No Evidence of False Reassurance among Women with an Inconclusive *BRCA1/2* Genetic Test Result

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Abstract

Background: **Little is known about how women who receive an inconclusive result from *BRCA1/2* testing interpret their result. Clinical observations suggest that some of them may be falsely reassured and, consequently, may not adhere to recommended surveillance. The purpose of this study is to evaluate whether women with inconclusive *BRCA1/2* test results are falsely reassured.**

Methods: **Participants were adult women with a family history suggestive of a germ-line mutation in either the *BRCA1* or the *BRCA2* gene who underwent genetic testing in the context of the interdisciplinary research program INHERIT BRCAs. Data were collected using selfadministered questionnaires at genetic counseling and 1 month after result disclosure. Reassurance was assessed through indicators of cancer risk perception, cancer worry, relief following result disclosure, painfulness of the test result, and its effect on quality of life.**

Results: **Five-hundred women (105 carriers, 140 noncarriers, and 255 inconclusive) were included in this analysis. Compared to noncarriers, women with inconclusive results had higher cancer risk perception, were more worried about cancer, were less relieved by their test result, and perceived their quality of life as being more adversely affected by it.**

Conclusion: **The differences observed between noncarriers and women who received an inconclusive result run counter to the hypothesis that the latter are falsely reassured following *BRCA1/2* testing. For clinicians, our findings show the value of taking precautions to fully explain to women that inconclusive results do not rule out the possibility that they still may face a higher risk of developing breast and/or ovarian cancer.** (Cancer Epidemiol Biomarkers Prev 2005;14(12):2862–7)

Introduction

Despite the identification of highly penetrant mutations in the *BRCA1* and *BRCA2* genes, which account for ~20% of the heritability of breast cancer, a large proportion of hereditary breast cancers are related to as-yet undiscovered susceptibility genetic variants (1-4). In our cohort of high-risk French-Canadian families, ~75% of tested families will receive an inconclusive genetic test result (5). A result is said to be inconclusive in the absence of a *BRCA1* or *BRCA2* mutation in the proband (6). If only partial testing—the search for known common and less frequent mutations—is done, a mutation may still be present in an untested portion of the genes. In this context, an inconclusive result provides the information that the individual is not a carrier of one of the mutations tested. However, if full *BRCA1/2* sequencing is carried out and still no mutation is identified at this stage, the familial cancer may be due to rare mutations outside the regions sequenced or large rearrangements, as well as due to a deleterious allele in another gene, or may be sporadic. Sequence variants for which the significance of the alteration is still unknown are also considered inconclusive test results (6).

Because of the unclear significance of such a result, patients getting an inconclusive result receive little information that they can use in medical decision-making. Moreover, clinical guidelines for cancer surveillance in the context of an inconclusive result are lacking (7-9). Despite counseling in which the possibility of an increased risk is discussed, there is growing concern that women receiving such a result may experience false reassurance about their cancer risk, which may in turn interfere with their screening behaviors (10, 11). To date, however, little is known about the psychosocial consequences of receiving an inconclusive *BRCA1/2* genetic test result. The purpose of this study is to assess whether women receiving an inconclusive *BRCA1/2* genetic test result are falsely reassured.

Materials and Methods

Participants. Eligible participants were French-speaking adult women with a family history suggestive of a germ-line mutation in either the *BRCA1* or *BRCA2* gene who underwent genetic testing from August 1998 to December 2004 in the context of the ongoing interdisciplinary research program Interdisciplinary Health Research International Team on Breast Cancer susceptibility (INHERIT BRCAs). Program participants were widely dispersed throughout the province of Quebec. Potential candidates for the breast/ovarian cancer genetic susceptibility testing program were

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referred by physicians from most regions of the province of Quebec but mainly from hospitals located in Quebec City, Montreal, Sherbrooke, Rimouski, and Jonquière. To be eligible for this study, they had to be informed of their test result at least 1 month before December 2004. Women who chose to be unaware of their test result were therefore excluded from the analyses. All subjects provided signed, informed consent.

Genetic Testing Program. In the INHERIT BRCAs research program, genetic counseling is provided to each participant in a pretest education session and a result disclosure session. Topics covered at the pretest session include standard subjects of informed consent for genetic testing (12) and consideration of potential psychological effects of possible test results on the participant. After obtaining a signed informed consent from each participant, genomic DNA was extracted from blood samples using standard procedures at the Cancer Genomics Laboratory at CHUQ/CHUL Research Center, Quebec City. More details about experimental and clinical procedures as well as the INHERIT BRCAs research program have been described elsewhere (5, 13-15). Overall, ~1 hour was spent with each participant for genetic counseling per se. The current analyses are based on 500 women from 196 high-risk French Canadian breast/ovarian cancer families.

These participants may have received a conclusive test result as carrier or noncarrier of the familial mutation or an inconclusive result when all individuals tested within a family were negative for the panel of *BRCA1/2* mutations analyzed. Briefly, the disclosed test results included genetic information from a panel of at least 14 mutations including (*a*) at least 7 of recurrent French Canadian mutations, which accounted for 84% of all mutation-positive families identified in our cohort, and (*b*) at least 7 other mutations previously reported in French-Canadian hereditary breast-ovarian cancer families or observed once by us in this cohort. Forty-two *BRCA1/2* positive families were identified by these analyses. When possible, additional analyses were carried out in 126 *BRCA1/2* inconclusive families using DNA samples isolated from 138 women affected with breast and/or ovarian cancer with the exception of four DNA samples which belonged to ''obligate carrier'' parents of cancer cases. These samples were sent to Myriad Genetic Laboratories/MDS Laboratory Services for a Comprehensive BRACAnalysis-BRCA1 and BRCA2 gene sequence analysis for susceptibility to breast and ovarian cancer. This additional approach led to the discovery of seven novel mutations found only once in seven different families in the current cohort. Confirmatory tests were done for each carrier or noncarrier of a known familial mutation on a second blood sample by the Molecular Diagnostic Laboratory, Alberta Children's Hospital, Calgary as well as by the Cancer Genomics Laboratory. For women receiving a result of carrier or noncarrier of a familial mutation, recommendations about cancer surveillance were reviewed (7-9, 16-18). For women receiving an inconclusive result, the likelihood of a higher risk estimated from their family history was explained and increased cancer surveillance was still recommended. In fact, based on the physician's clinical judgment, women with an inconclusive test result were often provided with cancer surveillance recommendations appropriate to *BRCA1/2* mutation carriers.

Data Collection. Starting in August 1998, all individuals tested for *BRCA1/2* mutations in the context of this research program were invited to participate in a longitudinal study aiming to elucidate the psychosocial consequences associated with *BRCA1/2* testing. Self-administered, mail-back questionnaires were used to assess quality of life, health-related behaviors, and factors possibly related to these outcomes at pretest and then 1, 12, and 36 months after result disclosure. Reminder calls were made to participants who did not return their questionnaire within 2 weeks. The current analyses include data collected at pretest and 1 month following *BRCA1/2* genetic test result disclosure.

Measures. A patient may be considered ''reassured'' when her/his concerns and worries about health are reduced (19). In this study, false reassurance among women having an inconclusive test result was primarily conceptualized as having an underestimated cancer risk perception which results in a sense of relief, a low level of worry, and the feeling that quality of life has improved following the test result disclosure.

We assessed reassurance 1 month post-disclosure through single items dealing with cancer risk perception, cancer worry, degree of relief and painfulness following result disclosure, as well as perceived influence of the test result on quality of life. *Cancer risk perception* was first assessed by asking participants to provide an absolute estimate of their lifetime risk of cancer in terms of percentage. Cancer risk perception was also evaluated using a five-point scale ranging from 1 (''very low'') to 5 (''very high''). These complementary approaches to the assessment of cancer risk perception were used because of the relatively low concordance between quantitative risk estimates and qualitative interpretation of risk (20). *Cancer worry* was measured by asking ''How worried are you about your risk of developing cancer?'' using a five-point scale ranging from 1 (''a lot less than before knowing my result'') to 5 (''a lot more than before knowing my result''). *Degree of relief* following result disclosure was measured by asking ''To what extent is knowing your test result a relief to you?'' using a four-point scale ranging from 1 (''no relief at all'') to 4 (''considerable relief''). *Degree of painfulness* of test result was assessed by asking ''To what extent is knowing your test result painful to you?'' measured on a four-point scale ranging from 1 (''not painful at all'') to 4 (''very painful''). Finally, the *perceived influence of test result on quality of life* was measured by asking ''To what extent has knowing your test result influenced your quality of life?'' using a five-point scale ranging from 1 (''decreased it a lot'') to 5 (''improved it a lot'').

The questionnaires also collected socio-demographic information and psychosocial characteristics possibly associated with reassurance. These included age, level of education, marital status, motivations for getting tested, knowledge about hereditary breast and ovarian cancer, and pretest cancer risk perception. To assess motivations for testing, we used a 22-item measure which included items developed by Lerman et al. (21). In this measure, participants were asked to indicate the level of importance they placed on various benefits, limitations, and risks of *BRCA1/2* testing using a four-point scale ranging from 1 (''not at all'') to 4 (''a lot''). Knowledge about hereditary breast and ovarian cancer was evaluated using a 19-item true-false measure. This measure included 11 items from Lerman's work addressing knowledge of inheritance of breast/ovarian cancer susceptibility and genetic testing and was complemented by 8 items developed by our group to assess knowledge about cancer risk, cancer risk factors, and confidentiality issues. Knowledge scores are expressed as a percentage of the maximum possible number of correct answers.

Analyses. Because of the extensive counseling provided in our research program, we hypothesized that women who received an inconclusive *BRCA1/2* test result would not be falsely reassured by their result. If this hypothesis were correct, these women would perceive themselves at higher risk of developing cancer than would noncarriers. They would also feel less relieved and more worried by their test result than noncarriers would. No specific hypotheses were formulated with respect to comparisons of women with inconclusive test result and carriers. The overall statistical approach aimed to compare women having an inconclusive result with noncarriers and carriers with respect to reassurance outcomes.

To identify potential confounders, the three study groups were first compared with respect to characteristics that might be associated with study outcomes including sociodemographic ones (age, education, marital status, having children), psychosocial characteristics (single item of the motivation scale assessing the perceived benefit ''to be reassured,'' knowledge about hereditary breast and ovarian cancer, pretest cancer risk perception), cancer status and genetic testing (full sequencing or search for common mutations). Because more than one subject per family was eligible and responses from family members might have been be correlated, we calculated the design effect for all outcomes (22). The design effect is the ratio of the true variance of a statistic (taking the intracluster correlation) to the variance of the statistic for a simple random sample with the same number of cases. However, because design effects were low, varying between 0.97 and 1.13, they were not taken into account in subsequent analyses.

Analyses done to compare reassurance outcomes varied according to the measurement scale of the outcome considered. For continuous outcomes, the normality assumption was first verified. Then, one-way ANOVA was carried out using the *BRCA1/2* test result as the main effect. The possible confounding effect on outcomes of a number of factors was examined using analysis of covariance. For ordinal outcomes, the test result groups were compared using ANOVA and analysis of covariance (to adjust for confounders) applied on the ranks of these variables (23). The Tukey-Kramer procedure was used to test all pairwise contrasts between means and ranks for continuous and ordinal variables, respectively.

In analyzing each outcome, variables identified as potential confounders were included simultaneously in adjusted models. Because the variable estimates of *BRCA1/2* test results adjusted for all potential confounders did not differ materially (<10%) from those adjusted for age, cancer status, knowledge about hereditary breast and ovarian cancer, and genetic testing approach, only the latter are reported in this article. In each model, we also assessed the interaction effect of *BRCA1/2* test result and cancer status. All significance levels are two sided. Statistical analyses were done using SAS software release 8.2 (24).

Results

From August 1, 1998 to December 31, 2004, 1,114 women were approached to receive genetic testing for *BRCA1/2* mutations in the context of our research program. Based on family history, 873 women were deemed eligible and proceeded with genetic testing. All women were then invited to participate in an ongoing psychosocial study, among whom 688 accepted (79%). As of December 2004, 618 had received their test results at least 1 month earlier and 535 (87%) completed the 1-month post-disclosure questionnaire. Because the present analysis was based on data collected at both pretest and 1 month post-disclosure, 25 women for whom we had post-disclosure data only were later excluded. We also excluded 10 women with a sequence variant of unknown significance, a type of inconclusive result which is conceptually different from the majority of inconclusive test results resulting from not finding any alteration on the *BRCA1* and *BRCA2* genes. Thus, the current analyses are based on 500 women (105 carriers, 140 noncarriers, and 255 women who had an inconclusive test result) from 196 families. Among the 245 women from families with a *BRCA1/2* mutation, 135 (55%) were recruited before the identification of the familial mutation. Of the 255 women who received an inconclusive result, 245 (96%) were recruited before any test result was disclosed within their family (data not shown).

Study groups differed on a number of socio-demographic, disease, and psychosocial characteristics (Table 1). Specifically, women who had an inconclusive test result were older than both carriers and noncarriers. In addition, women with an inconclusive result were more likely to have had cancer than noncarriers. In addition, women with an inconclusive result were less likely than carriers and noncarriers to be motivated by the desire to be reassured. Finally, knowledge scores about hereditary breast and ovarian cancer were slightly lower among women with an inconclusive result than among carriers and noncarriers. Lifetime cancer risk perception at pretest was higher among carriers than among noncarriers and women with an inconclusive result.

Among women who received an inconclusive test result and mutation carriers, lifetime cancer risk perception remained stable between the pretest education session and 1 month after *BRCA1/2* test result disclosure (Fig. 1). However, cancer risk perception among noncarriers decreased significantly following test result disclosure ($P < 0.0001$).

One month following result disclosure, women who received an inconclusive result differed statistically from noncarriers on a number of reassurance outcomes (Table 2). With respect to cancer risk perception, 31% of women who received an inconclusive result interpreted their personal risk as high or very high in comparison with 14% of the noncarriers. In addition, 39% of women with an inconclusive result reported being less worried about cancer than before they learned their result, compared with 64% of noncarriers. Also, 61% of women with an inconclusive result felt moderate or important relief following the result disclosure compared with 80% of the noncarriers. Finally, although the vast majority of participants in each test result group did not report any change in their quality of life, 14% of women with an

Table 1. Socio-demographic, disease, and psychosocial characteristics of participants at pretest education session according to *BRCA1/2* test result

Characteristics	Carriers (n = 105)	Noncarriers (n = 140)	Inconclusive (n = 255)
	n* (%)	n (%)	n (%)
Age at pretest (y)			
20-49	55 (52)	78 (56)	82 (32)
50-69	49 (47)	56 (40)	154 (60)
≥70	1 (1)	6 (4)	19 (7)
Mean ± SD	48.0 ± 11.5	48.0 ± 13.2	54.3 ± 10.5
Education (y)			
≤12	54 (52)	79 (56)	109 (43)
>12	49 (48)	61 (44)	144 (57)
Mean ± SD	12.8 ± 3.7	12.4 ± 3.5	13.2 ± 3.7
Living with a spouse			
Yes	76 (75)	100 (73)	181 (72)
No	25 (25)	37 (27)	70 (28)
Has children			
Yes	79 (77)	113 (83)	202 (81)
No	23 (23)	23 (17)	48 (19)
Cancer status			
Affected	68 (65)	19 (14)	121 (48)
Not affected	37 (35)	121 (86)	134 (52)
Genetic testing			
Full sequencing	6 (6)	1 (1)	77 (30)
Common mutations	99 (94)	139 (99)	178 (70)
Tested to be reassured			
Not at all	23 (23)	24 (17)	73 (30)
A little	16 (16)	15 (11)	55 (22)
Moderately	21 (21)	40 (29)	46 (19)
A lot	40 (40)	61 (44)	73 (30)
Cancer susceptibility testing knowledge scores			
Mean ± SD	61.7 ± 15.1	58.3 ± 16.6	56.8 ± 21.0
Pretest lifetime cancer risk perception			
Mean ± SD	48.2 ± 26.9	39.9 ± 24.2	40.4 ± 21.8

*Because of missing data, the number of participants does not always add to the total.

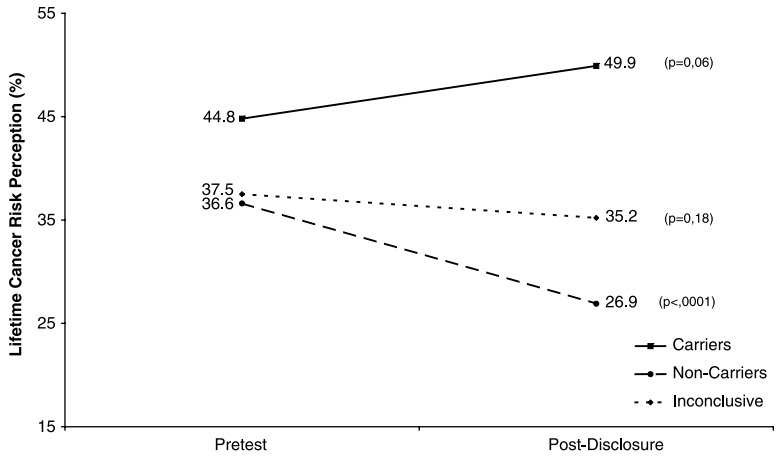

Figure 1. Lifetime cancer risk perception at pretest and 1 month post-disclosure according to *BRCA1/2* test result. *, *P* values adjusted for age (20-49, 50-69, 70+ years), cancer status, genetic testing approach, and cancer susceptibility testing knowledge.

inconclusive result perceived that their quality of life had improved following the result disclosure compared with 22% among noncarriers.

There were also several differences between women with an inconclusive result and carriers in reassurance outcomes. For instance, 62% of carriers interpreted their personal risk as high or very high compared with 31% of women who received an inconclusive result. In addition, 33% of the carriers reported being more worried about cancer than before they learned their result in comparison with 1% of women who received an inconclusive result. Finally, 24% of carriers reported that knowing their result was moderately to very painful compared with 3% of the women with an inconclusive result.

No statistically significant interaction was found between cancer status and test result for any of the reassurance outcomes assessed (data not shown).

Discussion

The differences observed between noncarriers and women who received an inconclusive test result in our research program tend to confirm the hypothesis that the latter were not falsely reassured by their test result. Overall, our findings suggest that the disclosure of an inconclusive test result does not modify women's perception of their lifetime risk of developing breast/ovarian cancer or another cancer. In fact, following disclosure of such a result, women in our study estimated their risk of developing cancer as higher than noncarriers who, on the other hand, reported a decrease in cancer risk perception after test result disclosure. In addition, the cognitive evaluation of cancer risk in women having tested inconclusive for *BRCA1/2* genes was consistent with their emotional response. Specifically, they were less relieved and

Table 2. Reassurance outcomes 1 month post-disclosure according to genetic test results

Outcomes	Carriers (a)	Noncarriers (b)	Inconclusive (c)	*P**	Group differences†
	n (%)	*n* (%)	*n* (%)		
Cancer risk					
Very low	2 (3)	13 (10)	19 (9)	<0.0001	a > b; a > c; b < c
Low	4 (5)	33 (26)	32 (15)		
Moderate	23 (30)	62 (50)	91 (44)		
High	27 (35)	16 (13)	52 (25)		
Very high	21 (27)	1 (1)	13 (6)		
Lifetime cancer risk perception (%)					
Mean ± SD	53.4 ± 23.4	30.4 ± 21.8	38.0 ± 24.1	<0.0001	a > b; a > c; b < c
Cancer worry					
A lot less than before	1 (1)	52 (42)	46 (22)	<0.0001	a > b; a > c; b < c
A little less than before	3 (4)	28 (22)	37 (17)		
Neither more nor less	49 (62)	44 (35)	127 (60)		
A little more than before	21 (27)	1 (1)	3 (1)		
A lot more than before	5 (6)	0 (0)	0 (0)		
Relief					
Not at all	48 (50)	5 (4)	40 (17)	<0.0001	a < b; b > c
Low	6 (6)	21 (16)	54 (22)		
Moderate	22 (23)	30 (23)	61 (25)		
Considerable	20 (21)	73 (57)	86 (36)		
Painfulness					
Not painful at all	43 (44)	120 (94)	220 (91)	<0.0001	a > b; a > c
Slightly painful	31 (32)	3 (2)	16 (7)		
Moderately painful	18 (19)	5 (4)	5 (2)		
Very painful	5 (5)	0 (0)	2 (1)		
Quality of life					
Decreased a lot	0 (0)	0 (0)	2 (1)	0.0019	a < b; b > c
Slightly decreased	8 (8)	0 (0)	0 (0)		
The same	79 (81)	99 (78)	207 (85)		
Slightly improved	8 (8)	9 (7)	20 (8)		
Improved a lot	2 (2)	19 (15)	15 (6)		

*Adjusted for age (20-49, 50-69, and 70+ y), cancer status, genetic testing approach, and cancer susceptibility testing knowledge scores.
†Based on adjusted analyses; $P < 0.01$.

were more concerned about their result than noncarriers. Still, the differences observed between women with inconclusive test results and carriers suggest that an inconclusive test result is not perceived or experienced in the same way as a positive result.

Despite a growing number of studies about the psychosocial implications of *BRCA1/2* susceptibility testing, women who receive an inconclusive test result remain an underresearched group (25-28). Parallel research on the implications of hereditary nonpolyposis colorectal cancer genetic testing suggests that an inconclusive test result might unrealistically reduce colon cancer fears and risk perception (27). Older data from the cystic fibrosis literature showed that the large majority of individuals who underwent incomplete genetic analysis described themselves as not having a mutation in the *CF* gene when asked 2 to 4 years after testing (29). However, differences between study populations, genetic syndromes, and measures may explain the apparent inconsistencies between these findings and ours.

Our findings are somewhat consistent with those reported by Schwartz et al. (26) among 279 high-risk women who underwent *BRCA1/2* genetic testing in a clinical setting. In that study, there were no differences in cancer risk perception assessed 6 months post-disclosure between mutation carriers and women with an inconclusive result. Unfortunately, the authors did not further compare cancer risk perception to that of noncarriers. In a qualitative study including 12 affected women with a *BRCA1/2* inconclusive test result, Hallowell et al. (25) reported a range of emotional reactions following an inconclusive result. Although a minority of women in the inconclusive group clearly misinterpreted their test result as necessarily meaning that the excess number of cancers in their family were not caused by a genetic mutation, a majority seemed to adequately understand the implications of an inconclusive result. Similarly, in our study, the absence of significant change in perceived risk among women with an inconclusive result suggests that most of them did not seem to be falsely reassured. Nevertheless, we also found that there might be a subgroup who may have misinterpreted the implications of their test result. Indeed, 1 month post-disclosure, 24% of women with an inconclusive result perceived their lifetime risk of cancer as low or very low. This is consistent with the observation that 22% of them also reported being a lot less worried about cancer than before result disclosure and that up to 36% reported being considerably relieved by their test result. Considering that a sizeable proportion of carriers also had low perceived risk and reported being less worried and relieved by their result, increasing the level of cancer awareness among this subgroup of women receiving inconclusive *BRCA1/2* test results will be a challenge for clinicians.

This study presented a number of challenges and potential limits that need to be considered in assessing our findings. First, false reassurance is not a well-defined concept and, to our knowledge, there is no existing validated instrument developed specifically to measure it. Approaches previously used to assess false reassurance in the context of genetic testing have been based on risk perceptions (27, 28), retention of information about the meaning of the test result (29), and intentions about behavior modification (28). In our study, we have gone further and conceptualized false reassurance in terms of cognitive and emotional components. Cancer risk perception, the cognitive dimension, was assessed at two different time points both qualitatively and quantitatively. The emotional dimension of false reassurance was evaluated using measures of cancer worry, relief, and painfulness, as well as perceived influence of test result on quality of life following test result disclosure. However, the use of several single items to measure reassurance is a potential limitation. These simple questions were not intended to provide an in-depth assessment of women's understanding of the meaning of their test result. The genesis and wording of these items emerged from our clinical experience and corresponds to the way women who underwent *BRCA1/2* testing talk about the effect of their test result. In addition, the observation that findings were consistent across these indicators suggests that they were measuring several aspects of the same construct. Thus, we believe that these items can be used as a starting point for the eventual development of a standardized measure of false reassurance in the context of genetic testing.

A second limitation stems from the fact that our participants were tested in a research setting. As a result, care must be taken before generalizing our findings to women tested for a *BRCA1/2* genetic predisposition in a clinical setting. However, it is unlikely that the study participants were a selected group of women tested in a research context. They came from a consecutive series of participants identified from several centers across the province of Quebec at the pretest education session. None was lost to follow-up and participation in the pretest and the 1-month questionnaires was high. Third, the confounding effects of a number of variables identified from the relevant literature and our clinical experience were assessed before the participants received their test result. All analyses were controlled for potential confounders for the outcomes under study. Thus, the observed similarities and differences are unlikely to be due to these potentially confounding factors. However, given that virtually all women whose results turn out to be inconclusive were recruited before any test result was available within their family, compared with 55% of women in the conclusive groups, we cannot exclude the possibility of residual confounding resulting from unmeasured factors related to differences in how women from those groups may have approached the testing process. Fourth, our findings cannot be extrapolated past the short period of time following result disclosure. As we are collecting data up to 36 months post-disclosure, there will eventually be additional reports on the stability of our findings over time. Until then, we hope our results will contribute stimulating future work in this important but neglected area.

Our findings have implications for the provision of genetic testing services. For clinicians, these results show the value of taking precautions to fully explain to individuals that inconclusive results do not rule out the possibility that they still may face a higher risk of developing breast or ovarian cancer. Because this concept may be difficult for patients to understand, pretest genetic counseling and result disclosure sessions generally lasted ~1 hour in our research program. With *BRCA1/2* testing gradually making its way into an already burdened clinical setting and because a majority of women eligible for *BRCA1/2* testing may turn out to have an inconclusive result, it is imperative to identify the components of genetic counseling that are most useful in helping patients understand the meaning of such a result.

Although our short-term results are encouraging, long-term studies are still needed to determine whether women who receive inconclusive results also adopt behaviors consistent with potentially increased risk. In a previous study carried out before the publication of the Women's Health Initiative study results (30), we have shown that the use of hormone replacement therapy among women who were undergoing *BRCA1/2* testing was relatively low and that receiving an inconclusive result did not seem to affect hormone replacement therapy use (31). Had these women been falsely reassured, we might have hypothesized an increase in their use of hormone replacement therapy. This finding is rather consistent with the idea that women receiving an inconclusive result would not be expected to modify their behavior because they have not received a definitive answer about their genetic risk status. Recently, van Dijk et al. (28) reported that disclosure of an inconclusive *BRCA1/2* test result did

not affect the mammogram intentions of both affected and nonaffected women. However, although intentions to have a mammogram may be predictive of the actual uptake, only longitudinal studies will help to assess the acceptability and use of cancer surveillance and risk reduction options in this particularly understudied population. Until specific guidelines for their follow-up and management are agreed on and implemented, women with inconclusive *BRCA1/2* test results will probably warrant special attention. To help clinicians in this regard, the National Comprehensive Cancer Network now emphasizes that those women should be offered research and individualized recommendations according to their personal and family history (32).

Because of the high proportion of women for whom the *BRCA1/2* gene test turns out to be inconclusive, it is important to find ways to keep them informed of developments in cancer genetics that could potentially help them clarify their risk status. In our research program, these women have the opportunity of enrolling in another study which aims to discover new cancer susceptibility genes. With the identification of new breast cancer susceptibility genes likely in the future, women with a current inconclusive *BRCA1/2* test result will eventually have to make decisions about being tested for those new susceptibility loci. Those who engage in further testing may well receive a second test result that might have different implications. Although there is a suggestion that a majority of women with an inconclusive result seem to understand the implications of their results globally, it should not be assumed that education and counseling can be reduced for women who might eventually undergo *BRCAX* testing. For them and others, information tools such as newsletters and seminars may be offered easily in both clinical and research settings (25).

Appendix A Contributors

The following members of the INHERIT BRCAs contributed to this research: Paul Bessette (Service de gynécologie, Centre hospitalier universitaire de Sherbrooke); Francine Durocher (Laboratoire de génomique des cancers, Centre de recherche du CHUL, CHUQ, and Faculté de Médecine, Université Laval); Bartha Maria Knoppers (Centre de recherche en droit public, Université de Montréal); Bernard Lespérance and Roxane Pichette (Département d'hématologie et d'oncologie, Hôpital du Sacré-Cœur de Montréal and Université de Montréal); Jean Lépine (Centre hospitalier régional de Rimouski); Louise Provencher (Centre des maladies du sein Deschênes Fabia, Hôpital du Saint-Sacrement, Centre hospitalier affilié universitaire de Québec); and Patricia Voyer (Clinique des maladies du sein, Carrefour de Santé de Jonquière).

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