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Short-term psychological impact of the *BRCA1/2* test result in women with breast cancer according to their perceived probability of genetic predisposition to cancer

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Background: The effect of *BRCA1/2* gene test result on anxiety, depression, cancer-related thought intrusion or avoidance and perceived control over cancer risk was assessed in breast cancer (BC) patients, according to their perceived probability of genetic predisposition to cancer.

Methods: Two hundred and forty-three (89% response rate) women with BC completed questionnaires after an initial genetic counselling visit (T1), of which 180 (66%) completed questionnaires again after receiving the *BRCA1/2* results (T2). The discrepancy between women's perceived probability of cancer genetic predisposition at T1 and the geneticist's computed estimates was assessed.

Results: In all, 74% of women received a negative uninformative (NU), 11% a positive *BRCA1/2* and 15% an unclassified variant (UV) result. On hierarchical regression analysis, in women with a positive *BRCA1/2* result (*vs* NU or UV), a lower perceived probability of cancer genetic predisposition than objective estimates at T1 predicted lower levels of anxiety at T2 ($\beta = -0.28$; $P<0.01$), whereas in women receiving a UV result (*vs* NU or positive *BRCA1/2*), a lower perceived probability of cancer genetic predisposition than objective estimates at T1 predicted higher levels of anxiety ($\beta = 0.20$; $P<0.01$), depression ($\beta = 0.19$; $P<0.05$) and intrusion ($\beta = 0.18$; $P<0.05$) at T2.

Conclusion: The type of *BRCA1/2* test result differently affects distress according to women's perceived probability of genetic predisposition before testing.

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Breast cancer (BC) is the most common cancer in women worldwide and a family history of BC is among the best recognised BC risk factors. In 15–30% of patients from high-risk families, BC is caused by a germline mutation in the *BRCA1* or *BRCA2* (*BRCA1/2*) gene (Wevers *et al*., (2011)). Women with BC who carry a mutation in the *BRCA1/2* gene have an increased risk of developing a second primary BC (Kirova *et al*, 2010). They also present up to 40% lifetime risk of developing ovarian cancer (Chen and Parmigiani, 2007).

BRCA1/2 testing is primarily proposed to women (index cases) in the family who developed BC as the probability of identifying a mutation is highest when testing starts with an affected woman. Identification of a *BRCA1/2* mutation in women with BC may inform potential decisions for preventive oophorectomy or mastectomy and can have implications for the relatives' cancer risks and the likelihood that cancer is due to a genetic mutation in the family.

Research on the psychological impact of *BRCA1/2* genetic testing initially focused on the response to a positive, compared with a negative, test result mainly in individuals unaffected with cancer (Meiser, 2005). Although women who received a *BRCA1/2* negative test result evidence a decrease in distress (Croyle *et al*, 1997; Schwartz *et al*, 2002), *BRCA1/2* mutation carriers may experience increased distress shortly after test result disclosure (Meiser *et al*, 2002; Van Roosmalen *et al*, 2004; Watson *et al*, 2004), which abates over the following years (Halbert *et al*, 2011; Graves *et al*, 2012).

However, in about 80% of cases, a *BRCA1/2* mutation in the first person tested in a BC high-risk family is not identified. In an additional 12.5% of cases, unclassified variants (UV), for which the effect on the protein function or the gene is still unknown, are detected (Vink *et al*, 2005). In BC patient index cases, a negative (i.e., no deleterious mutation found) or UV results are both 'uninformative', also referred as 'inconclusive'; such results do not significantly decrease the probability of cancer genetic predisposition in families with a high number of breast and ovarian cancer cases; however, no clear consensual risk management guidelines can be proposed (Gadzicki *et al*, 2011).

An uninformative *BRCA1/2* result may lead to potential distress (O'Neill *et al*, 2009), misunderstanding (Cypowyj *et al*., 2009), feeling less in control over the stress of cancer risk (Claes *et al*, 2004) or decisional conflicts (Rini *et al*, 2009). Previous results indicate lower levels of distress in women receiving an uninformative result compared with those receiving a positive *BRCA1/2* test result (Dorval *et al*, 2005; Beran *et al*, 2008; Smith *et al*, 2008), but risk management decisions have shown both no 'false reassurance' (i.e., women maintain appropriate risk management intentions) (Dorval *et al*, 2005; van Dijk *et al*, 2005) and infrequent surveillance (Vos *et al*, 2012).

Although emotional reactions to a negative uninformative (NU) (as opposed to a true negative where individuals are found non-carriers of their family's mutation) or UV results appears similar (van Dijk *et al*, 2004; Smith *et al*, 2008), a UV result has recently predicted genetic testing distress (O'Neill *et al*, 2009) and, associated with overestimation of cancer risk, has led to high distress and intention to undergo prophylactic interventions similar to that induced by a positive *BRCA1/2* test result (Vos *et al*, 2012), suggesting that the communication of these ambiguous results elicits a 'false alarm'.

High perceived cancer risks (Hopwood, 2000; Vos *et al*, 2010; 2012) or heredity likelihood (Vos *et al*, 2010; 2012), or high expectation of carrying a predisposing mutation (O'Neill *et al*, 2009), are often associated with high levels of distress. Perceptions of cancer risks or of the probability of genetic predisposition to cancer integrate knowledge (i.e., the recall of information gathered, e.g., from health-care professionals, relationships or the media) as well as feelings and subjective interpretations (van Dooren *et al*, 2004; Vos *et al*, 2012).

To our knowledge, only two studies prospectively addressed the emotional impact of *BRCA1/2* testing in BC patients considering separately a NU or UV result (O'Neill *et al*, 2009; Vos *et al*, 2012). So, this study was designed firstly to address the specific effect of the type of *BRCA1/2* test result received (positive *vs* NU or UV *vs* NU) on BC patients in terms of anxiety, depression, cancer-related thought intrusion or avoidance and perceived personal control.

Secondly, the *BRCA1/2* test result has been shown to affect distress via the perception of cancer risks (i.e., the recall of factual information associated with the test result and its interpretation; Vos *et al*, 2012). In the present study, we wanted to address of patients' risk perception before disclosure of test result. This perception may be related to genetic counselling, which may vary across cultures. In BC patients, cancer (recurrence) risk perception may be experienced not solely in relation to the genetic predisposition to cancer, so we only focused on the perceived probability of genetic predisposition to cancer as a moderator of psychological outcomes. We appraised how far BC patients' perception of the probability of genetic predisposition to cancer was from objective estimates.

We paid particular attention to the perceived probability of genetic predisposition to cancer because of the potential influence of inadequate expectations on emotional responses (Phelps *et al*, 2008; Hilgart *et al*, 2010) and the potential implication of this relationship on improvement of cancer genetic counselling communication.

To focus on the *BRCA1/2* test result and the discrepancy between perceived probability of carrying a predisposing mutation and objective estimates, we controlled for other potential factors of distress, including higher initial distress (Meiser, 2005; Smith *et al*, 2008), age (Schlich-Bakker *et al*, 2006), children (Meiser, 2005), recency of BC diagnosis (van Roosmalen *et al*, 2004), and high family pedigree-based risk (Meiser, 2005; van Dijk *et al*, 2006; O'Neill *et al*, 2009), being young when a parent was affected (van Oostrom *et al*, 2006).

PATIENTS AND METHODS

This study protocol was approved by the *Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé* (CCTIRS: Consultative committee for information management in health research – DGRI CCTIRS MG/CP°08.42) and by the *Commission Nationale Informatique et Libertés* (CNIL: French Information Technology and Privacy Commission). All recruited women provided written informed consent.

Participants and procedure. From November 2008 to December 2009, women aged >18 years, eligible for *BRCA1/2* testing and the first woman to be tested in the family (index case) with a personal history of BC were consecutively recruited at the cancer genetic counselling unit of the Ensemble Hospitalier Institut Curie, Institut Gustave Roussy (June-December 2009) and Tenon Hospital (March–September 2009) in the Paris region (France). A minimum sample size of 200 was required to allow for comparisons between *BRCA1/2* deleterious *vs* NU or UV *vs* NU test results. Women with a personal history of ovarian cancer or a major psychiatric disorder were not included.

The study objectives were explained to the women on the day of the initial cancer genetic counselling visit (T1) and, when they agreed to participate, they were given questionnaires to fill in at home and return within 2 weeks. At the *BRCA1/2* test result notification visit (T2), they received another set of questionnaires to be filled in at home and returned within 2 weeks. When necessary, a reminder call was made at both the time points.

Questionnaires not received within 21 days of the genetic visit were considered to be missing.

Genetic counselling. In our centres, at the initial genetic consultation with a geneticist or a genetic counsellor, patients are informed about hereditary cancer risks and the genetic testing process. The hereditary risk is evaluated and, if testing is indicated, patients are provided with further medical information. Although practice may vary across clinicians, information most systematically provided at that time comprises the risk of genetic predisposition to cancer, cancer risks (breast or ovarian) and the probability that an index case may be a carrier of a *BRCA1/2* mutation. The probability of genetic predisposition to cancer is provided in terms of 'moderate', 'high' or 'very high'. No figure is provided and patients are not informed of the possibility of receiving a UV.

At disclosure of the *BRCA1/2* test result, women receiving an uninformative *BRCA1/2* test result are generally told that no deleterious gene mutation was found, which does not preclude a possible yet unknown genetic predisposition explaining the family history of cancer. When a UV is identified, women are told that this result does not allow for concluding that a causal mutation was found; however, clinicians will be kept informed whether this mutation is reclassified as deleterious in the future.

Instruments

Outcome measures. General distress (i.e., anxiety and depression) was measured by the Hospital Anxiety and Depression French version, anxiety (HADS-Anxiety) and depression (HADS-Depression) subscales (Zigmond and Snaith, 1983; Razavi *et al*, 1990).

The Impact of Event Scale (IES) (Horowitz *et al*, 1979) measuring psychological reactions (i.e., thoughts or feelings of intrusion or avoidance) to a stressful event (i.e., in this case cancer risks) has been validated in the setting of hereditary BC risk to address cancer-specific distress (Thewes *et al*, 2001). Items of the HADS-Anxiety and -Depression and IES-Intrusion and Avoidance scales both concern frequency of thoughts or feelings during the previous week.

The Perceived Personal Control (PPC) scale consists of a measure of the genetic counselling impact (Berkenstadt *et al*, 1999). This concept is central to 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*' (Thompson, 1981). Recent validation studies recommend a one-dimension scale (Smets *et al*, 2006; McAllister *et al*., (2012)). A PPC French version measuring perceived personal control over the genetic risk of cancer was produced following a forward–backward translation process.

All these outcome measures, completed at both T1 and T2, presented adequate internal consistencies with Cronbach's alpha >0.70.

Predictor measures. Perceived probability of genetic predisposition to cancer assessed at T1 and perceived risks of breast or ovarian cancer assessed at T2 were each measured by two items; the first in terms of absolute figure using a visual analogue scale ranging from 0% ('no risk') to 100% ('maximum risk') and the second in terms of comparative figure to age-matched general population women, using a five-level categorical scale with responses ranging from 'much lower' to 'much higher'. As the absolute and comparative evaluations for each perceived probability or risks assessed were strongly correlated ($r=0.41$ for perceived probability of genetic predisposition to cancer; $r=0.50$ for BC risk perception, $r=0.53$ for ovarian cancer risk perception), scores of the absolute and comparative evaluation items were standardised and their sum was averaged providing a total score based on a two-item scale.

Objective estimates of cancer genetic predisposition probability were expressed as a percentage, computed at T1 by the genetic counsellor. The model used is derived from the results of the segregation analysis published by Claus *et al* (1991) and is based on the LINKAGE programme developed by Lathrop and Lalouel (1984). The use of the LINKAGE programme allows taking into account the number of breast and ovarian cancers in the family, their distribution among relatives and the age at onset of BCs and thus estimating the probability that a dominant, highly penetrant allele is running in the family whatever the gene involved. These values represented reference points according to which the woman's perceived probability of genetic predisposition to cancer was compared and the degree of discrepancy of their perception with objective figures estimated.

Statistical analysis. For each multi-item scale, missing data were replaced by the mean value of the scale when at least half of the items on that scale had been completed. All items of psychometric instruments presented $<1\%$ of missing data; however, individual risk or probability perception items comprised 1–27% of missing responses.

The discrepancy between objective estimates and perceived probability of genetic predisposition to cancer was computed using standardized residuals of the objective cancer genetic predisposition probability variable regressed on the perceived probability of genetic predisposition to cancer-dependent variable. Mean (s.d.) of this variable was 0.00 (1.00) ranging from -2.34 to 2.06; a positive value indicates lower perceived probability of genetic predisposition to cancer than objective estimates.

Multiple regression analyses were performed on the dependent outcome variables that is, HADS-Anxiety, HADS-Depression, IES-Intrusion, IES-Avoidance and PPC at T2. For each regression model, we controlled for sociodemographic (age, education level above secondary school or not, having a partner or not, daughters or not), clinical data, time interval between initial genetic counselling visit and *BRCA1/2* test result notification, breast and ovarian cancer risk perception at T2, perceived cancer genetic predisposition probability and its difference with respect to objective estimates, as well as for T1 scores of the outcome variable. Due to our sample characteristics, recency of the BC diagnosis was measured using the dichotomised 'undergoing treatment' or 'in remission' variable. Family cancer history and being young when a parent was affected was assessed by the number of relatives diagnosed with breast or ovarian cancer before 50 years of age. We also assessed the number of deceased relatives in different regression models and also tested regression models without all risk perception variables as covariates. This led to similar statistical results (not reported). Hierarchical multiple regressions were performed (Tabachnick and Fidell, 2007) in which these covariates were introduced into a first block, the *BRCA1/2* result into a second block and the interaction between the degree of discrepancy between the perceived probability of genetic predisposition to cancer and objective estimates and the *BRCA1/2* result into a third block.

Interaction graphs represent the relationship, for the different *BRCA1/2* results, between the degree of discrepancy between the perceived probability of genetic predisposition to cancer and objective estimates assessed at T1 and the variables at T2 representing anxiety, depression, intrusion or avoidance and perceived personal control over cancer risk, in the multiple regression models, setting continuous covariates (e.g., age, number of affected relatives) at the mean and dichotomous covariates at the mode (e.g., having a partner).

Statistical analyses were performed with SPSS software version 18.0 (IBM, Somers, NY, USA) and interaction graphs were drawn and their estimates computed using *R* 2.15.0.

RESULTS

Sample characteristics. Two hundred and seventy-three women were recruited. Of these, 30 (11%) at T1 and, of the 243 respondents at T1, 63 (23%) at T2 did not provide evaluable data for the following motives: unwilling to participate in the study (13 women), not returning or completing questionnaires within the protocol time frame (74), declining to attend the second cancer genetic counselling visit (3) or deceased (3). Respondents and non-respondents at T1 differed significantly only in terms of medical status ($P=0.006$) (Table 1).

Non-respondents at T2 did not differ in terms of treatment status, type of *BRCA1/2* test result or psychological assessment at T1, except for a tendency to a higher mean HADS-Depression score ($P=0.07$).

Mean age (s.d.) of the respondent sample was 47.3 (11.4); 65% exhibited an education level above high school and 52% were undergoing treatment. The mean (s.d.) clinical objective estimate of the probability of a genetic predisposition to cancer on the 0–100% scale was: 42.5 (29.2) with women spread over each probability category from low ($\leqslant 20$) (32%) to moderate (>20–$\leqslant 40$) (20%), high (>40–$\leqslant 80$) (31%) and very high (>80) (16%) (Table 1).

Among respondents at T2 (66% response rate), 133 (74%), 20 (11%) and 27 (15%) received a negative, deleterious mutation or UV result at a mean (s.d.) time of 11 (3) months after their initial cancer genetic counselling visit (Table 2).

BRCA1/2 test results and objective probability of genetic predisposition to cancer were strongly correlated ($P=0.001$). Mean objective probabilities (s.ds.) were 40.7 (28.6), 70.2 (24.4) and 38.5 (28.1) ($F(2,214)=10.26$, $P<0.001$) for negative, positive and UV results, respectively

Psychological assessment. As shown in Table 3, mean scores for anxiety (7.8 and 8.2), depression (3.6 and 3.7), intrusions (7.2 and 9.1) and avoidance (9.9 and 10.9) at T1 and at T2, respectively, were low to moderate and only significantly different for intrusions ($P=0.002$); the mean score was moderate for perceived personal control (11.9 and 11.8); 24, 3, 8 and 14% of women at T1 and 31, 2, 11 and 18% of women at T2 presented a level of anxiety, depression, intrusion or avoidance requiring psychology professional attention, respectively.

For respondents at both T1 and T2 ($n=180$), mean (s.d.) of absolute perceived probability of genetic predisposition to cancer assessed at T1 was 48.3 (25.6); 23.6% and 23.7% of women presented a higher or lower perceived probability of genetic predisposition to cancer than objective estimate by $\geqslant 25\%$ on the 0–100% scale, respectively (Table 3).

As shown in Table 4, for the perceived probability of genetic predisposition to cancer assessed at T1 on the 0–100% one-item absolute scale, means were significantly different across the clinician-computed estimate categories (respectively: $F(3,192)=8.0$, $P<0.001$, $\eta^2=0.11$). The concordance correlation coefficient (Lin, 1989) between objective estimate of predisposition probability and the two-item standardised scale predisposition probability perception was .31 ($P<0.001$).

Hierarchical regression analyses. In hierarchical regression analysis (Table 5), the percentage of explained variance (adjusted R^2) for anxiety, depression, intrusions, avoidance and perceived personal control at T2 ranged from 23–30% (all $P<0.001$). Among covariates, anxiety was also predicted by being on treatment rather than in remission ($\beta=0.17$, $P<0.05$) and higher ovarian cancer risk perception ($\beta=0.16$, $P<0.05$); avoidance was predicted by an increased time interval since the initial cancer genetic counselling visit ($\beta=0.21$, $P<0.01$); and perceived personal control was predicted by lower ovarian cancer risk perception ($\beta=-0.17$, $P<0.05$).

Adding the *BRCA1/2* result to the model did not significantly improve the predictions. However, addition in a third block of the combined effect of the degree of discrepancy between the perceived probability of genetic predisposition to cancer and

Table 1. Descriptive characteristics at initial consultation (T1)

	Respondents (*N* = 243)	Non-respondents (*N* = 30)
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	
Family status (*N*/%)		
Living with a partner (*N*/%)	193 (79)	12 (71)
Missing data	—	13
Having children (*N*/%)	184 (76)	25 (86)
Missing data	—	1
Having daughters (*N*/%)	148 (61)	19 (65)
Medical status (*N*/%)[a]		
Under treatment	127 (52)	14 (87)
In remission	116 (48)	2 (13)
Missing data	—	14
Number of first-degree relatives with cancer		
Mean (s.d.)	1.2 (1.0)	1.4 (1.2)
Number of sceond-degree relatives with cancer		
Mean (s.d.)	1.8 (1.4)	1.6 (1.3)
Objective estimate of cancer genetic predisposition risk (*N*/%)[b]		
(Mean/s.d.)	42.5 (29.2)	49.0 (31.8)
⩽ 20%	73 (32)	10 (36)
> 20% to ⩽40%	45 (20)	2 (7)
> 40% to ⩽80%	71 (31)	10 (36)
> 80%	37 (16)	6 (21)
Missing data	17	2

[a]Significant difference between respondents and non-respondents at $P<0.01$.
[b]According to Claus model.

Table 2. Descriptive characteristics after *BRCA1/2* test result notification consultation (T2)

	Respondents (*N* = 180)	Non-respondents (*N* = 63)
***BRCA* test result (*N*/%)**		
Negative uninformative (NU)	133 (74)	42 (84)
Positive *BRCA1/2*	20 (11)	1 (2)
Unclassified variant (UV)	27 (15)	7 (14)
Length of time between initial and *BRCA1/2* test result notification consultation (days)		
Mean (s.d.)	321.3 (85.9)	328.2 (108.6)

Table 3. Psychological assessment at initial (T1) and after *BRCA1/2* test result notification (T2)

	T1 (*N* = 243)	*T2* (*N* = 180)	*T* test (*P*)
Perceived probability of genetic predisposition to cancer			
Two-item standardised scale score (−2.8 to 1.61]		—	—
Mean (s.d.)	−0.02 (0.08)		
Missing data	7		
Perceived probability of genetic predisposition to cancer			
Absolute figure (0–100%) (*N* = 180)[a]		—	—
Mean (s.d.)	48.3 (25.6)		
N/% higher perceived probability/objective estimates[b]	34 (23.6)		
N/% lower perceived probability/objective estimates[b]	34 (23.7)		
Missing data	36		
HADS-Anxiety score (0–21)			
Mean (s.d.)	7.8 (4.3)	8.2 (4.5)	−1.81 (0.07)
Percentage of clinical case (score >10)[c]	24	31	
Missing data	—	1	
HADS-Depression score (0–21)			
Mean (s.d.)	3.6 (3.2)	3.7 (3.1)	−1.27 (0.20)
Percentage of clinical case (score >10)[c]	3	2	
Missing data	—	1	
IES (risk of cancer)-Intrusion score (0–35)			
Mean (s.d.)	7.2 (7.7)	9.1 (8.5)	−3.15 (0.002)
Percentage of clinical case (score >20)[d]	8	11	
Missing data	2	2	
IES (risk of cancer)-Avoidance score (0–40)			
Mean (s.d.)	9.9 (9.3)	10.9 (9.6)	−0.93 (0.35)
Percentage of clinical case (score >21)[d]	14	18	
Missing data	2	2	
PPC scale total score (0–18)			
Mean (s.d.)	11.9 (3.8)	11.8 (4.0)	0.99 (0.32)
Missing data	—	1	

[a]Computed only for respondents at both T1 and T2.
[b]Figures provided by women falls outside a range of ±25%.
[c]Distress threshold from Hopwood *et al* (1991).
[d]Distress threshold from Horowitz *et al* (1979).

objective estimate, and test result was significant for HADS-Anxiety ($F(144, 2)$ change = 8.18, $P<0.001$), HADS-Depression ($F(144, 2)$ change = 3.64, $P<0.05$) and IES-Intrusion ($F(144, 2)$ change = 3.2, $P<0.05$).

A higher perceived probability of genetic predisposition to cancer compared with objective estimate predicted higher levels of anxiety in women with a positive *BRCA1/2* compared with women receiving a NU or UV result, and a lower perceived probability of genetic predisposition to cancer compared with objective estimate predicted lower levels of anxiety ($\beta = -0.28$, $P<0.01$) (Table 5; Figure 1). On the contrary, compared with women receiving a NU or positive *BRCA1/2* test result, a higher perceived probability of genetic predisposition to cancer compared with objective estimate in women with an UV result predicted lower levels of anxiety ($\beta = 0.20$, $P<0.01$) (Table 5; Figure 1), depression ($\beta = 0.19$, $P<0.05$) and thought intrusion ($\beta = 0.18$, $P<0.05$), whereas a lower perceived probability of genetic predisposition to cancer compared with objective estimates predicted higher levels of these latter outcomes. The degree of discrepancy between perceived probability of genetic predisposition to cancer and objective estimates by *BRCA1/2* test results had no effect on IES-Avoidance and PPC (see Supplementary Figures 1–4 and Table 5).

Table 4. Mean (s.d.) absolute perceived probability of genetic predisposition to cancer by Claus model-based objective estimates categories computed at T1

Objective estimates of cancer genetic predisposition categories	Perceived probability of genetic predisposition to cancer absolute scale (0-100%)[a]
⩽20%	37.9 (27.6)
>20% to ⩽40%	48.4 (23.2)
>40% to ⩽80%	50.0 (24.4)
>80%	63.2 (22.0)

Means are significantly different: $F(3,192) = 8.0$, $P<.001$, $\eta^2 = 0.11$.
[a]Due to missing data on the one-item absolute figure scale, $N = 196$.

DISCUSSION

This prospective study addressed the effect of *BRCA1/2* testing on anxiety, depression and cancer-specific distress and perceived personal control in BC patients, considering the type of *BRCA1/2* result received and the degree of discrepancy between their perceived probability of genetic predisposition to cancer and objective estimates before test disclosure. After controlling for covariates, the effect of receiving a positive *BRCA1/2* or a UV result compared with a NU result did not predict higher levels of general or specific distress and did not affect perceived personal control over cancer risk. Increased distress has been evidenced in carriers after *BRCA1/2* testing (van Dijk *et al*, 2004; 2006; Dorval *et al*, 2005; Beran *et al*, 2008; Smith *et al*, 2008; Hamilton *et al*, 2009), whereas decrease in distress was observed in women receiving an uninformative result (Hamilton *et al*, 2009), with comparable emotional reactions to receipt of a NU and UV result (van Dijk *et al*, 2004; Smith *et al*, 2008) but higher distress in UV (O'Neill *et al*, 2009). However, the lack of association between the type of *BRCA1/2* test result and distress is in line with Bennett *et al* (2008) and Vos *et al* (2010), who also found no relation between assigned risk status and emotional distress underlining the major role of the woman's interpretations of the genetic test result meaning.

An effect of the *BRCA1/2* test result became apparent when taking into account the perception of the probability of genetic predisposition to cancer relative to objective estimates before test disclosure. In women with a positive *BRCA1/2* result compared with those with a NU or UV result, a higher perceived probability of genetic predisposition to cancer compared with objective estimates before testing predicted higher levels of anxiety after notification of a *BRCA1/2* test result. These women, who presented higher appraisals of their probability of genetic predisposition to cancer, were probably already anxious and, as they were

Table 5. Predictors of anxiety, depression, intrusion, avoidance or perceived personal control at *BRCA1/2* test result notification consultation (final model β)

	HADS-Anxiety	HADS-Depression	IES-Intrusion	IES-Avoidance	Perceived Personal Control
Score at T1	0.46***	0.50***	0.41***	0.43***	0.45***
Age	−0.00	−0.11	−0.05	−0.08	0.09
Education	0.06	0.07	−0.10	−0.05	−0.04
Having a partner	0.03	−0.02	0.03	0.01	−0.06
Having daughters	0.11	0.07	0.00	−0.10	−0.04
Under treatment (*vs* in remission)	0.17*	0.02	0.13	0.13	0.04
Relatives diagnosed of breast or ovarian cancer <50 years old	−0.00	0.03	−0.05	−0.08	0.05
Lapse of time between initial and second genetic consultation	0.09	−0.02	0.13	0.21**	0.03
BC risk perception at T2	0.04	0.07	−0.11	−0.11	−0.04
OC risk perception at T2	0.16*	0.12	0.16	0.16	−0.17*
Perceived probability of genetic predisposition	−0.01	−0.03	0.04	0.00	−0.08
Objective estimates *vs* perceived probability of genetic predisposition difference	−0.05	−0.12	0.01	0.14	0.13
Block 1 (control variables): F(df); R^2; Adjusted R^2	**5.06 (148,12)***; 0.29; 0.23**	**5.22 (148,12)***; 0.30; 0.24**	**4.18 (148,12)***; 0.25; 0.19**	**5.26 (148,12)***; 0.30; 0.24**	**5.60 (148,12)***; 0.31; 0.26**
Positive *BRCA* (*vs* NU)	0.31**	0.14	0.21*	0.02	0.05
UV (*vs* NU)	0.03	−0.00	0.14*	0.05	0.03
Block 2 (+ BRCA1/2 test result): F change(df); R^2change; Adjusted R^2	**1.26 (146,2); 0.01; 0.24**	**0.32 (146,2); 0.003; 0.23**	**2.68 (146,2); 0.03; 0.21**	**0.33 (146,2); 0.003; 0.24**	**1.30 (146,2); 0.01; 0.26**
Objective *vs* perceived probability of genetic predisposition difference × positive *BRCA*	−0.28**	−0.09	−0.10	−0.04	0.12
Objective *vs* perceived probability of genetic predisposition difference × UV	0.20**	0.19*	0.18*	−0.05	0.02
Block 3 (+ interactions): F change(df); R^2change; Adjusted R^2	**8.18 (144,2)***; 0.07; 0.30**	**3.64 (144,2)*; 0.03; 0.26**	**3.2 (144,2)*; 0.03; 0.23**	**0.21 (144,2); 0.002; 0.23**	**0.68 (144,2); 0.01; 0.26**

Abbreviations: BC = breast cancer; HADS = Hospital Anxiety and Depression Scale; IES = Impact of Event Scale; OC = ovarian cancer; UV = unclassified variant. *$P<0.05$; **$P<0.01$; ***$P<0.001$.

anticipating a positive *BRCA1/2*, their worries were confirmed when they were notified about this result. On the contrary, women who received a positive *BRCA1/2* test result but who presented a lower perceived probability of genetic predisposition to cancer compared with objective estimates displayed lower levels of anxiety than those receiving a UV or NU test result, suggesting possible minimisation or denial of thoughts related to cancer genetic risks in these women.

In women receiving an UV test result, a higher perceived probability of genetic predisposition to cancer compared with objective estimates predicted lower levels of anxiety after notification of *BRCA1/2* test results compared with women receiving a positive *BRCA1/2* or NU test result. This result may reflect the relief of these women when they were informed that their cancer risk was lower than if they carried a *BRCA1/2* mutation. However, in women receiving a UV test result compared with those informed of a positive *BRCA1/2* or NU test result, a lower perceived probability of genetic predisposition to cancer compared with objective estimates before test result notification predicted higher levels of anxiety, depression and intrusion. In these women who approached cancer genetic testing with confidence, the uncertainty raised by this ambiguous result may have elicited increased distress. As suggested by Vos *et al* (2010), a UV, although indicating the presence of a gene modification of unknown clinical significance, may have been interpreted as harmful. The effect of receiving a UV result rather than a positive *BRCA1/2* result on depression may be related to the lack of clearly defined risk management recommendations leaving women uncertain about the actions to be taken to cope with increased cancer-related anxiety.

During the initial cancer genetic consultation, most women were informed of their cancer genetic predisposition probability using the verbal categories 'low', 'moderate', 'high' or 'very high'. So, we expected a difference between objective risk estimates and patients' perception of their probability of genetic predisposition to cancer in addition to the deviance between objective information and perception resulting from psychological processes (Pilarski, 2009). About one half of this sample of women either presented a higher (24%) or a lower (24%) perceived probability of genetic predisposition to cancer compared with the clinician's objective probability estimates, which is in line with a recent review of genetic risk perception accuracy (Smerecnik *et al*, 2009). Our results highlight the role of woman's inappropriate expectations combined with the *BRCA1/2* test result on emotional reactions. Women were not informed of the possibility of receiving a UV result, so they only expected to receive either a positive or

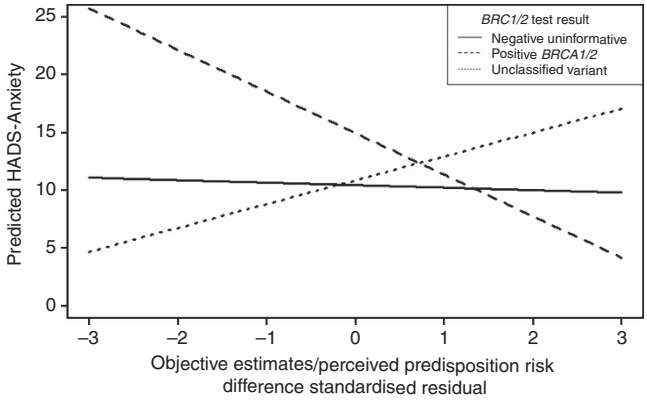

Figure 1. HADS-Anxiety level at T2 according to discrepancy between perceived probability of genetic predisposition to cancer and objective probability estimates for positive *BRCA1/2*, NU and UV test result. *Note:* a negative or positive value in abscise reflect an over or under estimation of predisposition risk.

a negative result but not a positive-UV, which may have been more puzzling than receiving a clear positive or negative (even uninformative) result.

At the *BRCA1/2* test result disclosure, both women who received a NU or a UV result were similarly warned that possible development in genetics could explain women's family history of cancer in the future and so it seems that evocation of a 'mutation' convey a worrisome connotation.

A level of anxiety and avoidance requiring psychological care was observed in, respectively, 24% and 14% of the women after the initial cancer genetic counselling visit and in 31% and 18% after notification of *BRCA1/2* test results, indicating psychological strain during this genetic testing process in a significant number of these women either on BC treatment or survivors. These figures are in line with those published in the literature showing that about one quarter of subjects undergoing genetic risk assessment will experience emotional distress at some time (Bennett *et al*, 2008; Power *et al*, 2011). As we assessed distress after the initial cancer genetic counselling visit and after communication of the *BRCA1/2* test results, we only report the short-term emotional response during the genetic testing process. However, it is important to consider that some of these women may want to decide on their cancer risk management at that time and may therefore potentially make their decisions in a troubled emotional state.

BRCA1/2 testing is increasingly proposed to BC patients at the time of BC diagnosis (Meiser *et al*, 2008) or treatment (Schlich-Bakker *et al*, 2008). However, these circumstances may encompass additional stress. In addition, BC patients invited to undergo *BRCA1/2* testing may be less well prepared for the test results than women who decide by themselves to attend cancer genetic counselling clinics for *BRCA1/2* genetic testing. Although no effect of a BC diagnosis (Schlich-Bakker *et al*, 2006; Smith *et al*, 2008) or lower distress in women unaffected with BC, especially those receiving an uninformative test result (Hamilton *et al*, 2009) has been evidenced, in this study, women on BC treatment presented higher anxiety than survivors, which is in line with studies showing a risk of psychological distress in the case of a more recent BC diagnosis (Bonadona *et al*, 2002; Van Roosmalen *et al*, 2004).

BRCA1/2 test results, either alone or combined with perceived probability of genetic predisposition to cancer, had no effect on perceived personal control over cancer risk. This may be related to the limited efficacy of breast and especially ovarian cancer surveillance and the difficult decision-making regarding prophylactic interventions. Information on cancer risk management alternatives may help to increase the degree of control (Bennett *et al*, 2008). By contrast, as expected in view of the clinical features of ovarian cancer, a higher perception of ovarian cancer risk also lowered perceived personal control.

The generalisability of these results is limited for the following reasons. First, they reflect reactions of women with BC attending French cancer genetic services whereas genetic testing delivery and counselling may vary cross-culturally. Second, inclusion criteria planned for a homogeneous clinical sample in order to limit medical factors could explain variation in distress, but in consequence this study results cannot represent the psychological reactions of other populations such as healthy women or those with ovarian cancer or more advanced cancer. Third, among eligible patients, comparisons between respondents and non-respondents at T1 demonstrated significant differences on medical status (i.e., women currently on BC treatment were less likely to answer the questionnaires) and the effect of *BRCA1/2* result could only be assessed on the 66% of the eligible patients who provided questionnaire responses at T2. Finally, this study should be replicated given its small sample size relative to the number of predictors assessed and the number of women provided with a positive *BRCA1/2* or a UV test result.

CONCLUSIONS

The results of this study indicate that women affected with BC undergoing *BRCA1/2* gene testing who presented a higher perceived probability of genetic predisposition to cancer than objective estimates and who received a positive *BRCA1/2* test result presented higher levels of anxiety than those receiving a NU or UV result, probably because their worries were confirmed. In addition, women who presented a lower perceived probability of genetic predisposition to cancer than objective estimates and who received a positive *BRCA1/2* test result evidenced lower levels of anxiety than those receiving a NU or UV result, which could suspect denial and possibly risk of surveillance neglect requiring closer attention by clinicians.

These findings also highlight that, in women receiving an UV test result, a higher perceived probability of genetic predisposition to cancer compared with objective estimates predicted lower levels of anxiety, suggesting relief in these women. However, those who presented a lower perceived probability of genetic predisposition to cancer than objective estimates and who received a UV test result were more anxious than those receiving a NU or positive *BRCA1/2* test result, suggesting that they misinterpret this gene modification as being harmful, especially as they did not expect such result.

During the initial cancer genetic counselling, patients should be informed of the different possible *BRCA1/2* test results. Particular attention should be paid to exploring the women's perception of their probability of genetic predisposition to cancer by facilitative communication skills so as to correct misperception and facilitate emotional adjustment at *BRCA1/2* test result disclosure.

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