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Research Article

Long-Term Psychosocial Outcomes of *BRCA1/BRCA2* Testing: Differences across Affected Status and Risk-Reducing Surgery Choice

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Abstract

Background: Numerous studies have documented the short-term impact of *BRCA1/BRCA2* (*BRCA1/2*) testing; however, little research has examined the long-term impact of testing. We conducted the first long-term prospective study of psychosocial outcomes in a U.S. sample of women who had *BRCA1/2* testing.

Methods: Participants were 464 women who underwent genetic testing for *BRCA1/2* mutations. Prior to testing, we measured sociodemographics, clinical variables, and cancer specific and general distress. At long-term follow-up (Median = 5.0 years; Range = 3.4–9.1 years), we assessed cancer-specific and genetic testing distress, perceived stress, and perceived cancer risk. We evaluated the impact of *BRCA1/2* test result and risk-reducing surgery on long-term psychosocial outcomes.

Results: Among participants who had been affected with breast or ovarian cancer, *BRCA1/2* carriers reported higher genetic testing distress ($\beta = 0.41$, $P < 0.0001$), uncertainty ($\beta = 0.18$, $P < 0.0001$), and perceived stress ($\beta = 0.17$, $P = 0.005$) compared with women who received negative (i.e., uninformative) results. Among women unaffected with breast/ovarian cancer, *BRCA1/2* carriers reported higher genetic testing distress ($\beta = 0.39$, $P < 0.0001$) and lower positive testing experiences ($\beta = 0.25$, $P = 0.008$) than women with negative results. Receipt of risk-reducing surgery was associated with lower perceived cancer risk ($P < 0.0001$).

Conclusions: In this first prospective long-term study in a U.S. sample, we found modestly increased distress in *BRCA1/2* carriers compared with women who received uninformative or negative test results. Despite this modest increase in distress, we found no evidence of clinically significant dysfunction.

Impact: Although a positive *BRCA1/2* result remains salient among carriers years after testing, testing does not seem to impact long-term psychologic dysfunction. *Cancer Epidemiol Biomarkers Prev; 21(3); 445–55. ©2012 AACR.*

Introduction

BRCA1/BRCA2 (*BRCA1/2*) gene testing is now part of routine care for women with significant family histories of breast or ovarian cancer (1, 2). The clinical utility of *BRCA1/2* testing is evidenced by high rates of risk-reducing surgeries by *BRCA1/2* carriers over the long term (3–8) and the resultant decrease in morbidity and mortality (9). In contrast, little is known about long-term psychosocial outcomes of *BRCA1/2* genetic testing, particularly in the context of risk-reducing surgery.

Numerous studies (10–16) have described the short-term psychosocial impact of *BRCA1/2* genetic testing in the year after receipt of results. Mixed evidence suggests that *BRCA1/2* mutation carriers may experience higher distress than noncarriers in the months following testing (16, 17), but such differences typically dissipate 1 year postresult (10, 14). In fact, comparisons between carriers and age-matched general populations reveal no differences on psychosocial outcomes at 1 year posttesting (10). The few studies that explored the psychosocial impact of receiving uninformative *BRCA1/2* results reported decreased distress and worry over time (15, 18).

We are aware of 3 small studies that have evaluated the long-term impact of testing. Two studies focused on people unaffected with cancer and found no differences on psychosocial outcomes between carriers and noncarriers at 3 years (11) or 5 years posttesting (19). The third study, using a cross-sectional design with a sample of U.S. women, focused on genetic testing–specific concerns 7

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Note: Institutional Review Board approval was granted for this study and all participants provided informed consent.

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years posttest (20). Results indicated statistically significant, but not clinically significant, greater genetic testing distress in *BRCA1/2* carriers compared with noncarriers (20).

Likewise, few studies have evaluated the impact of risk management choices on long-term psychosocial outcomes. In a large sample of high-risk women in the Netherlands (most of whom had not had *BRCA1/2* testing), risk-reducing oophorectomy was associated with reduced worry and perceived risk (21). Similarly, in a French cohort sample, risk-reducing surgery was associated with lower perceived cancer risk (22).

This study is the first to prospectively examine long-term psychosocial outcomes in a large U.S. sample. Given differences in risk management decisions, health care systems, and participant demographics, data from European samples may not generalize to the United States. This study extends prior research in several ways. First, unlike some prior studies (11, 16), this study includes individuals with and without cancer. Second, whereas prior work has largely focused on a limited number of psychosocial outcomes, we included a broad range of outcomes spanning specific ratings of genetic testing distress to more global perceived daily stress. Third, in contrast to the only other long-term study with a U.S. sample (20), our prospective design allows us to control for pretest psychosocial functioning levels. Finally, this study evaluated psychosocial outcomes within the context of risk-reducing surgery choices.

Materials and Methods

Study population

We identified participants through the Lombardi Comprehensive Cancer Center (LCCC) Familial Cancer Registry (FCR). Participants were eligible if they were female, 25 to 75 years old, had received *BRCA1/2* test results at LCCC, and were at least 3 years postdisclosure at the time of this study. Methods for this study and characteristics of FCR participants are described elsewhere (8, 23). Briefly, at the time participants in this article received genetic counseling/testing, all counseling and testing at LCCC was conducted through research protocols. Participants in this article came from 1 of 4 genetic studies: two observational studies (24, 25) of short-term genetic counseling outcomes and 2 intervention trials (26, 27). One trial evaluated a psychosocial telephone counseling intervention for mutation carriers (26) and the other evaluated an interactive decision aid for mutation carriers (27). This article includes 26 mutation carriers who had been randomized to the intervention arms of one of the trials; we thus controlled for randomization to intervention arm in subsequent analyses. All participants in this article had completed a baseline assessment prior to genetic counseling, received genetic counseling/testing, and had been followed for 12 months as part of their initial participation. This article describes an additional long-term follow-up assessment.

We mailed letters of invitation to 655 potentially eligible FCR participants who had consented to recontact for future studies. Of the 655 eligible FCR participants, we lacked accurate contact information for 26 (4%), yielding 629 women. Of the 629, 118 (18.7%) declined participation and 47 (7.5%) could not be reached after repeated attempts. Our final sample ($N = 464$) represents 73.8% of those eligible and for whom we had correct contact information. Compared with eligible nonparticipants, participants were more likely to be married and less likely to be Jewish ($P < 0.05$).

Procedures

Mailed invitation packets described the study and included Institutional Review Board (IRB)-approved consent documents, a printed version of the survey, a stamped postcard to decline participation, and a telephone number if the participant preferred to complete the survey by phone. Potential participants could decline participation by telephone or mail. Women interested in participating completed the 30-minute survey by print or telephone. Our IRB approved the research protocol, and all participants provided informed consent.

Measures

Control and predictor variables. *Sociodemographics.* We assessed age, race, education, marital status, employment status, income, and religion.

Time since receipt of test result. We calculated the time between receipt of test results and current study completion; we dichotomized time at the median of 5 years.

Genetic test result. Results were classified as "positive" if a woman was found to have a deleterious mutation, "negative" if she was found not to carry a mutation previously identified in her family, and "uninformative" when no mutation was detected in the first tested person in a family.

Personal/family cancer history. We assessed personal cancer history of the participants and the number of first and second degree relatives affected with breast or ovarian cancer.

Time since cancer diagnosis. We stratified women affected with cancer into those diagnosed less than 10 years ago versus those diagnosed more than 10 years ago. We selected 10 years as this value was closest to the mean time since diagnosis (10.4 years).

Pretesting distress. We measured cancer-specific distress prior to genetic testing using the 15-item, highly reliable (alpha = 0.88), Impact of Event Scale (IES; ref. 28). For general distress, 87 participants completed the 20-item State Trait Anxiety Inventory (STAI; ref. 29) and 366 participants completed the anxiety subscale of the Brief Symptom Inventory (BSI; ref. 30). Both measures are reliable (alphas = 0.85–0.91). We z-scored the STAI and BSI and used these as a composite measure of general pretest distress.

Risk-reducing surgeries. We assessed receipt of risk-reducing mastectomy (RRM) and risk-reducing bilateral

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salpingo-oophorectomy (RRBSO) with face-valid interview items described in prior reports (8).

Outcome variables. *Perceived risk for breast and ovarian cancer.* We assessed perceived risk for developing breast and ovarian cancer using a numeric perceived risk item (31, 32). Women responded with a number between 0 ("definitely won't get breast cancer") and 100 ("definitely will get breast cancer"). For individuals affected with cancer, we asked their perceived risk of developing cancer again. We used separate items for breast and ovarian cancer perceived risk.

Perceived stress. We assessed perceived stress using the 4-item version of the psychometrically sound Perceived Stress Scale (33). Responses were made on a 5-point scale ranging from "never" to "very often." Internal consistency in this study was good (alpha = 0.82).

Distress. We assessed cancer-specific distress at the long-term follow-up using the IES (described above; alpha at follow-up = 0.89). We measured genetic testing distress with the 21-item Multi-Dimensional Assessment of Cancer Risk Assessment (MICRA; ref. 34). The MICRA has subscales measuring distress, uncertainty and positive experiences related to the genetic test result. Subscale alphas ranged from 0.81 to 0.85.

Statistical analysis

After generating descriptive statistics to characterize the sample, we conducted separate analyses for women affected with breast or ovarian cancer and for women unaffected with cancer. For affected women, we compared those who tested positive to those who received an uninformative genetic test result. For unaffected women, we compared those with a positive result to those with a definitive negative test result. We identified potential confounders for inclusion in multivariate models by first evaluating bivariate predictors of our psychosocial outcomes using *t* tests (with Satterthwaite's approximation for unequal variances when appropriate) and Pearson correlation coefficients. To be conservative, we included potential confounders with bivariate associations at the $P < 0.10$ level in our multivariate models.

Next we conducted a series of multiple regression models with hierarchical variable entry to evaluate the independent effect of test result on each outcome after adjusting for confounders identified in bivariate analyses. To minimize the number of multivariate models, we conducted multivariate modeling only for the outcomes that were statistically significantly associated ($P < .05$) with test result in bivariate analyses. Finally, in analyses limited to carriers, we evaluated the impact of risk-reducing surgery on psychosocial outcomes by including RRM and RRBSO status in regression models, again adjusting for all variables with bivariate associations at the $P < 0.10$ level.

We have organized the results as follows: sample characteristics, results for women affected with cancer, results for women unaffected with cancer, and then results related to risk-reducing surgery among *BRCA1/2* carriers and psychosocial outcomes.

Results

Sample characteristics

Sample characteristics by affected/unaffected status are displayed in Table 1 and Table 2. Overall, 144 (31%) participants received positive results, 261 (56.1%) received uninformative results, and 60 (12.9%) received definitive negative results. The mean age of the participants was 52.5 (SD = 10.1); women received *BRCA1/2* results a median of 5.0 years prior (range = 3.4–9.1 years; SD = 1.2 years). Most participants were white (92%), college educated (95%), employed (57%), and married (77%). The majority was affected with breast cancer (72%); only 4% ($n = 18$) had ovarian cancer, and 4 women had both breast and ovarian cancer. Affected women were on average 10.4 years postdiagnosis (SD = 6.9). Participants had a mean of 2.3 (SD = 1.6) relatives affected with breast or ovarian cancer.

Psychosocial outcomes among affected women

As displayed in Table 1, test result was not statistically significantly associated with long-term cancer distress, genetic testing positive experiences, or perceived breast or ovarian cancer risk. Thus, we did not conduct further multivariate analyses among affected women for these variables. Test result (positive vs. uninformative) was statistically significantly associated with genetic testing distress [Satterthwaite $t(99.5) = 5.44$, $P < .001$], uncertainty (Satterthwaite $t(129) = 2.79$, $P = 0.006$) and perceived stress ($t(352) = 3.08$, $P = 0.002$)]. We then proceeded with multivariate modeling for these outcomes.

Genetic testing distress. *Distress subscale.* As displayed in Table 3, we used multiple regression to examine the independent impact of test result among women affected with cancer, adjusting for potential confounders identified in bivariate analyses (Table 1). Specifically, we adjusted for potential confounders by entering variables with a bivariate association of $P < 0.10$ (age, education pretest cancer-specific distress and anxiety, intervention arm and RRBSO status) in step 1. These confounders accounted for 10% of the variance in genetic testing distress ($R^2 = 0.10$, $P < 0.0001$). When entered on the next step, test result (positive vs. uninformative) accounted for an additional 10% of the variation in long-term genetic testing distress ($\Delta R^2 = 0.10$, $F = 45.6$, $P < 0.0001$). Among women affected with cancer, *BRCA1/2* carriers reported higher levels of long-term genetic testing distress compared with women who received uninformative test results ($\beta = 0.45$, $P < 0.0001$).

Uncertainty subscale. As displayed in Table 3, we used multiple regression to examine the independent impact of test result on uncertainty among women affected with cancer, adjusting for potential confounders identified in bivariate analyses (Table 1). We entered potential confounders with a bivariate association of $P < 0.10$ (race, age, pretest cancer distress, and pretest anxiety) in step 1. These potential confounders accounted for 10% of the variance in genetic testing uncertainty ($R^2 = 0.10$, $P < 0.0001$). Test result (positive vs. uninformative)

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Table 1. Bivariate predictors of psychosocial outcomes among affected women

Variable	Perceived stress	Perceived BC risk	Perceived OC risk	Cancer distress	MICRA distress	MICRA uncertainty	MICRA positive
Genetic test result							
Positive ($n = 97$)	5.1 (3.2)[a]	28.4 (27.3)	20.7 (27.8)	12.8 (14.8)	3.5 (5.5)[b]	6.5 (8.1)[b]	7.4 (5.8)
Uninformative ($n = 260$)	4.0 (3.0)	34.5 (26.3)[c]	17.1 (19.4)	12.7 (12.4)	0.4 (1.4)	4.0 (5.5)	7.9 (7.7)
RRM							
No ($n = 259$)	4.2 (3.0)	36.8 (26.2)	17.9 (20.4)	12.7 (13.0)	1.1 (2.9)	4.7 (6.4)	7.8 (7.4)
Yes ($n = 98$)	4.4 (3.2)	22.6 (25.2)[b]	18.6 (25.5)	12.7 (13.2)	1.8 (4.3)	4.5 (6.2)	7.6 (6.6)
RRBSO							
No ($n = 254$)	4.2 (3.1)	34.7 (26.7)	21.3 (22.5)	13.0 (12.8)	1.0 (3.0)	4.5 (6.0)	7.9 (7.4)
Yes ($n = 103$)	4.5 (3.1)	27.8 (26.2)[a]	10.5 (18.5)[b]	12.0 (13.7)	1.9 (4.2)[c]	5.2 (7.2)	7.4 (6.8)
Education							
<College ($n = 12$)	2.7 (3.1)	25.1 (28.9)	20.2 (31.4)	6.4 (10.0)	0.4 (0.9)	4.2 (4.0)	8.3 (6.9)
College + ($n = 345$)	4.3 (3.1)[c]	33.0 (26.6)	18.0 (21.7)	12.9 (13.1)[c]	1.3 (3.4)[a]	4.7 (6.4)	7.7 (7.2)
Religion/ethnicity							
Non-Jewish ($n = 222$)	4.1 (3.0)	33.0 (27.5)	18.9 (22.6)	12.1 (12.8)	1.2 (3.1)	4.7 (6.3)	7.8 (7.1)
Jewish ($n = 135$)	4.5 (3.1)	32.4 (25.3)	16.7 (20.9)	13.8 (13.5)	1.4 (3.8)	4.6 (6.4)	7.7 (7.4)
Race							
Non-Caucasian ($n = 23$)	4.1 (3.9)	24.8 (23.3)	14.7 (19.5)	20.2 (17.0)[a]	1.5 (3.5)	9.0 (9.6)[a]	10.8 (7.7)[a]
Caucasian ($n = 326$)	4.3 (3.0)	33.1 (26.8)	18.3 (22.3)	12.3 (12.7)	1.2 (3.4)	4.3 (5.8)	7.6 (7.1)
Marital status							
Unmarried ($n = 83$)	4.7 (3.1)	35.7 (27.5)	19.2 (21.9)	13.0 (13.7)	1.1 (3.0)	4.5 (6.7)	7.1 (7.3)
Married/partner ($n = 274$)	4.1 (3.0)	31.9 (26.4)	17.8 (22.0)	12.6 (12.9)	1.3 (3.5)	4.7 (6.3)	8.0 (7.2)
Employment							
Not full time ($n = 159$)	4.1 (3.1)	33.9 (28.0)	20.5 (23.2)[c]	11.7 (12.8)	1.4 (3.4)	4.4 (6.6)	8.0 (7.0)
Full time ($n = 198$)	4.4 (3.0)	31.9 (25.6)	16.2 (20.8)	13.5 (13.2)	1.2 (3.4)	4.9 (6.2)	7.5 (7.4)
Annual income							
<85,000 USD ($n = 86$)	4.6 (3.0)	34.6 (28.3)	21.9 (25.5)	13.7 (14.3)	1.3 (3.1)	5.6 (7.4)	9.1 (7.5)
≥85,000 USD ($n = 238$)	4.1 (3.0)	32.1 (26.6)	17.3 (21.0)	12.9 (12.8)	1.3 (3.6)	4.6 (6.2)	7.7 (7.1)
Years since testing							
<5.0 y ($n = 186$)	4.3 (3.1)	32.4 (26.1)	18.2 (21.8)	13.4 (13.4)	1.3 (3.3)	4.5 (6.0)	8.5 (7.5)[a]
≥5.0 y ($n = 171$)	4.3 (3.1)	33.2 (27.4)	18.0 (22.3)	11.9 (12.6)	1.2 (3.5)	4.9 (6.8)	6.9 (6.8)
Time since Ca diagnosis							
<10 y ($n = 221$)	4.4 (3.0)	34.8 (25.9)[a]	19.1 (22.9)	13.9 (12.9)[a]	1.3 (3.4)	4.9 (6.3)	7.6 (7.3)
10+ y ($n = 135$)	4.0 (3.1)	27.8 (26.6)	16.6 (20.6)	10.8 (13.3)	1.2 (3.4)	4.2 (6.5)	8.0 (7.1)
Intervention arm							
No intervention ($n = 343$)	4.3 (3.1)	32.9 (26.6)	18.2 (21.9)	13.0 (13.2)[a]	1.1 (3.2)	4.7 (6.4)	7.8 (7.3)
Intervention ($n = 14$)	3.4 (2.2)	30.9 (29.6)	16.1 (25.3)	5.3 (6.2)	4.6 (5.3)[a]	4.6 (4.7)	6.7 (5.5)
Continuous predictors							
Age (M = 54.1, SD = 9.6)	$r = -0.10$[a]	$r = -0.00$	$r = -0.06$	$r = -0.16$[a]	$r = -0.10$[a]	$r = -0.12$[a]	$r = 0.07$
FDRs w/Br/Ov cancer (M = 1.0, SD = 1.0)	$r = -0.03$	$r = 0.05$	$r = 0.05$	$r = -0.10$[a]	$r = 0.05$	$r = 0.06$	$r = -0.02$
Relatives w/Br/Ov Cancer (M = 2.1, SD = 1.4)	$r = -0.02$	$r = 0.04$	$r = 0.04$	$r = -0.08$	$r = 0.03$	$r = 0.02$	$r = -0.05$
Pretest cancer distress (M = 20.5, SD = 14.4)	$r = 0.30$[b]	$r = 0.15$[a]	$r = 0.16$[a]	$r = 0.41$[b]	$r = 0.18$[a]	$r = 0.17$[a]	$r = -0.03$
Pretest anxiety (M = 0.08, SD = 1.0)	$r = 0.37$[b]	$r = 0.09$	$r = 0.02$	$r = 0.39$[b]	$r = 0.12$[a]	$r = 0.22$[b]	$r = -0.08$

NOTE: Values are means (SD) for categorical predictors and Pearson correlations for continuous predictors.
Abbreviations: RRM, Risk reducing mastectomy; RRBSO, Risk reducing bilateral salpingo-oophorectomy; USD, United States Dollars; FDRs, First-degree relatives.
[a]$P < 0.01$.
[b]$P < 0.05$.
[c]$P < 0.10$.

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Table 2. Bivariate predictors of psychosocial outcomes among unaffected women

Variable	Perceived stress	Perceived BC risk	Perceived OC risk	Cancer distress	MICRA distress	MICRA uncertainty	MICRA positive
Genetic test result							
True negative ($n = 60$)	4.3 (3.0)	38.8 (23.1)	21.9 (20.1)	10.7 (13.9)	0.9 (2.2)	4.0 (5.7)	9.8 (8.2)[b]
Positive ($n = 47$)	4.3 (3.1)	42.5 (31.8)	23.0 (23.4)	10.5 (11.7)	2.6 (4.6)[a]	5.1 (6.7)	6.1 (5.8)
RRM							
No ($n = 90$)	4.2 (2.9)	44.6 (25.2)	22.5 (20.3)	9.7 (12.6)	1.8 (3.8)[a]	4.4 (6.3)	8.4 (7.7)
Yes ($n = 17$)	4.8 (3.4)	18.5 (27.6)[b]	22.0 (27.8)	15.3 (13.4)[c]	0.7 (1.3)	4.9 (5.2)	6.8 (6.7)
RRBSO							
No ($n = 76$)	4.4 (3.1)	41.4 (26.2)	27.3 (22.2)	10.8 (13.3)	1.7 (3.4)	4.8 (6.3)	8.7 (7.7)
Yes ($n = 31$)	4.1 (2.8)	37.8 (29.9)	10.4 (14.0)[b]	10.2 (12.1)	1.5 (3.9)	3.6 (5.7)	6.9 (6.7)
Education							
<College ($n = 9$)	4.6 (2.5)	32.8 (27.3)	27.0 (21.6)	4.7 (6.1)	1.2 (1.9)	2.3 (2.3)	11.4 (7.8)
College+ ($n = 98$)	4.3 (3.1)	41.1 (27.2)	22.0 (21.6)	11.1 (13.2)	1.7 (3.7)	4.7 (6.4)[a]	7.8 (7.4)
Religion/ethnicity							
Non-Jewish ($n = 73$)	4.3 (3.1)	43.4 (27.5)[c]	24.0 (21.5)	10.0 (13.3)	1.9 (3.8)	4.6 (6.8)	8.9 (7.8)
Jewish ($n = 34$)	4.4 (2.8)	33.8 (25.6)	18.9 (21.4)	12.0 (12.0)	1.2 (2.9)	4.1 (4.5)	6.6 (6.5)
Race							
Non-Caucasian ($n = 5$)	5.6 (4.3)	34.0 (24.3)	25.0 (20.9)	12.6 (12.6)	2.2 (2.6)	5.6 (6.3)	10.2 (7.2)
Caucasian ($n = 101$)	4.2 (3.0)	40.4 (37.4)	22.0 (21.5)	10.3 (12.9)	1.6 (3.6)	4.3 (6.2)	8.0 (7.5)
Marital status							
Unmarried ($n = 25$)	5.1 (3.0)	49.5 (28.9)[c]	24.8 (23.5)	12.2 (13.3)	0.6 (1.6)	2.5 (3.1)	9.0 (9.2)
Married/partner ($n = 82$)	4.1 (3.0)	37.6 (26.2)	21.6 (20.9)	10.1 (12.8)	2.0 (3.9)[a]	5.1 (6.7)[a]	7.9 (6.9)
Employment							
Not full time ($n = 42$)	4.1 (2.9)	33.4 (25.5)	17.2 (18.6)	10.0 (12.8)	1.4 (3.3)	4.2 (6.6)	8.5 (7.0)
Full time ($n = 65$)	4.5 (3.1)	45.0 (27.5)[a]	25.7 (22.7)[a]	10.9 (13.0)	1.8 (3.8)	4.6 (5.9)	7.9 (7.8)
Annual income							
<85,000 USD ($n = 33$)	5.0 (3.3)	44.5 (27.7)	29.6 (24.5)[a]	15.0 (15.0)[a]	2.1 (3.7)	5.3 (7.5)	10.5 (7.6)[a]
≥85,000 USD ($n = 70$)	4.0 (2.9)	37.5 (27.1)	18.8 (19.3)	8.8 (11.6)	1.3 (3.1)	4.0 (5.4)	7.0 (7.1)
Years since testing							
< 5.0 y ($n = 55$)	4.3 (3.0)	41.5 (27.4)	20.4 (17.7)	11.5 (13.4)	1.5 (3.4)	4.7 (7.1)	9.2 (7.4)
≥5.0 y ($n = 52$)	4.3 (3.1)	39.2 (27.2)	24.5 (24.9)	9.7 (12.3)	1.8 (3.7)	4.2 (5.1)	7.0 (7.4)
Intervention arm							
No intervention ($n = 95$)	4.32 (3.0)	40.69 (27.2)	22.2 (22.1)	10.6 (12.9)	1.40 (3.1)	4.33 (6.2)	8.39 (7.7)
Intervention ($n = 12$)	4.17 (3.4)	38.0 (28.0)	23.8 (16.7)	10.3 (13.0)	3.58 (6.0)	5.42 (6.1)	6.17 (5.2)
Continuous predictors							
Age ($M = 47.4$, $SD = 9.7$)	$r = 0.09$	$r = -0.15$	$r = -0.24$	$r = -0.05$	$r = -0.16$	$r = -0.21$[a]	$r = -0.10$
FDRs w/Br/Ov Cancer ($M = 1.8$, $SD = 1.3$)	$r = 0.03$	$r = -0.02$	$r = -0.02$	$r = 0.13$	$r = -0.03$	$r = -0.04$	$r = 0.03$
Relatives w/Br/Ov Cancer ($M = 3.3$, $SD = 1.7$)	$r = 0.15$	$r = -0.02$	$r = -0.07$	$r = 0.17$[a]	$r = -0.08$	$r = -0.09$	$r = 0.06$
Pretest cancer distress ($M = 15.0$, $SD = 14.6$)	$r = 0.26$[a]	$r = 0.07$	$r = 0.20$[a]	$r = 0.53$[b]	$r = 0.29$[a]	$r = 0.49$[b]	$r = 0.21$[a]
Pretest anxiety ($M = -0.25$, $SD = 0.84$)	$r = 0.23$[a]	$r = 0.05$	$r = 0.01$	$r = 0.49$[b]	$r = 0.02$	$r = 0.19$[a]	$r = 0.03$

NOTE: Values are means (SD) for categorical predictors and Pearson correlations for continuous predictors.

Abbreviations: RRM, Risk reducing mastectomy; RRBSO, Risk reducing bilateral salpingo-oophorectomy; USD, United States Dollars; FDRs, First-degree relatives.

[a] $P < 0.01$.

[b] $P < 0.05$.

[c] $P < 0.10$.

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Table 3. Impact of *BRCA1/2* test result on psychosocial outcomes among women affected by cancer

Variable	Total R^2	ΔR^2	df	Final β
Genetic testing distress				
Model 1	0.10[a]	0.10[a]	6, 347	
Age				0.02
Education				0.03
Randomized to intervention				0.08
Pretest cancer distress				0.12[b]
Pretest cancer anxiety				0.06
Risk reducing oophorectomy				−0.09
Model 2	0.20[a]	0.10[a]	7, 346	
Genetic test result				0.41[b]
Genetic testing uncertainty				
Model 1	0.10[a]	0.10[a]	4, 343	
Age				−0.04
Race				−0.19[b]
Pretest cancer distress				0.04
Pretest anxiety				0.21[b]
Model 2	0.13[a]	0.03[b]	5, 342	
Genetic test result				0.18[b]
Perceived stress				
Model 1	0.16[a]	0.16[a]	4, 349	
Age				0.01
Education				0.10[c]
Pretest anxiety				0.30[a]
Pretest cancer distress				0.14[b]
Model 2	0.18[a]	0.02[b]	5, 348	
Genetic test result				0.14[b]

NOTE: Bivariate predictors ($P < 0.10$) were entered in Model 1. Test result was entered in Model 2 and the change in R^2 was tested for significance. Reference for test result is uninformative. Standardized betas (β) represent betas in the final model.

[a]$P < 0.0001$.

[b]$P < 0.01$.

[c]$P < 0.05$.

accounted for an additional 3% of the variation in genetic testing uncertainty ($\Delta R^2 = 0.03$, $P = 0.0005$). Affected carriers reported greater long-term uncertainty relative to affected uninformatives ($\beta = 0.18$, $P = 0.0005$).

Perceived stress. As displayed in Table 3, we used multiple regression to examine the independent impact of test result on perceived stress among women affected with cancer, adjusting for potential confounders identified in bivariate analyses (Table 1) by entering those variables with a bivariate association of $P < 0.10$ (education, age, pretest cancer distress and anxiety). As shown in Table 3, confounders accounted for 16% of the variation in perceived stress ($R^2 = 0.16$, $P < 0.0001$). Genetic test result (positive vs. uninformative), entered in step 2, accounted for an additional 2% of the variation in perceived stress ($\Delta R^2 = 0.02$, $P = 0.005$). Affected women who received a positive test result reported statistically significantly higher levels of long-term perceived stress compared with affected uninformatives ($\beta = 0.14$, $P = 0.005$).

Psychosocial outcomes among unaffected women

As displayed in Table 2, test result (positive vs. true negative) was not associated with cancer distress, perceived stress, genetic testing uncertainty, perceived breast cancer risk, or perceived ovarian cancer risk among women unaffected with cancer. Thus, we did not conduct further multivariate analyses for these outcomes. In bivariate analyses, test result was statistically significantly associated with genetic testing distress (Satterthwaite $t(63) = -2.29$, $P = 0.03$) and positive experiences (Satterthwaite $t(104) = 2.70$, $P = 0.008$) among unaffected women. We proceeded with multivariate modeling for these 2 outcomes.

Genetic testing distress. *Distress subscale.* As displayed in Table 4, we used multiple regression to examine the independent impact of test result on genetic testing distress among unaffected women, adjusting for potential confounders identified in bivariate analyses (Table 2). We adjusted for potential confounders by entering variables with a bivariate association of $P < 0.10$ (marital status, pretest cancer distress, and receipt of RRM). These confounders, entered in step 1, accounted for 13% of the variance in genetic testing distress ($R^2 = 0.13$, $P = 0.003$). Test result (positive vs. negative), entered in step 2, accounted for an additional 12% of the variance in genetic testing distress ($\Delta R^2 = 0.12$, $P = 0.0001$). Among unaffected women, *BRCA1/2* carriers reported higher genetic testing distress compared with *BRCA1/2* negatives ($\beta = 0.39$, $P < 0.0001$).

Genetic testing positive experiences. As displayed in Table 4, we used multiple regression to examine the independent impact of test result on genetic testing distress among unaffected women, again adjusting for potential confounders identified in bivariate analyses (Table 1). As before, we adjusted for potential confounders by entering variables with a bivariate association of $P < 0.10$ (income and pretest cancer distress). When entered in step 1, these confounders accounted for 8% of the variance in positive experiences ($R^2 = 0.08$, $P = 0.04$). Test result (positive vs. true negative) accounted for an additional 6% of the variance ($\Delta R^2 = 0.06$, $P = 0.008$). Specifically, unaffected *BRCA1/2* carriers reported lower positive experiences compared with unaffected women who received negative test results ($\beta = -0.25$, $P = 0.008$).

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Table 4. Long-term impact of *BRCA1/2* test results on psychosocial outcomes among women unaffected by cancer

Variable	Total R^2	ΔR^2	df	Final β
Genetic testing distress				
Model 1	0.13[a]	0.13[a]	3, 103	
Marital status				0.13
Pretest cancer distress				0.31[a]
Risk reducing mastectomy				−0.36[a]
Model 2	0.25[b]	0.12[b]	4, 102	
Genetic test result				0.39[b]
Genetic testing positive experiences				
Model 1	0.08[a]	0.08[a]	3, 99	
Income				−0.18[c]
First-degree relatives w/breast/ovarian cancer				0.06
Pretest cancer distress				0.20[a]
Model 2	0.14[a]	0.06[a]	4, 98	
Genetic test result				−0.25[a]

NOTE: Bivariate predictors ($P < 0.10$) were entered in Model 1. Test Result was entered in Model 2 and the change in R^2 was tested for significance. Reference for test result is True Negative. Standardized betas (β) represent betas in the final model.

[a]$P < 0.0001$.

[b]$P < 0.01$.

[c]$P < 0.10$.

Impact of risk-reducing surgery on distress outcomes among BRCA1/2 mutation carriers. To examine the impact of risk-reducing surgery on psychosocial outcomes, we conducted a series of regressions limited to *BRCA1/2* mutation carriers ($n = 144$).

RRM. After excluding 13 carriers with bilateral breast cancer or ovarian cancer, 48% ($n = 63$) of carriers had RRM. The only outcome associated with RRM was perceived risk for breast cancer ($t(119) = 5.22$, $P < 0.0001$). In a multiple regression in which we controlled potential confounders [affected status, pretest anxiety, and distress (due to association with RRM uptake in previous reports; ref. 8)], RRM was independently associated with reduced perceived breast cancer risk among *BRCA1/2* carriers ($\Delta R^2 = 0.18$, $P < 0.0001$, $\beta = -0.44$, $P < 0.0001$; see Table 5).

RRBSO. After we excluded 13 carriers with bilateral breast cancer and/or ovarian cancer and 13 carriers who reported BSO for reasons other than breast or ovarian cancer prevention, 73% ($n = 86$) of carriers had RRBSO. In bivariate analyses, RRBSO was statistically significantly associated only with genetic testing distress [$t(115) = 2.18$, $P = 0.03$], perceived ovarian cancer risk [$t(113) = 6.90$, $P < 0.0001$], and perceived breast cancer risk [$t(107) = 2.25$, $P = 0.03$]. Thus, we proceeded with multivariate analyses for these outcomes.

For genetic testing distress, after adjusting for potential confounders (education, number of relatives with breast/ovarian cancer, and pretest distress), receipt of RRBSO was marginally associated with decreased genetic testing distress among *BRCA1/2* carriers ($\Delta R^2 = 0.02$, $\beta = -0.16$, $P = 0.06$; see Table 5). For perceived ovarian cancer risk, after adjusting for the potential confounder of age, RRBSO was independently associated with reduced perceived ovarian cancer risk among *BRCA1/2* carriers ($\Delta R^2 = 0.24$, $\beta = -0.58$, $P < 0.0001$; see Table 5). For perceived breast cancer risk, after controlling for confounders (affected status, pretest anxiety, and pretest cancer-specific distress), RRBSO was not related to perceived breast cancer risk among *BRCA1/2* carriers ($\Delta R^2 = 0.02$, $P = 0.10$; see Table 5).

Discussion

To our knowledge, this is the first U.S. report to prospectively examine long-term psychosocial outcomes following *BRCA1/2* testing in a large sample of women affected and unaffected with cancer. Prior studies have focused on psychosocial outcomes during the year following testing (10, 14), have focused only on unaffected individuals (11, 19, 22), or were not prospective (20). For women both affected and unaffected with cancer, genetic test results seem to impact certain long-term psychosocial outcomes.

Approximately 5 years after testing, women who received positive *BRCA1/2* results reported greater genetic testing distress than women who received uninformative or negative results. This contrasts with prior studies with shorter follow-ups (10, 14), but it is consistent with a recent cross-sectional study that assessed genetic testing concerns a median of 7 years posttesting (20). The impact of *BRCA1/2* results on genetic testing distress remains statistically significant even after controlling for the receipt of risk-reducing surgery. Our measure of genetic testing distress, the MICRA, may be more sensitive than more global distress measures used in prior studies. Indeed, the MICRA was specifically designed to measure distress associated with receipt of a positive *BRCA1/2* result (34). The present findings suggest that a positive *BRCA1/2* result remains salient years after testing, perhaps due to ongoing decisions about risk management or worry over family members' cancer risk (35). Whether these results have clinical or behavioral implications is not yet clear. Despite elevations in genetic testing distress among carriers, our

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Table 5. Impact of risk reducing surgery on psychosocial outcomes among *BRCA1/2* mutation carriers

Variable	Total R^2	ΔR^2	df	Final β
Impact of risk reducing mastectomy				
Perceived breast cancer risk				
Model 1	0.05[a]	0.05[a]	3, 117	
Affected status				−0.15[a]
Pretest cancer distress				0.01
Pretest anxiety				0.18[a]
Model 2	0.23[b]	0.18[b]	4, 116	
Risk reducing mastectomy				−0.44[b]
Impact of risk reducing oophorectomy				
Perceived breast cancer risk				
Model 1	0.08[c]	0.08[c]	5, 105	
Affected status				−0.26[c]
Pretest cancer distress				−0.01
Pretest anxiety				0.11
Model 2	0.11[a]	0.02[a]	4, 104	
Risk reducing oophorectomy				−0.16[a]
Perceived ovarian cancer risk				
Model 1	0.06[c]	0.06[c]	1,113	
Age				0.07
Model 2	0.30[b]	0.24[b]	2, 112	
Risk reducing oophorectomy				−0.58[b]
Genetic testing distress				
Model 1	0.14[c]	0.14[c]	4, 112	
Education				0.08
Total relatives with breast/ovarian cancer				−0.16[c]
Pretest cancer distress				0.33[c]
Pretest anxiety				−0.06
Model 2	0.16[c]	0.02[d]	5, 111	
Risk reducing oophorectomy				−0.16[a]

NOTE: Bivariate predictors ($P < 0.10$) were entered in Model 1. For RRM outcomes, RRM was entered in Model 2 and the change in R^2 was tested for significance. Reference for RRM is no RRM. For RRBSO outcomes, RRBSO was entered in Model 2 and the change in R^2 was tested for significance. Reference for RRBSO is no RRBSO.

[a] $P < 0.0001$.

[b] $P < 0.01$.

[c] $P < 0.05$.

[d] $P < 0.10$.

results suggest that genetic testing distress is unrelated to more global psychologic dysfunction. This mirrors an earlier report in which distress due to high-risk cancer status was unrelated to general psychologic functioning (36) and the recent long-term follow-up by Hughes Halbert and colleagues (20). More research is needed to determine whether elevated genetic testing distress has clinical implications.

Unique to this study was our measurement of perceived stress. Among affected women, *BRCA1/2* carriers exhibited greater perceived stress 5 years posttesting compared with uninformatives. The Perceived Stress Scale is designed to measure global stress and not psychologic symptoms (33). Thus, it is possible that the Perceived Stress Scale better captures subtle influences of a positive *BRCA1/2* result on everyday functioning compared with traditional assessments of psychologic symptoms in previous studies. These results—together with our findings of elevated genetic testing distress—suggest that *BRCA1/2* carriers continue to experience slightly higher levels of perceived stress compared with women who receive uninformative or true negative *BRCA1/2* results. Whether such modest elevations in perceived stress are clinically relevant or actionable is not clear. The seminal work of Cohen and colleagues suggests that perceived stress can have important physiologic effects (37). Future research can explore whether elevated perceived stress impacts psychosocial or physical functioning in *BRCA1/2* carriers.

Somewhat surprisingly, affected women with positive results reported statistically significantly more uncertainty

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related to genetic testing than women who received uninformative results. Given clear risk management guidelines for *BRCA1/2* carriers, and the lack of such guidance for women with uninformative results, the increased uncertainty among positives warrants further examination. Perhaps the experience of uncertainty among carriers relates to lingering risk management questions. For example, several theoretical approaches suggest that health-related decision making is impacted by emotions [e.g., Peters and colleagues' work (38); Lazarus's cognitive-motivational-relational theory (39)] and are relevant to outcomes such as decisional conflict (40). Although we evaluated the impact of test result on genetic testing distress and uncertainty separately, these outcomes are correlated ($r = 0.53$, $P < 0.0001$) and the factors that underlie their association may also be responsible for the present results related to greater uncertainty in *BRCA1/2* carriers compared with women with uninformative results. Future research that carefully explores the psychologic and emotional pathways relevant to genetic testing distress may help explain these specific findings.

BRCA1/2 results were unrelated to perceived risk for breast or ovarian cancer, likely reflecting the high uptake of risk-reducing surgery in our sample and the impact of risk-reducing surgery on perceived risk. For example, among *BRCA1/2* carriers, uptake of RRM and RRBSO were associated with lower perceived breast and ovarian cancer risk, respectively. This is consistent with the substantially decreased objective risk following these procedures (9, 41, 42). Of note, the decrease in perceived risk following risk-reducing surgery did not translate to reduced distress over the long term. Given that distress and worry reduction are frequently cited reasons for obtaining risk-reducing surgery (43), our findings may be relevant to women considering such surgery. However, these results should be interpreted cautiously due to the relatively small number of *BRCA1/2* carriers without RRBSO at follow-up.

The present findings should be considered in the context of study limitations. Data were drawn from a single institution and all participants were previously enrolled in clinical research studies, thus limiting the generalizability of results. Despite the single site, women were referred to our center by diverse community providers across a large metropolitan area. Although our sample has characteristics similar to patients seen at other large cancer genetics referral centers, the homogeneity in education level of participants and the lack of racial diversity warrant caution in interpretation of results. Our finding that women of Jewish descent were less likely to participate in the study is interesting and deserves attention in future prospective studies. In other work, we found a similar but marginal trend in which men and women of Jewish descent were less likely to enroll in a familial cancer registry (44). However, the reasons for lower participation remain unclear. Finally, results should also be interpreted cautiously given the large number of comparisons we conducted. Rather than adjusting for multiple comparisons, we opted to minimize the chance of a Type II error by maintaining a traditional alpha level. Importantly, with 2 exceptions (e.g., genetic test result and perceived stress among affected women, $P = 0.005$; genetic test result and positive genetic testing experiences among unaffected women, $P = 0.008$), the statistically significant multivariate comparisons we found were significant at a level of $P \leq 0.0005$.

Despite these limitations, this is the first U.S. study to prospectively evaluate a broad range of long-term psychosocial outcomes in a cohort of *BRCA1/2* tested women. We found evidence of modestly increased perceived stress in affected carriers and increased genetic testing distress in both affected and unaffected carriers; however, we did not find evidence for clinically significant dysfunction. Furthermore, although risk-reducing surgeries appropriately lower perceptions of cancer risk among *BRCA1/2* carriers, we did not find evidence to support broader psychosocial benefits. Future research can confirm our results with representative cohorts and examine whether elevated genetic testing distress or perceived stress is clinically meaningful.

Disclosure of Potential Conflicts of Interest

The authors do not have any financial conflicts to disclose.

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Long-Term Psychosocial Outcomes of *BRCA1*/*BRCA2* Testing: Differences across Affected Status and Risk-Reducing Surgery Choice

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