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Emotional Distress Following Genetic Testing for Hereditary Breast and Ovarian Cancer: A Meta-Analytic Review

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Abstract

Objective—Meta-analysis was used to synthesize results of studies on emotional consequences of predictive genetic testing for *BRCA1/2* mutations conferring increased risk of breast and ovarian cancer.

Design—Studies assessing anxiety or cancer-specific distress before and after provision of test results ($k = 20$) *were* analyzed using a random-effects model. Moderator variables included country of data collection and personal cancer history of study participants.

Main Outcome Measures—Standardized mean gain effect sizes were calculated for mutation carriers, noncarriers, and those with inconclusive results over short (0–4 weeks), moderate (5–24 weeks), or long (25–52 weeks) periods of time following testing.

Results—Distress among carriers increased shortly after receiving results and returned to pre-testing levels over time. Distress among noncarriers and those with inconclusive results decreased over time. Some distress patterns differed in studies conducted outside the US and for individuals with varying cancer histories.

Conclusion—Results underscore the importance of time; changes in distress observed shortly after test-result disclosure frequently differed from the pattern of distress seen subsequently. Although emotional consequences of this testing appear minimal, it remains possible that testing may affect cognitive and behavioral outcomes, which have rarely been examined through meta-analysis. Testing may also affect understudied subgroups differently.

Keywords

predictive genetic testing; hereditary breast and ovarian cancer; *BRCA1/2* gene mutations; emotional distress; meta-analysis

Breast cancer is the most prevalent cancer in women, apart from skin cancer, and is the second-leading cause of women's cancer deaths (American Cancer Society, 2007; US Cancer Statistics Working Group, 2006). As many as 10% of breast cancers are due to heredity (Claus, Schildkraut, Thompson, & Risch, 1996), with the majority caused by mutations in the tumor suppressor genes *BRCA1* (Miki et al., 1994) or *BRCA2* (Wooster et al., 1995). Female *BRCA1/2* gene mutation carriers have a 35–84% chance of developing breast cancer, and a 10–

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50% chance of developing ovarian cancer, by age 70 (US Preventive Services Task Force, 2005). By comparison, the average woman has a 7–10% chance of developing breast cancer and a 1–2% chance of developing ovarian cancer in her lifetime (Offit, 1998). Male carriers are at increased risk for breast, prostate, and pancreatic cancer (Liede, Karlan, & Narod, 2004). It is now possible to identify those at risk for developing such cancers through *predictive genetic testing*.

Predictive genetic testing can identify asymptomatic individuals who carry gene mutations which put them at increased risk for developing a specific disorder and for passing disease-causing mutations to their offspring. Prior to testing, individuals are usually evaluated to confirm a high likelihood of hereditary cancer, and are then counseled on personal risk levels and the process of predictive genetic testing (Lerman & Shields, 2004). Testing may reveal one's status as a mutation carrier or noncarrier. Carriers possess a gene mutation previously identified either within their family or within a particular ethnic group, such as the common founder mutations present in the Ashkenazi Jewish population. Noncarriers do not possess a mutation previously identified in their family. Sometimes results are inconclusive whereby either no known mutations, or genetic variations of unknown association with cancer risk, are identified.

Although learning one's testing results may promote efforts toward disease prevention, health experts have expressed concern about potential adverse emotional, cognitive, and behavioral consequences of such knowledge (Lerman & Croyle, 1996; Lerman & Schwartz, 1993). With high levels of public and media interest in genetic testing (e.g., Gwyn, Vernon, & Conoley, 2003; Pear, 2008), and the recent availability of widely-advertised mutation-detection products such as the BRAC*Analysis*® blood test (Myriad Genetic Laboratories Inc., 2007), it is critical to examine how people respond to learning their *BRCA1/2* mutation status.

People pursuing predictive genetic testing often believe their risk for developing or passing on the disorder is high, and undergo testing to reduce feelings of uncertainty, aid decisions about reproduction, and understand risk to family members (Andrews, Meiser, Apicella, & Tucker, 2004; Lobel, Dias, & Meyer, 2005; Meiser & Dunn, 2000; Struewing, Lerman, Kase, Giambarresi, & Tucker, 1995). However, specific characteristics of a genetic mutation, namely its *inheritance* and *penetrance*, influence the degree of certainty about one's future health provided by genetic testing. *BRCA1/2* mutations are inherited equally by men and women in an autosomal dominant manner. Their dominant expression means inheriting one copy from either parent confers an increased risk of cancer. Thus, offspring of a *BRCA1/2* carrier have a 50% chance of inheriting the mutation. Because *BRCA1/2* mutations display incomplete penetrance, some who inherit the gene may not develop cancer due to genetic or environmental factors. Mutation carriers may perform frequent screening with breast self-exams, clinical breast exams, mammograms, and transvaginal ultrasounds, explore chemoprevention with drugs such as tamoxifen, or undergo prophylactic mastectomy or oophorectomy. Prophylactic surgery dramatically reduces disease risk; yet, no method eliminates risk completely, and the risk-reducing efficacy of these methods may differ between cancers and between specific *BRCA1/2* gene mutations (Domchek & Weber, 2006).

This particular constellation of features in hereditary breast and ovarian cancer (HBOC), especially incomplete gene penetrance and varying effectiveness of screening and prevention behaviors, may produce unique emotional consequences for people at risk of carrying *BRCA1/2* mutations. They may be faced with uncertainty and stress about whether to be tested, whether and when they will develop breast or ovarian cancer, how severe their disease may be, and whether prevention strategies will be effective. In addition, genetic testing results have implications for the health of family members, personal relationships, future plans including reproductive decisions, and insurance availability and discrimination (Lerman & Shields,

2004; Marteau & Richards, 1996). Thus, *BRCA1/2* testing may elicit anxiety, anger, depression, or guilt (Croyle, Smith, Botkin, & Baty, 1997; Lerman, Croyle, Tercyak, & Hamann, 2002).

Baum and colleagues (1997) have developed a framework to understand reactions to genetic testing from a stress and coping perspective. In this framework, emotional distress following testing is influenced by factors including disease characteristics (e.g., severity, preventability), test result received (carrier, noncarrier, or inconclusive), amount of uncertainty remaining after testing, and the extent to which uncertainty is reduced by testing. By applying this framework to HBOC, specific predictions about emotional distress from *BRCA1/2* testing can be made. Mutation carriers are likely to experience no change or an increase in distress after receiving test results: Whereas some uncertainty may be resolved with knowledge of one's mutation status, questions about the occurrence, timing, severity, course, and preventability of cancer may elevate distress. Similarly, people with inconclusive results may experience no change or an increase in distress. Noncarriers are likely to experience a decrease in emotional distress after learning that their risk is no more than average. Baum et al. also describe how other variables, in conjunction with gene mutation status, may contribute to emotional consequences of testing. For HBOC, these variables likely include availability and quality of genetic counseling and medical surveillance, time since testing, age, gender, and personal cancer history (Croyle, Achilles, & Lerman, 1997; Watson et al., 2004).

Empirical investigations of the emotional sequelae of predictive *BRCA1/2* mutation testing have not consistently upheld predictions based upon the Baum et al. (1997) framework. Although a few studies have found increases in distress among women who test positive for *BRCA1/2* mutations (e.g., Meiser et al., 2002; van Roosmalen et al., 2004), others have reported no change in pre- to post-test distress for carriers (e.g., Lerman et al., 1996; Lodder, Frets, Trijsburg, Meijers-Heijboer et al., 2001). Several studies report a decrease in distress for noncarriers (e.g., Lodder, Frets, Trijsburg, Meijers-Heijboer et al., 2001; Meiser et al., 2002), but questions exist about the magnitude of this effect, as well as the possibility of distress due to "survivor guilt" (Lerman & Croyle, 1996). The course of distress experienced by those with inconclusive results is also unclear; as these may be misinterpreted by testers and the lack of definitive information may elevate distress (Bish et al., 2002; Dorval et al., 2005).

Two recent investigations examined research on emotional effects of predictive genetic testing for HBOC. One systematic review of 4 studies of women undergoing *BRCA1/2* mutation testing (Butow, Lobb, Meiser, Barratt, & Tucker, 2003) concluded that noncarriers experience a decrease in distress from before testing through shortly after receiving test results; mutation carriers' cancer-related distress increases, but global depression and anxiety remain relatively constant. Schlich-Bakker, ten Kroode, and Ausems' (2006) systematic review of 8 studies concluded that testing does not lead to increased distress among breast cancer patients. While providing a valuable analysis, these non-quantitative reviews are limited in their ability to provide firm conclusions about the effects of predictive cancer genetic testing. Each reviewed a small number of studies, and neither examined characteristics of the testing context nor of study participants that may moderate the impact of predictive genetic testing on emotional reactions.

The Present Study

Meta-analysis was used to examine effects of *BRCA1/2* mutation testing on anxiety and cancer-specific distress. Cancer-specific distress was included because testing may produce situationally-relevant distress including concerns about medical surveillance, prophylactic surgery, communication of results to family members or friends, reproductive decisions, and sexuality (Claes et al., 2003; Moyer & Lobel, 2006). Examining changes in both measures provides a more comprehensive description of the emotional consequences of *BRCA1/2* testing

and allows for the possibility that testing affects one type of distress but not another (e.g., Butow et al., 2003). Prior research suggests that emotional consequences of testing may vary by gene mutation status. Thus, changes in distress from pre- to post-testing experienced by carriers, noncarriers, and those with inconclusive results were compared. Consistent with past findings and with the Baum et al. (1997) framework, we hypothesized that noncarriers would experience a decrease in distress from before testing to after receiving results, and carriers and those with inconclusive results would experience stable levels of distress or an increase in distress. We also expected that emotional effects of testing would be strongest immediately after result disclosure, and would diminish with time as individuals adapt.

We explored two potential moderators. The country where data were collected may affect distress because of national or cultural differences in genetic counseling, attitudes toward testing and HBOC, and access to insurance and medical treatment (Lerman & Shields, 2004). Personal cancer history may also moderate distress, as cancer survivors may be less uncertain about HBOC than those without the disease.

Method

Study Identification and Selection

Bibliographic databases (PsycINFO, PubMed, and Web of Science) were searched in April 2007 and June 2008 using the keywords: (*breast cancer* or *BRCA**) and (*gene* test**, *gene* counsel**, *gene* screen**, *DNA test**, or *DNA screen**) and (*psycholog**, *psychosocial*, *distress*, *anxiety*, *depression*, or *worry*). This produced 1,154 human studies published in English. Inspection of abstracts and references cited by relevant articles resulted in 73 potentially-eligible studies.

Studies were eligible if they were published in a peer-reviewed journal or as a dissertation, included participants over age 18, used a prospective design with an emotional distress variable quantitatively assessed prior to genetic testing and up to one year after the provision of test results, reported results needed to calculate an effect size (e.g., sample means and standard deviations reported separately for each mutation status group), did not involve a comparison of treatment or counseling interventions, and included individuals explicitly participating in *BRCA1/2* genetic testing. Authors of 8 potentially-eligible studies were contacted for additional data; 3 authors provided the requested information. Methods were examined to prevent inclusion of studies from overlapping samples; when there was overlap, the study with the largest sample was selected. Based on these criteria, 20 studies were included.

Emotional Distress Constructs and Measures

Anxiety—State anxiety was assessed with the state anxiety subscale of the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), General Health Questionnaire (GHQ28; Goldberg & Hillier, 1979), short form of the Hopkins Symptom Checklist (HSCL-25; Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974), anxiety subscale of the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), anxiety subscale of the Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983), and anxiety subscale of the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971). Four studies (Manne et al., 2004; O'Neill et al., 2006; Ozakinci, 2004; Schwartz et al., 2002) reported a combined anxiety- and depression-subscale score; their data were used to calculate effect sizes for anxiety. When multiple measures of anxiety were reported in a study, data from the STAI, the most commonly used measure, were used to calculate the effect size.

Cancer-specific distress—Measures of cancer-specific distress included the avoidance and intrusion subscales of the Impact of Event Scale (IES; Horowitz, Wilner, & Alvarez, 1979), the Cancer Worry Scale (CWS; Lerman & Croyle, 1994; Lerman, Trock, Rimer, & Jepson, 1991), and experimenter-designed items. The total IES was the most frequently used measure. Thus, it was used whenever multiple measures were reported. When data were provided separately for the avoidance and intrusion subscales of the IES, effect sizes were calculated for each and then averaged. As shown in Table 1, all studies using the IES specified the distressing event as cancer, hereditary cancer, or risk for cancer, except one (Ozakinci, 2004), which specified genetic testing. To maintain conceptual consistency, the CWS was used for this study.

Data Abstraction and Statistical Analyses—The standardized mean gain effect size (*d*) was used to examine changes in emotional distress from before testing to after the provision of results, with positive effect sizes indicating increased distress. Descriptive information was abstracted for moderator analyses including country of data collection (US vs. elsewhere) and personal cancer history of study participants (history vs. no history). Analyses were conducted with Comprehensive Meta-Analysis Version 2.0 (Borenstein, Hedges, Higgins, & Rothstein, 2005). Random-effects aggregate effect sizes are reported, as recommended (Schmidt, Oh, & Hayes, in press).

Results

Sample sizes ranged from 10 to 279 (M = 108.6; SD = 75.1), resulting in a total of 2,171 predominantly female (95.2%) participants (664 carriers, 794 noncarriers, 713 individuals with inconclusive testing results) with sample mean ages ranging from 35.2 (SD = 10.6) to 57.0 (SD = 10.0) years. Sixteen studies reported anxiety and 18 reported cancer-specific distress data. Length of time between disclosure of genetic test results and post-result psychological assessment was short (0–4 weeks) for 15 studies, moderate (5–24 weeks) for 13, and long (25–52 weeks) for 6. Eight studies were conducted in the US and 12 were conducted in Australia or Europe; 14 studies reported participants' personal cancer history (see Table 1). Associations of *BRCA1/2* mutation testing with anxiety and cancer-specific distress are presented for each of the three gene mutation status groups over the three elapsed time periods (Table 2). The magnitude of aggregate effect sizes was evaluated in terms of Cohen's (1988) recommendations: $d \leq .20$, small; = .50, medium; and $\geq .80$, large.

Anxiety

For studies in which a short period of time had elapsed between disclosure of test results and anxiety assessment, individual effect sizes ranged from −3.85 to .85. The effect sizes for carriers and noncarriers from one study (Kinney et al., 2005) were statistical outliers and removed from analyses as is recommended (Lipsey & Wilson, 2001), resulting in effect sizes ranging from −1.03 to .85. For studies assessing anxiety after a moderate period of time, effect sizes ranged from −.46 to .40. Data for anxiety after a long period of elapsed time were only available for carriers and noncarriers; effect sizes ranged from −.49 to .21.

There were significant differences in the magnitude of anxiety changes experienced by carriers, noncarriers, and those with inconclusive results after a short period of time (mixed effects $Q(2) = 22.41$, $p < .001$), but no difference in the magnitude of such changes after a moderate period of time (mixed effects $Q(2) = 2.47$, $p = .29$), nor between the changes experienced by carriers and noncarriers after a long period of time (fixed effects $Q(1) = .59$, $p = .44$). Although carriers experienced a small increase in anxiety shortly after receiving their results ($d = .22$, $p < .001$), their anxiety was not different from pre-testing levels after a moderate ($d = -.03$, $p = .68$) or long ($d = -.03$, $p = .83$) period of time. Noncarriers experienced a small-to-medium

decrease in anxiety after a short period of time ($d = -.33$, $p = .008$), and a small decrease after a moderate period of time ($d = -.22$, $p = .02$). Noncarriers' anxiety after a long period of time was equivalent to their pre-testing levels ($d = -.06$, $p = .71$). Anxiety levels of testers with inconclusive results were similar to pre-testing levels after both a short ($d = -.10$, $p = .20$) and moderate period of time ($d = -.12$, $p = .11$). One study (Andrews et al., 2004) reported data allowing calculation of an effect size for the change in anxiety experienced by those with inconclusive results after a long period of time, revealing no change in distress ($d = -.003$).

Country of data collection significantly moderated the change in anxiety experienced by noncarriers: Noncarriers in the US experienced greater decreases in anxiety after a short ($d = -.84$, $p = .002$) and moderate ($d = -.45$, $p < .001$) period of time than did those in Australia or Europe ($d = -.21$, $p = .08$ and $d = -.09$, $p = .04$, respectively). Neither country of data collection nor cancer history moderated the experience of anxiety after a long period of time.

Cancer-specific distress

Individual effect sizes ranged from −1.13 to .94 for studies assessing cancer-specific distress a short period of time following testing. Effect sizes for carriers in one study (Kinney et al., 2005) and for noncarriers in another (Ozakinci, 2004) were statistical outliers and were removed from analyses, resulting in effect sizes ranging from −.68 to .94. For studies in which a moderate period of time had elapsed between the disclosure of test results and the distress assessment, individual effect sizes ranged from −.78 to .51. Effect sizes for the change in cancer-specific distress after a long period of elapsed time ranged from −3.03 to .21. The effect size for one study (Plon, Peterson, Friedman, & Richards, 2000) was an outlier and removed from analyses; effect sizes then ranged from −.69 to .21.

There were significant differences in the distress changes experienced by carriers, noncarriers, and those with inconclusive results after a short (mixed effects $Q(2) = 25.37$, $p < .001$), moderate (mixed effects $Q(2) = 15.71$, $p < .001$), and long (mixed effects $Q(2) = 7.40$, $p = .03$) period of time. Whereas carriers experienced a small increase in cancer-specific distress soon after receiving results ($d = .27$, $p < .001$), their distress was equivalent to pre-testing levels after both a moderate ($d = -.01$, $p = .94$) and long ($d = -.15$, $p = .18$) period of time. Noncarriers experienced a small decrease in cancer-specific distress shortly after learning their mutation status ($d = -.25$, $p = .008$), and a small-to-medium decrease after a moderate ($d = -.42$, $p < .001$), and long ($d = -.47$, $p < .001$) period of time. Testers with inconclusive results experienced a small decrease in distress after a short period of time ($d = -.18$, $p = .04$) and a small-to-medium decrease after a moderate ($d = -.34$, $p < .001$) and long ($d = -.39$, $p < .001$) period of time.

Country of data collection significantly moderated noncarriers' changes in cancer-specific distress experienced after a short period of time: Those in the US experienced greater decreases in distress ($d = -.68$, $p < .001$) than those in Australia or Europe ($d = -18$, $p = .03$). Cancer history moderated changes in distress for both carriers and testers with inconclusive results. After a moderate period of time, carriers with a personal cancer history experienced a small decrease in distress ($d = -.20$, $p = .006$) while the distress of those without one did not change ($d = .08$, $p = .43$). Among testers with inconclusive results, those without a cancer history experienced greater decreases in distress after a short ($d = -.50$, $p < .001$) and long ($d = -.57$, $p < .001$) period of time than those with one ($d = -.22$, $p = .001$ and $d = -.21$, $p = .002$, respectively).

Since studies using the IES differed in the distressing event specified, we also examined whether the referent of the measure (cancer, hereditary cancer, or risk for cancer) moderated changes in cancer-specific distress. This variable significantly moderated changes in distress for noncarriers shortly after receiving their results (mixed effects $Q(2) = 13.74$, $p = .001$): Only studies measuring concerns about "cancer" reported a significant decrease in distress ($d = -$.

32, $p < .001$). IES referent also moderated changes in distress for carriers after a moderate period of time (mixed effects $Q(1) = 5.16$, $p = .02$). Studies measuring concerns about "hereditary cancer" reported a small decrease in distress among carriers ($d = -.16$, $p = .002$), whereas concerns about "risk for cancer" did not change ($d = .11$, $p = .31$).

Evaluating the Clinical Significance of Changes in Emotional Distress—To interpret the clinical significance of changes in distress experienced by testers, effect sizes were translated into values from the most commonly used measures of emotional distress (Table 3). The weighted mean pre-testing level of anxiety (calculated from studies using the STAI) was 38.2 ($SD_{pooled} = 11.1$). This value is similar to published norms (Spielberger, 1983) for working women ages 19–39 years who have an average state anxiety score of 36.2 ($SD = 11.0$). Women with ovarian cancer ages 22–76 years (Bodurka-Bevers et al., 2000) had an average score of 34.6 ($SD = 12.4$). The weighted mean pre-testing level of cancer-specific distress (calculated from studies using the IES) was 14.7 ($SD_{pooled} = 12.8$). This value is similar to that for women ages 25–58 years with a family history of breast cancer ($M = 14.1$, $SD = 14.3$), but is greater than for women without a family history of cancer ($M = 2.4$, $SD = 6.7$; Lloyd et al., 1996).

Discussion

Findings from this meta-analysis of 20 studies were largely consistent with predictions. Soon after receiving test results, carriers' emotional distress increased slightly. However, carriers' distress returned to pre-testing levels with additional time. Whereas noncarriers experienced decreases in both general and cancer-specific distress soon after testing, only the reduction in cancer-specific distress persisted over time. This reduction may correspond to increased certainty about their mutation status and cancer risk. Contrary to expectations, those with inconclusive results experienced decreases in cancer-specific distress. This decrease was similar in magnitude to that observed in noncarriers. While only two studies provided long-term data on the cancer-specific distress of those with inconclusive results, they indicate that this decreased distress endured. These findings suggest that people may be misinterpreting inconclusive results as an indicator of reduced cancer risk rather than understanding that they may possess an unidentified mutation that could confer increased risk. This is worrisome if such misunderstanding impairs screening and other relevant health behaviors. Additional research is needed to investigate this group's long-term emotional responses, risk perceptions, and health behaviors to determine whether testing is affecting them adversely.

Moderator analyses revealed greater decreases in distress for noncarriers in the US than those in Australia or Europe. While the small number of studies required combining countries outside the US, it remains likely that cultural and national differences in attitudes toward genetic testing, availability of follow-up care and insurance coverage, privacy of medical information, and aspects of genetic counseling influence individuals' emotional responses to predictive genetic testing (Lerman & Shields, 2004). Cancer history also moderated testers' cancer-specific distress. Consistent with prior research (Croyle, Smith et al., 1997), carriers with a personal cancer history experienced less distress upon learning their results than carriers without a history. Additionally, testers without a personal cancer history who received inconclusive results experienced the greatest reductions in distress; these individuals may be most likely to misinterpret test results.

The experiences of men, those of varying races or ethnicities, and of different socioeconomic strata undergoing *BRCA1/2* testing are rarely reported, yet these variables could be important moderators of emotional distress. Motivations for testing and the stigma associated with being a carrier may differ by gender (Lodder, Frets, Trijsburg, Tibben et al., 2001) and race or ethnicity (Andrews et al., 2004; Kinney et al., 2005). It is notable that the only study in this meta-analysis that reported on a predominantly African-American sample (Kinney et al.,

2005) produced effect sizes that were statistical outliers when compared to other studies, with carriers and noncarriers experiencing large decreases in anxiety, and carriers experiencing large decreases in cancer-specific distress. Similarly, two (Ozakinci, 2004; Plon et al., 2000) of the three studies based exclusively on Ashkenazi Jewish women produced outlier effect sizes. Unique experiences, such as the unknown accuracy of *BRCA1/2* testing in people of varying ethnicity (Nanda et al., 2005) or the greater risk for HBOC faced by Ashkenazi women (Plon et al., 2000), may help to explain these findings. Socioeconomic status may also influence the course of emotional distress following testing, as learning one's mutation status can raise concerns about insurance coverage, employment discrimination, and access to medical care.

Results of this study highlight the importance of time in relation to emotional state following testing. Changes in distress observed shortly after disclosure of test results frequently differed from the pattern of distress seen subsequently. Often, testers returned to their pre-testing emotional state with additional time. However, it is important to compare testers' baseline levels of emotional distress with those of the general population. Testers' pre-testing anxiety was similar to that of both the general population and cancer patients. However, testers' pre-testing cancer-specific distress was much greater than that of women without a family history of cancer. Members of HBOC families who are eligible for testing experience elevated distress as a result of their high-risk status (Coyne, Kruus, Racioppo, Calzone, & Armstrong, 2003), and the testing context may be especially upsetting for these individuals, contributing to their greater cancer-specific distress (Lerman & Schwartz, 1993; Moyer & Lobel, 2006). General anxiety measures may be too generic to capture the types of distress most relevant to this population. As indicated by moderator analyses of the IES referent, differences in the phrasing of cancer-specific distress measures may also influence how individuals respond to these assessments. Furthermore, it is possible that genetic testing contributes to emotional reactions not examined in this study, such as guilt or anger, or to adverse cognitive and behavioral outcomes, which have rarely been examined through meta-analysis.

A limitation of this research is the small number of studies that were available for many of the statistical comparisons. Although a reasonable number of studies have been conducted on emotional distress resulting from *BRCA1/2* testing, many studies failed to report results needed to calculate effect sizes. Failsafe *N* values, however, provide little support for publication bias. An additional limitation is that numerous studies failed to report the timing of administration of the pre-testing distress measure. Among studies that did, differences existed in when the pre-testing assessment occurred. For instance, some studies assessed distress immediately after an initial genetic counseling session; others administered distress measures during a later follow-up visit, such as when blood was drawn. Thus, it is unlikely that across studies a consistent length of time elapsed between the pre-testing measures of distress and the provision of results. Such variability may have influenced the results of this meta-analysis.

Overall, findings indicate that *BRCA1/2* testing does have emotional consequences, but these appear to be minimal over time. Among mutation carriers, whose testing outcome was most unfavorable, levels of general and cancer-specific distress increased slightly but distress returned to pre-testing levels over time. Noncarriers received the most favorable result, and appeared to benefit from it, as evidenced by small, short-term decreases in anxiety and larger, long-term decreases in disease-specific distress. Testers with inconclusive results also experienced a slight decrease in cancer-specific distress soon after learning their mutation status, and this decrease endured over time. Thus, for most people, *BRCA1/2* testing did not dramatically increase distress, but this may be attributable to the extensive genetic counseling that accompanied testing in the studies analyzed. As testing becomes more available in less controlled clinical settings, emotional responses may differ. Understudied subgroups may also have unique experiences or perceptions that lead to different emotional outcomes. Their responses to predictive cancer genetic testing should be examined with culturally appropriate,

situationally-specific measures. Such studies will benefit researchers, clinicians, and patients, further clarifying the balance between risks and benefits of predictive genetic testing.

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Table 1

Descriptive Information for Studies Included in the Meta-Analysis

Study	Gene Mutation Status Groups	Length of Elapsed Time	Emotional Distress Construct & Measure	Country of Data Collection	Personal Cancer History of Study Participants
Andrews et al., 2004	- Carrier - Inconclusive[a]	- Short (1–2 weeks) - Moderate (16 weeks) - Long (52 weeks)	- Anxiety: STAI - CSD: IES, *risk for cancer*	Australia/Europe	- History (Carrier, Inconclusive) - No history (Carrier, Inconclusive)
Bish et al., 2002	- Inconclusive	- Short (1 week) - Moderate (24 weeks)	- Anxiety: HADS - CSD: CWS	Australia/Europe	- History (Inconclusive)
Claes et al., 2005	- Carrier - Noncarrier	- Long (52 weeks)	- Anxiety: STAI - CSD: IES, *cancer*	Australia/Europe	- No history (Carrier, Noncarrier)
Dudok de Wit et al., 1998	- Carrier - Noncarrier	- Short (1 week) - Moderate (24 weeks)	- CSD: IES, *hereditary cancer*	Australia/Europe	—
Kinney et al., 2005	- Carrier - Noncarrier	- Short (4 weeks) - Moderate (16 weeks)	- Anxiety: STAI - CSD: Experimenter scale	US	—
Lodder, Frets, Trijsburg, Meijers-Heijboer, et al., 2001	- Carrier - Noncarrier	- Short (2 weeks)	- Anxiety: HADS - CSD: IES, *cancer*	Australia/Europe	- No history (Carrier, Noncarrier)
Lodder, Frets, Trijsburg, Tibben, et al., 2001	- Carrier - Noncarrier	- Short (1–3 weeks)	- Anxiety: HADS	Australia/Europe	- No history (Carrier, Noncarrier)
Manne et al., 2004[b]	- Carrier - Noncarrier - Inconclusive	- Moderate (24 weeks)	- Anxiety: BSI - CSD: IES, *hereditary cancer*	US	- No history (Noncarrier)
Meiser et al., 2002	- Carrier - Noncarrier	- Short (1–2 weeks) - Moderate (16 weeks) - Long (52 weeks)	- Anxiety: STAI - CSD: IES, *risk for cancer*	Australia/Europe	- No history (Carrier, Noncarrier)
O'Neill et al., 2006	- Inconclusive	- Short (4 weeks) - Moderate (24 weeks)	- Anxiety: BSI - CSD: IES, *risk for cancer*	US	- History (Inconclusive)
Ozakinci, 2004	- Carrier - Noncarrier - Inconclusive	- Short (1–2 weeks) - Moderate (24 weeks)	- Anxiety: POMS - CSD: CWS	US	—
Plon et al., 2000	- Inconclusive[a]	- Long (52 weeks)	- CSD: Experimenter item	US	- No history (Inconclusive)
Reichelt et al., 2004	- Carrier - Noncarrier	- Moderate (6 weeks)	- Anxiety: HADS - CSD: IES, *cancer*	Australia/Europe	- No history (Carrier, Noncarrier)
Schwartz et al., 2002[c]	- Carrier - Noncarrier - Inconclusive	- Moderate (24 weeks)	- Anxiety: HSCL-25 - CSD: IES, *hereditary cancer*	US	- History (Carrier, Inconclusive) - No history (Carrier, Noncarrier)
Smith, 2003	- Carrier - Inconclusive[a]	- Short (1 week) - Moderate (12 weeks)	- Anxiety: STAI - CSD: IES, *risk for cancer*	US	—

Study	Gene Mutation Status Groups	Length of Elapsed Time	Emotional Distress Construct & Measure	Country of Data Collection	Personal Cancer History of Study Participants
Tercyak et al., 2001	- Carrier - Noncarrier	- Short (0 weeks)	- Anxiety: STAI	US	—
van Dijk et al., 2006	- Carrier - Noncarrier - Inconclusive	- Short (4 weeks) - Long (28 weeks)	- CSD: IES, *cancer*	Australia/Europe	- History (Carrier, Inconclusive) - No history (Carrier, Noncarrier, Inconclusive)
van Oostrom et al., 2007[c]	- Carrier - Noncarrier	- Short (1 week) - Moderate (24 weeks)	- CSD: IES, *hereditary cancer*	Australia/Europe	
van Roosmalen et al., 2004	- Carrier	- Short (2 weeks)	- Anxiety: STAI - CSD: IES, *hereditary cancer*	Australia/Europe	- History (Carrier) - No history (Carrier)
Watson et al., 2004[c]	- Carrier - Noncarrier	- Short (4 weeks) - Moderate (16 weeks) - Long (52 weeks)	- Anxiety: GHQ28 - CSD: IES, *risk for cancer*	Australia/Europe	- No history (Carrier, Noncarrier)

Note. Dashes indicate that information was either not included in the original article, or was not provided in a manner that could be coded for the meta-analysis. STAI = State Anxiety subscale of the Spielberger State-Trait Anxiety Inventory; CSD = Cancer-specific distress; IES = Impact of Event Scale, measure referent listed in italics; HADS = Hospital Anxiety and Depression Scale; CWS = Cancer Worry Scale; BSI = Brief Symptom Inventory; POMS = Profile of Mood States; HSCL-25 = Hopkins Symptom Checklist; GHQ28 = General Health Questionnaire.

[a] Although this publication categorizes testers as noncarriers or as receiving negative results, study details indicate that these participants likely received uninformative negative results. Therefore, data for these participants were categorized as "inconclusive" for the present analysis.

[b] Approximately half of the participants in Manne et al., 2004 were also included in Schwartz et al., 2002. To correct for sample overlap, the total number of participants in Manne et al., 2004 was divided by half for the present analysis.

[c] Author(s) provided additional data to enable this study to be included in the meta-analysis.

Table 2

Analysis of Emotional Distress Following BRCA1/2 Mutation Testing

Length of Elapsed Time	Emotional Distress Construct	Gene Mutation Status	Fail-safe					Moderator Analyses (mixed-effects model unless otherwise noted)	
			k	*N*	*d*	95% CI	Homogeneity test	Country	Cancer History
Short	Anxiety	Carrier	9	33	.22***	.11 to .33	$Q(8) = 8.42$	$Q_B(1) = 1.61^a$	$Q_B(1) = 1.01^a$
		Noncarrier	6	50	−.33**	−.58 to −.09	$Q(5) = 27.13^{***}$	$Q_B(1) = 4.62^{*}$	–
		Inconclusive	5	–	−.10	−.26 to .05	$Q(4) = 9.62^{*}$	$Q_B(1) = .82^a$	–
	Cancer-Specific Distress	Carrier	10	109	.27***	.13 to .41	$Q(9) = 28.07^{***}$	$Q_B(1) = .05^a$	$Q_B(1) = .59^a$
		Noncarrier	7	69	−.25**	−.44 to −.06	$Q(6) = 41.00^{***}$	$Q_B(1) = 11.56^{***}$	–
		Inconclusive	6	41	−.18*	−.35 to −.01	$Q(5) = 28.90^{***}$	$Q_B(1) = 2.78$	$Q_B(1) = 5.68^{*}$
Moderate	Anxiety	Carrier	8	–	−.03	−.18 to .12	$Q(7) = 18.16^{**}$	$Q_B(1) = 2.91$	$Q_B(1) = .32$
		Noncarrier	6	39	−.22*	−.40 to −.04	$Q(5) = 23.38^{***}$	$Q_B(1) = 23.07^{***}$	–
		Inconclusive	7	–	−.12	−.27 to .03	$Q(6) = 26.09^{***}$	$Q_B(1) = 2.12$	–
	Cancer- Specific Distress	Carrier	11	–	−.01	−.14 to .13	$Q(10) = 32.62^{***}$	$Q_B(1) = 1.40^a$	$Q_B(1) = 5.07^{*}$
		Noncarrier	9	283	−.42***	−.65 to −.18	$Q(8) = 91.72^{***}$	$Q_B(1) = .89$	–
		Inconclusive	7	179	−.34***	−.46 to −.22	$Q(6) = 18.94^{***}$	$Q_B(1) = .66^a$	–
Long	Anxiety	Carrier	4	–	−.03	−.30 to .24	$Q(3) = 5.27$	–	–
		Noncarrier	3	–	−.06	−.36 to .25	$Q(2) = 6.87^{*}$	–	–
		Inconclusive	–	–	–	–	–	–	–
	Cancer-Specific Distress	Carrier	5	–	−.15	−.37 to .07	$Q(4) = 14.17^{**}$	–	$Q_B(1) = .82^a$
		Noncarrier	4	94	−.47***	−.56 to −.38	$Q(3) = 1.54$	–	–
		Inconclusive	2	–	−.39***	−.49 to −.30	$Q(1) = .33$	–	$Q_B(1) = .11.39^{***}$

* $p \leq .05$;

** $p \leq .01$;

*** $p \leq .001$

Q_B Between-groups heterogeneity for categorical moderators;

[a] Fixed-effects model

Table 3

Examination of the Clinical Significance of Effect Sizes in Terms of Representative Measures of Emotional Distress

Emotional Distress Construct (Representative Measure)	Pre-testing $M_{weighted}$ (SD_{pooled})	Gene Mutation Status	*M* after Short Length of Elapsed Time	*M* after Moderate Length of Elapsed Time	*M* after Long Length of Elapsed Time
Anxiety (STAI)	38.17 (11.10)	Carrier	40.61	37.84	37.84
		Noncarrier	34.51	35.73	37.50
		Inconclusive	37.06	36.84	–
Cancer-Specific	14.70 (12.81)	Carrier	18.16	14.57	12.78
Distress (IES)		Noncarrier	11.50	9.32	8.68
		Inconclusive	12.39	10.34	9.70

Note. STAI = State Anxiety subscale of the Spielberger State-Trait Anxiety Inventory; IES = Impact of Event Scale