Original article

Effect on perceived control and psychological distress of genetic knowledge in women with breast cancer receiving a *BRCA1/2* test result

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ABSTRACT

Information provision during *BRCA1/2* genetic counseling is complex and expected to be increasingly so with gene panel testing. This prospective study evaluated whether genetic knowledge in counselees with breast cancer (BC) after a pre-test genetic counseling visit (T1) enhance their feeling of personal control while minimizing distress after the notification of BRCA1/2 result (T2).

At T1, 243 (89% response rate) counselees completed questionnaires on genetic knowledge (BGKQ), perceived cancer genetic risk; of which, at T2, 180 (66%) completed the BGKQ again, scales of anxiety/depression, distress specific to genetic risk, and perceived control. Multilevel models were performed accounting for clinician, and testing an effect of knowledge on psychological outcomes according to the adequacy of counselees' perceived genetic predisposition to cancer.

The mean knowledge score was moderate at T1, decreased while not significantly differing by *BRCA1/2* test result at T2. Knowledge at T1 had no direct effect on psychological outcomes, but in counselees who over-estimated their cancer genetic risk, higher knowledge at T1 predicted higher specific distress at T2.

In BC affected counselees who over-estimate their cancer genetic risk, higher *BRCA1/2* pre-test genetic knowledge seem to lead to increased specific distress. Identifying these BC affected counselees who over-estimate their genetic cancer risk and helping them to interpret their genetic knowledge instead of providing them with exhaustive genetic information could minimize their distress after test result receipt.

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1. Introduction

A diagnosis of breast cancer (BC) at a young age or a significant family history of BC, are among criteria for cancer predisposition gene testing [1]. Among the hereditary cancer gene panels now available [2], the *BRCA1* or *BRCA2* genes are commonly tested.

Women with BC who carry a mutation in the *BRCA1 or BRCA2* gene have, respectively, a cumulative of 44.1% and 33.5% risk to develop contralateral BC, 25 years post diagnosis [3], as well as a 12.7% and 6.8% risk to develop an ovarian cancer [4].

National guidelines recommend embedding cancer genetic testing within a framework of genetic counseling [1]. Its main function is to provide counselees with relevant information in order to increase personal control [5−8], to facilitate medical decision-making about cancer gene testing [9], about cancer risk management options [10−13] and sharing genetic information with concerned family relatives [14,15] and to minimize psychological

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distress [16].

Genetic counseling confronts to large quantities of information involving complex statistic and genetic concepts [17,18] coupled to perceptions of cancer risk and worry [19]. Intricacies also involve the communication of uninformative gene test results. Indeed in the context of *BRCA1/2* gene testing, in about 80% of index cases (first person tested in the family, usually BC affected), a mutation is not identified (i.e.: the result is negative uninformative (NU)), and in an additional 12.5% cases, an unclassified variant (UV) is found [20]. Such results do not significantly decrease the probability of cancer genetic predisposition in families with a high number of breast or ovarian cancer cases; but no clear consensual risk management recommendation can be proposed [21].

Counselees' genetic knowledge reflects the recall of information obtained from genetic counseling among different sources. If gain in breast genetic knowledge is highlighted after genetic counseling [14,22—24], it is not clear whether an increased level of breast genetic knowledge contributes to enhancing psychological outcomes such as perceived control over one's health or psychological well-being. In view of recent development in BC risk multi-gene testing and the cumulative information that may be offered to counselees [25], it seemed relevant to assess the specific psychological impact of genetic knowledge. Although high-risk women affected with BC may exhibit specific care needs [26,27], to our knowledge, only one study specifically addressed genetic knowledge in these women [13]. However it is not known whether and for which of these women genetic knowledge is beneficial.

A critical factor is the perception of hereditary cancer risk [28,29]. Discrepancies have been highlighted between counselees' and clinicians' evaluations of cancer risks [30].

Genetic counseling is expected to produce similar cognitive effects, i.e. improving knowledge as well as cancer risk perception accuracy. However, it has been shown that after genetic counseling, knowledge may increase while cancer risk perception remained largely inaccurate [5,7,10]. Although distress may decrease after genetic counseling [5,7,10], an inadequate perceived probability of genetic predisposition to cancer has been associated with higher levels of distress [29,31].

To the best of our search, no study simultaneously assessed the respective and interactive effect of knowledge and risk perception on psychological distress. So, as part of a prospective study exploring the psychological impact of the *BRCA1/2* test result in women affected with BC [31], we examined whether breast genetic knowledge after an initial genetic consultation improved counselees' perceived personal control while minimizing psychological distress after the *BRCA1/2* test disclosure. We also assessed whether the adequacy of counselees' perceived probability of genetic predisposition affected the psychological effect of knowledge. We hypothesized: 1) higher perceived personal control and lower distress after the communication of the *BRCA1/2* test result in women displaying higher genetic knowledge prior to testing; and 2) higher distress after the communication of the *BRCA1/2* test result in women overestimating their cancer genetic risk and evidencing higher knowledge prior to testing.

2. Methods

The protocol was approved by the *Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé* (CCTIRS MG/CP°08.42) and by the *Commission Nationale Informatique et Libertés* (CNIL). All recruited women provided written informed consent.

2.1. Study design

The design of this multicenter study described elsewhere [31] is displayed in Fig. 1. The main effects tested are depicted as plain arrows. The modifying effect of the adequacy of counselees' perceived probability of genetic predisposition on the relationship
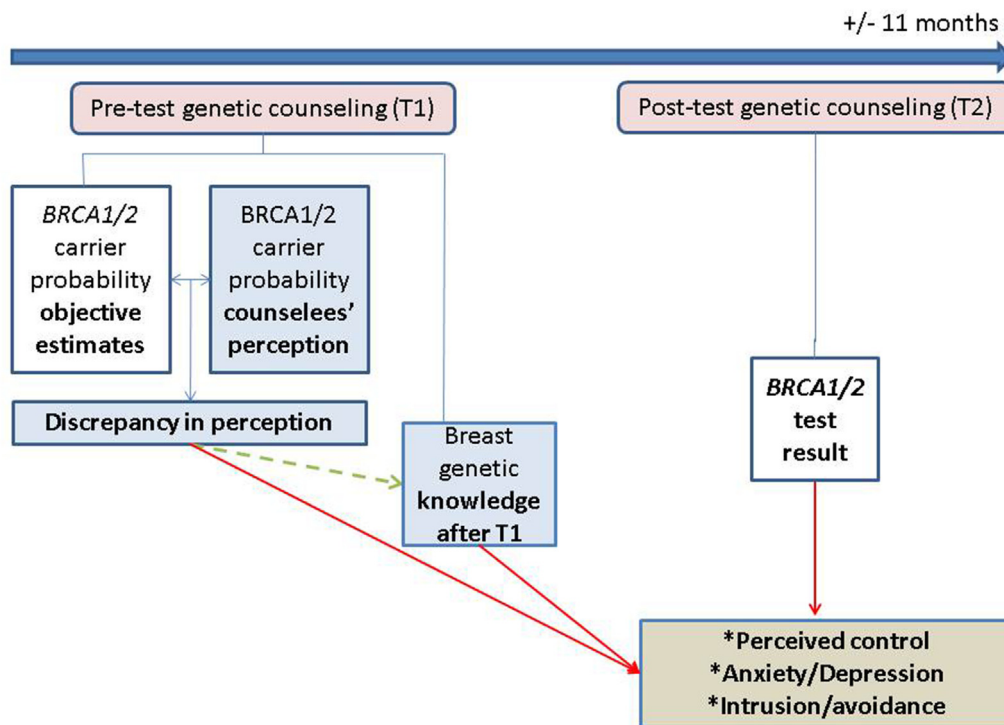

Fig. 1. Design of analyses testing the modifying effect of discrepancy between counselees' perceived probability of genetic predisposition to cancer and objective estimates, on the relationship between knowledge at T1 and psychological outcomes after notification of the *BRCA1/2* test result[a]. [a] Main effect tested depicted as plain arrows and interaction as dashed arrow.

between knowledge after the initial genetic consultation (here labeled 'discrepancy in perception') and psychological outcomes after *BRCA1/2* test result disclosure is shown as a dashed arrow.

For these analyses, we controlled for factors evidenced to be related to knowledge, the *BRCA1/2* test result, as well as anxious preoccupation about the personal BC diagnosis to specifically address the psychological outcomes linked to the specific experience of cancer genetic risk.

We did not assess an effect of genetic knowledge at T2 as this was measured at the same assessment time as the psychological outcomes and so would not allow for determining the direction of the relationship between these variables.

2.2. Procedure

From November 2008 to December 2009, women over the age of 18 years, eligible for *BRCA1/2* testing and the first woman to be tested in the family (index cases), with a personal history of BC were consecutively recruited by six medical geneticists or certified genetic counselors, at three cancer genetic counseling units in the Paris region (France).

On the day of the initial cancer genetic counseling visit (T1), women were given questionnaires to fill in at home within 2 weeks. At the *BRCA1/2* test result notification visit (T2 – at a mean (standard deviation) time of 11 (3) months), they received a similar set of questionnaires also to fill in within 2 weeks.

2.3. Counseling at the initial genetic consultation

In our centers, at the initial genetic consultation with a geneticist or a genetic counselor, patients are informed about hereditary cancer risks and the genetic testing process. Although practice may vary across clinicians, information most systematically provided at that time comprises the pattern of inheritance, cancer risks (breast or ovarian) and their medical management.

2.4. Psychological assessments

2.4.1. Knowledge

Breast genetic knowledge was assessed at T1 and T2 using the 27-item Breast Genetic Knowledge Questionnaire (BGKQ) [32]. This questionnaire addresses knowledge of information typically included in genetic counseling for breast cancer. It was translated in a forward-backward process from English into French. The geneticists and genetic counsellors involved in the study positively judged its content validity according to their clinical practice. Items with correct responses are listed in the supplementary material (table a). Internal consistencies (Cronbach's alpha coefficients) of the scale were 0.78 at T1 and 0.79 at T2.

2.4.2. Predictors

Women's perceived probability of genetic predisposition to cancer was measured at T1 on a scale ranging from 0 to 100 [31].

Objective estimates of cancer genetic predisposition probability were expressed as a percentage, computed at T1 by the clinician. The model used was derived from the results of segregation analyses [33]. These values represented reference points according to which the extent of women's over- or underestimation of their probability of being a carrier of a *BRCA1* or *BRCA2* mutation was estimated. A positive value indicates underestimation of one's probability of carrying a BRCA1/2 mutation.

The Mental Adjustment to Cancer Anxious Preoccupation subscale (MAC AP) French version [34] was used at T1 to assess difficulty in coping with the personal BC diagnosis. This scale internal consistency was 0.76.

2.4.3. Outcomes

The Perceived Personal Control (PPC) scale [35] measures coping with health threats and refers to the "*beliefs that one has at one's disposal a response that can influence the aversiveness of an event*" [36].

General distress was measured by the Hospital Anxiety and Depression French version, anxiety (HADS-Anxiety) and depression (HADS-Depression) subscales [37].

The Impact of Event Scale (IES) was used to measure specific psychological distress (*i.e.* thoughts or feelings of intrusion or avoidance) to hereditary cancer risk [38].

All these outcomes, measured at T2, presented adequate internal consistencies with Cronbach's alpha estimates above 0.70.

2.5. Statistical analysis

Statistical analyses were performed with R software (version 3.3.0).

Bivariate multilevel analyses explored covariates of knowledge, including age, education level (above secondary school or not), family cancer history (number of relatives diagnosed with breast or ovarian cancer before age 50 years), closeness of the BC diagnosis ('undergoing treatment' or 'being in remission'), 'discrepancy in perception', anxious preoccupation, and the *BRCA1/2* test result. To respect the two-level hierarchical structure of patients (level 1) nested in clinicians (level 2), we controlled for the random effect of clinicians on knowledge [39].

Secondly multivariate multilevel models were fitted on the dependent outcome variables, *i.e.* PPC, HADS-Anxiety, HADS-Depression, IES-Intrusion, IES-Avoidance at T2, controlling for the random effect of clinicians on these outcomes. Each model included the knowledge covariates identified among those cited above, the type of *BRCA1/2* test result, and knowledge at T1 (main effect: plain arrows in Fig. 1), and interaction (i.e. dashed arrow in Fig. 1).

The interaction significance was estimated by comparing multivariate multilevel models including the main effects and the interaction against the models including the main effects only using the likelihood ratio test (LR). The retained final model exhibited a significant likelihood ratio test (Chi^2 test, 1° of freedom).

To describe the significant interaction, a cross-tabulation of variables representing 'discrepancy in perception', and knowledge level categorized into terciles, provides the mean (standard deviation) predicted outcome values.

3. Results

3.1. Sample characteristics

Two hundred and seventy-three women were recruited. Of these, 30 (11%) at T1 and 63 (23%) at T2, did not provide evaluable data. Compared to non-respondents, respondents at T1 were only more likely to be in remission than still under BC treatment ($p = 0.006$) (Table 1). Non-respondents at T2 did not differ in terms of knowledge, perceived probability of genetic predisposition to cancer and anxious preoccupation assessed at T1, and the type of *BRCA1/2* test result (data not shown).

Table 1 provides the descriptive socio-demographic, clinical and psychological data collected at T1 or T2. Among the 180 respondents at T2, 133 (74%), 20 (11%) and 27 (15%) received a negative, deleterious mutation or UV result, respectively.

3.2. Psychological assessment

At T1, compared to objective estimates, 23.6% of women overestimated and 23.7% of women underestimated their probability of

Table 1
Descriptive characteristics of study sample.

	Respondents at T1 (N = 243)	Non respondents at T1 (N = 30)	Respondents at T2 (N = 180)		
Socio-demographic and clinical data					
Age (years)					
Mean (s.d.)	47.3 (11.4)	49 (13.5)	–		
Education level N(%)					
<High school	84 (35)	–	–		
≥High school	156 (65)				
Missing data	*3*				
Medical status N(%)[a]					
Under treatment	127 (52)	14 (87)	–		
In remission	116 (48)	2 (13)			
Missing data	*–*	*14*			
Number of 1st d° relatives with cancer					
Mean (s.d.)	1.2 (1.0)	1.4 (1.2)	–		
Number of 2nd d° relatives with cancer					
Mean (s.d.)	1.8 (1.4)	1.6 (1.3)	–		
Objective estimate of cancer genetic predisposition risk N(%)[b]					
≤20%	73 (32)	10 (36)	–		
>20%–≤40%	45 (20)	2 (7)			
>40%–≤80%	71 (31)	10 (36)			
>80%	37 (16)	6 (21)			
Missing data	*17*	*2*			
BRCA test result N(%)[c]					
Negative uninformative (NU)	–	–	133 (74)		
Positive *BRCA1/2*	–	–	20 (11)		
Unclassified variant (UV)	–	–	27 (15)		
Psychological data					
Perceived probability of genetic predisposition to cancer[d]					
N/% higher perceived probability than objective estimates[e]	34 (23.6)	–	–		
N/% lower perceived probability than objective estimates[e]	34 (23.7)	–			
Missing data	*36*	*–*			
MAC-Anxious preoccupation					
N/ % clinical cases (score > 15)[f]	19 (8)	–	–		
HADS-Anxiety					
N (%) clinical case (score > 10)[g]	–	–	56 (31)		
HADS-Depression					
N (%) clinical case (score > 10)[g]	–	–	4 (2)		
IES (risk of cancer)-Intrusion					
N (%) clinical case (score > 20)[h]	–	–	20 (11)		
IES (risk of cancer)-Avoidance					
N (%) clinical case (score > 21)[h]	–	–	32 (18)		
PPC scale total score [0–18][i]					
Mean (s.d.)	–	–	11.8 (4.0)		
BGKQ total score [0–27][j]	18.6 (4.2)		NU: 17.0 (4.7)	*BRCA1/2+:* 18.9 (3.3)	UV: 16.3 (4.2)
Mean (s.d.)			17.1 (4.5)		

[a] Significant difference between respondents and non-respondents at p < .01.
[b] According to Claus model.
[c] NU: negative uninformative; *BRCA1/2+*: positive; UV: unclassified variant.
[d] For respondents at both T1 and T2 (n = 180).
[e] Figures provided by women falls outside a range of plus or minus 25%.
[f] Mental Adjustment to Cancer (MAC)- Anxious Preoccupation coping clinical threshold from Cayrou et al. (2003).
[g] Hospital Anxiety and Depression Scale (HADS) clinical thresholds from Hopwood et al. (1991).
[h] Impact of Event Scale (IES) Intrusion/avoidance clinical thresholds from Horowitz et al. (1979).
[i] Perceived Personal Control (PPC).
[j] Breast Genetic Knowledge Questionnaire (BGKQ) mean difference: p < .001.

genetic predisposition to cancer by more than 25% (Table 1).

At T1, 8% of the women evidenced anxious preoccupation requiring psychology professional attention and at T2, 31%, 2%, 11% and 18% presented, respectively, a level of anxiety, depression, intrusion or avoidance demanding such consideration.

3.2.1. Knowledge

The frequency of correct responses across the breast genetic knowledge 27-item questionnaire at T1, and by *BRCA1/2* test results at T2, is displayed in table a. of the supplementary material.

The mean (standard deviation) total breast genetic knowledge score at T1 was moderate (18.6 (4.2)) and significantly decreased at T2 (17.1 (4.5)). For the NU, *BRCA1/2* + and UV results, these values were 17.0 (4.7), 18.9 (3.3) and 16.3 (4.2) respectively, which were not significantly different. Among the three BGKQ items that showed significant accuracy difference, women receiving a positive *BRCA1/2* test result presented higher knowledge on two items (i.e., "*A father can pass down a breast cancer gene mutation to his daughters*" and "*Select the procedure than is NOT appropriate for the detection of ovarian cancer*").

Counselees' younger age and higher education level were significantly related to higher knowledge at both T1 and T2 (Table 2). Discrepancy in perception (i.e. counselees' underestimation of the probability of having a *BRCA1/2* mutation) was significantly related to higher knowledge at T2, and higher anxious preoccupation was significantly related to higher to knowledge at T1. Family cancer history, BC diagnosis closeness and the *BRCA1/2* test result were not related to knowledge (Table 2).

3.3. Multivariate multilevel models

The multivariate multilevel models, interaction and main effects estimates are detailed (table b) and depicted (figure a) in the supplementary material. There seemed to be no direct effect of T1 knowledge level on any of the psychological outcomes at T2. However a significant interaction between knowledge level and 'discrepancy in perception' at T1 on IES-Intrusion scores at T2 was observed, that is, a higher level of knowledge at T1 predicted higher IES-Intrusion scores after *BRCA1/2* test result disclosure in women who over-estimated their risk of having a *BRCA1/2* mutation (Table 3). This was also the case for women who presented a more adequate genetic risk perception who revealed higher IES-Intrusion mean scores for a high knowledge level.

Younger age and under-estimation of the risk of having a *BRCA1/2* mutation predicted an increase in perceived personal control. Anxious preoccupation about personal BC diagnosis significantly increased all distress outcomes. A *BRCA1/2* + and UV test result significantly increased the level of IES-Intrusion (Table b of supplementary material).

4. Discussion

This prospective study evaluated breast genetic knowledge in counselees affected with BC after the initial genetic consultation and its effect on psychological outcomes after receiving the *BRCA1/2* test result. Breast cancer genetic knowledge may be improved after counseling but cancer risk perception often remains inaccurate [5,7,10]. This study was meant to add to current knowledge in the field of breast cancer clinical genetics by clarifying how counselees' genetic knowledge affects their psychological distress accounting for their cancer risk perception.

An indirect effect of knowledge was revealed when taking into account the adequacy of women's perceived probability of genetic

Table 3
IES-Intrusion scores at T2 according to the level of breast genetic knowledge and the discrepancy between counselees' perceived probability of genetic predisposition to cancer and objective estimates at T1.[a]

Discrepancy in perception[b,c]	Level of knowledge[b]		
	Low	Medium	High
Over-estimation	5.0 (4.6)	10.0 (4.3)	11.3 (3.4)
Adequate	7.2 (4.7)	9.3 (4.6)	10.1 (4.0)
Underestimation	9.5 (3.9)	9.0 (3.1)	9.6 (4.7)

[a] Figures in cells represent the IES-Intrusion predicted mean (standard deviation) scores; range [0–35].
[b] Discrepancy in perception and level of knowledge variables are categorized by tercile.
[c] Discrepancy in perception refers to the discrepancy between objective estimates and perceived probability of genetic predisposition.

predisposition to cancer relative to objective estimates. Indeed, in women who over-estimated their risk of having a *BRCA1/2* gene mutation, a higher level of knowledge after the initial genetic consultation increased the distress specific to genetic risk after the notification of test result (regardless of the type of result). Worry in these women who presented higher appraisals of their genetic predisposition to cancer may have been accentuated by the information provided during the initial genetic counseling, which may have persisted after the test result notification. So, it could be alleged that women who overestimated their probability of carrying a *BRCA1/2* mutation were not disturbed by a deficit in genetic knowledge but instead by amplified anxious thoughts when confronted to increased knowledge. It should be noted that some of these women may want to decide on their cancer risk management after receipt of their genetic test result and may therefore potentially make their decisions in a troubled emotional state.

This finding has potentially important clinical implications. During the initial genetic counseling consultation, the perception of genetic predisposition to cancer in counselees affected with BC at high genetic risk should be checked. Discussing with them about what they already know prior to *BRCA1/2* gene testing, helping them to interpret this knowledge instead of striving to provide exhaustive genetic details [40] could contribute to minimize their worries about cancer genetic risk after the notification of their genetic test result.

In contrast to over-estimation of the risk of genetic predisposition to cancer, underestimation seemed to be more beneficial in

Table 2
Factors associated to counselees' level of breast genetic knowledge after the initial genetic consultation (T1) and after *BRCA1/2* test result notification (T2).[a,b]

	Knowledge	
	T1	T2
Age	−0.095 (−4.0)***	−0.073 (−2.4)*
Education	2.51 (4.6)***	2.29 (3.3)***
Relatives diagnosed of breast or ovarian cancer < 50 years old	0.081 (0.1)	1.245 (1.8)
Under treatment (versus in remission)	−0.027 (−0.1)	−0.430 (−0.63)
Assessment at T1		
Discrepancy in perception (i.e., underestimation)[c]	0.382 (1.3)	0.984 (2.9)**
Anxious preoccupation	0.241 (2.8)**	0.126 (1.1)
Assessment at T2		
BRCA test result[d]		
NU vs Positive		−1.038 (−1.043)
UV vs Positive	−	−0.135 (−0.114)

[a] Bivariate multilevel models accounting for the random effect of different clinicians.
[b] Figures in cells = bivariate unstandardized b (Student *t*-test),*p value < 0.05;**p value < 0.01;***p value < 0.001.
[c] Discrepancy in perception refers to the discrepancy between objective estimates and perceived probability of genetic predisposition (positive estimate value = counselees' under-estimation of genetic predisposition to cancer).
[d] NU: negative uninformative; *BRCA1/2*+: positive; UV: unclassified variant.

terms of psychological outcome. Indeed women who underestimated their cancer genetic risk displayed higher perceived personal control after the *BRCA1/2* test result notification. These women did not probably suspect a possible causal heredity to their BC diagnosis. Less acquainted to this possibility they may have gained more control from the information entailed to *BRCA1/2* test result notification. Or in line to the inverted u-shape relationship between stress and cognition [41], they were not as worried as those women who overestimated their possible cancer genetic predisposition and so perceived more control following receipt of the test result.

Overall, breast genetic knowledge assessed after the initial genetic consultation had no direct effect on perceived personal control over cancer risks or on psychological distress after *BRCA1/2* test disclosure. The absence of knowledge effect is unexpected as other studies showed an overall significant enhancement in perceived personal control [5–7] and decrease in anxiety [5,6] concomitant to increased knowledge at a similar time after an initial genetic consultation.

However these latter studies included healthy counselees in addition to BC affected counselees. In this study, a moderate mean level of knowledge was found after the initial genetic consultation which decreased subsequently, while not differing significantly by type of *BRCA1/2* test result. These figures are in line with those reported for similar BC affected counselees and assessment-time [9,13] and may reflect that women affected with BC often confronted with fear of BC recurrence [42] may need more than standard genetic counseling [43] to address their information needs on cancer risks.

For two items (i.e., paternal inheritance and ovarian cancer management), women receiving a *BRCA1/2+* test result exhibited significant better knowledge scores. Referring to the genetic counseling content in our practices this was expected, which underscores that genetic clinicians could achieve a number of their information goals.

An anxious preoccupation coping with the personal BC diagnosis independently predicted higher levels in all psychological distress outcomes. Hence, women's emotional reactions to their disease superseded the hypothetical minimizing effect of genetic knowledge on distress.

As previously noted [31], receiving a *BRCA1/2* positive or UV result increased intrusion. However, neither the family cancer history - as in other studies [10,44,45] – nor the type of test result affected knowledge at both assessment times. So specific worries related to BC genetic risk could not have been attenuated by the information on cancer genetic risk and medical management that is generally provided based on these counselees' characteristics.

The generalizability of these results is limited as they reflect reactions of women affected with BC attending French cancer genetic services and addresses healthy counselees at high BC risk. No assessment of genetic knowledge before the initial genetic consultation was performed so the correct knowledge responses in these women may also reveal recall of information from other sources than genetic counseling. The wrong knowledge responses may also reflect that the information had not been provided during counseling.

Assessment of knowledge at T2 and psychological outcomes were simultaneous and so we could not ascertain a specific psychological effect of knowledge after the notification of the *BRCA1/2* test result. However an effect of knowledge after the initial genetic consultation could be estimated based on the prospective assessment of psychological outcomes after the genetic test result disclosure. So this study provides relevant information on the role of pre-test genetic knowledge conditional to perceived probability of genetic predisposition to cancer, on short term post-test result psychological reactions.

This data collection was concomitant to the single *BRCA1* or *BRCA2* gene testing whereas gene panel testing is now increasingly performed for BC risks. New specific breast genetic knowledge topics related to BC gene panel testing (i.e. testing of moderate-penetrance genes, higher rates of detecting UVs [46]) may presently confront counselees to even more complex information and psychological effects that should be monitored.

5. Conclusions

Breast genetic knowledge after an initial genetic counseling consultation did not seem to improve psychological outcomes in counselees affected with BC at high genetic risk. The knowledge exhibited in those who overestimated their risk of genetic predisposition to cancer could increase psychological distress shortly after the notification of the *BRCA1/2* test result. Identifying these BC affected counselees and helping them to interpret their genetic knowledge could minimize their distress after test result receipt.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.breast.2016.10.024.

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