier *versus* a noncarrier was nonsignificant for each of the three post-test interviews. However, when we introduced the interaction term between gender and carrier status, we found that carriers were significantly less likely to report a desire for future children than noncarriers among females but not males. For example, 59% of male noncarriers and 86% of male carriers would like to have additional children in the 4-month interview. Among women, the pattern was reversed with 67% of noncarriers and 28% of carriers reporting a preference for more children. The reduction in fertility intentions among female carriers *versus* noncarriers (and an insignificant difference between male carriers and noncarriers) also occurred at the 1-year and 2-year interviews.

Table 3 reports results from logistic regression models that used the composite dependent variable where we compared persons who have reported wanting additional children at all three post-test interviews with everyone else. Again, female mutation carriers, in relation to female noncarriers, reported a significantly lower interest in having additional children while there was an insignificant difference among males (Gender × Carrier mutation;  $P = 0.01$ ). When the sample was restricted to women (Female-only sample in Table 3), where we controlled for age, marital status, and baseline fertility intentions, female carriers were less likely to want additional children [odds ratio (OR) 0.12, 95% confidence interval (95% CI) 0.01–1.23;  $P = 0.0744$ ] in relation to noncarriers. No significant differences were found among in the male-specific subsample (results not shown).

Table 3 also shows that persons who do not know their mutation status have significantly lower intentions to have additional children than noncarriers (OR 0.09, 95% CI 0.01–0.75;  $P = 0.027$ ). This association was suggestive in the time-specific models (Table 2) and became increasingly stronger with the passage of time and finally becoming significant by the 2-year interview ( $P = 0.026$ ).

By using the composite measure that compares persons who reported wanting additional children at all three post-test interviews with everyone else may

**Table 3. Effects of *BRCA1* mutation status on composite fertility intentions based on multiple logistic regressions**

| Variable                                      | Main effects |          |           |             | Main effects + interaction |          |        |             | Females only: main effects |          |       |             |         |
|---|--------------|----------|-----------|-------------|----------------------------|----------|--------|-------------|----------------------------|----------|-------|-------------|---------|
|   | Estimate     | <i>P</i> | OR        | 95% CI      | Estimate                   | <i>P</i> | OR     | 95% CI      | Estimate                   | <i>P</i> | OR    | 95% CI      |         |
| Intercept                                     | 13.41        | 0.001    |           |             | 15.74                      | 0.0012   |        |             | 11.24                      | 0.0139   |       |             |         |
| UMS (=1)                                      | -2.18        | 0.03     | 0.11      | 0.02 0.81   | -2.45                      | 0.0267   | 0.09   | 0.01 0.75   | -2.9                       | 0.0385   | 0.06  | 0.01 0.86   |         |
| <i>BRCA1</i> mutation carrier (=1)            | -0.42        | 0.65     | 0.66      | 0.11 3.96   | 0.25                       | 0.8237   | 1.29   | 0.14 12.07  | -2.13                      | 0.0744   | 0.12  | 0.01 1.23   |         |
| Age baseline                                  | -0.58        | <0.0001  | 0.56      | 0.42 0.74   | -0.67                      | 0.0001   | 0.51   | 0.37 0.72   | -0.52                      | 0.0015   | 0.60  | 0.43 0.82   |         |
| Wants additional children baseline (=1)       | 0.46         | 0.661    | 1.58      | 0.21 12.09  | 0.64                       | 0.615    | 1.90   | 0.16 23.11  | 0.44                       | 0.7482   | 1.56  | 0.1 23.81   |         |
| Married (=1)                                  | 3.49         | 0.015    | 32.62     | 1.97 539.60 | 4.02                       | 0.0152   | 55.51  | 2.17 >999   | 3.22                       | 0.0319   | 24.97 | 1.32 471.56 |         |
| Female(=1)                                    | -2.01        | 0.012    | 0.13      | 0.03 0.65   | -3.23                      | 0.0039   | 0.04   | 0.00 0.35   |                            |          |       |             |         |
| Female × <i>BRCA1</i> mutation interaction    |              |          |           |             | -7.20                      | 0.01     | <0.001 | <0.001 0.17 |                            |          |       |             |         |
| Model likelihood ratio ( <i>df</i> ) <i>P</i> |              |          | 81.38 (6) | <0.0001     |                            |          |        | 90.80 (7)   | <0.0001                    |          |       | 52.20 (5)   | <0.0001 |

Note: (=1), the variable is a dummy variable.

overlook the possibility that subjects change their minds. When we created a new trichotomous variable that again considers preferences across all three interviews (*i.e.*, an ordinal variable with three categories: always wants children, varies between wanting and not wanting children, and never wants children), we used an ordinal logistic regression model. The results yielded nearly identical conclusions as those reported in Table 3.

From the 2-year interview, we examined the association between mutation status and whether subjects made an explicit change in the number of children they wish to have because of their test result. While the previous models show that at least among females, being a mutation carrier was associated with lower intentions to have additional children, this explicit question about linking genetic test results to reproductive decision-making resulted in only seven affirmative responses. Nonetheless, there is preliminary support in this model that suggested that carriers are 5.46 times more likely (95% CI 0.92–32.46) to have altered their family planning more than noncarriers because of their test results [*i.e.*, 16% (4 of 25) altered the number of children they wanted among carriers and 3.2% (2 of 62) among noncarriers; the *P* value for the age-sex adjusted difference is 0.0621; the justification for adjusting the analysis for age and sex only was that the dependent variable is skewed with very few people reporting having made making such a change].

We also examined fertility intentions among the spouses of tested individuals (18 husbands, 14 wives). No husband with a carrier wife indicated a desire for additional children (0 of 6), while half of the husbands of noncarrier wives did (6 of 12;  $\chi^2 = 4.5$ , *df* = 1, Fisher's exact *P* = 0.054). One wife out of the three carrier husbands and 27% of wives of noncarrier husbands (3 of 11) wanted additional children ( $\chi^2 = 0.024$ , *df* = 1, Fisher's exact *P* = 0.99). While we were not able to interview more spouses of reproductive age for this study, these exploratory results suggest that the impact of being a female carrier translated into a reduction in the husband's fertility intentions, but there was no comparable effect among wives of male carriers.

## Discussion

We examined fertility intentions among 101 individuals of reproductive age from a high-risk kindred who participated in a study on genetic counseling and testing for a *BRCA1* gene mutation. To our knowledge, no study has systematically examined the fertility intentions of individuals receiving genetic information and testing for breast cancer and ovarian cancer susceptibility. Our results were consistent with our hypothesis that female gene mutation carriers were less likely to want additional (or any) children compared with female noncarriers. We found no effect of mutation status on fertility intentions among men.

Individuals who chose not to be tested and who did not know their mutation status were less likely to want additional children than noncarriers. It is not yet clear what may motivate these subjects to limit their family size. Apparently, these individuals were especially anxious about what would happen to them should they learn that they were carriers, an anxiety that may alter their intentions to have additional children. However, we were unable to identify a characteristic that clearly differentiated these individuals from those who chose to be tested, including pretesting assessments of their likelihood of being a mutation carrier or, as some have suggested, depression (4). Given the potential impact that genetic testing has on tested persons and their spouses, we examined the quality of the marriage prior to testing and found somewhat more marital strain before testing among UMS individuals in relation to those who were tested. Controlling for pretest marital strain did not mediate the association between not knowing one's mutation status and lower fertility intentions. More research is justified so that we may better understand the motives of individuals from high-risk families who are offered testing but choose to forgo it.

The effects of the burgeoning genetic technology on reproductive issues have been long been a concern of ethicists and scholars examining the ethical, legal, and social implications of genetics and genetic testing (30–32). The American Society of Human Genetics, the National Society of Human Genetics, the National Advisory Council for Human Genome Research, and the National Breast Cancer Coalition have all called for

a careful and continued evaluation of genetic testing before broader clinical testing and population screening is implemented. The speed and success of the Human Genome Project has certainly heightened questions about reproduction with the attendant increase in the number of genetic tests for late-onset diseases such as those for mutations of the *BRCA1/BRCA2* genes. The increasing availability of predictive genetic testing clearly suggests a need for more research on its consequences for reproductive decision-making.

It was surprising that little work had been conducted regarding the association between predictive testing and fertility choices for two reasons. First, the long-standing concerns among ethicists about fertility outcomes among persons choosing predictive testing would suggest more research in this arena. Second, high-risk individuals often indicated that they chose testing to learn about cancer risks for their existing children's but also for their future children and grandchildren, all with an eye toward prevention, early detection, and cure (33, 34). The majority of respondents in our study of K2082 also reported a motivation for being tested was to learn about the cancer risks for their children, realized and potential.

Our study of fertility intentions necessarily focused on a sample where future fertility was a possibility. The sample analyzed here was therefore restricted to fertile men and women. This strategy had some important implications for studies seeking to understand the association between testing and fertility intentions. We have reported elsewhere (35) that after testing, carrier women were significantly more likely to have bilateral oophorectomies than noncarrier women. This is a surgical procedure that was presented as a possible consideration in our study protocol for female carriers. While more carrier women had their ovaries removed than noncarrier women, the majority of reproductive-aged carriers did *not* have oophorectomies. This observation suggests that more concerned carrier women who were fertile became surgically sterile and hence were not asked about their fertility intentions. It is plausible that these same women, prior to their surgery, would have strong views about future childbearing (that were not asked about future childbearing because they were sterile). This scenario suggests that the estimated association reported here between fertility intentions and mutation status among women may be conservative.

We have also found that carrier women were more likely than noncarrier women to have had oophorectomies *before* they learned that they were carriers. Such an association is explicable because carrier women have more affected female relatives, information that physicians may use to base their recommendation for a surgical intervention. This observation too suggests that studies considering the fertility effects of genetic testing among *fertile* women may be biased because some of the high-risk women (mutation carriers who do not yet know they are) will have surgically induced sterility.

Not all subjects who were initially invited into the study chose to participate. We know that persons with no or few affected close relatives are less likely to participate (results not shown), a feature that suggests that non-carriers are less prone to be involved in the study. Accordingly, we suggest that this means that our analysis

includes the more anxious noncarriers, thereby making them more like mutation carriers. This potential bias has the effect of making our results conservative. Given the longitudinal nature of our study, the sample also experienced attrition over time. The loss of sample size and the somewhat greater propensity of known noncarriers to drop out also serve to reduce statistical power and to bias our results toward the null. Again, these methodological issues serve to make our results conservative.

Nearly all subjects in this kindred were identified as practicing members of the Church of Jesus Christ of Latter-day Saints. Accordingly, subjects hold values that encourage large families. Indeed, it was these values that facilitated this study because a preference for many children, on average, provided the opportunity for us to also observe wide variations in fertility intentions. The impact of perceived genetic susceptibility and family cancer history on fertility intentions in other populations may also be significant because these populations are more likely to have preferences for smaller families. For example, in a lower fertility group such as Ashkenazi Jews with a high risk for *BRCA1/BRCA2* mutations, the effects might lead to childlessness. Accordingly, the effects that mutation testing reported here are likely to be conservative because the predisposition of these subjects will be toward pronatalism' unlike other populations where the desire for childbearing might be less firmly entrenched.

Genetic testing for breast cancer susceptibility has largely been conducted on large at-risk families. This raises a question about whether these families are representative of families in the larger population. At present, research families have provided the only longitudinal data that can help us to anticipate the likely outcomes that may occur when larger-scale community testing occurs. Given that entire families have been invited to participate in these initial research protocols, family members were able to provide support to each other and likely discussed their results with one another (36). Individuals contemplating testing outside of a research study will be less likely to have the same level of family support and involvement of medical researchers when compared with research families. For this analysis, the effects of testing on fertility intentions among members of the K2082 kindred (as well as with other kindreds enrolled in research projects) may differ from the effects that arise in the general community.

This study was based on a large kindred identified from a common founder comprising over 100 nuclear families studied over a 2-year period following testing. This was the first study that has observed longitudinally a large number of tested individuals at risk for a common late-onset cancer to determine how genetic test results affected family planning decision-making. Further work is needed to determine whether reduced fertility intentions translate into an actual reduction in reproduction.

### Acknowledgments

We thank Diana Lane Reed, Deb Ma, and Jean Wylie for their invaluable assistance with this analysis.

### References

1. Codori A-M, Brandt J. Psychological costs and benefits of predictive testing for Huntington's disease. *Am J Med Genet* 1994;54:174-84.

2. Codori A-M, Slavney PR, Young C, Miglioretti DL, Brandt J. Predictors of psychological adjustment to genetic testing for Huntington's disease. *Health Psychol* 1997;16:36-50.
3. Croyle RT, Smith KR, Botkin JR, Baty B, Nash J. Psychological responses to BRCA1 mutation testing: preliminary findings. *Health Psychol* 1997;16:63-72.
4. Lerman C, Hughes C, Lemon SJ, et al. What you don't know can hurt you: adverse psychologic effects in members of BRCA1-linked and BRCA2-linked families who decline genetic testing. *J Clin Oncol* 1998;16:1650-4.
5. Marteau TM, Dundas R, Axworthy D. Long-term cognitive and emotional impact of genetic testing for carriers of cystic fibrosis: the effects of test result and gender. *Health Psychol* 1997;16:51-62.
6. Smith KR, West JA, Croyle RT, Botkin JR. Familial context of genetic testing for cancer susceptibility: moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. *Cancer Epidemiol Biomarkers & Prev* 1999 Apr; 8(4 Pt 2):385-92.
7. Tibben A, Timman R, Bannink EC, Duijvenvoorden HJ. Three-year follow-up after presymptomatic testing for Huntington's disease in tested individuals and partners. *Health Psychol* 1997;16:20-35.
8. Wiggins S, Whyte P, Huggins M, et al. The psychological consequences of predictive testing for Huntington's disease. *N Engl J Med* 1992;327:1401-5.
9. Zick CD, Smith KR, Mayer RN, Botkin JR. Genetic testing, adverse selection, and the demand for life insurance. *Am J Med Genet* 2000; 93:29-39.
10. King MC, Rowell S, Love SM. Inherited breast and ovarian cancer: what are the risks? What are the choices? *JAMA* 1993;269:1975-80.
11. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994;266(5182):66-71.
12. Easton DF, Ford D, Bishop DT and the Breast Cancer Linkage Consortium. Breast and ovarian cancer incidence in BRCA1-mutation carriers. *Am J Hum Genet* 1995;56:265-71.
13. Devilee P. BRCA1 and BRCA2 testing: weighing the demand against the benefits. *Am J Hum Genet* 1999;64:943-8.
14. Easton D. Breast cancer genes—what are the real risks? *Nat Genet* 1997;16:210-1.
15. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003 May;72(5):1117-30.
16. Thompson D, Easton DF. Breast cancer linkage consortium cancer incidence in BRCA1 mutation carriers. *J Natl Cancer Inst* 2002 Sep 18;94(18):1358-65.
17. Bonadona V, Sallat P, Desseigne F, et al. Cancer patients who experienced diagnostic genetic testing for cancer susceptibility: reactions and behavior after the disclosure of a positive test result. *Cancer Epidemiol Biomarkers & Prev* 2002;11:97-104.
18. Kessler S. Psychological aspects of genetic counseling; VI. A critical review of the literature dealing with education and reproduction. *Am J Med Genet* 1989;34:340-53.
19. Nance MA, Sevenich EA, Schut LJ. Knowledge of genetics and attitudes toward genetic testing in two hereditary ataxia (SCA 1) kindreds. *Am J Med Genet* 1994;54:242-8.
20. Johnson WG, Lucel PR, Chatkupt S, et al. Reduced fecundity in male ALS gene-carriers. *Am J Med Genet* 1995;59:149-53.
21. Pridmore SA. Relative fertility of unaffected siblings of the Huntington's disease families in Tasmania. *Med J Aust* 1990;153: 588-9.
22. Morrison PJ, Johnston WP, Nevin NC. The epidemiology of Huntington's disease in Northern Ireland. *J Med Genet* 1995;32:524-30.
23. Lodder LN, Frets PG, Trijsburg RW, Meijers-Heijboer EJ, Klijn JGM, Niermeijer MF. Attitudes towards termination of pregnancy in subjects who underwent presymptomatic testing for the BRCA1/BRCA2 gene mutation in The Netherlands. *J Med Genet* 2000;37(11):883-4.
24. Botkin JR, Croyle RT, Smith KR, et al. A model protocol for evaluating the behavioral and psychosocial effects of BRCA1 testing. *J Natl Cancer Inst* 1996;88:872-82.
25. Goldgar D, Fields P, Lewis CM. A large kindred with the 17q-linked breast and ovarian cancer: genetic, phenotypic, and genealogical analysis. *J Natl Cancer Inst* 1994;86:200-9.
26. Baty B, Venne V, McDonald J, Croyle R, Botkin J. Genetic counseling protocols for BRCA1 testing. *J Genet Counsel* 1997;6:223-44.
27. Horowitz M, Wilner N, Alvarez W. The Impact of Event Scale: a measure of subjective stress. *Psychosom Med* 1979;41:209-18.
28. Zilberg NJ, Weiss DD, Horowitz MJ. Impact of Event Scale: a cross-sectional validation study and some empirical evidence supporting a conceptual model of stress response syndromes. *J Consult Clin Psychol* 1982;50:407-14.
29. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986 Mar;42(1):121-30.
30. Motulsky A. Impact of genetic manipulation on society and medicine. *Science* 1983;219:135-40.
31. Annas E, editor. Gene mapping: using law and ethics as guides. New York: Oxford University Press, 1992.
32. Andrews LB, Fullarton JE, Holtzman NA, Motulsky AG. Assessing genetic risks: implications for health and social policy. Washington DC: National Academy Press; 1994.
33. Lynch HT, Lemon SJ, Durham C, et al. A descriptive study of BRCA1 testing and reactions to disclosure of test results. *Cancer* 1997;79(11): 2219-28.
34. Richards CS, Ward PA, Roa BB, et al. Screening for 185delAG in the Ashkenazim. *Am J Hum Genet* 1997;60(5):1085-98.
35. Botkin JR, Smith KR, Croyle RT, et al. Genetic testing for a BRCA1 mutation: Prophylactic surgery and screening behavior in women 2 years post testing. *Am J Med Genet* 2003 Apr 30;118A(3):201-9.
36. Smith KR, Zick CD, Mayer RN, Botkin JR. Voluntary disclosure of BRCA1 mutation tests results. *Genet Test* 2002;6:89-93.