article

Putting it all behind: long-term psychological impact of an inconclusive DNA test result for breast cancer

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Purpose: An inconclusive DNA-result for breast cancer may leave women with uncertainty that cannot be relieved. We assessed the influence of beliefs women held about their inconclusive DNA-result on psychological well-being and whether women had been able to put the period of DNA testing behind them. **Methods:** In total, 215 women completed a baseline and a follow-up questionnaire 2.5 till 7 years after DNA test disclosure. Within the group of 147 women who received an inconclusive result (either a personal result or the result of an affected family member) multiple regression analyses were applied to investigate the relevance of women's personal beliefs. **Results:** Personal beliefs and ambivalence about an inconclusive DNA-result were associated with cancer-related worry and distress ($P < 0.05$). Moreover, these beliefs seemed to be an especially strong predictor of whether women had been able to leave the period of DNA testing behind them, even after controlling for all measures of psychological distress ($P < 0.001$). **Discussion:** Psychological distress measures may provide an important but incomplete picture of how women make sense of an inconclusive DNA-result. These findings underscore the importance of discussing counselees' beliefs and expectations openly to enhance well-being and adaptation on the long term. ***Genet Med* 2008:10(10):745–750.**

Key Words: *Genetic testing, inconclusive result, breast cancer, psychological, distress*

Since the identification of the *BRCA1* and *BRCA2* genes, many individuals have requested genetic testing for hereditary breast and ovarian cancer. From meta-analytic studies we now know that *BRCA* mutation testing does not, on the whole, lead to high levels of distress.[1,2]

These studies were based on women from families in which a *BRCA* mutation had been detected previously and who were offered informative testing. However, the majority of women receive an uninformative or inconclusive result, that is, a negative result in the absence of a mutation detected previously within the family. Because of the limitations of current genetic technology genetic susceptibility cannot be ruled out, and because of the possibility of deleterious mutations in as yet unidentified genes, these women remain at increased risk of developing breast cancer on the basis of the pedigree-based risk assessment.

Usually, women's DNA-samples are preserved for possible future testing using new technological advances. The inconclusiveness of the result may make it hard to regard this as a closed chapter and adapt to a somewhat uncertain risk status. In other words, it may be important to know whether women can put the period of genetic testing behind them, and whether they can cope with the ongoing uncertainty about their cancer risk and the risk for their female relatives.

This may be even more applicable to unaffected women who have asked an affected relative to take the test on their behalf. It may be very unsatisfactory if this relative receives an inconclusive test result, particularly when multiple cases of cancer have been observed in the family. Consequently, their perception and beliefs may be that the cancer is still hereditary. The absence of the option of a personal mutation test may leave the women with additional uncertainty that cannot be relieved.

Data on women who receive an inconclusive result in the absence of a known *BRCA1/2* mutation are relatively scarce. Despite concern about the possible harmful effects of continuing uncertainty associated with the result, levels of distress do not increase,[3,4] although no data are available about psychological functioning several years after DNA test disclosure. Moreover, levels of distress may be an incomplete outcome measure for understanding the impact of the continuing uncertainty and ambivalence that is associated with an inconclusive DNA test result. Our purpose was to assess how women evaluate such a result and whether they manage to make sense of it.

In the current study, we present results from a long-term follow-up study that was conducted up to 7 years after women received an inconclusive DNA test result. To have a measure of comparison for the psychological functioning of women with

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an inconclusive result, we also included women with conclusive DNA test results, namely (1) women with a positive DNA test result (i.e., a pathogenic *BRCA1* or *BRCA2* mutation was detected), and (2) women with a true negative DNA test result, that is a negative result regarding a *BRCA* mutation that has previously been detected within the family. First, we report on levels of worry and cancer-specific distress, but we focus in particular on whether women with an inconclusive DNA test result have managed to put the genetic testing behind them. Second, we explore the factors associated with psychological adaptation after an inconclusive result. Finally, it was explored whether it was more difficult to adjust to an inconclusive DNA test result that is not based on a personal blood sample.

METHODS

Participants and procedures

The present study was a follow-up study, the participants being women who had participated in an earlier prospective study of risk perception and informed decision-making among women at risk for familial breast cancer (Chances and Choices study). In the initial study, we invited all women who had received genetic counseling in the period between 1998 and 2002 at Leiden University Medical Center, and met the inclusion criteria of being at least 18-years old, with sufficient understanding of the Dutch language and not having received genetic counseling elsewhere. To participate, if the mutation was not detected in the family previously, women were eligible for DNA testing if the probability of detecting a mutation was about 10% or more. As the probability in women with a personal history of breast or ovarian cancer is commonly higher, unaffected women could approach an affected family member to take the test on their behalf. Some unaffected women underwent a personal test. All women who underwent DNA testing or who had asked a family member to take the test on their behalf participated in a disclosure counseling session. In this session, the personal implications of the DNA test result were discussed, and screening advice was provided in accordance with women's pedigree-based residual risk. Finally, all women received a letter summarizing all the information that had been established. Hence, the genetic counseling procedure was similar for women who did not receive a personal DNA test. We published a more detailed description of the counseling procedure elsewhere.[5]

For the follow-up study, we first searched medical records to see whether the women were still alive and whether their addresses had changed. Subsequently, we asked all women who had completed the last questionnaire of the previous study (i.e., about 1 year after DNA test disclosure) once again for their informed consent. In addition, we asked the women whether their medical status had changed. We did this so that we could send all participants a questionnaire tailored to their personal situation by mail. All participants received an initial mailed questionnaire, and 1 year later they received a final mailed questionnaire. We now report on all the women who completed this final questionnaire.

Measures

Sociodemographic and medical variables

All available information about the women's personal history of breast cancer (no, yes), risk status ($<$30% or $\geq$30%), *BRCA1/2*-test result, age, education (high-level, low-level), marital status, and number of children was collected from medical records and questionnaire data. More specifically, we asked about changes between the period of the DNA test result and the follow-up study with regard to health, prophylactic surgery, and present DNA test status.

Perceived likelihood of having inherited a deleterious mutation

We asked women who had received an inconclusive DNA test result the following question: "You may sometimes have wondered if you have inherited a characteristic or gene which increases your chances of developing breast cancer. What do you think the likelihood is that you have inherited such a characteristic/gene?" Women could respond on a 9-point scale ranging from 0 "nonexistent" through 4 "neither high nor low" to 9 "it is certain, the genetic mutation has been detected."

Personal beliefs regarding an inconclusive DNA test result

We measured "ambivalence regarding an inconclusive DNA test result" using six items on a 5-point scale ranging from 1 "totally disagree" to 5 "totally agree." Items were for example "Whatever the result of the DNA testing, I think that breast cancer is a hereditary problem in my family," "Now I have clarity about my risk of developing breast cancer (again)" and "I have mixed feelings about the DNA test result." The reliability of the scale was good ($\alpha = 84$).

Women who did not undergo a personal DNA test, but who had to rely on the inconclusive DNA test of an affected family member instead, were asked three additional questions regarding "ambivalence about not being tested personally." Items were "It's a shame I didn't undergo DNA testing myself," "It does not worry me at all that the DNA testing was done on my relative and not on me personally," "I have the idea that they might well detect something in me." The reliability of the scale was sufficient ($\alpha = 69$).

Psychological functioning

Coming to terms scale. Psychological adjustment was measured using seven newly constructed items which could be rated on a 5-point scale ranging from 1 "totally not applicable" to 5 "fully applicable." Items were "I have put the genetic testing for breast cancer behind me," "In fact, I never think about it any more," "It is somehow always on my mind," "I feel that the genetic testing is something that happened a long time ago," "The slightest thing can start me thinking about it again," "I have come to terms with the genetic testing," "I think about it regularly, even when there's no obvious reason to do so." The

reliability of the scale was good ($\alpha = 85$). Throughout the text, we will refer to this measure as "adjustment."

Breast-cancer-specific distress. Breast-cancer-specific distress was measured using 15 items of the Impact of Events Scale,[6] tailored to breast cancer, which assesses the level of intrusion and avoidance on a 4-point scale ranging from 0 "not at all," 1 "seldom," 3 "sometimes," to 5 "often." The reliability of the scale was very good ($\alpha = 91$). We will refer to breast-cancer-specific distress in the text as "distress" or "IES."

Breast-cancer worry. We assessed breast-cancer-related worries using a single item: "During the last 2 weeks, how often did you worry about developing breast cancer (again)?" on a 4-point scale ranging from 1 "almost never" to 4 "almost all the time."[7] Throughout the text, we will refer to this measure as "worry."

Statistical analysis

The SPSS 14.0 statistical package was used to analyze the data. Frequencies were used to describe the study population and psychological functioning. We used *t* tests and χ^2 to assess possible response bias concerning the characteristics of women who provided informed consent for this follow-up study. To investigate differences that were associated with different DNA test results, we conducted analysis of variances, and if significant, additional *t* tests. To assess differences between baseline and current levels of psychological functioning, we used analysis of variances with repeated measures and paired *t* tests.

In all further analyses, we focused on the group of women who received an inconclusive DNA test result. *t* Tests and χ^2 were used to assess whether women with a personal history of breast or ovarian cancer differed in terms of psychological functioning from women who were unaffected. Similarly, we tested whether women who had a relatively high risk differed from women with a relatively low risk after an inconclusive DNA test result. We used Pearson correlations to investigate whether other medical, sociodemographic, or psychological characteristics were associated with levels of distress and adjustment.

Finally, we investigated whether associations with our new measure "adjustment" remained significant if we controlled for levels of worry and cancer-specific distress. To put it differently, we wanted to determine whether adjustment would make a unique contribution to our understanding of the significance of an inconclusive DNA test result. In addition, we wanted to control for medical variables and psychological functioning reported before DNA test disclosure. Regarding the baseline level of psychological functioning, we obviously had no baseline measures of personal adjustment. We therefore decided to control for both baseline levels of worry and baseline levels of cancer-specific distress. The baseline levels refer to the measurement in between the first counseling session and DNA test disclosure. Summarizing, for each multiple regression analysis we controlled for baseline levels of distress and worry, long-term follow-up levels of distress and worry, residual risk ($<30\%$ or $\geq 30\%$), having had a personal history of breast cancer (yes, no), and years since DNA test result. Finally, we conducted all analyses in the subgroup of women who received a personal DNA test (i.e., exclusion of women with a familial inconclusive DNA result). As the pattern of results remained very stable, we only report the overall analyses.

RESULTS

Participants

Of the 303 women who had participated in our earlier study and received a DNA test result, six had died. Seven women had received a so-called variant of uncertain significance; we excluded them from this study. Of the 290 remaining women we invited for the current follow-up study, 216 provided written informed consent and completed our final questionnaire (response rate 74.5%). The follow-up period ranged from 2.5 years to 7 years after DNA test disclosure (mean 4.4 years, SD 1.0 year). Of the women who were unaffected in the period of the DNA test result, eight had developed breast cancer and one had developed ovarian cancer in the follow-up period. These women were diagnosed more than 1 year before completing our final questionnaire. Only one woman, a *BRCA*-mutation carrier, received a cancer diagnosis <6 months before completing the questionnaire, she was excluded from analyses.

No differences were observed between the women who chose to participate in the follow-up study and the women who did not (i.e., DNA status, personal history of cancer, age, having children, marital status, and level of education).

Participant characteristics

Among the women who had initially received an inconclusive DNA test result, two were informed that a *BRCA* mutation had been found. In total, 37 women had learned that they had inherited a *BRCA1* or *BRCA2* mutation, 31 had received a true negative DNA test result, and 147 had received an inconclusive result. Of the latter group, 62 of 64 women with a personal history of breast cancer had received a personal DNA test result. Two women had received an inconclusive DNA test result from a relative who was affected as well. Of the 83 unaffected women, 13 had received a personal DNA test result, whereas 70 had received a DNA test result from a family member's blood sample. (We identified nine mutually related family members. As exclusion of these women did not change the pattern of results, we decided to include them in the analyses.) As shown in Table 1, the DNA-result groups differed in several respects from each other.

Inconclusive DNA test result

An inconclusive versus a conclusive DNA test result

Table 1 displays the mean scores on psychological functioning and predisclosure levels of worry and cancer-specific distress. Overall, the levels of worry and cancer-specific distress were lower than before DNA test disclosure (worry $t = 6.00$, $P < 0.0001$; distress $t = 5.51$, $P < 0.001$). Subsequent *t* tests showed that these decreases applied to all three DNA-result

Table 1
Characteristics of the study population

Variable	Inconclusive (n = 147)	BRCA-mutation (n = 37)	True negative (n = 31)
Sociodemographic			
Age, mean (SD)	43.6 (10.3)[a]	40.4 (10.4)[a]	43.8 (11.2)[a]
Married or cohabiting: yes	121 (82%)[a]	30 (81%)[a,b]	29 (94%)[b]
Children: yes	119 (81%)[a]	22 (59%)[b]	26 (84%)[a]
Educational level: high	49 (34%)[a]	13 (35%)[a]	8 (25%)[a]
Medical			
Personal history of breast cancer: yes	64 (44%)[a]	22 (59%)[a]	—
Breast cancer risk: ≥30%	67 (48%)[a]	37 (100%)[b]	—
Psychological functioning			
Adjustment to risk status, mean (SD)	23.0 (6.3)[a]	22.3 (6.4)[a]	28.5 (4.9)[b]
IES: impact of Events scale, mean (SD)	16.2 (13.8)[a]	13.3 (11.7)[a]	4.0 (6.9)[b]
Baseline IES, mean (SD)	20.3 (13.9)[a]	21.3 (14.8)[a]	10.1 (10.2)[b]
Breast cancer worry, mean (SD)	1.7 (0.8)[a]	1.8 (1.4)[a]	1.2 (0.4)[a]
Baseline breast cancer worry, mean (SD)	2.5 (1.6)[a]	2.8 (2.0)[a]	2.3 (2.3)[b]

[a,b]Within each row, values that do not share the same superscript differ in a statistically significant manner ($P < 0.05$).

groups (inconclusive result: worry $t = 5.13$, $P < 0.0001$; distress $t = 3.66$, $P < 0.001$; *BRCA*-mutation carrier: worry $t = 2.25$, $P < 0.03$; distress $t = 3.52$, $P = 0.001$; true negative result: worry $t = 2.45$, $P < 0.02$; distress $t = 2.75$, $P = 0.011$). Furthermore, on the follow-up, the DNA-result groups differed on all psychological functioning measures (worry $F = 4.48$, $P = 0.013$; IES $F = 11.78$, $P < 0.001$; adjustment $F = 11.14$, $P < 0.001$: Table 1). *t*-Tests revealed that these differences could be attributed to the divergent responses of women with a true negative result. They reported the highest level of adjustment and relatively low scores on distress measures, whereas *BRCA* mutation carriers and women with an inconclusive result had highly comparable scores.

Sociodemographic and medical characteristics

No associations between psychological functioning and sociodemographic variables could be observed (i.e., age, having children, marital status, education). Regarding medical characteristics, women with a personal history of breast cancer did not differ from unaffected women with regard to the level of adjustment and worry ($P > 0.24$). However, women with a personal history of breast cancer reported higher levels of cancer-specific distress (IES $t = 2.39$, $P = 0.018$). Among the women with a personal history of breast cancer, time since diagnosis was not related to distress and adjustment ($P > 0.11$). Please note that having a personal history of breast cancer was very much confounded with having a personal DNA-test. Hence, it may also be concluded that women who had a personal test expressed higher levels of cancer-specific distress.

Furthermore, women with a relatively high risk status differed from women with a relatively low residual risk; they had much lower levels of adjustment ($t = 4.69$, $P < 0.001$), and higher levels of cancer-specific distress ($t = 2.03$, $P = 0.045$). Regarding worry, no differences were observed (worry $P = 0.13$). Women who received a personal DNA-test had a somewhat lower risk status than women who asked a family member to take the test on their behalves ($\chi^2 = 9.25$, $P = 0.002$). Finally, the time since DNA test disclosure was not significantly associated with psychological adjustment (adjustment $P = 0.24$, worry $P = 0.29$). Only for the cancer-specific distress could we observe a trend: women who had received their inconclusive DNA test result more recently reported higher levels of cancer-specific distress ($r = -0.16$, $P = 0.053$).

Perceived likelihood after an inconclusive DNA test result

Among the women who had a personal inconclusive DNA test, 15% said that their personal risk of having inherited a *BRCA* mutation was nonexistent. Among the women who did not have a personal test this percentage was 3%. Furthermore, in both groups (i.e., personal test and no personal test) one woman said that the mutation had actually been detected. A higher perceived risk of having inherited a *BRCA* mutation was related to worse psychological functioning. Women with a relatively high perceived risk reported in particular a much lower level of adjustment (Table 2).

Ambivalence regarding an inconclusive DNA test result

Quite a few women reported having mixed feelings or being somewhat ambivalent about their inconclusive DNA test result (mean = 2.99, SD = 99; 75 women score >3). Women who reported more uncertainty or ambivalence regarding their DNA test result reported higher levels of distress, and much lower levels of adjustment (see Table 2). Forty-seven percent of

Table 2
Pearson correlations between personal beliefs regarding an inconclusive DNA test result and psychological functioning

	Adjustment	Worry	IES
Adjustment—coming to terms with counseling information	—	−0.45[a]	−0.45[a]
Worry—about cancer risk		—	0.64[a]
Perceived likelihood carrier self (0–8) M = 3.58, SD = 2.09	−0.46[a]	0.27[b]	0.18[c]
Ambivalence about the DNA test result scale (scale 1–5) M = 2.99, SD = 0.99	−0.56[a]	0.24[b]	0.22[b]
Regret not having a personal DNA test, if applicable (1–5) M = 2.90, SD = 1.27	−0.50[a]	0.36[b]	0.31[b]

[a]$P < 0.001$.
[b]$P < 0.01$.
[c]$P < 0.05$.

the women with a nonpersonal result thought it was a pity that they had not had a personal test (i.e., score >3). Women who regretted more strongly not having undergone a personal test reported higher levels of distress and much lower levels of adjustment (Table 2).

Personal adjustment after an inconclusive DNA test result

Our measure of personal adjustment seemed to be strongly related to personal beliefs about an inconclusive DNA test result (Table 2). We wondered whether associations would remain significant if we controlled for levels of worry and cancer-specific distress. For each regression analysis we controlled for baseline levels of distress and worry, long-term follow-up levels of distress and worry, residual risk, having had a personal history of breast cancer, and years since DNA test result. The analyses showed that, independent of other psychological measures, adjustment remained very strongly related to beliefs regarding an inconclusive DNA test result (risk perception $\beta = -0.35$, $P < 0.0001$; ambivalence about the inconclusive DNA test result $\beta = -0.43$, $P < 0.0001$; regret at not having had a personal test $\beta = -0.36$, $P = 0.001$).

DISCUSSION

Our results suggest that women who receive an inconclusive DNA test result do not report adverse psychological consequences several years after test disclosure. Furthermore, their level of psychological functioning was comparable with that of women who learn that they carry a *BRCA* mutation. These long-term follow-up findings are in line with reports about the psychological functioning in the short term of women with an inconclusive result.[3,4,8,9] However, it should be noted that their psychological functioning was significantly worse than that of women who received a true negative DNA test result.

We found that women's beliefs regarding an inconclusive result are associated with their psychological functioning. For example, women who report feeling uncertain or ambivalent about their inconclusive DNA test result reported higher levels of worry and distress. This is in line with O'Neill et al.[10] who reported that women with a higher perceived risk and lower levels of tolerance for ambiguity reported the highest levels of distress 6 months after receiving an inconclusive DNA test result. Moreover, we found that beliefs regarding an inconclusive DNA test result were very strongly related to whether the women had come to terms with their result and their risk status. It was remarkable that beliefs regarding an inconclusive result remained very significantly related to adjustment, even if we adjusted for all measures of distress and worry. Cancer-related worries and distress may provide an important but incomplete picture on how women adapt to their inconclusive result. The measure of adjustment may be a very relevant indication of the impact of an inconclusive result, as women differ in whether they can cope with the uncertainty of an inconclusive result. It should be noted however, that most measures (e.g., psychological adaptation, beliefs regarding an inconclusive result) were newly developed and need to be validated in follow-up studies.

In a previous article about women with an inconclusive DNA test result, we reported that women with a personal history of breast cancer reported higher levels of distress and worry 6 months after DNA test disclosure than unaffected women.[9] Although women with a personal history of breast cancer reported more cancer-specific distress than unaffected women, we no longer found long-term effects on other measures of psychological functioning. This may be due to the longer follow-up period of the current study: a new breast cancer in the family usually triggers suspicions about whether breast cancer is hereditary. Thus, many women with a personal history of breast cancer start genetic counseling quite soon after their cancer diagnosis, which creates an additional stressor.[11] It is likely that the uncertainty and intense feelings of stress associated with a breast cancer diagnosis diminish over time. We should note a limitation to our conclusions regarding the effect of breast cancer: Because having a personal history of breast cancer was confounded with having a personal test, it is possible that the effect regarding breast cancer distress can be attributed to having received a personal test.

Although the likelihood that a high-risk mutation is actually present is lower after an inconclusive test result, the residual risk depends on the family history of breast and ovarian cancer. The present follow-up results confirm our previous findings that a relatively low or high risk status is an important determinant of psychological functioning in women who receive an inconclusive DNA test result.[9] Consistent with this, women who indeed perceive their risk of actually carrying a *BRCA* mutation as higher have the greatest difficulty in coming to terms with their risk status, which is especially true for women with a more suspicious family history of breast or ovarian cancer. This underscores an important clinical factor: the likelihood that a high-risk mutation is actually present is lower after an inconclusive test result, but this is especially true for women with a less suspicious family history of breast or ovarian cancer. Moreover, the influence of risk status corroborates an important but subtle difference with regard to the primary aim of DNA-mutation testing within the group of women with an inconclusive result. Whereas women with a relatively low risk may opt for testing to obtain additional reassurance from the finding that no *BRCA* mutation has been proven, others with a relatively strong family history may undergo DNA testing with the motive of revealing a *BRCA* mutation. Because of an inconclusive result they cannot confirm the etiology of their own or their family cancer history, and they are unable to provide a new opportunity for conclusive DNA testing for their unaffected family members.

It may be useful for counselors and other physicians to acknowledge the clinical and psychological heterogeneity of test applicants who receive an inconclusive result. It is important to note that psychological heterogeneity does not only apply to emotional functioning (i.e., cancer-related distress), but also to cognitive representations. The apparent importance of personal beliefs reflects the assumptions of the Self Regulation

Theory, which postulates that both cognitive representations and emotional processes are important in coming to terms with (the threat of) illness.[12–14] Moreover, as personal beliefs are modifiable, clinicians' may address these beliefs to enhance psychological well-being. Regarding risk beliefs, it should be noted that only a small minority of women reported false reassurance from an inconclusive test result.[5,15] Still, our results underscore the value of fully explaining the meaning and consequences of an inconclusive result. Not only must women's expectations before *BRCA* testing be addressed, but also the issue of how women are planning to come to terms with an inconclusive result. This may be particularly important if the result does not derive from a personal blood sample. Our results showed that quite a few women who did not undergo a personal test report difficulties with this procedure. Women who have problems with the lack of a personal test seem to have higher levels of worry and cancer-specific distress. Moreover, they seem to adapt less easily to their risk status. Further research will have to make clear what might be helpful in enabling women with an inconclusive result to cope with the uncertainty and to adjust to their risk status. For example, women may be willing to be kept up-to-date on the discovery of new breast-cancer mutations, since this may provide greater certainty about their risk status.

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