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Prognostic factors for hereditary cancer distress six months after BRCA1/2 or HNPCC genetic susceptibility testing

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ABSTRACT

This study explored predictors for hereditary cancer distress six months after genetic susceptibility testing for a known familial BRCA1/2 or HNPCC related mutation, in order to gain insight into aspects relevant for the identification of individuals needing additional psychosocial support. Coping, illness representations, experiences with cancer in relatives and family system characteristics were assessed in 271 applicants for genetic testing before result disclosure. Hereditary cancer distress was assessed prospectively up to six months after disclosure. Regression analysis revealed that the pretest level of distress, complicated grief, the number of affected first-degree relatives and strong emotional illness representations were factors that best explained hereditary cancer distress. Other significant predictors were illness coherence, passive coping, distraction seeking, being aged <13 years when a parent was affected by cancer and family communication. Individuals who may benefit from additional support may be identified before result disclosure using a short instrument assessing the relevant aspects.

1. Introduction

Genetic testing for a cancer predisposition has become a usual component of clinical practice over the last years and will become more common as knowledge on the early detection and prevention of malignancies is increasing. Hereditary nonpolyposis colorectal cancer (HNPCC) and hereditary breast and ovarian cancer due to a BRCA1/2 mutation are the most prevalent hereditary cancer syndromes. Both imply a high risk of developing cancer from 25 years onwards that may induce fear of intense physical suffering, of death and of leaving children and loved ones behind far before the time that would be appropriate in the family life cycle.[1] In spite of elevated cancer risks for themselves and their children, difficult choices concerning risk management and a potential psychological vulnerability due to early experiences with can-

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cer in relatives, most mutation carriers have shown to cope well with the knowledge of their genetic status.[2] Nevertheless, a considerable proportion of 10–20% of individuals undergoing genetic testing for a BRCA1/2 or HNPCC associated mutation reports clinically elevated distress levels.[3–5]

In current practice genetic counselors refer a small proportion of their counselees to a specialised mental health professional for additional support. Insight into the mechanisms involved in the development of hereditary cancer distress could be useful for the identification of individuals who may benefit from additional support and for the development of counselling interventions. To date, many predictive factors have been documented, but no studies have evaluated a broad range of vulnerability factors and their mutual relevance simultaneously. Moreover, most studies have focused on distress shortly before or after result disclosure. Temporary feelings of distress, worry and despair shortly before and after receiving the genetic test result may reflect working through a stressful life event, indicative of adaptive coping. Individuals who continue to be distressed after the first turmoil of genetic susceptibility testing is over should be more a concern to health care professionals.[6] Finally, many predictors reported in the literature like age, cancer status or having children are too general to be used as indications for referral to mental health professionals and provide minimal insight into the underpinnings of psychological maladjustment that is necessary to develop counselling interventions.

Leventhal's model of self-regulation of health and illness[7] has been put forward as a useful framework to understand the emotional and cognitive reaction to genetic cancer susceptibility testing.[8] This model posits that individuals create their own understanding of an illness or health threat (*i.e.* illness representations), which determines coping responses, health behaviour and finally psychological well-being. Illness representations, coping behaviours and emotional adjustment may be influenced by earlier experiences with cancer in the family and by the familial and the social environment.[7,9]

This paper reports findings from a prospective multi-centre research project that studied psychological adjustment to genetic susceptibility testing for an identified pathogenic gene mutation in BRCA1/2 or one of the HNPCC related genes. The objective of the present study was to explore the contribution of illness representations, coping and two potential underlying factors of the Leventhal's model,[7,9] i.e. experiences with cancer in the family and family functioning, to hereditary cancer distress six months after result disclosure.

2. Patients and methods

2.1. Patients

Applicants for genetic susceptibility testing of a known familial pathogenic gene mutation in either BRCA1/2 or a HNPCC related gene (MSH2, MLH1 or MSH6) aged 18 and over were asked to participate in a psychological study. Applicants were eligible for the study if they had a relative with an identified gene mutation, irrespective of cancer status and of the decision to proceed with genetic testing. We excluded individuals with insufficient proficiency in Dutch and males from BRCA1/2 mutation families because they are not at significantly increased risk of developing cancer. Accrual took place from January 2003 to October 2004 at the University Medical Centers of Rotterdam, Leiden and Groningen.

2.2. Procedure and design

Applicants for genetic testing received at least two counselling sessions. Blood sampling generally took place at the end of the first counselling session if the applicant proceeded with genetic testing. The test result was disclosed during a counselling session 6–10 weeks after blood sampling. The three participating centres adhered to the national guidelines on genetic counselling and therefore the same cancer risks were communicated.

The first questionnaire, containing all predictive measures, was mailed one week after the first counselling session. Participants received a second and a third questionnaire, containing the outcome measure, two weeks and six months after result disclosure. The study procedure was approved by the medical ethics committees of the participating institutions.

2.3. Measures

2.3.1. Predictive measures

Demographic and medical history information: Data were obtained on age, gender, marital status, having children, year of birth of children, educational level, employment status and religion. Medical information was gathered on cancer status, pretest genetic risk, genetic test result, having consulted a social worker, psychologist or psychiatrist and having used psychopharmacological medication in the past.

Experiences with cancer in the family: Information was gathered on which relatives developed cancer and died of cancer. Participants having a parent affected by cancer were categorised according to three developmental phases at the time of the parental cancer diagnosis: children (participant was younger than 13 years), adolescents (between 13 and 20 years) and adults (older than 20 years). Perceived closeness to affected relatives was assessed by a Likert type 5-point scale item. Participants also noted the time since learning when a gene mutation was identified in the family and whose relatives were found to be a mutation carrier.

Grief symptoms were assessed using the inventory of complicated grief[10] that was designed to identify problematic grief reactions and has been validated in the Dutch population.[11]

Illness representations were assessed by the IPQ-R.[12] The items were anchored on hereditary cancer. Subscales with satisfactory reliability were used in the analyses (Table 1).

Cancer risk perception: Recalled risk was assessed by an estimate of the chance for a mutation carrier to develop breast or colon cancer. Individuals rating the risk to develop breast or colon cancer for mutation carriers as higher than 85% were defined as over-estimators. Affective risk was assessed by: 'Independent of my actual risk, I feel my risk of developing cancer is 'not likely' to 'very likely".[13]

Coping was assessed by the Utrecht Coping List-29[14] that was anchored to coping with hereditary cancer. Subscales with satisfactory reliability were used in the analyses (Table 1).

Table 1 – Overview of subscales of the Illness Perception Questionnaire Revised (IPQ-R) and the Utrecht Coping List 29 (UCL-29)

Scale	Examples of items	α[a]
Cognitive representations (IPQ-R)		
Consequences	It is a serious condition, it has major consequences on my life	0.72
Personal control	There is a lot which I can do to control it, I have the power to influence it	0.73
Treatment control	Treatment will be effective in curing it, there is little to be done to improve it (r)	0.72
Illness coherence	The symptoms are puzzling to me (r), it does not make any sense to me (r)	0.70
Emotional representations	When I think about it I get upset, I get depressed when I think about it	0.85
Coping (UCL-29)		
Social support seeking	Sharing worries, showing feelings, looking for understanding	0.84
Distraction seeking	Seeking distraction, meeting happy company, thinking about other things	0.77
Active coping	Observe the problem, think of different options, make directed action plans	0.79
Passive coping	Pessimistic view, feeling overwhelmed, feeling incapable of dealing with it	0.70
Moderate demands	Changing own demands, needs, priorities	0.75

(r) reverse scored.
a Cronbach's alpha.

Familial communication style concerning hereditary cancer was measured at the first assessment by the Openness to Discuss Hereditary Cancer in the Family Scale.[15] The scale provides an assessment of communication in the nuclear family and in the family of origin.

Perceived social support from partner, parents and siblings was assessed by the following two items: 'I feel supported by my partner/parents/siblings in this phase of the genetic testing process' and 'With my partner/parents/siblings I can share all my worries concerning hereditary cancer', to be answered on a 5-point scale.

Nuclear family functioning was measured with the Dutch validated version of the Family Adaptability and Cohesion Evaluation Scales.[16]

Differentiation: The extent to which individuals felt differentiated to their parents was assessed with the Differentiation in the Family System Scale.[17] Differentiation was defined as both a sense of emotional connectedness (support and involvement) and a sense of separateness (autonomy, uniqueness, and freedom of personal expression).

2.3.2. Outcome measure

Hereditary cancer related distress was assessed with the Impact of Event Scale Revised.[18] The scale has been used extensively in studies on adjustment to genetic susceptibility testing and has satisfactory psychometric properties.[19] Participants scoring equal to or higher than the cutoff (26) on the intrusion and avoidance subscales were considered to have a clinically significant level of distress that likely reflects a need for psychological or psychiatric support.[20]

2.4. Statistical methods

Demographic and clinical characteristics of the study sample were analysed using exact tests for categorical variables and *T*-tests for continuous variables. The numbers of patients having a clinically significant level of distress at each measurement were determined (IES $\geqslant$ 26).

The method of linear regression was used to identify potential prognostic variables that could predict hereditary cancer distress six months after result disclosure. The prognostic variables were selected in three steps. First, all potential prognostic variables were entered individually, adjusted for age, gender, test result and cancer syndrome. Second, all variables having *P*-values less than or equal to 0.10 in the individual analysis were entered into a multiple, category-specific analysis (for example, all illness representations together), adjusted for age, gender, test result and cancer syndrome. Third, factors with *P*-values less than or equal to 0.10 in the category-specific analyses were entered into a multiple analysis, followed by the backward elimination procedure ($P_{in} < 0.050$ and $P_{out} > 0.051$).

At each step, it was investigated whether the independent variables were highly inter-correlated by Variance Inflation Factors (VIFs). Models having a VIF $\geqslant 4$ were modified in the sense that the variable(s) causing multicollinearity were eliminated. In order to evaluate the predictive capacity of the final model, the percentage of the explained variance (adjusted R^2) was presented. To evaluate the capacity of the final model in predicting a clinically elevated level of hereditary cancer distress six months after result disclosure, the area under the receiver operating characteristic (ROC) curve was calculated. The area under the curve (AUC) is a measure for the probability of correctly identifying individuals having clinically elevated distress levels. An AUC of 1.0 means that the model is able to identify all distressed individuals perfectly.

Several variables had 'obligatory' missing values that were given a value of zero if that could be defended. For example, not all participants had lost a family member due to cancer and had filled in the Inventory of Complicated Grief. Individuals without a deceased relative were then attributed a value of zero. Otherwise, dummy variables were created.

3. Results

3.1. Study population

In the study 271 patients participated. Non-participants (23%, $n = 81$) and participants who were lost to follow-up (3%, $n = 7$) did not differ from participants with regard to age, gender,

offspring, cancer syndrome, pre-test genetic risk and cancer status. Non-participants however more often refrained from genetic testing than participants ($\chi^2 = 9.4$; $P < .01$). Participants belonged to 96 different BRCA1/2 and 45 different HNPCC mutation families (1.92 individuals per family, range 1–12) (Table 2).

3.2. Scale reliability

All scales and subscales that were used in the study were found to have a reliability (Cronbach's alpha) of >.70 (for more details see[21]).

3.3. Prevalence of clinically elevated distress

Before receiving the test result, 22.1% of the participants had a clinically elevated level of hereditary cancer related distress. Two weeks after test result disclosure, 29.3% reported elevated distress levels, and 14.1% six months after disclosure. Individuals from BRCA1/2 and HNPCC families did not differ significantly with regard to the prevalence of clinically elevated distress.

3.4. Individual prognostic factors for hereditary cancer distress six months after result disclosure

Table 3 displays the individual and category-specific models for hereditary cancer distress six months after test result disclosure. Factors with P-values less than or equal to 0.05 will be discussed. Participants reporting more hereditary cancer distress six months after result disclosure more frequently had a history of consulting a professional for psychological support and of using psychopharmacological medication. They were more distressed and worried at the first measurement. Their representations of hereditary cancer were more emotional and less coherent. Furthermore, they perceived hereditary cancer to have more serious consequences and they perceived less treatment control. They overestimated the risk of developing cancer more frequently. They reported more frequently to have a passive coping style, to distract themselves with other activities and to moderate their demands, expectations and priorities in order to cope with hereditary cancer. They reported more complicated grief, more affected first-degree relatives and more frequently having been younger when their parent was affected by cancer. They perceived

Table 2 – General and demographic characteristics of the study population, and mean level of hereditary cancer distress before and six months after test result disclosure

	BRCA1/2 (N = 175)		HNPCC (N = 96)		P
	%	n	%	n	
Age					
Mean (SD)	42.5 (12.1)		41.0 (13.3)		0.40
Gender					
Women	100.0	175	66.7	64	
Men	0.0	0	33.3	32	
Marital status					
Married or cohabiting	77.1	135	81.3	78	0.55
Single, divorced, widowed	22.9	40	18.7	18	
Having children					
Yes	69.1	121	67.7	65	0.89
No	30.9	54	32.3	31	
Education					
<High school	26.3	46	18.8	18	0.28
Some college	48.0	84	55.2	53	
>College	25.7	45	26.0	25	
Cancer status					
Unaffected	90.9	159	94.8	91	0.34
Affected	9.1	16	5.2	5	
Pretest genetic risk					
⩾50%	70.3	123	76.0	73	0.34
25%	23.4	41	19.8	19	
<25%	6.3	11	4.2	4	
DNA-test					
Yes	92.0	161	95.8	92	0.31
No	8.0	14	4.2	4	
Carrier status					
Mutation carrier	37.9	61	29.3	27	0.17
Non-carrier	62.1	100	70.7	65	
Hereditary cancer distress predisclosure					
Mean (SD)	24.3 (18.1)		16.8 (16.7)		<0.05[a]
Hereditary cancer distress 6 months postdisclosure					
Mean (SD)	11.5 (12.6)		8.9 (12.1)		0.37[a]

a P-value adjusted for sex, age, having children, cancer status and pretest genetic risk.

Table 3 – Selection of prognostic factors for hereditary cancer distress six months after genetic test result disclosure, adjusted for age, gender, test result and cancer syndrome

	Univariate analyses			Category specific analyses		
	β	P-value	R^{2a}	β	P-value	R^2
Medical variables						
Psychosocial professional in past	0.16	0.01	0.02	0.14	0.03	0.09
Psychopharmacological medication in past	0.18	0.00	0.03	0.12	0.07	
Distress predisclosure						
Hereditary cancer distress	0.56	0.00	0.31	0.56	0.00	0.36
Cancer worry	0.39	0.00	0.13	–0.01	0.99	
Illness representations						
Emotional representations	0.43	0.00	0.19	0.37	0.00	0.21
Illness coherence	0.28	0.00	0.08	0.17	0.01	
Consequences	0.16	0.01	0.03	0.01	0.92	
Treatment control	–0.15	0.02	0.03	–0.04	0.50	
Personal control	–0.13	0.05	0.02	–0.04	0.59	
Risk perception						
Overestimation of risk	0.15	0.02	0.02	0.14	0.02	0.09
Affective risk	0.11	0.08	0.01	0.11	0.09	
Coping						
Passive coping	0.36	0.00	0.14	0.28	0.00	0.21
Distraction seeking	0.30	0.00	0.10	0.15	0.02	
Moderate demands	0.22	0.00	0.05	0.07	0.28	
Experiences with family illness						
Complicated grief	0.34	0.00	0.13	0.39	0.00	0.26
Aged <13 years when parent affected	0.13	0.03	0.02	0.14	0.02	
Number of first-degree relatives affected	0.15	0.03	0.03	0.06	0.46	
Mean closeness to affected relatives	0.17	0.08	0.03	0.05	0.51	
Family system characteristics						
Open communication partner, children	–0.37	0.00	0.14	–0.26	0.01	0.18
Open communication parents, siblings	–0.24	0.00	0.07	–0.12	0.20	
Differentiation to mother	–0.18	0.02	0.03	–0.10	0.24	
Support partner	–0.14	0.02	0.02	–0.06	0.46	

a Not adjusted for age, gender, test result and cancer syndrome β, standardised regression coefficient; R^2, R^2 adjusted for shrinkage.

the communication within the family with regard to hereditary cancer as less open, the relationship with their mother as less differentiated and they reported to receive less support from their partner.

Potential predictive variables that were *not* significantly associated with hereditary cancer distress were gender, marital status, having inhabiting children, religious background, practicing a religion, cancer status, pretest genetic risk, genetic testing decision, centre of accrual, seeking social support, active coping, having a sibling identified as a mutation carrier, having a mother, father, sister or brother affected by or deceased due to cancer, number of relatives affected by or deceased due to cancer, time since learning about the familial mutation, cohesion, adaptation, differentiation to father and support from parents and siblings.

3.5. *The final prognostic model*

Factors with *P*-values less than or equal to 0.10 in the category-specific analyses were having a history of consulting a psychosocial professional in the past or of psychopharmacological medication, hereditary cancer distress before result disclosure, emotional representations, illness coherence, overestimating the cancer risk, affective risk, passive coping, distraction seeking, complicated grief, being aged <13 years when a parent was affected by cancer and communication style with partner and children. These variables and the control variables (age, gender, test result and cancer syndrome) were entered into a multiple analysis, followed by the backward elimination procedure. The final model contained negative test result, hereditary cancer distress before result disclosure, complicated grief, number of first degree relatives affected by cancer and emotional representations (Table 4).

Table 4 – Final model for hereditary cancer distress six months after genetic test result disclosure

	β	P-value	R^2	AUC
Negative genetic test result	–0.16	0.00	0.41	0.87
Hereditary cancer distress predisclosure	0.40	0.00		
Complicated grief	0.17	0.00		
Number of first-degree relatives affected	0.17	0.00		
Emotional representations	0.17	0.01		

β-standardised regression coefficient; R^2 – R^2 adjusted for shrinkage; AUC, area under the curve predicting *clinically elevated* levels of hereditary cancer distress.

Explained variance of the final model was 41%; the AUC in predicting clinically elevated levels of hereditary cancer distress was 87%.

4. Discussion

This prospective study aimed at identifying psychological characteristics that have prognostic significance for hereditary cancer distress in individuals from families with an identified BRCA1/2 or HNPCC related mutation. Significant predictive factors for hereditary cancer specific distress six months after result disclosure were baseline complicated grief, the number of affected first-degree relatives, having more intense emotional representations and, congruent with other studies,[2] the pretest level of distress. Some of these factors may reflect an underlying personal vulnerability factor like neuroticism or a lack of ego-strength. Neuroticism has been found to relate to greater symptom reporting and may as well predispose to complicated grief. Notwithstanding the potential contribution of this personality factor, our data suggest that also other vulnerability factors exist.

A key finding was that several experiences with cancer in the family were significantly related to hereditary cancer distress, especially the number of first-degree relatives affected by cancer and having a parent affected by cancer at a young age. These findings contribute to the emerging evidence that individuals at increased risk of cancer who have been involved in a relative's cancer process,[22] have lost a parent to cancer,[23,24] were exposed to cancer more frequently[25,26] and at a younger age[27] may become psychologically more vulnerable. Unresolved loss has been reported to be one of the most important reasons to refer women at increased risk of breast cancer to a mental health professional.[3] Of importance is the individual reaction to illness and loss experiences. Individuals who are confronted with these experiences and who are psychologically more vulnerable may report more complicated grief and more hereditary cancer distress than individuals who are psychologically more robust.

Another important finding was that family system characteristics significantly contributed to hereditary cancer distress. Especially an open way of communicating about hereditary cancer with relatives was of importance. Similar findings have been reported in studies on women from BRCA1/2 mutation families 6 months[28] or 5 years after genetic testing.[15] Furthermore, feeling supported by the partner was found to buffer distress, as was found in similar studies.[26,29]

The way individuals perceived hereditary cancer and the way they coped with hereditary cancer was significantly related to hereditary cancer distress too. Having more intense emotional representations of hereditary cancer and feeling that hereditary cancer is hard to grasp (illness coherence) predicted distress in particular. In line with others,[25,30] also a low perceived control over developing cancer and more serious perceived consequences contributed to distress. With regard to coping styles, especially passive coping and distracting oneself were important predictors of distress. So, individuals feeling that nothing can be done to cope with hereditary cancer and individuals avoiding hereditary cancer by distracting oneself were more vulnerable, while more active coping styles did not significantly moderate distress.

Strengths of our study are the prospective study design, low drop out rate, large study sample and broad range of predictive variables. Our study sample was representative for clinical samples presenting at family cancer clinics. Some methodological limitations should be considered as well. Screening for psychological distress by using self-report questionnaires may be inadequate and may result in an overestimation of psychological morbidity.[4] Furthermore, we have used a cutoff score for the Impact of Event Scale in some of the analyses that has not been widely validated. In future studies, using an additional clinical interview in order to improve the validity of the outcome variable is recommended. Finally, the relationships between vicarious illness experiences, family characteristics, illness representations and coping remain to be explored.

In practical terms, several experiences with cancer in relatives, family characteristics, illness representations and coping styles are to be taken into account when psychological adjustment is evaluated. Particularly, we would suggest to assess pretest feelings of distress, complicated grief, the number of affected first-degree relatives and emotional representations in order to identify psychological vulnerable individuals. Early identification and referral to mental health professionals may reduce future psychological suffering. Early identification could be implemented easily in clinical practice by filling out a short instrument assessing the predictive factors before disclosing the genetic test result. Useful psychological interventions for referred patients may aim at reconstructing the past family history, identifying inadequate family coping and communication and helping to express worries and to change inadequate thoughts and perceptions.

Conflict of interest statement

None declared.

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