

Short Communication

Uptake of Offer to Receive Genetic Information about *BRCA1* and *BRCA2* Mutations in an Australian Population-Based Study

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Abstract

Research on the utilization of genetic testing services for mutations in *BRCA1* and *BRCA2* has focused on women with a strong family history of breast and ovarian cancer. We conducted a population-based case-control-family study of Australian women diagnosed with invasive breast cancer before age 40 years, unselected for family history, and tested for germ line mutations in *BRCA1* and *BRCA2*. Case subjects found to carry a deleterious mutation and their relatives who had given a research blood sample were informed by mail that the study had identified "genetic information" and were offered the opportunity to learn more. Those interested were referred to a government-funded family cancer clinic. Of 94 subjects who received the letter, 3 (3%) did not respond and 38 (40%) declined to learn their result (16 declined the referral, 10 accepted

but did not attend a clinic, and 12 attended a clinic but declined testing), and 12 (13%) remain "on hold." The remaining 41 (44%) chose to learn their result (3 of whom already knew their mutation status). There was no evidence that the decision to learn of mutation status depended on age, gender, family history, or having been diagnosed with breast cancer. Of 19 families with more than one participant, in 11 (58%) there was discordance between relatives in receiving genetic results. Although in Australia genetic testing is offered free of charge and insurance issues are not a major consideration, we found considerable reluctance, indecision, and unexplained variability both between and within case families in the desire to know their mutation status. (Cancer Epidemiol Biomarkers Prev 2004; 13(12):2258-63)

Introduction

Germ line mutations in *BRCA1* and *BRCA2* are associated, on average, with at least a 10-fold increase in breast cancer risk but only explain a small proportion of familial aggregation of that disease. Although individuals with early-onset breast cancer or a strong family history of breast or ovarian cancer are more likely to have a germ line mutation in *BRCA1* or *BRCA2*, a substantial proportion of affected carriers do not seem to have a family history of breast or ovarian cancer (1). Genetic testing for breast cancer susceptibility can identify individuals at increased risk and has potential benefits in

terms of early detection. Prophylactic surgery can be offered to carriers (2), although further steps need to be taken to improve our understanding of the possibilities for prevention in carriers. Genetic counseling and testing for cancer predisposition produce psychological benefits and improve the accuracy of risk perception, whereas "this is still a young field of research, with many unanswered questions" (3).

In general, testing is carried out in Family Cancer Clinics on self-selected and physician-referred women with a strong family history of breast and/or ovarian cancer. Moreover, it is now becoming possible to increase the proportion of tested individuals found to be carriers by offering mutation testing to newly diagnosed cases, with targeting of the offer based on their age at diagnosis, cancer family history, and, in a proportion of cases, the pathologic features of their tumor (4). The future of genetic testing for breast cancer susceptibility is moving beyond the traditional setting of multiple-case families. In this study, the opportunity for genetic information came about as a result of the women being involved in an

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Australian population-based study of early-onset breast cancer (unselected for family history) and appropriate referrals were arranged for women to attend Australian Family Cancer Clinics.

Research on the uptake of genetic testing for breast cancer has to date mainly focused on attitudes toward and intentions to undergo genetic testing in the general population (5-8), among women attending a health service (9-12), and among women with a family history of breast cancer (13-17). Those that consider the actual utilization of genetic testing have considered only women with a strong family history and have been based either in a clinical or in a family history-based research setting (18-23). It has been found that although intention to undergo testing is high, uptake is low and varies depending on the population studied and the extent of family history. A priori one might expect females and those with a strong family history of breast cancer to be more inclined to pursue genetic testing; however, previous studies have been inconclusive (21-23). It is difficult to predict how age might influence the decision.

The Australian Breast Cancer Family Study provided a novel opportunity to analyze the responses to an offer of genetic testing among a group of individuals who were not self-selected and did not necessarily exhibit a strong family history but who were found by the research study to carry a deleterious mutation in *BRCA1* or *BRCA2*. We conducted a population-based case-control-family study of women diagnosed with primary invasive breast cancer before age 40 years, unselected for family history, and tested for mutations in *BRCA1* and *BRCA2*. In Australia, it is considered ethically responsible to give research participants an opportunity to decide whether they wish to know any clinically significant genetic information (24). To do so it was suggested they attend a family cancer clinic, where a new blood sample could be taken for testing in an accredited testing laboratory. Mutation carriers and their family members were offered this opportunity and their responses were monitored and analyzed to determine the uptake and acceptability of testing.

Materials and Methods

Subjects. The Australian Breast Cancer Family Study is a population-based case-control-family study of breast cancer (25, 26). Approval for this study was obtained from the Ethics Committees of The University of Melbourne, The Cancer Council Victoria, and The Cancer Council New South Wales. Eligible case subjects were identified from the Victorian and New South Wales cancer registries as those women younger than 40 years at diagnosis of a first primary invasive breast cancer between January 1, 1992, and December 31, 1998, and living in the Melbourne or Sydney metropolitan areas. The subjects were selected independent of family history. Of 1,208 selected eligible case subjects, 856 (71%) participated in the study (27). Participation included completing an interviewer-administered family cancer history questionnaire, which involved construction of a pedigree covering all known first- and second-degree adult relatives of the case subject. In addition, each case subject was asked to approach their living adult relatives (siblings, parents, and both maternal and paternal grandparents and aunts) to invite

them to participate in the study. Consenting relatives were interviewed and asked to provide additional information for the pedigree and family cancer history questionnaire. All case subjects and selected relatives were asked to provide a blood sample for genetic research.

Mutation Testing. Extensive testing for germ line mutations in *BRCA1* and *BRCA2* was done as described in Dite et al. (27). In brief, all DNA samples were screened with a protein truncation test covering exon 11 of *BRCA1* and each of exons 10, 11, and 27 of *BRCA2*. Manual sequencing of all coding and flanking intronic regions in *BRCA1* and *BRCA2* was carried out for 72 of the 85 case subjects with two or more first- or second-degree relatives with breast or ovarian cancer, and for *BRCA1* only, in randomly selected groups of 91 case subjects (47 with at least one first- or second-degree relative with breast cancer and 44 with none). All participants who provided a blood sample were screened for the Ashkenazi founder mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*) and for duplication of exon 13 in *BRCA1*.

Extensive testing in *BRCA1* and *BRCA2* identified many genetic variants. Only those variants known to have clinically significant implications were regarded as "mutations" in this study. Briefly, this included all protein truncating mutations, except for 10204, A > T *BRCA2* (28), and variations 5' to this in *BRCA2*. Missense variants were regarded as clinically significant based on published literature such as Brzovic et al. (ref. 29; for C61G, *BRCA1*).

Offer of Genetic Information. In accordance with the ethical obligation to inform participants of any clinically significant information identified by the study, a letter was sent to all case subjects identified by the research study as mutation carriers and to all of their relatives from whom a blood sample was obtained. This letter was worded so as not to imply that a mutation had definitely been detected, but to inform participants that this was a possibility and to make clear the process they would undergo if they chose to learn more about genetic testing and to have a diagnostic test and receive their results (see Fig. 1).

Participants were asked to indicate on an attached form whether they were interested in proceeding. As well as indicating whether they would or would not like to consider knowing this information, they could also indicate that they would like more information before making a decision.

Those who indicated that they did not wish to know what the study had found were not contacted any further, and those who indicated either that they would like to consider knowing this information or that they would like more information were contacted and offered referral to an appropriate government-funded family cancer clinic and testing was carried out in a laboratory accredited by the National Association for Testing Authorities, Australia. At these clinics (free of charge to referred individuals), genetic counseling was done by trained professionals and included discussion of current knowledge about breast cancer genes and the possible clinical and psychosocial effect of the presence or absence of a mutation in these genes. In this study, if the participant chose to proceed, a small blood sample was taken and tested in a laboratory for the family mutation. Initial testing was done for research purposes only; the results of

... It has become possible to test for specific breast cancer genes. We have been recently undertaking some research in this area, although the full implications are unlikely to be known for several years. We have performed some testing on some of the genes in some participants, but have yet to test all participants fully on all breast cancer genes. We anticipate that a small proportion of the people who participated will have inherited a change in one of these genes.

We are writing to find out if participants want to know whether we have been able to identify a change in any breast cancer gene. For participants who want to know we will need to organise an appointment with a clinical genetics service at a mutually convenient time and place, free of charge. The clinical genetics service will explain what it means to have or not have inherited a change in this gene so that you can make an informed choice as to whether you wish to proceed further...

Figure 1. An excerpt from the letter sent to case subjects identified as mutation carriers and their relatives from whom a blood sample was obtained.

this testing were communicated to the testing laboratory and then the sample taken in the clinic was tested in a National Association for Testing Authorities-accredited laboratory to verify the mutation found in the research laboratory. Appropriate counseling and clinical management was then provided in accordance with the National Health and Medical Research Council-approved Guidelines on Familial Aspects of Cancer (30).

Statistical Analyses. Associations between the independent variables and decisions about genetic testing were assessed using the Pearson's χ^2 test and multivariable logistic regression. All statistical analyses were done with SPSS version 11.5.0.

Results

The first letters were mailed in 1997, and by April 30, 2003, 109 participants from 34 families had been sent a letter. Their participation or otherwise was followed up until September 5, 2003, at which time 5 were known to be deceased and 10 could not be reached.

Figure 2 illustrates the responses of the remaining 94 participants at each step of the process. For example, 74% ticked "yes" or "more information" on the form, and of these 79% attended a clinic, 73% of those had a mutation test, and 95% of those tested have to date received their results. (Of the 9 who ticked more information, to date only 2 have attended a clinic: 1 has received results and 1 is on hold). When combined with the 3 participants who already knew their mutation status, a total of 41 (44%) have received their results. A total of 38 (40%) declined the offer either to the mailed letter (16), to the clinical referral (10), or to the mutation testing (12). The remaining 15 (16%) either did not respond to the mailed letter or are on hold at one of the steps. On hold indicates that the participant has not refused the next step but has also failed to proceed.

Table 1 shows the percentages of participants who proceed through the various steps of the process by different participant characteristics. The only percentage that differed significantly between subgroups was a greater positive response to the letter from the younger group of participants ($P = 0.01$). The percentage receiving

results was greater for women, probands, those affected by cancer, and individuals with a strong family history, but none of these associations was significant either singly or in combination (all P s > 0.2).

A total of 19 families included more than one person. Of these, three were fully concordant in receiving genetic results, and five were fully concordant in not receiving genetic results. In the remaining 11 families (58%), there was at least some discordance in receiving results. Table 2 shows the degree of discordance in these 11 families. In 7 families, only one person differed from the rest of the family; in the remaining 4 families, the discordance was greater, with at least two family members responding differently to at least two other family members.

Discussion

This Australian study of receiving genetic test results for mutations in *BRCA1* and *BRCA2* was novel in that it was done on a population-based series of women with incident breast cancer who were diagnosed before age 40 and their relatives. A substantial proportion of cases found to carry a mutation did not report having a family history of breast or ovarian cancer (31), and only a small proportion of the families had a sufficiently strong history of breast or ovarian cancer that they would have been considered appropriate candidates for genetic testing according to the National Guidelines (32). Although genetic counseling through an accredited family cancer clinic was offered free of charge, we found that just less than half of the participants who were approached chose to receive their test results and 13% were undecided. We also found that there was substantial discordance within families with respect to the choice to receive genetic test results. In this population, there is considerable reluctance, indecision and unexplained variability both between and within case families in their desire to know their mutation status, although at least one family member has been recently diagnosed with early-onset disease.

Previous studies of genetic testing utilization have focused either on self-selected and/or physician-referred family cancer clinic attendees or on women otherwise identified to be at high risk of breast cancer due to their

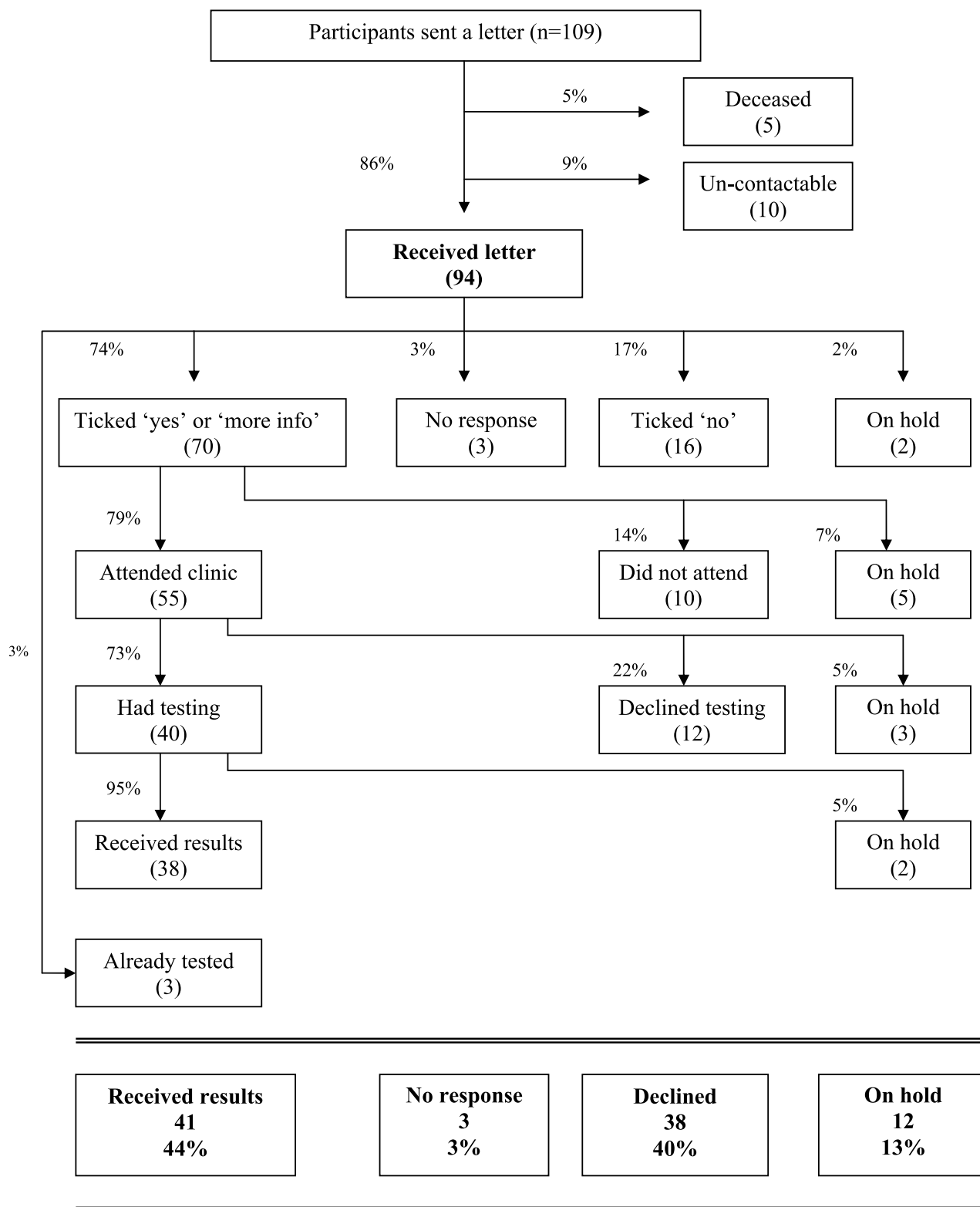


Figure 2. The responses of participants at each step in the process of receiving genetic information.

Table 1. Responses of participants at particular steps in the process of receiving genetic information by individual characteristics

Variables	<i>n</i>	Ticked "yes" or "more information" on form (%)	Attended clinic (%)	Had predictive testing (%)	Received results (%)
Gender					
Male	21	67	57	33	33
Female	70	80	61	47	44
Age (y)					
25-49	48	88	62	46	42
50-94	43	65	58	42	42
Subject status					
Proband	31	81	55	48	48
Relative	60	75	63	42	38
Cancer status					
Affected	43	79	60	49	49
Unaffected	48	75	60	40	35
Reported family history					
Strong*	63	78	63	48	44
Weak/none [†]	28	75	54	36	36
Total	91 [‡]	77	60	44	42

*One or more first-degree relatives have had breast cancer.

[†]No first-degree relative has had breast cancer.

[‡]Participants already tested (*n* = 3) excluded from this table.

strong family history (18-23). Rates of uptake of genetic test results observed in these multiple-case families ranged from 10% in a sample recruited through a cancer registry (18) to 26% (19), 38% (23), and 43% (21) in clinic-based samples to 55% of a Jewish volunteer, community-based sample who were invited to attend an education session (22) and to 84% of attendees at a French clinic (although these represented only 27% of those eligible to attend; ref. 20). Analyzing differences within samples, one study reported that younger women were more likely to be tested than men (23), and another that women, affected individuals, and those with a strong family history were more likely to pursue testing, whereas age had no effect (21). Yet another reported that older participants were more interested in testing than younger participants, but that gender, cancer status, and family history were not significantly associated with uptake (22). We found no evidence of an association between uptake of genetic testing and any of these variables, although small effects would not have been detectable. There is large, unexplained variation in uptake across studies and no strong, consistent predictors of uptake within studies.

Table 2. Display of the discordance within families regarding the decision to receive genetic results

		No/on hold (no. family members)				
		0	1	2	3	4+
Yes (no. family members)	0	-	-	2	2	1
	1	-	2	1	2	
	2	2	1		1	1
	3	1			1	
	4+		1	1		

■ Discordant families

Our study, based on women diagnosed with breast cancer before age 40 and their families, has shown, as have others, that intention to undergo genetic testing is not a good indicator of actual uptake. Of the 91 participants who received a letter and did not already know their result 70 indicated a positive intention, but only 38 of them (54%) went on to receive their results. Of those who had attended a family cancer clinic, however, 69% chose to receive their results. Although some studies have reported high (>90%) rates of intention to undergo testing (15, 17), studies of uptake like ours have found substantially lower percentages actually go on to receive their results. These findings need to be tested in other populations.

In this group of individuals (a third of whom have a weak or no family history; see Table 1) the reasons for uptake are not known. Even for those who were affected, the rate of uptake (49%) was not significantly different from those unaffected (35%; *P* = 0.14). Further study is needed to understand the motivations and considerations of this particular group because new knowledge about pathology could lead to targeted testing of newly diagnosed cases irrespective of family history, rather than relying on self-referral of mostly unaffected women to a genetics service. This study needs to be conducted in other populations to assess the effect of different health care systems as well as different social, ethical, and legal frameworks. The findings outlined here provide an important starting point for developing protocols to optimize the future use of genetic testing for breast cancer susceptibility in the wider population.

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