Experiences and interpretations of *BRCA1/2* testing among women affected by breast or ovarian cancer who received a negative result

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Abstract

The aim of this study was to retrospectively describe the genetic testing motives and experiences of women with a previous breast and/or ovarian cancer diagnosis, who received negative *BRCA1/2* results including variants of unknown significance and no pathogenic variant detected. One hundred and thirteen women (mean age 56.17 years) were recruited from a familial cancer centre in metropolitan Australia, an average 3.4 years after undergoing testing. Participants completed a self-report questionnaire focusing on the retrospective experience of and motives for undergoing *BRCA1/2* testing. The study found that the primary motives for undergoing *BRCA1/2* testing were (a) to know more about whether their cancer was hereditary, and (b) to have more certainty about the risk of their children developing cancer. In terms of perceptions of personal risk, 35% of women perceived that their risk of breast cancer to be the same or lower than the general population and 80% believed the negative test result to mean that a risk-conferring gene had not been detected. Yet, the average estimate of the likelihood that their cancer was hereditary was 48 out of a possible 100. Psychologically, women did not interpret the negative *BRCA1/2* result as a positive outcome. Half were not relieved by the result and were as or more worried than before. Psychological morbidity was high with 17%, 100%, and 36% experiencing clinically significant depression, anxiety, and cancer-specific distress, respectively. Self-ratings of the likelihood that their cancer was hereditary were more closely associated with their personal family cancer histories than with measures of psychological distress. These results have implications for adherence to risk-reducing behaviours and quality of life. Given that these women are not routinely followed up in clinical practice, these findings highlight the importance of post-test genetic counselling and longer-term follow-up for women with negative *BRCA1/2* results. Additional time and emotional support from

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genetic counsellors may help this group of women make sense of the meaning of their test result and adjust psychologically, particularly to uncertainty around the cause of their family history.

Keywords Breast/ovarian cancer · *BRCA1/2* · Negative result · Genetic testing · Motives · Experiences

Introduction

By age 85, the risk of breast and ovarian cancer in Australian women is 1 in 8 (Cancer Council Australia 2017a) and 1 in 81 (Cancer Council Australia 2017b), respectively. Globally, one in 18 women will develop breast cancer in their lifetime (Tao et al. 2015), and 220,000 women will develop ovarian cancer each year (Jayson et al. 2014). Women born with a variant in the *BRCA1/2* tumour suppressor genes are at a significantly greater risk of breast and ovarian cancer than those without these variants (Antoniou et al. 2003; Narod 2002). Variants in the *BRCA1/2* genes confer an estimated 27 to 87% lifetime risk of breast cancer and an 11 to 68% lifetime risk of ovarian cancer (Kuchenbaecker et al., 2017). Genetic testing has enabled women to determine whether they have inherited a *BRCA1/2* variant and in doing so, inform decisions about their risk-management behaviours. When a *BRCA1/2* test is undertaken, it can yield three types of results:

- (i) A conclusive positive result (a family-specific *BRCA1/2* variant)
- (ii) No variant detected (the result does not reveal a pathogenic *BRCA1/2* variant)
- (iii) A variant of unknown significance (VUS: a variant is identified in *BRCA1/2*; however, it is not known whether it is pathogenic).

Given the variability within the human genetic code, germline *BRCA1/2* variants only account for between 5 and 10% (Silva et al. 2014) and 10–15% (Karakasis et al. 2016) of breast and ovarian cancer familial clusters, respectively. Consequently, the majority of women affected by cancer who undergo *BRCA1/2* testing do not receive a conclusive positive result and instead, must contend with the uncertainty of either no variant being detected or a VUS result (henceforth collectively referred to as a negative result). Until relatively recently, when no pathogenic variant was found in a person who was the first member of their family to undergo *BRCA1/2* testing, this result was considered *uninformative* rather than truly negative. However, with advances in genetic testing technology, clinical confidence in these negative results has increased dramatically—such that the absence of a pathogenic variant in *BRCA1/2* is now considered almost definitively negative. Although the majority of women continue to receive negative *BRCA1/2* results, much of the previous psychosocial research has focused on women with a positive *BRCA1/2*

result. Little is known about the experience of genetic testing and counselling among women who have received a negative result, including their perception of risk and their understanding and interpretation of the genetic information provided.

One study reporting on women's interpretations of different *BRCA1/2* results found that while women were mostly correct in their understanding of positive and true negative results, interpretation of uninformative negative results was more challenging (Hanoch et al. 2014). Approximately 50% of the women felt that they had learned nothing from these results, while the other 50% interpreted them to mean that their cancer risk was the same as that of the average woman (Hanoch et al. 2014). Another study included a sample of women both affected and unaffected by breast or ovarian cancer, who had all undergone *BRCA1/2* testing, the majority (74.5%) receiving a negative result (Vos et al. 2012a). This study reported inaccuracies between women's perception of risk and the information that had actually been communicated to them through genetic counselling (Vos et al. 2012a). Significant disparities were also found between their actual cancer risks (as communicated by the health professional) and both (a) their recalled and interpreted cancer risk, and (b) their recalled and interpreted likelihood of cancer being heritable. Furthermore, women who received an uninformative negative result specifically were less likely to have undergone risk-reducing surgery or surveillance and expressed less intent to engage in risk-reducing surgery or surveillance activities, as compared with women with positive results. This suggests they may have felt falsely reassured by their test results. The authors concluded that genetic counselling needs to better address the potential for misinterpretation after an uninformative negative *BRCA1/2* test result.

Other research has focused on the association between risk interpretation and psychological distress, and findings have been inconsistent. One study reported that women's recollections and interpretations of the communicated cancer risks over the short-term were the strongest predictors of psychological well-being, such that the higher the women interpreted their likelihood of a hereditary cancer, the greater the negative psychological impact (Vos et al. 2012b). Both Vos et al. (2012a) and Vos et al. (2012b) found an association between perceptions of higher cancer risk and likelihood of hereditary cancer and increased short-term distress, which was seen to decline over time. Beran et al. (2008) reported that distress declined over a period of 12 months after testing (Beran et al. 2008), and others have also reported that initially

elevated levels of distress following an uninformative negative test result declined over time among the majority of women (O'Neill et al. 2009). However, a meta-analysis found that receiving an uninformative negative result was associated with decreases in cancer-specific distress, similar to those observed among non-carriers (Hamilton et al. 2009). These decreases were maintained over time, and the authors concluded that women misinterpreted a negative result to mean a definitively reduced cancer risk. Overall, the authors found little evidence of an effect of *BRCA1/2* testing on distress. Subsequent research found no association between *BRCA1/2* test results and anxiety levels, and the authors concluded that levels of anxiety were instead associated with pre-testing levels of perceived genetic predisposition to cancer (Bredart et al. 2013). It follows that our understanding of the intermediate and long-term psychological sequelae of a negative *BRCA1/2* result is not entirely clear.

Information is also limited regarding the factors motivating women with family and personal histories of breast/ovarian cancer to undergo *BRCA1/2* testing. While several studies have reported the motivations of women with a family history of breast cancer, they excluded those with a personal history of breast cancer (Bowen et al. 1999; Brain et al. 2000) or only discussed motivations when a *BRCA1/2* variant had been identified (Jeffers et al. 2014; Van Asperen et al. 2002). To date, the *BRCA1/2* genetic testing motivations of women with a personal history of breast cancer, as well as the relative uncertainty of a negative *BRCA1/2* status, have yet to be explored.

Within a sample of women with breast or ovarian cancer with a negative *BRCA1/2* result, the aims of the present study were to:

1. Describe their retrospective motives for undergoing *BRCA1/2* testing.
2. Understand their experience of genetic testing, including interpretation of a negative result and risk perceptions of breast and ovarian cancer.
3. Understand the intermediate to long-term associations between the perception of the likelihood of cancer being hereditary and psychological measures of depression, anxiety, neuroticism and cancer specific distress, and family history of cancer.

Method

Participants for the present study were recruited as a part of a broader study of the psychological and behavioural outcomes of women at an increased risk of breast and/or ovarian cancer. The records of the Familial Cancer Centre (FCC) at the Royal Melbourne Hospital, a large tertiary hospital institution in metropolitan Melbourne, Australia, were searched for women with

a breast and/or ovarian cancer diagnosis who had attended the FCC between the years 2005 and 2010, and had undergone *BRCA1/2* genetic testing and received a negative result, which includes a VUS or no pathogenic variant detected. Other inclusion criteria were: being over 18, fluency in English, and being free of an intellectual disability or cognitive impairment that would hinder informed consent or participation.

Procedure

The names of women identified through the FCC were cross-referenced with a state-wide cancer registry, to ensure that they had not subsequently died. FCC records were searched from 2005 to 2010 and identified 319 potential participants. Three did not have postal addresses, so questionnaires were sent out to the remaining 316 women. In 2011, potential participants were mailed the following information: (a) documents describing the nature and the purpose of the study and inviting them to take part, (b) a self-report questionnaire, and (c) a consent form. Women were asked to return the completed questionnaire along with their informed written consent in a reply paid envelope. The study received institutional ethics approval (HREC No: 2010.285).

Measures

Self-report questionnaires were used to collect data relating to the experience and interpretation of genetic testing, including motives for undergoing testing, as well as socio-demographic, clinical, and psychological information (detailed below).

Socio-demographic characteristics

Data collected were age, residential location, living arrangements, highest level of education, occupational status, relationship status, and gross annual household income. Clinical information collected were type of cancer diagnosis (initial and recurrence), cancer treatments, age at first cancer diagnosis, age at most recent cancer diagnosis), date of genetic testing, and number of relatives with any cancer/breast cancer/deceased following cancer. Although relatives with ovarian cancer were also reported, the number was very low ($n = 24$ in total); therefore, this information was not utilised further in the present study.

Breast and ovarian cancer experience: treatment and family cancer history

Participants were asked about their age at diagnosis and the types of cancer treatment they received at the time for their breast and/or ovarian cancer. For family cancer history, participants were asked to provide details of up to five family members who had been diagnosed with cancer. They were also

asked to include their relationship to each relative, the type of cancer diagnosed in the relative, and whether the relative was deceased as a result of cancer.

Motives for undergoing testing

Thirteen statements based on previous work were developed to assess motives for undergoing genetic testing (Brain et al. 2000; Julian-Reynier et al. 1998). Participants were asked to nominate all motives that applied. Examples include ‘I wanted to know if cancer in my family is hereditary’, ‘I wanted more certainty about the risk of my children getting cancer’, and ‘my doctor advised me to get tested’. Participants were also given the opportunity to list other motives not mentioned in the list.

Risk perception, interpretation and understanding of the *BRCA1/2* testing process

Participants were asked about anticipated outcomes of *BRCA1/2* testing. Namely, whether *before they were tested*, they suspected or expected that *BRCA1/2 mutation would be identified using the technology at the time*, *BRCA1/2 mutation would not be identified using the technology at the time*, *BRCA1/2 mutation of uncertain significance would be identified*, *no idea/did not think about it*, *others*. Participants were asked whether, before testing, they had considered the possibility that they would receive result that they did (yes/no); whether they expected to receive more genetic information in the future (yes/no); whether they thought the genetic counselling process was complete (yes/no); and the extent of relief and worry arising from knowledge of the *BRCA1/2* test result. To measure interpretation of their genetic risk, participants were asked: ‘Based on your test result, what do you think is the likelihood that you have inherited a gene that increases your chances of having cancer again?’ Response options were: *non-existent*, *very unlikely*, *unlikely*, *likely*, *very likely*, *certain* and *no information can currently be given about my risk*. They were also asked: ‘On a scale of 0 (no chance at all) to 100 (absolutely certain), what do you think the likelihood is that your cancer is hereditary (genetically transmitted?)’ Responses were not directly compared to any objective information, but interpreted within the context that participants were counselled about the possibility of carrying an as yet unknown genetic variant (see below). For perceived relative risk of breast cancer, participants were asked ‘Compared to the average Australian woman, my risk of developing breast cancer (again) is...’ with response options of: *much lower*, *a bit lower*, *the same*, *a bit higher* and *much higher*. Absolute risk was assessed by asking ‘Regardless of the risk of the average Australian woman, on a scale of 0 (no chance at all) to 100 (absolutely certain), what do you believe your risk is of developing breast cancer (again) in your lifetime?’

Responses to these items were compared to information that would have been given at the time, based on the Australian National Breast and Ovarian Cancer Centre (NBOCC) guidelines for assessing family history (NBOCC 2010). All participants would have been counselled about being ‘potentially’ high risk, which was communicated as a 25–50% lifetime risk for breast cancer. Only a small number of women in the study had personal or family histories of ovarian cancer, and given that less specific lifetime risk information would have provided at the time, no risk perception data relating to ovarian cancer are presented here.

Psychological measures

Anxiety symptoms were assessed with the Hospital Anxiety Depression Scale anxiety subscale (HADS-A), a 7-item self-report scale used to assess the presence of anxiety states in medical outpatients (Zigmond and Snaith 1983). Higher scores represent greater symptom severity. Scores range from 0 to 21, with ≥ 8 indicating possible, and ≥ 11 indicating probable, clinically significant anxiety (Bjelland et al. 2002; Singer et al. 2009). The HADS has well established psychometric properties (Bjelland et al. 2002) and is recommended for use in oncology populations (Singer et al. 2009).

Depressive symptoms were measured using the Centre for Epidemiological Studies Depression Scale (CES-D; Radloff 1977). Scores range from 0 to 60. Higher scores represent more severe depressive symptomology, with scores of 16 or higher considered indicate of significant symptoms of depression (Radloff 1977). The CES-D has high internal consistency and has been reported with Cronbach’s alpha coefficients ranging from .85 to .90 (Radloff 1977). This tool has also been recommended for use in cancer populations (Vodermaier et al. 2009).

Cancer-specific distress was measured using the Impact of Events Scale (IES). The IES consists of 15 items capturing intrusive and avoidant thoughts and behaviours, associated (in this case) with breast and/or ovarian cancer, and occurring in the past week (Horowitz et al. 1979). Items are scored on a 4-point Likert-scale of 0 = ‘not at all’, 1 = ‘rarely’, 3 = ‘sometimes’ and 5 = ‘often’. Scores range from 0 to 75. Scores of 0–8 are considered subclinical, scores from 9 to 25 are in the mild range, scores from 26 to 43 are considered moderate and scores of 44 and above indicate severe distress. The IES has been shown to have good reliability and validity (Joseph 2000; Thewes et al. 2001).

Neuroticism was measured with the 10-item Neuroticism scale of the International Personality Item Pool Five Factor Personality Inventory (IPIP) (Goldberg 1999). The IPIP is a public-domain alternative to major commercial inventories assessing domain constructs of the Five Factor Model of personality (Goldberg et al. 2006). Responses on the Neuroticism scale are scored on a 5-point Likert-type scale, with higher scores representing greater neuroticism. Scores range from 0

to 50. There are no cut-offs for this measure, as personality is considered a dimensional construct. The IPIP-N has been shown to have strong internal consistency (Cronbach's $\alpha = 0.775$) and acceptable discriminate, concurrent and predictive validity (Buchanan et al. 2005; Gow et al. 2005). Neuroticism was included as a measure because there is a well-established association between high levels of neuroticism, experience of health care and subjective perceptions of mental and physical quality of life (Stafford et al. 2015).

Data analysis

Data were analysed using SPSS version 23.0. Descriptive and frequency statistics were calculated for all clinical, demographic and psychological measures. The three aims of the study were addressed as follows: First, motives were ranked in order from most nominated to least nominated; second, participants' experiences and interpretation of their *BRCA1/2* test results were described; and third, examination of psychological morbidity and trait neuroticism was addressed by reporting of depression, anxiety, cancer-specific distress and levels of neuroticism scores. Spearman rank correlations were conducted between perceptions of the likelihood that cancer is hereditary and family cancer history and psychological measures. These Spearman rank correlations were Bonferroni-adjusted for multiple comparisons ($\alpha = .001$ [.05/28]).

Results

Study participation

Of the 316 study packs mailed to potential participants, 18 study packs were returned to sender, seven women declined to take part, one questionnaire was returned incomplete and was excluded, and 177 questionnaires were not returned due to unknown reasons. A total of 113 questionnaires were returned with informed consent (37.9% response rate). Descriptive analyses were conducted on the questionnaire data of these 113 recruited participants (Fig. 1).

Demographic characteristics of the sample

The demographics of the sample are detailed in Table 1. The age range of the women in the sample was 27 to 84 years, with a mean age of 56.17 years. On average, 3.4 years had lapsed between genetic testing and study participation. The majority (83%) of the participants were in a committed relationship. Approximately half of the sample lived in the Melbourne metropolitan area (48%), were in paid employment (54%) and had a total gross family income above AUD \$62,348 (44%). Notably, 17% of the sample declined to answer the income question.

With regard to education, about one third (32%) of the cohort reported having a Bachelor's or higher university degree.

Personal and family cancer history

The clinical and family cancer history characteristics of the sample are described in Table 2. The original diagnosis for the majority of women was breast cancer (95%). The average age at diagnosis was 45.12 years ($SD = 11.19$), and the average time between original cancer diagnosis and data collection was 11.2 years. On average, 7.6 years lapsed between the date of the original cancer diagnosis and genetic testing. Approximately one quarter of women (27%) reported experiencing a recurrence and/or new primary diagnosis since their original diagnosis. Just over a quarter of the sample (27%) had undergone prophylactic oophorectomy and 10% had had a bilateral mastectomy. Of the other treatment options available, for both the first diagnosis and recurrent diagnosis, chemotherapy was the most utilised (59% and 35%, respectively). On average, each of the women had 2.24 relatives with cancer ($SD = 1.25$), 1.94 of these relatives had had breast cancer, and 1.12 relatives had died of cancer ($SD = 0.96$).

Retrospective motives for undergoing genetic testing

Table 3 describes participants' motives for undergoing *BRCA1/2* testing. The most frequently endorsed motives were 'to know if cancer in my family is hereditary' (80%), for 'more certainty about the risks of my children getting cancer' (76%), and 'more certainty about my own risks of getting cancer again' (50%). The least endorsed motives were family planning (6%) and being asked by a family member to undergo testing (13%).

Perceptions and interpretations and understanding of the *BRCA1/2* testing process

Table 4 describes the perceptions and interpretations of the *BRCA1/2* genetic testing process from the perspective of the participants. The largest proportion of women (39%) anticipated (i.e., reflecting back to their thoughts prior to being tested) that the testing process would identify a *BRCA1/2* variant; however, a further 33% reported that they had either no idea or did not think about it. Regarding perceptions of the likelihood that they had inherited a cancer-conferring gene after receiving the test results, overall, nearly half of participants believed that they did not inherit a pathogenic variant (49.6%). Approximately 31% thought that it likely/very likely/certain that they had inherited a risk-conferring gene, and 16% of women interpreted their result as meaning *no information can be currently be given about my risk*. Regarding ratings of risk perception on a scale of 0 to 100, the average (SD) rating of the likelihood that their cancer was hereditary

Fig. 1 Participant recruitment flow diagram

was 47.81(33.69). The mean rating of perception of absolute breast cancer risk was 40 out of 100, and approximately 60% of women perceived their relative risk of breast cancer to be *a bit* or *much higher* than the average Australian woman. The size of the standard deviations of the risk perception ratings suggest that women's responses were spread out over a wide range of values.

In terms of the women's understanding of the genetic counselling process, before the testing occurred, 29% of women had not considered the notion that they would receive the result that they did, 53% did not expect to receive more information in the future and 59% believed the genetic counselling process to be complete. Half of the women (48%) reported feeling relieved by their test result, and half the women (50%) reported being just as—if not more—worried since receiving their test results.

Psychological characteristics

Table 5 describes the psychological characteristics of the sample. The mean levels of depression (CES-D), anxiety (HADS-A), Neuroticism (IPIP-N) and cancer-specific distress (IES) were 9.85, 13.15, 23.15 and 19.61 respectively. All participants (100%) met the threshold for probable anxiety on the HADS (score ≥ 8), of whom 10 met the threshold for clinical anxiety (≥ 11). On the depression scale, 17% of participants met the threshold for likely major depression (CES-D ≥ 16), and on the IES, 36% (38 women) had scores showing at least

moderate cancer-related distress. Among these 38 women, nine had scores indicative of severe distress. There was a significant association between scoring ≥ 16 on the CES-D and experiencing at least moderate cancer-related distress on the IES (scores ≥ 26) ($\chi^2 = 8.95$, $df = 1$; $p = .003$). A total of 67% of women who met the threshold for depression also met the threshold for at least moderate cancer-related distress. Given that 100% of participants had probable levels of anxiety, this may be associated with depression and distress.

Associations between psychological characteristics, family cancer history and risk perception

Significant positive associations were found between perceptions of the likelihood that cancer is hereditary and total number of relatives with breast cancer ($r(83) = .437$, $p < 0.001$), total number of relatives deceased following cancer ($r(84) = .374$, $p < 0.001$), and total number of relatives with cancer ($r(84) = .492$, $p < 0.001$). However, the perception of the likelihood that cancer is hereditary was not significantly associated with any psychological measures. All psychological measures were significantly positively correlated with each other.

Discussion

The outcome of *BRCA1/2* gene variant testing is most frequently a negative result. This was the case at the time that

Table 1 Demographics characteristics of the sample ($N = 113$)

Characteristic	Total $N = 113$
Age, years, M (SD) [range]	56.17 (13.5) [28.9–85.2]
Time between genetic testing and study participation (years), M (SD) [range]	3.4 (1.8) [1.5–9.1]
Residential area	
Metropolitan Melbourne, n (%)	54 (48)
Non-metropolitan–regional, n (%)	30 (27)
Mon-metropolitan–rural, n (%)	29 (26)
Relationship status	
Married/cohabiting, n (%)	94 (83)
Single/never married, n (%)	5 (4)
Separated/divorced, n (%)	6 (5)
Widowed, n (%)	8 (7)
Highest level of education	
Primary school, n (%)	3 (3)
Some secondary school, n (%)	32 (28)
Completed secondary school, n (%)	12 (11)
Diploma/Certificate, n (%)	29 (26)
Apprenticeship, n (%)	1 (1)
Bachelor or other higher degree, n (%)	36 (32)
Occupational status	
Unemployed, n (%)	4 (4)
Paid employment, n (%)	61 (54)
Home duties, n (%)	21 (19)
Retired, n (%)	23 (20)
Other, n (%)	1 (1)
Missing, n (%)	2 (2)
Total annual gross family income (AU \$)	
\$0 to \$20,748, n (%)	10 (9)
\$20,749 to \$41,548, n (%)	19 (17)
\$41,549 to \$62,348, n (%)	12 (11)
\$62,348 to 83,148, n (%)	17 (15)
More than \$83,149, n (%)	33 (29)
Prefer not to answer, n (%)	19 (17)
Missing, n (%)	3 (3)

these data were collected and continues to be the commonest outcome today. The most substantial change since the data were collected is the meaning attributed to a negative *BRCA1/2* result. Genetic counselling in the period to which this manuscript relates (2005–2010) would have included a ‘potentially’ high cancer risk assessment for these women taking into account family history, the concept of polygenic risk, the small chance of a missed *BRCA1/2* variant and the possibility of as yet unknown major breast cancer genes. In 2018, levels of clinical understanding of negative *BRCA1/2* results have increased dramatically, and the absence of a pathogenic variant in *BRCA1/2* is now thought of almost definitively as a true negative *BRCA1/2* result. Risk assessment now also involves genetic testing for other hereditary breast cancer genes and personalised risk calculation. While the findings of

this study need to be interpreted in the context of what was current knowledge during data collection, they bear clinical relevance to the genetic counselling experience of the many women who receive negative results today. This study also describes the motivations for undergoing *BRCA1/2* genetic testing in this group of women. These data add to our knowledge, as the motives of women with a family and a personal history of cancer have not been well documented.

The predominant motives for most women to undergo testing were the desire to learn more about the genetic nature of their cancer risk and the potential impacts on their family. In this respect, the uncertainty of a negative result might have been and may continue to be particularly distressing, as 39% of women anticipated that testing would indeed identify a *BRCA1/2* variant. Prior research investigating the testing

Table 2 Clinical and family cancer history characteristics (*N* = 113)

Characteristic	Total sample, <i>N</i> = 113
Age when first diagnosed, M (SD) [range]	45.12 (11.19) [24–79]
Time between original cancer diagnosis and study participation (years), M (SD) [range]	11.2 (9.9) [1.5–40.5]
Time between original cancer diagnosis and genetic testing (years), M (SD) [range]	7.6 (9.7) [0–37.3]
Original cancer diagnosis	
Breast cancer, <i>n</i> (%)	107 (94.7)
Ovarian cancer, <i>n</i> (%)	6 (5.3)
Subsequent cancer diagnosis	
None, <i>n</i> (%)	82 (72.6)
Recurrence, <i>n</i> (%)	9 (8)
New diagnosis, <i>n</i> (%)	16 (14.2)
Recurrence and new diagnosis, <i>n</i> (%)	5 (4.4)
Missing, <i>n</i> (%)	1 (0.9)
Treatment (first diagnosis)	
Surgery—lumpectomy, <i>n</i> (%)	61 (54.0)
Surgery—unilateral mastectomy, <i>n</i> (%)	43 (38.1)
Surgery—bilateral mastectomy, <i>n</i> (%)	9 (8.0)
Surgery—bilateral oophorectomy, <i>n</i> (%)	7 (56.2)
Radiation, <i>n</i> (%)	57 (50.4)
Chemotherapy, <i>n</i> (%)	67 (59.3)
Hormone therapy, <i>n</i> (%)	45 (39.8)
Targeted therapy, <i>n</i> (%)	12 (10.6)
Treatment (recurrence [<i>n</i> = 34])	
Surgery—lumpectomy, <i>n</i> (%)	11 (9.7)
Surgery—unilateral mastectomy, <i>n</i> (%)	13 (11.5)
Surgery—bilateral mastectomy, <i>n</i> (%)	3 (2.7)
Surgery—bilateral oophorectomy, <i>n</i> (%)	6 (5.3)
Radiation, <i>n</i> (%)	8 (23.5)
Chemotherapy, <i>n</i> (%)	12 (35.3)
Hormone therapy, <i>n</i> (%)	12 (35.3)
Targeted therapy, <i>n</i> (%)	4 (10.3)
Prophylactic oophorectomy	
Yes, <i>n</i> (%)	30 (26.5)
No, <i>n</i> (%)	79 (69.9)
Missing, <i>n</i> (%)	4 (3.5)
Prophylactic mastectomy	
No still have both breasts, <i>n</i> (%)	59 (52.2)
One breast removed, <i>n</i> (%)	24 (21.2)
Both breasts removed, <i>n</i> (%)	11 (9.7)
Missing, <i>n</i> (%)	19 (16.8)
Total nr of relatives with cancer, M (SD) [range]	2.24 (1.25) [1–5]
Total nr of relatives with breast cancer, M (SD) [range]	1.94 (1.2) [0–5]
Total nr of relatives died of cancer, M (SD) [range]	1.12 (0.96) [0–4]

nr number

motives of women at increased risk of breast and/or ovarian cancer is limited with inconsistent findings. One study of women likely to approach genetic assessment services indicated that women's primary motives were to establish their

personal risk (Brain et al. 2000) and concluded that these women were utilising their genetic testing results in their decisions about risk management. The participants in that study, however, were women identified as having a family history of breast

Table 3 Motives for undergoing testing ranked in order of most to least endorsed

Motive	n	%
To know if cancer in my family is hereditary	90	80
More certainty about the risks of my children getting cancer	86	76
More certainty about my own risks of getting cancer again	57	50
Help with scientific research	46	41
Doctor advised me to get tested	45	40
Worried about getting cancer again	39	35
Should I have a prophylactic mastectomy (removal of one or both breasts to reduce your chances of having cancer again)	28	25
Should I have a prophylactic oophorectomy (removal of ovaries to reduce your chances of having cancer again)	27	24
Should I be having more surveillance (e.g., more frequent mammograms)	22	20
Wanted to plan my future	17	15
Asked by a family member to get tested	15	13
Should I have a family	7	6

cancer, and women with a previous breast and/or ovarian cancer diagnosis were excluded unlike those in the present study. Of the research that included women with a personal history of breast cancer (30% of a study with 322 participants), women with a history of breast cancer who had not yet undergone *BRCA1/2* testing were less concerned about their own personal risk and were more motivated by knowing more about the risk status of their offspring (Van Asperen et al. 2002). A recent retrospective qualitative study of 33 *BRCA1/2* positive women with a previous diagnosis of breast and/or ovarian cancer also reported that the main motivation for genetic testing was to better understand the risk faced by their family, particularly their children (Jeffers et al. 2014). This is consistent with the finding of the present study, where the two most endorsed motives were wanting to find out whether cancer in the family was hereditary (80%) and the risk to offspring (76%).

The current findings provide insight into how this group of women interpreted their negative results on average 3 years after undergoing genetic testing. In the period from 2005 to 2010, women were counselled that the possibility of harbouring a risk-conferring gene remained, despite a *BRCA1/2* negative result. Thus, a negative result was framed as an uninformative result at the time. Despite this, in this study, the perceived likelihood of inheriting a cancer-conferring genetic variant was considered to be likely/very likely/certain by 31% of women, while just under half the women considered this outcome to be very unlikely or unlikely and a small number considered it non-existent (3.5%).

The possibility that women did not have an accurate understanding of their test results is further evidenced in their reports of perception of relative risk of breast cancer. While just over 60% of participants perceived their risk as higher than that of the average Australian woman (which would match the information provided during genetic counselling), 20% of women perceived their risk of breast cancer as being lower

than population level and a further 15% viewed their risk as equivalent to population level. Yet, women estimated their lifetime risk appropriately at an average of 40 out of 100. The size of the standard deviation ($SD = 30$) observed in women's perceptions of relative breast cancer risk indicates the large amount of variance in this measure in our sample. The overall implication is that approximately 3 years after genetic testing, women with negative *BRCA1/2* results have inconsistent representations of their personal cancer risk. This may reflect a poor understanding of population risk levels, or a general lack of understanding about the genetic testing outcome and its meaning in the context of personal risk estimation. This is a concern as far as under-estimation of risk may influence adherence to appropriate risk management strategies. Previous research has reported that women draw from their personal experience when interpreting genetic risk (Maheu and Thorne 2008), which could potentially account for the estimations of genetic risk observed in the current study. It is also possible that the way risk information was presented when genetic testing results were delivered may have played a role. Prior research has shown that diverse factors may impact upon understanding of genetic test results including presentation style, numeracy, presentation format and communication style (Hanoch et al. 2014). In this study, perceptions of the likelihood that cancer is hereditary were strongly and positively associated with the number of relatives with breast cancer, the number of relatives who died of cancer and the number of relatives with cancer. This would suggest that in the process of ensuring that women with negative results have an accurate understanding of the meaning of their results, particular attention paid to the role of family cancer history is contributing to women's individual representations of their risk.

We found that a negative *BRCA1/2* test result was not experienced psychologically as a positive outcome for many

Table 4 Anticipated versus reported results and other features of testing, among affected women with breast and/or ovarian cancer who have undergone *BRCA1/2* genetic testing and received a negative result

Feature of testing	Anticipated	Reported
Anticipated versus perceived result		
<i>BRCA1/2</i> mutation would be/has been identified, <i>n</i> (%)	44 (38.9)	
<i>BRCA1/2</i> mutation would not/has not been identified, <i>n</i> (%)	14 (12.4)	92 (81.4)
<i>BRCA1/2</i> mutation of uncertain significance would be/has been identified, <i>n</i> (%)	5 (4.4)	5 (4.4)
No idea/did not think about it, <i>n</i> (%)	37 (32.7)	3 (2.7)
Other, <i>n</i> (%)	6 (5.3)	7 (6.2)
Missing, <i>n</i> (%)	7 (6.2)	6 (5.3)
Perceptions of likelihood of inheriting a cancer-conferring genetic variant		
Non-existent, <i>n</i> (%)	4 (3.5)	
Very unlikely, <i>n</i> (%)	9 (8.0)	
Unlikely, <i>n</i> (%)	43 (38.1)	
Likely, <i>n</i> (%)	24 (21.2)	
Very likely, <i>n</i> (%)	8 (7.1)	
Certain, <i>n</i> (%)	3 (2.7)	
No information can currently be given about my risk, <i>n</i> (%)	18 (15.9)	
Missing, <i>n</i> (%)	4 (3.5)	
Cancer risk perception		
Relative cancer risk: compared to the average Australian woman, my risk of developing breast cancer (again) is:		
Much lower, <i>n</i> (%)	17 (15)	
A bit lower, <i>n</i> (%)	5 (4.4)	
The same, <i>n</i> (%)	17 (15)	
A bit higher, <i>n</i> (%)	40 (35.4)	
Much higher, <i>n</i> (%)	29 (25.7)	
Missing, <i>n</i> (%)	5 (4.4)	
Absolute breast cancer risk perception, M (SD) [<i>n</i>]	39.63 (30.47) [102]	
Likelihood cancer is hereditary, M (SD) [<i>n</i>]	47.81 (33.69) [104]	
Considered outcome of result before testing		
Yes, <i>n</i> (%)	67 (59.3)	
No, <i>n</i> (%)	33 (29.2)	
Missing, <i>n</i> (%)	13 (11.5)	
Expect to receive more information in the future		
Yes, <i>n</i> (%)	48 (42.5)	
No, <i>n</i> (%)	60 (53.1)	
Missing, <i>n</i> (%)	5 (4.4)	
Belief that genetic counselling process is completed		
Yes, <i>n</i> (%)	67 (59.3)	
No, <i>n</i> (%)	41 (36.3)	
Missing, <i>n</i> (%)	5 (4.4)	
Relief from test results		
None or some relief, <i>n</i> (%)	54 (47.7)	
Quite a bit or considerable relief, <i>n</i> (%)	54 (47.7)	
Missing, <i>n</i> (%)	5 (4.4)	
Worry associated with test results		
Was not worried before and still not worried, <i>n</i> (%)	43 (38.1)	
As worried, or more worried than before, <i>n</i> (%)	57 (49.5)	
Missing, <i>n</i> (%)	14 (12.4)	

women in our sample. Three years after testing, about 50% of participants reported little or no relief from their negative

result and approximately 50% were as or more worried by their result. Rates of psychological morbidity were also high.

Table 5 Anxiety, depression, impact of events, and neuroticism means (M) and standard deviations (SD) of the sample

Psychological characteristic	<i>n</i>	<i>n</i> (%) scoring above clinical cut-off	M (SD)	Range
HADS-A	110	110 (100)	13.15 (1.76)	9.80–16.00
CES-D	110	19 (17)	9.85 (8.95)	0–44
IES	106	38 (36)	19.61 (16.32)	0–71
IPIP-N	109	Not applicable	23.15 (7.78)	10–41

HADS-A Hospital anxiety and Depression Scale-Anxiety, *CES-D* Centre for Epidemiologic Study Depression Scale, *IES* Impact of Events Scale, *IPIP-N* International Item Pool Five Factor Inventory-Neuroticism

*HADS-A cut-off ≥ 8 indicating probable anxiety; CES-D cut-off ≥ 16 indicating depressive illness; IES cut-off ≥ 26 indicating moderate cancer-specific distress

All participants (100%) met the threshold for probable anxiety on the HADS of whom 10 met the threshold for clinical anxiety, 17% were likely depressed and 36% had evidence of at least moderate cancer-related distress. Among the 38 women with high scores on the IES, nine had scores indicative of severe distress related specifically to thoughts of developing cancer. Comparing these data with similar studies is challenging, due to the use of different validated measures and clinical cut-offs. There are no local norms for the self-report measures used; however, the extent of psychological morbidity in this study is much higher than that reported in the most recently published Australian national survey of mental health and well-being (Australian Bureau of Statistics 2008) which found 12-month prevalence rates of depressive episode and anxiety disorders among women to be 5.1% and 18%, respectively. Even though self-report measures are likely to overestimate prevalence relative to structured clinical interview which was used in the national survey, these scores reflect a significant burden of psychological distress that is likely to impact on general quality of life. It is beyond the scope of the current study to pinpoint the cause of this morbidity, and there are likely multiple contributing factors apart from genetic status. Nonetheless, women with negative results are seldom followed up by genetic counselling services after testing, so options for detecting this distress in routine care are very limited. A possible clinical implication is for genetic counsellors to provide women with information about potential future psychological reactions to negative results, with advice to visit their primary care physician in the presence of pervasive or chronic mood or anxiety symptoms.

In this study, more than half of the sample indicated that they did not expect to receive more information in the future and almost 60% believed the genetic counselling process to be complete. These were reasonable assumptions, as women would have been advised that the genetic counselling process was complete unless there was new information available in the future. However, over one third of women did not believe that the genetic counselling process was completed. This finding suggests that many women may still be expecting further genetic information to become available, despite the reality of this being very small. Sometimes, patients are re-contacted if a new test method becomes available, and women with VUS

results may be contacted in the future if a current variant is reclassified as pathogenic (Bredart et al. 2013; Kalia 2015). The exact proportion of participants with VUS results in this sample is not known, but data from the recruitment site show that approximately 10% were in this category. It is possible that this group of participants have very different perceptions of risk and uncertainty compared to those who received an uninformative negative result, but this was not examined in our study.

This study has a number of limitations. The clinical meaning of a negative *BRCA1/2* test result has changed since these data were collected. Although only 3 years on average had lapsed between genetic testing and study participation, the retrospective nature of the study design meant that data regarding perceptions of risk, relief and worry about testing were collected after the actual experience of testing. As such, responses are prone to recall bias and may have been coloured by experiences that have occurred since the time of testing (Lindberg et al. 2017). Indeed, while data regarding the diagnosis of cancer among relatives of participants were collected, the dates of these diagnoses were not collected. The relative extent to which the experience of *BRCA1/2* testing was influenced by family experience prior to and after genetic testing is not known; however, in order to qualify for *BRCA1/2* testing, a family history would have had to exist prior to testing for the majority of women. Another limitation is the wording of the questions asked. Given that these women have had a diagnosis of cancer, they could have interpreted the questions around the risk of developing another cancer either as a new primary cancer or a recurrence. Similarly, it is possible that the woman may not have comprehended the difference between the concepts of hereditary cancer risk as opposed to cancer risk. Furthermore, there may have been confusion for women about whether the questions referred to their feelings at the time of testing or at the time they received the questionnaire. Within the sample, data from women with VUS results were not analysed separately to data from women with uninformative negative results—information that would have strengthened the results. The study was also cross-sectional in nature, which precludes any notion of causality. Another limitation is the potential for sampling bias, which may affect the generalizability of the findings. A third of women were well educated

and held a Bachelor or other higher degree (32%); 54% were in paid employment and 44% had an annual gross family income above AU\$62,348. This is consistent with previous data showing that genetic counselling and testing are often under-utilised by women from minority or disadvantaged groups (Sheppard et al. 2013). It has also previously been reported that women of lower socioeconomic status are less likely to be enrolled into breast cancer research studies (Gross et al. 2005). Other factors impacting upon the generalizability of the sample are that approximately 6% of potentially eligible participants could not be contacted due to either a lack of address or the incorrect address, and that the response rate from the mail out was about 38%. A response rate of 38% is lower than other mail-out surveys in similar cohorts of 61% (Ganz et al. 1998) and 46% (Caan et al. 2005), although a more recent study from the US reported an overall response rate of just 34% (Jensen et al. 2016). The lowered response rate may reflect of a reported downturn in mail-out survey response rates (Baruch and Holtom 2008). Characteristics of the 177 non-responders are not known, and it is possible that these women were from underserved or minority groups with poor English comprehension. These women may also have poorer mental and physical health inhibiting their participation. These potential sources of bias demonstrate the need for better understanding of the genetic testing experience of women from underserved or disadvantaged sectors. Finally, while validated measures of psychological morbidity were used in this study, comparison with other studies is complicated by use of different cut-offs and measures, and comparison with the general population is made difficult due to the absence of normative data using the same instruments. Additionally, it is acknowledged that prevalence may be overestimated in self-report studies but also often underestimated in mailing studies.

This study also has a number of strengths. There are very few studies examining the motives and experiences of women undergoing *BRCA1/2* testing (Brain et al. 2000; Julian-Reynier et al. 1998; Van Asperen et al. 2002) and even fewer in recent years, despite the increasing number of women undergoing testing (Jeffers et al. 2014). While all previous studies included samples of women at an increased risk for breast and/or ovarian cancer, none focused specifically on women with a previous cancer diagnosis and a negative *BRCA1/2* test result. These results also describe and report on associations between other variables of interest previously implicated in this research. This includes the role of cancer risk perception and personal experiences of cancer including the number of relatives with breast cancer, the number of relatives with cancer and the number of relative that had died from cancer. Finally, despite the retrospective nature of the study and changes in genetic testing technology, our data contribute to the dearth of literature on women with negative *BRCA1/2* results, a group that are seldom followed up in clinical care and research settings.

Conclusion

The present study aimed to describe the motives, experiences and interpretations of *BRCA1/2* genetic testing of women with a previous breast and/or ovarian cancer diagnosis and a negative result. These women are an understudied population, and our findings add to the very limited literature on their experience and interpretation of testing. Our findings suggest that these women were mostly motivated to undergo testing to discover whether their cancer was hereditary; they anticipated that a *BRCA1/2* variant would be detected and had a range of representations about their personal cancer risk as well as their perceived estimation of genetic predisposition. Risk perception correlated most strongly with familial cancer history. Half of the women living with a negative *BRCA1/2* result reported no relief from the genetic testing process, and rather were as worried or more worried by it. Rates of psychological morbidity were very high, with women reporting not only symptoms of general anxiety and depression, but also cancer-specific-related anxiety symptoms. These findings emphasise counselling issues to consider both at pre- and post-test genetic counselling, such as the expectation of a *BRCA1/2* variant being detected and understanding a genetic test result in relation to personal and hereditary cancer risk. The findings highlight that more attention should be paid to the emotional needs of women undergoing genetic counselling for breast cancer risk who have negative results. Genetic counsellors are trained and skilled in providing counselling about managing uncertainty; however, they are often under-resourced in terms of the time needed to provide the additional psychosocial support and follow-up required to help this large group of patients with their understanding and psychological acceptance of a negative *BRCA1/2* result. Genetic counsellors in the FCC (from which the current sample were drawn) routinely convey test results in person or by phone, and provide a written summary of the discussion for women who receive a negative *BRCA1/2* result (the majority of women undergoing testing). This work highlights the ongoing impact and psychological burden that genetic test results may have (despite a negative result), and how genetic counselling can play a key role helping patients understand risk information and aid psychological adjustment to their results. Specifically, the findings point to the need for longer-term clinical follow-up of this group. The issues raised from the study findings may serve to inform current and future directions and models of care for women with a *BRCA1/2* negative result.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human studies and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants included in the study.

Animal studies No animal studies were carried out by the authors for this article.

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