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Psychological impact of genetic testing in women from high-risk breast cancer families

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Abstract

Psychological adjustment in 90 women (30 carriers and 60 non-carriers) who had undergone genetic testing for mutations in *BRCA1* and *BRCA2* breast/ovarian cancer susceptibility genes was compared with that of 53 women who were not offered genetic testing. Women were assessed prior to genetic testing and 7–10 days, 4 and 12 months after carrier status disclosure using self-administered questionnaires. Compared with women not offered testing, mutation carriers had significantly higher breast cancer distress 7–10 days ($t=2.80$, $P=0.005$) and 12 months ($t=2.01$, $P=0.045$) post-notification. Non-carriers showed a significant decrease in state anxiety 7–10 days post-notification ($t=2.27$, $P=0.024$) and in depression 4 months post-notification ($t=2.26$, $P=0.024$), compared with women not offered testing. These data show that non-carriers derive psychological benefits from genetic testing. Women testing positive may anticipate a sustained increase in breast cancer distress following disclosure, although no other adverse psychological outcomes were observed in this group.

Keywords: Psychological impact; Genetic counselling; Hereditary breast cancer

1. Introduction

Two breast-cancer-associated genes (*BRCA1* and *BRCA2*) have been identified, making it possible, once the family-specific mutation is identified, to accurately distinguish between mutation carriers and non-carriers in women currently unaffected by cancer. Mutation detection provides carriers with the possibility of improving survival through an increased focus on early detection and preventative strategies. Non-carriers return to population risk levels and can therefore resume population screening, possibly alleviating both their anxiety and the costs associated with the high-risk screening programme. Whether these potential benefits are realised in practice needs to be evaluated, as do potential psychological costs, if any.

There are few data currently available that assess the short-term psychological effects for women tested for gene mutations in *BRCA1* and *BRCA2*, and to our knowledge no long-term data are currently available on the psychological impact of genetic testing for breast and ovarian cancer susceptibility. For non-carriers, a decline in distress was found two weeks [1] and one month after testing [2] compared with baseline levels of distress. However, carriers did not show increases in depression and functional impairment one month after testing [2,3]. These previous studies included both individuals affected and unaffected by cancer [1,2] and men

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and women [2]. Because they include members of *BRCA1*-linked families who have been participating in research studies for many years, generalisability of these results to familial cancer clinic populations and current clinical practice may be limited [1,2].

A recent Dutch study provides prospective data on psychological adjustment amongst women approaching a familial cancer clinic 1–3 weeks post genetic testing for breast/ovarian cancer susceptibility gene mutations [4]. Anxiety and depression levels of mutation carriers and non-carriers were significantly different, with non-carriers showing a decrease in anxiety and depression [4]. Carriers by contrast became slightly more anxious and depressed 1–3 weeks post-disclosure compared with baseline [4]. These findings are similar to Croyle and colleagues, who found that carriers were more anxious than non-carriers one to two weeks post-testing [1]. In summary, most previous studies on the short-term impact of genetic testing for *BRCA1/2* mutations found that non-carriers, but not carriers, derived psychological benefits [1,2,4].

Lerman and colleagues found that individuals with high pre-testing levels of breast cancer distress who declined testing were significantly more likely to be depressed one month after testing was declined, while depression rates amongst non-carriers decreased and those of carriers remained unaltered [3]. No significant differences between non-carriers and those who declined testing and had low to moderate levels of breast cancer distress were found [3]. The inclusion of a test decliners comparison group is a strong feature of this study. However, given that test decliners have been found to differ from those who accept testing, with test acceptors exhibiting higher levels of breast cancer distress pre-testing [5], it is important to replicate this study with a different, more comparable control group.

A recent study by Tercyak and colleagues examined the impact of individual differences in information-seeking style on psychological adjustment in women undergoing testing both while anticipating results (ie. after providing a blood sample), and following disclosure of results [6]. Individuals with a tendency to monitor for threatening information were more likely to be distressed while anticipating genetic testing results. There was no association between information-seeking style and psychological adjustment once testing results had been disclosed [6].

Because attitudes towards genetic testing [7] and insurance contexts have been shown to vary cross-culturally, generalisations from these studies to the Australian context can only be undertaken cautiously. The objective of our study was to investigate the long-term psychological impact of genetic testing in carriers and non-carriers; the times at which negative outcomes are most likely; factors likely to facilitate or hinder psychological adjustment and the potentially moderating influence of individual information-seeking styles. As the impact of genetic testing is likely to be different for patients who have already been affected by cancer compared with those currently unaffected, only unaffected women are included. The current study includes a control group of women not eligible for testing to control for the passage of time and potential measurement effects. The following hypotheses were tested. (i) Non-carriers will have decreased psychological distress levels compared with untested women in the short-term (2-weeks follow-up), medium-term (4 months) and long-term (12-months). (ii) Carriers will not experience the same psychological benefits. Specifically there will be no changes of distress level compared with untested women at any one of the follow-up time points in this group. (iii) Individual differences in information-seeking styles at baseline will interact with testing outcome and influence psychological adjustment.

2. Patients and methods

2.1. Participants

Data were collected as part of a comprehensive assessment of attitudes to genetic testing, and uptake of breast cancer screening and prophylactic surgery uptake in women at increased risk of developing hereditary breast/ovarian cancer [8]. Unaffected women with a family history of breast/ovarian cancer who approached one of fourteen familial cancer clinics and six associated outreach clinics in five Australian States (New South Wales, Victoria, South Australia, Queensland and Western Australia) between November 1996 and October 2000 were eligible for the study. These familial cancer clinics provide a comprehensive service, which includes risk assessment, genetic testing, and advice regarding cancer surveillance and prophylactic strategies [9]. Only women who have never had breast or ovarian cancer were included in the study. Women were ineligible if they were unable to give informed consent; or had limited literacy in English, since data were collected using self-report questionnaires. The study was approved by 16 institutional ethics committees and signed informed consent was obtained.

Currently women at risk of developing hereditary breast cancer who have an affected, living relative willing to provide a blood sample are eligible for genetic testing, because the test is informative only when a known mutation is segregating in a particular family [10]. Women who were only being tested for founder mutations (such as those common in the Ashkenazi Jewish population) were not eligible to participate in the study.

Familial cancer clinic staff invited women to participate in the study during the pre-clinic telephone call

before initial face-to-face genetic counselling. Questionnaires, consent forms, and reply-paid envelopes were then mailed out by the co-ordinating research centre. Women were subsequently telephoned by the central research staff and given further information about the study and issues of informed consent. Participants were asked to return the completed questionnaire and consent form before attending the familial cancer clinic, where possible. Follow-ups questionnaires were mailed 7–10 days, 4 months and 12 months post-disclosure for those women who received testing results. Each time a woman received a testing result, this triggered the start of an analogous mail out of follow-up questionnaires to a recently recruited control participant whenever there was one available. Reminder calls were made as required.

2.2. Statistical analysis

Data were analysed using SPSS 7.0 (Statistical Program for the Social Sciences) for univariate analyses and MlwiN version 1.02 for multilevel regressions [11]. Descriptive statistics were used to describe the sample in terms of sociodemographic, clinical and psychological characteristics. To identify potential baseline confounder variables, the study and control groups were compared with respect to sociodemographic, clinical and psychological variables at baseline, using χ^2 tests for categorical variables and one-way analysis of variance for continuous data. Variables with significant associations with the study group were assessed for their associations with the outcome variables to identify confounding variables that would require inclusion as covariates. This was followed by repeated measures linear regression to explore differences in psychological outcomes between testing groups. This analysis was undertaken using multilevel (or hierachical) modelling, which is useful when there are differing numbers of observations per patient. Such models consider repeated observations (level 1) to be 'nested' within patients (level 2) [11].

2.3. Measures

2.3.1. Demographic characteristics

At baseline, age, educational level, marital status and number of biological children were assessed.

2.3.2. Baseline mutation carrier risk

To provide an estimate of risk pre-genetic testing, clinic staff made a judgment on whether the participant was at either 50 or 25% mutation carrier risk based on their family history of disease. An approximate 25% mutation carrier risk would apply to a woman from a high-risk family whose closest affected relative or relative with a known *BRCA1/2* mutation is second degree. A woman from a high-risk family who has either a first-degree affected relative or unaffected relative with a known pathogenic *BRCA1/2* mutation would be classified as being at 50% mutation carrier risk.

2.3.3. Miller Behavioural Style Scale

This 8-item scale is a validated measure of coping in threatening situations and possible responses to these situations [12]. In particular, it measures the coping styles of monitoring versus blunting. Specifically the scale asks subjects to imagine four hypothetical stress-invoking scenes of a largely uncontrollable nature. Each scene is followed by eight statements that represent different strategies for dealing with the stressful event. The Miller Behavioural Style Scale has been shown to be largely unrelated to, and distinct from, trait measures of anxiety and depression and is included in the present study as a moderating variable in the analysis.

2.4. Outcome measures administered at all time points

2.4.1. Impact of Event Scale

This is a 15-item pre-validated scale that measures intrusive thoughts and avoidant thinking about a specific stressful event [13,14]. Individuals at increased risk of developing hereditary breast cancer may construe their being at risk as a continuous, rather than specific, trauma. In a previous validation study of women with a family history of breast cancer, the intrusion and the avoidance subscales have been found to be highly consistent with Cronbach's alpha of 0.84 and 0.91, and a test-retest reliability of $r = 0.75$ and 0.78, respectively [15]. In the current study, the particular stressor was concern about being at risk of developing breast cancer. Participants were asked to rate symptoms of distress (for example, 'I had strong waves of feelings about being at risk of breast cancer') on a scale ranging from 'Not at all' to 'Often' over the previous one-week period.

2.4.2. State component of the State-Trait Anxiety Inventory (STAI-State)

The STAI-State Scale has well-documented psychometric properties [16]. It measures state anxiety, that is, transitory anxiety. The STAI-State asks respondents to indicate how they feel 'right now, at this moment' and to rate particular symptoms (for example, 'I feel strained') on a scale ranging from 'not at all' to 'very much so' [16]. Scores range from 20 to 80.

2.4.3. Beck Depression Inventory

This is a 21-item standardised instrument designed to measure severity of depression [17]. The Beck Depression Inventory was selected on the basis of its well-documented psychometric properties and its wide acceptance for assessing depression in psychiatric patients and detecting possible depression in normal populations [17]. Test–retest reliability correlations for

nine studies of non-psychiatric patients ranged from 0.60 to 0.90 [17]. Scores range from 0 to 63.

2.4.4. Satisfaction with the decision to undergo testing

Women who were tested were asked whether they felt either pleased, unsure or regretted having had the test 12 months post-disclosure.

3. Results

3.1. The sample

The sample divides into those who were eligible for testing and received either a positive result (carriers) or a negative result (non-carriers), and those who were ineligible for testing because they did not have a living affected relative from whom a blood sample could be taken ('not tested' group). Ninety women received genetic testing results. Of these, 30 were found to be carriers and 60 non-carriers. Women received testing results between one month and 33 months after completion of baseline assessment (median 2.5 months). Fifty-three women who could not be tested were recruited into the control group.

The mean age of participants was 40 years (S.D. = 11.1). Sixty-six per cent of the participants were married or living together. Seventy-two per cent had post-school qualifications, compared with 37% of women in the general Australian population [18]. Clinic staff judged 85% of participants to be at a 50% mutation carrier risk, and 15% at a 25% mutation carrier risk. For logistic reasons, a significant number of questionnaires (33%) were completed after initial face-to-face counselling at the familial cancer clinic. Prior prophylactic surgery was also assessed as a potential confounder. One carrier and one woman not offered testing had had a bilateral prophylactic mastectomy prior to genetic testing. Six carriers, nine non-carriers and two women not offered testing had had a prophylactic oophorectomy prior to testing. There were no significant differences by testing group in the number of women who had undergone bilateral prophylactic mastectomy and/or oophorectomy pre-testing with $P = 0.64$ and $P = 0.80$, respectively. To identify potential baseline confounding variables, all groups were compared with respect to age, family history variables (mutation carrier risk, presence of ovarian cancer in family history) and whether questionnaires were completed before or after the initial counselling. Only one variable had a significant association with the study group: presence of ovarian cancer in family history ($\chi^2 = 28.29$, $P < 0.001$). Perhaps not surprisingly, carriers and non-carriers were significantly more likely to have a family history that included ovarian cancer in addition to breast cancer (73% and 58%, respectively), compared with women who were not tested due an unavailability of an affected relative (19%). This reflects the higher likelihood of successful mutation detection in breast/ovarian families, compared with those with breast cancer only [19]. However, the presence of ovarian cancer was not associated with changes in any of the psychological outcomes at any assessment point, and therefore was unlikely to be a confounding variable. No significant differences were observed by group status with regard to whether baseline questionnaires were completed prior to or after face-to-face counselling.

We have previously reported that 89% of women eligible for participation in the study returned the baseline questionnaire [20]. Of the 143 participants who had returned baseline questionnaires, 114 also returned the 12-months questionnaire (overall follow-up rate of 80%). The follow-up rates by group were as follows: carriers—73%, non-carriers—77% and untested women—87%. There were no statistically significant differences between women who were retained and those lost to the 12-months follow-up ($n = 29$). Specifically, there were no statistically significant differences in age, education level, type of family history (breast cancer only versus breast and ovarian cancers) and baseline breast cancer distress, state anxiety and depression.

3.2. Satisfaction with decision to undergo predictive genetic testing

Twelve months after disclosure of the testing result, 64 women (90%) reported feeling pleased to have had the test, six (8%) feeling unsure, and one woman (1%) regretted having had the test. Amongst women reporting feeling unsure, three were carriers and three non-carriers. The participant who regretted having had the test was a carrier. Table 1 shows mean breast cancer distress (total score), state anxiety and depression scores for carriers, non-carriers and untested women across all of the assessment points.

3.3. Impact of testing on psychological outcomes

Three carriers underwent bilateral prophylactic mastectomy and one bilateral oophorectomy within 12 months of being notified of their carrier status. Due to the small number of carriers who had undergone prophylactic surgery, is unlikely that surgery would have moderated distress among mutation carriers. Table 2 shows the final hierarchical regression models for total breast cancer distress (as measured on the Impact of Event Scale), state anxiety and depression over time. No significant interactions between monitoring style and group were found for any of the three psychological outcomes, with $P = 0.46$, $P = 0.68$ and $P = 0.45$ for breast cancer distress, state anxiety and depression, respectively. The final model for breast cancer distress

Table 1
Mean (*M*) psychological outcome scores by testing group (raw scores)

Measure	Baseline		7–10 Days		4 Months		12 Months	
	N	M (S.D.)	N	M (S.D.)	N	M (S.D.)	N	M (S.D.)
Breast cancer distress (total score)								
Carriers	30	13.1 (13.1)	25	21.2 (14.4)	25	17.7 (18.6)	20	16.1 (14.9)
Non-carriers	59	13.4 (14.6)	43	13.9 (16.1)	47	8.1 (13.5)	42	8.2 (14.2)
Not tested	51	16.0 (14.8)	45	14.9 (12.3)	50	13.1 (13.5)	43	12.3 (14.8)
State anxiety								
Carriers	25	36.1 (11.2)	24	38.5 (13.8)	26	36.8 (15.3)	22	31.7 (10.5)
Non-carriers	53	33.6 (12.1)	43	31.6 (11.1)	48	32.2 (10.8)	46	36.2 (12.9)
Not tested	47	33.6 (10.7)	46	36.8 (12.1)	48	36.3 (14.2)	46	39.0 (12.2)
Depression								
Carriers	25	5.5 (5.7)	24	5.3 (6.2)	26	6.2 (8.7)	22	4.0 (5.1)
Non-carriers	50	6.3 (6.7)	44	5.7 (7.0)	50	3.6 (5.4)	46	5.4 (6.4)
Not tested	47	5.9 (5.6)	47	7.2 (6.8)	48	6.4 (6.3)	46	6.9 (7.00)

S.D. standard deviation.

Table 2
Summary of final hierarchical regression models on psychological outcomes ($N = 143$)[a]

	Coefficient	Standard error	*P* value
Breast cancer distress			
Intercept	15.8	2.1	<0.001
Carriers × time 2 (interaction)[b]	8.5	3.0	0.005
Carriers × time 4 (interaction)[b]	6.4	3.2	0.045
State anxiety			
Intercept	33.0	1.8	<0.001
Carriers × time 4 (interaction)[b]	−8.3	3.1	0.007
Non-carriers × time 2 (interaction)[b]	−5.7	2.5	0.024
Depression			
Intercept	6.1	1.0	<0.001
Non-carriers × time 3 (interaction)[b]	−2.9	1.3	0.024

[a] Only significant interaction effects between mutation status and assessment time are shown.
[b] Reference group is women who were ineligible for testing because they have no living affected relative from whom a blood sample could be taken.

shows that carriers had significantly higher breast cancer distress 7–10 days ($t = 2.80$, $P = 0.005$) and 12 months ($t = 2.01$, $P = 0.045$) post-notification than those who were untested, and a trend for higher breast cancer distress was observed 4 months post-notification ($t = 1.93$, $P = 0.054$). Compared with untested women, carriers showed a statistically significant decrease in state anxiety 12 months post-notification ($t = 2.70$, $P = 0.007$), and non-carriers similarly showed a statistically significant decrease in state anxiety 7–10 days post-notification ($t = 2.27$, $P = 0.024$). Non-carriers also showed a trend for lower state anxiety than those untested 4 months post-notification ($t = 1.84$, $P = 0.066$). Non-carriers showed a statistically significant decrease in depression scores 4 months post-notification ($t = 2.26$, $P = 0.024$). Multilevel regressions were repeated with type of family history (ovarian cancer present or not present in family history) and the 'before/after counselling' variable included as covariates. Findings remained unchanged.

4. Discussion

Before discussing the implications of these findings, the strengths and limitations of this study should be noted. The high follow-up rate (80% at 12 months follow-up) and the lack of differences between those lost to follow-up and those retained is a strength of the study. To our knowledge, this study provides data on the long-term outcomes of genetic testing for the first time, and the high follow-up rate allows us to generalise to women approaching familial cancer clinics for genetic testing. Several of our findings approached, but failed, to reach

statistical significance, indicating a situation where effect sizes are moderate and the sample size is limited. Thus, even though we included almost all Australian familial cancer clinics and collected data for four years, our sample size may have been inadequate. Having said this, it should be noted that the number of unaffected women included in previous studies are similar, with the number of carriers assessed at baseline ranging from 22 to 31 [2,4,6]. Given the sample size limitations of these studies, meta-analysis would clearly be the most powerful strategy to address the impact of genetic testing in currently unaffected women.

Amongst carriers, we found statistically significant increases in breast cancer distress 7–10 days and 12 months post-notification and a trend towards a statistically significant increase four months post-notification, indicating a sustained long-term increase in breast cancer distress in response to receiving a positive test result. This finding is consistent with previous studies that included a measure of breast cancer distress. Lodder and colleagues found that carriers showed a slight increase in cancer-related distress 1–3 weeks post-testing [4]. In a preliminary report of the British multicentre study, Watson and colleagues described significantly increased cancer worry in carriers at the 1-month follow up [21]. Our study is the first, however, to show that this increase in cancer distress is long-lasting.

We also found that carriers showed statistically significant decreases in state anxiety 12 months post-disclosure. This finding seems as likely to reflect Type I error as it is to be real, given the lack of changes amongst carriers in state anxiety 7–10 days and 4 months post-disclosure. If, however, we assumed that this decrease in state anxiety at 12 months is not just a statistical aberration, it is unclear why no changes were observed from baseline state anxiety levels 7–10 days and 4 months post-notification. One possible explanation may be that a prolonged period of time may be needed for carriers to derive psychological benefits. What is clear from our findings though is that the impact of testing on carriers may be more complex than formerly assumed, with carriers potentially deriving both psychological costs and benefits from predictive testing.

Consistent with previous studies and in support of what was hypothesised, we observed statistically significant decreases in anxiety amongst non-carriers 7–10 days post-notification and a decrease at 4 months that approached, but failed, to reach statistical significance. In addition, we observed statistically significant decreases in depression four months post-testing. These results show that non-carriers derive psychological benefits from genetic testing, although it is perhaps surprising that these women's breast cancer distress did not show a more dramatic fall after testing confirmed their non-carrier status.

Based on a large body of literature that demonstrates that individuals with a monitoring information-seeking style are more likely to focus on negative outcomes, thereby generating distress, we had hypothesised that carriers high in monitoring would be most vulnerable. We found no significant interaction between testing result and a tendency to monitor for threatening information. Although we cannot rule out type II error, this is consistent with the findings by Tercyak and colleagues, who studied the short-term impact of testing [6].

5. Clinical implications

These data are useful in counselling women considering predictive genetic testing about the potential impact of genetic testing. Our data show that, on average, non-carriers derive psychological benefits from genetic testing, while women testing positive may anticipate an increase in breast cancer distress following disclosure. Clearly, in some women, high breast cancer distress may be psychologically disabling. Given the strong correlations between baseline breast cancer distress and subsequent levels of breast cancer distress [22], women are likely to benefit from routine assessment of breast cancer distress to identify those with elevated breast cancer distress. These women are arguably most at risk if testing demonstrates carrier status, and should be counselled that genetic testing may exacerbate their anxiety about developing breast cancer.

These psychological costs amongst carriers must be balanced against benefits of genetic testing. Genetic testing is an important step in the decision-making process about prophylactic mastectomy and/or oophorectomy since it can provide a definitive answer concerning a woman's mutation status and therefore risk. Evidence for a significant reduction of risk and mortality from bilateral prophylactic mastectomy has now become available [23], and recent studies also show that prophylactic mastectomy reduces psychological morbidity and anxiety in women at increased risk [24,25].

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