FAMILY MATTERS

Adjustment to genetic cancer susceptibility testing

Iris van Oostrom

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Aanpassingsproblemen na voorspellend genetisch onderzoek
naar een aanleg voor kanker

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Your children are not your children.
They are the sons and daughters of life's longing for itself.
They come through you but not from you,
and though they are with you, yet they belong not to you.
You may give them your love but not your thoughts.
For they have their own thoughts.
You may house their bodies but not their souls,
for their souls dwell in the house of tomorrow,
which you cannot visit, not even in your dreams.
You may strive to be like them, but seek not to make them like you.
For life goes not backward nor tarries with yesterday.

Khalil Gibran The prophet 1923

CONTENTS

CHAPTER 1

Introduction

Cancer is generally feared because it is associated with death and severe physical suffering. It is one of the most common causes of death in the Netherlands. Breast and colon cancer are the most prevalent types of cancer among women. Frequently occurring types in men are cancer of colon, lung and prostate. About 5% of colorectal and breast cancer arises as a result of a mutation in an inherited cancer susceptibility gene. Knowledge about these cancer susceptibility genes has been accumulating in an impressive manner over the last decades, resulting in the clinical availability of genetic testing from the mid-nineties onward.

Through genetic testing, an individual's risk to develop cancer can be determined more precisely. This can reduce feelings of uncertainty about the risk one has to develop cancer at some point in life. Another advantage is that individuals testing negative for the mutation can be discharged from unnecessary and possibly invasive early detection and/or prevention strategies. Genetic testing has several psychosocial implications, especially for mutation carriers. It implies knowing to be at high risk to develop cancer at an early stage in life, while often having witnessed the devastating impact of cancer on close family members. It implies going to hospitals regularly for screening with the possibility of hearing bad news, or opting for far-reaching preventive options like prophylactic surgery. It implies that you can pass on or may have passed on the susceptibility to your own children, who will have to face the same fate. It means that other close family members are also at increased risk to develop cancer. Finally, it may imply more difficulties in obtaining life insurance, mortgage or insurances for disablement.

This thesis aims at understanding the psychosocial consequences of genetic susceptibility testing for a predisposition to develop breast cancer and colorectal cancer and to identify risk factors for maladjustment. We focus on individuals from families with a known mutation in the *BRCA1* or *BRCA2* genes (breast cancer) or one of the HNPCC-related genes (colorectal cancer). The two conditions are comparable according to Rolland's psychosocial typology[1] with regard to the likelihood of developing cancer, the timing of clinical onset in life cycle, overall clinical severity and availability of prevention and treatment options.

CLINICAL ASPECTS OF HEREDITARY CANCER AND GENETIC CANCER SUSCEPTIBILITY TESTING

BRCA1/2 and HNPCC

Hereditary Breast and Ovarian Cancer, caused by a germline mutation in *BRCA1/2* and Hereditary Non-Polyposis Coli (HNPCC), also named Lynch syndrome, are the two most common hereditary cancer syndromes. *BRCA1* and *BRCA2* are the two responsible genes for Hereditary Breast and Ovarian Cancer. Women with a germline mutation in one of these genes have an increased risk to develop breast cancer from 25 years onwards and ovarian cancer from

35 years onwards (Table 1)[2-4]. Male mutation carriers do not have a significantly increased risk to develop cancer; their lifetime risk for breast cancer is about 1% (*BRCA1*) to 7% (*BRCA2*). HNPCC is caused by a germline mutation in one of the DNA mismatch repair genes *MSH2, MLH1* or *MSH6.* Male and female carriers of a mutation in one of these genes are at increased risk to develop colorectal cancer from 25 years onward[5-7]. Female mutation carriers have an additional increased risk of endometrial cancer from 35 years onwards. The mode of inheritance of both syndromes is autosomal dominant, implying that each mutation carrier has a chance of 50% to pass the mutation on to a child.

Genetic testing for a *BRCA1/2* or HNPCC related mutation is offered from age 18 onwards. The uptake of individuals at 50% risk of carrying a known familial *BRCA1/2* or HNPCC related mutation is 57% in our clinic[8, 9]. Motivations to opt for genetic testing were obtaining certainty about the risk to develop cancer, the necessity of risk management and the risk for offspring[10, 11].

Table 1. Medical consequences of *BRCA1/2* or HNPCC related gene mutations

	Gene	Cumulative life time risk	Risk reducing interventions		Starting at age
BRCA	*BRCA1*	Breast cancer 50-85%	**Breasts**	Breast self- examination (every month)	25
				Clinical breast examination (every 6 months)	25
		Ovarian cancer 40-60%		Mammography, MRI (every year)	25
				Prophylactic bilateral mastectomy	
	BRCA2	Breast cancer 50-85%	**Ovaries**	Vaginal ultrasonography	30-35
				Assessment of serum CA125 levels	30-35
		Ovarian cancer 15-20%		Prophylactic bilateral salpingo-oophorectomy	40
HNPCC	*MSH2*	Colon cancer 60-90%	**Colon**	Colonoscopy, gastroscopy (every two years)	20-25
				(Sub)total colectomy	
	MLH1	Endometrial cancer 30-60%	**Endometrium**	Vaginal ultrasonography	30-35
				Asessment of serum CA125 levels	30-35
	MSH6	Other cancer <15%	**Other**	Depending on family history	

Early detection and/or prevention

Several early detection and prevention strategies are available for female *BRCA1/2* mutation carriers. In the Netherlands, *BRCA1/2* mutation carriers are recommended to visit a specialist for clinical breast examination twice a year, to have an annual MRI and/or mammography and to

perform monthly breast-self examination starting at age 25[12]. Regular breast screening however can not prevent the development of breast cancer and it is not guaranteed that a tumor will be detected at an early stage[13, 14]. Prophylactic bilateral mastectomy (PM) is a radical alternative for breast screening that has proved to be effective in preventing the development of breast cancer[15, 16]. Important differences exist between countries in the uptake of PM. In France the acceptability of PM amongst specialists and patients is low, whereas in England, Canada and the Netherlands the acceptability is quite high[17, 18]. Half of the mutation carriers in the Rotterdam Family Cancer Clinic opted for PM in the nineties[8], although this number is currently decreasing. On the psychological level, PM has shown to diminish concerns about developing cancer[19, 20], but may have negative consequences on self-esteem, sexual relationships and feelings of femininity[19, 21]. From age 35 years onwards, *BRCA1/2* mutation carriers are furthermore recommended to visit a specialized gynecologist yearly for vaginal sonography and serum CA125 assessment. Current gynecological screening techniques have not proved to be effective in detecting tumors at an early stage[14]. Mutation carriers are therefore offered prophylactic bilateral salpingo-oophorectomy (PBSO) from age 40 onwards. PBSO has shown to reduce the risk of developing breast and ovarian cancer[22, 23], but may result in menopausal symptoms and in compromised sexual functioning[24, 25].

Carriers of a mutation in one of the HNPCC related genes are recommended to have a colonoscopy every one to two years from age 20-25 onwards[12]. Colonoscopy is currently the most effective strategy to detect premalignant polyps and small adenomas. These can be removed during the procedure. Colonoscopy has proved to be effective in reducing colorectal cancer incidence and mortality in mutation carriers[26-28]. Gynecological examination is recommended to female mutation carriers from age 30-35 onwards, but the effectiveness of this screening may be limited[29]. Dependent on family history, screening for other HNPCC related cancers can be recommended. The effectiveness of these screening procedures is unsure too. The compliance to screening recommendations generally improves after genetic testing[30, 31]. In the Netherlands carriers of an HNPCC related mutation are generally compliant to recommended screening[32, 33].

Other hereditary cancer syndromes

Familial atypical multiple-mole melanoma syndrome (FAMMM), hereditary prostate cancer and familial paragangliomas resemble *BRCA1/2* and HNPCC with regard to the age of onset (mainly in adulthood), penetrance (not 100%) and availability of screening. For several reasons, these cancer syndromes were not subject of this study. Genetic testing for hereditary prostate cancer is not available yet and genetic testing for a FAMM related mutation is currently less informative than for a *BRCA1/2* or HNPCC related mutation. Non-carriers of the mutation with atypical nevi still have to continue dermatological screening. Familial paragangliomas differ from *BRCA1/2* and HNPCC in that only paternal inheritance results in the expression of the phenotype, also called genomic imprinting.

Other predispositions to cancer differ from *BRCA1/2* and HNPCC in their age of onset of symptoms, penetrance or mode of inheritance. *MYH* associated polyposis (MAP) is characterized by a recessive mode of inheritance. Multiple Endocrine Neoplasia type 1 and type 2a and 2b, Familial Adenomatous Polyposis Coli (FAP), Von Hippel Lindau disease, Peutz-

Jeghers syndrome and Li-Fraumeni syndrome (*P53*) have in common that tumors may develop in childhood. Genetic testing for these syndromes can be offered in childhood depending on the medical benefits of screening. For example, screening for FAP (characterized by a high number of polyps in the colon) is recommended from age 10 years onwards. The screening is burdensome and may cause complications. Genetic testing of children at risk of FAP may prevent unnecessary and burdensome screening in non-carrier children. For Li-Fraumeni syndrome (characterized by sarcoma's, breast tumors and multiple other tumors at a young age) currently no effective screening is available. Genetic susceptibility testing in childhood is therefore currently discouraged.

Procedure of genetic testing

In the Netherlands, genetic services are provided at departments of Clinical Genetics or Family Cancer Clinics. After application, the genetic counselor studies the provided pedigree information, verifies cancer diagnoses and attempts to diagnose the cancer susceptibility syndrome at hand. 'Diagnostic' genetic testing is offered if a certain genetic susceptibility is suspected. A blood sample of one or more affected relatives is required to search for a mutation. If affected relatives do not want to have the test or are deceased, two or more relatives at risk of 50% of having the mutation can be tested, but these results are less conclusive. About four to six months after blood sampling the genetic test result is available. In the majority of cases of diagnostic tests, no mutation is detected. With such an inconclusive result, uncertainty prevails and counselees and their relatives frequently have to continue their hospital visits for examinations in view of the family history. Individuals receiving an inconclusive result were not found to misunderstand their test result[34], though several studies have suggested that some individuals may misinterpret the result[35-37]. In some rare cases, a variant of uncertain clinical significance (VUCS) is found. This result was also found to be rather well-understood[37-39], although clinical evidence shows that confusion exists about risk management options (personal communication, J. Vos).

If a mutation is detected, genetic susceptibility testing becomes available for relatives at risk. The counselor always provides a 'family letter' with information for distribution amongst relatives. When relatives apply for genetic susceptibility testing, they receive at least one pretest counseling session. Because only the presence of the family specific gene mutation is tested, this testing takes about 4-8 weeks for *BRCA1/2* mutations and about 2-3 months for mutations in an HNPCC related gene. Results are disclosed in a face-to-face session with the counselor. The counseling is concluded with a personal letter including the main findings, conclusions and recommendations for screening and risk management.

Tasks of genetic counselors

Because genetic testing can produce lifelong knowledge about increased cancer risks and can have far-reaching implications, genetic counseling is an essential component of genetic testing. The counselor's task is to provide complete and clear information about cancer risks and implications of genetic testing, and to help making personally relevant decisions that will result in the best possible adjustment both in the short and the long term[40]. Counselors not only have to support the decision making process by providing relevant information, but also by helping

the counselee to gain insight into his or her individual motives, perceptions and capabilities of coping with the result[41].

Furthermore, the counselor's task is to broaden the scope from individual to family processes. Pressure may occur within the family in having genetic testing performed or not. The counselees may find it difficult to ask relatives to cooperate and to inform them about the genetic susceptibility[42]. Second and third degree relatives and relatives with whom the relationship is perceived as distant or conflicted have been found to remain frequently uninformed[43-47]. Informing children may be experienced as emotionally burdensome and may be avoided[48, 49]. Counselors have to stimulate the counselee in informing relatives in a sensitive manner and help the counselee to anticipate on the reactions of different family members.

Another important task of the genetic counselor is to estimate the counselees' strengths, weaknesses and need for additional support. Counselees can be referred to a specialized social worker or psychologist on the counselor's and/or the counselees' request[50]. Currently, no standardized method is used to assess strengths, weaknesses and the need for referral. Counselors refer their counselees based on their clinical experience. It is unknown what criteria are used and whether these are effective in identifying individuals who need additional counseling and support.

PSYCHOSOCIAL ASPECTS OF GENETIC TESTING FOR *BRCA1/2* OR A HNPCC RELATED MUTATION

Psychological distress as outcome of genetic testing

The psychological impact of genetic susceptibility testing for a *BRCA1/2* or HNPCC related mutation has been studied extensively by assessing the levels of psychological distress shortly before or after blood sampling, shortly after result disclosure and several weeks to months after result disclosure[39, 57-69] (For recent reviews see[51-56]). At the time of blood sampling, counselees show somewhat elevated anxiety levels and quite low depression rates. Shortly after result disclosure, distress rates drop in non-carriers and remain stable or increase in mutation carriers. At that time, mutation carriers are generally more distressed than non-carriers. In the months after result disclosure, distress levels decrease in mutation carriers and non-carriers. After a year, generally no significant differences between carriers and non-carriers are reported, except for cancer worry[64]. Two studies have found a different pattern. They reported a decrease in depression in mutation carriers from pre- to post-test and an increase in depression in non-carriers[65, 70], but these changes were not significant or may be due to methodological causes such as missing values. No studies have investigated psychological well-being in mutation carriers longer than one year post-disclosure.

A question of debate has been whether individuals from families with an increased presence of cancer are psychologically more vulnerable than the general population. Early studies on individuals at increased risk have expressed concern about their psychological well-being[71-74]. One study found stronger cortisol responses to daily stressors in women at familial risk for breast cancer than for comparable women without a family history of breast cancer[75].

Studies on individuals undergoing genetic cancer susceptibility testing have reported that a considerable proportion of 10-27% is clinically distressed[10, 11, 76-80]. Distress levels are however equal to or even lower than those in the general population or in a primary care population[65, 66, 78, 79, 81]. It has been suggested that genetic susceptibility testing is not distressing[82]. Another explanation for the low distress rates is that individuals who present for genetic testing are self-selected and less vulnerable than individuals refraining from genetic testing. Indeed, women who declined *BRCA1/2* genetic testing have been found to be more distressed than women who opted for testing[83].

Predictors of psychological distress

Whereas the proportion of counselees suffering from clinically elevated distress may be comparable to figures that have been reported for the general population, this does not mean that distressed individuals should go unintended. Psychological suffering may be reduced by early identification of vulnerable individuals and referral to a mental health professional for additional support. Therefore, insight is needed into characteristics and mechanisms predicting psychological adjustment. Several predictors have been documented to date.

The most frequently reported predictor of posttest distress was the level of pretest distress[84]. Other suggested predictors for distress were younger age[77, 85, 86], lower education[85], being unmarried[86], gender[87], having children[87], being unaffected[58] or affected[69] by cancer, and declining genetic testing[83]. These predictors are however too general to be used for selection of individuals to be referred to mental health professionals. They are furthermore not very informative in the sense of understanding the underpinnings of psychological maladjustment and of developing treatment interventions. Finally, most studies attempting to understand how individuals respond to the notification of a genetic cancer risk lack a theoretical basis[88].

Other outcomes

Remarkably few studies have concentrated on other outcomes of genetic testing than psychological distress (anxiety, depression, intrusions, worries, general mental health). One such understudied outcome is the impact of genetic testing on the structure and dynamics of family relationships[89]. Besides anecdotal evidence[42], only two recent studies have evaluated family relationships after genetic testing. One study evaluated changes in cohesion, expressiveness and conflict in close family relationships of individuals from families with a known *BRCA1/2* gene mutation[90]. Participants reported feeling closer to family members as a result of genetic testing. A Belgian study[39, 67] assessed the impact of genetic testing on family relationships in individuals opting for genetic susceptibility testing for a *BRCA1/2* or an HNPCC related mutation. A minority reported changes and these were mainly positive. Unfavourable changes may however have been overlooked due to the small sample sizes of these studies. More studies in larger samples are needed to explore the impact of genetic susceptibility testing on family relationships. Especially more information is needed on the nature of the impact on family relationships.

Conclusion

In conclusion, studies on the psychosocial implications of genetic cancer susceptibility testing have mainly focused on psychological distress up to one year after result disclosure. Self-referred individuals generally adjust well to genetic susceptibility testing with appropriate counseling. No adverse psychological consequences have been reported due to genetic testing. Several topics have been understudied. The long-term impact of genetic testing on psychological distress has not been sufficiently documented. Studies reporting on other outcomes, such as the impact of genetic testing on family relationships are scarce. Finally, insufficient and a-theoretical knowledge exists on the underlying mechanisms causing maladjustment in a small proportion of individuals.

THEORETICAL BACKGROUND

Several theories from health psychology have been put forward as useful models to understand the psychological implications of genetic cancer susceptibility testing[88, 89, 91-93]. We will elaborate on Leventhal's Common Sense Model of Self-Regulation and on two potential underlying factors of the model: experiences with cancer in the family and family system characteristics.

Leventhal's Model of Self-Regulation

Leventhal's Common Sense Model of Self-Regulation of Health and Illness[94] may be a useful framework to understand the cognitive, emotional and behavioral reactions to genetic cancer susceptibility testing[91-93]. This model posits that individuals create their own understanding of a health threat (i.e. *illness representations*), which determine *coping responses**, health behavior and finally psychological well-being. Cognitive processes evaluate the health threat and try to regulate it by problem-focused coping. Problem focused coping consists of behaviors attempting to reduce the health threat, like seeking information or opting for genetic testing. Simultaneously, emotion-focused processes regulate the emotional consequences of the health threat. Emotion-focused processes may be unconscious processes like minimization or more conscious processes like seeking social support. The simultaneous cognitive and emotion-focused processes evolve over time and mutually affect each other. The cognitive and emotional processes will be influenced by personal and vicarious experiences with the illness and by the social and familial context.

A growing body of research in health psychology has supported Leventhal's model[95]. Within the field of hereditary and familial cancer, no empirical studies have evaluated illness representations, risk perception, distress and their determinants simultaneously. Some studies have examined the relationship between some illness representations and psychological well-being. Perceiving more control over developing cancer[86], less serious consequences[39, 67, 96] and more curability[67] were found to be related to psychological well-being. Perceiving a higher risk to develop cancer was found to be related to cancer related distress[97-104]. Risk perception and several cognitive illness representations were found to be interrelated as well[105].

* Coping has been defined by Leventhal *et al.* as "the cognitive and behavioral actions we take (or do not take) to enhance health and to prevent, treat (cure or control) and rehabilitate from illness"

A few studies have focused on coping mechanisms. Having a monitoring coping style, i.e. being very vigilant to threatening information, was associated with more psychological distress in women opting for *BRCA1/2* genetic testing[106], but not in colorectal cancer patients undergoing genetic testing for HNPCC[85], nor in individuals having received genetic test results[63, 107, 108]. Having a passive coping style has been found to be related to psychological distress in individuals at increased familial risk and in individuals opting for genetic testing[39, 67, 109].

Experiences with cancer in relatives

It has been suggested that earlier experiences with cancer in the family affect psychological adjustment to genetic testing[52, 110]. Experiences with affected or deceased relatives may therefore be an underlying factor of the model of self-regulation. They may affect adjustment directly, but also indirectly by influencing illness representations and coping[88]. Of note, illness experiences may furthermore affect the normal development of the family and its individual members. Stress or illness will push the family towards transition and increased cohesion[1, 111]. These processes may not fit with the developmental cycle of the family or its individual members. For example, when a parent develops cancer, it may compromise the developmental step to leave the home of the parents[112]. This likely aggravates the impact of the illness experience.

Some studies have demonstrated that experiences with cancer in the family affect emotional adjustment to the notification of an increased cancer risk. Women with a family history of breast cancer have been found to report more breast cancer-related distress if they had lost a mother[101] or one of their parents[113] to cancer, or if they were closely involved in a sister's breast cancer[114]. Colorectal patients opting for genetic testing for an HNPCC related mutation reported more anxiety if they were under 25 years at the time of a close relatives cancer diagnosis[115]. Distress levels in unaffected women presenting for *BRCA1/2* genetic testing were related to the number of affected relatives and a young age of onset in the family[10, 116]. Finally, the test result of other family members has been found to impact on distress levels[59, 117]. In conclusion, a negative relationship may exist between psychological distress and several experiences with cancer in close relatives, like having experienced parental cancer or loss during childhood or adolescence, grief symptoms and the total number of affected relatives.

Family system characteristics

Human beings do not function in isolation, but share health-related cognitions and beliefs with their social environment and family members[89, 118]. Besides beliefs, the family also influences coping procedures and psychological adjustment[94]. The family system may therefore be conceived as another underlying factor of the model of self-regulation. Moreover, hereditary cancer is a family affair that affects all family members directly or indirectly. The impact of the family on individual illness representations, coping and psychological adjustment may therefore be more profound in case of hereditary cancer and genetic testing.

Remarkably few studies have explored the impact of family system characteristics on psychological adjustment to genetic cancer susceptibility testing. Most studies have focused on the transmission of information regarding the genetic susceptibility within the family[44-49, 119-122], which is a different topic. Only the protective effect of *support from family members* has been

well documented. Less support and more protective buffering** resulted in higher distress levels in women opting for *BRCA1/2* mutation testing and in colorectal cancer patients undergoing genetic testing for HNPCC[68, 85, 116, 123, 124].

Besides social support, several other family system characteristics may be related to psychological adjustment. Olson *et al.* have posited the Circumplex Model of Marital and Family Systems[125, 126]. This model describes *family functioning* in terms of cohesion and adaptability. Cohesion is defined as the emotional bond between family members. Families high in cohesion are highly interrelated and enmeshed, while families low in cohesion can feel alienated and disengaged from each other. Adaptability is defined as the ability to change a power structure, roles and rules when the family encounters stress. Families high in adaptability have been described as chaotic, while families low in adaptability can be described as rigid. Moderate levels of cohesion and adaptability would be the most functional for family and individual adjustment. Indeed, cohesion has been found to buffer distress in individuals at familial risk of breast cancer[116].

Another important family system characteristic could be *differentiation to parents*. Differentiation is defined as the extent to which an individual feels separated from the parents without damaging these important relationships[127]. Differentiation in adolescence is essential for psychological adjustment[128] and mid-life well-being[129]. Finally, it can be expected that the quality of *family communication* regarding hereditary cancer is related to psychological adjustment. Families of cancer patients who were able to act openly and express feelings directly, were found to be less psychologically distressed[130].

AIM AND OUTLINE OF THIS THESIS

Study aims

The first aim of this thesis is to understand the psychosocial consequences of genetic susceptibility testing for a *BRCA1/2* or an HNPCC related mutation. Several topics that have been underreported in literature were studied, like the long-term consequences of genetic cancer susceptibility testing and the impact of genetic testing on family relationships. The second aim is to understand the psychological mechanisms that are related to psychological adjustment from a theoretical perspective. We have used Leventhal's Model of Self-Regulation as a theoretical framework[94]. Specifically, the contribution of coping and illness representations, family system characteristics and experiences with cancer in the family were studied. Enhanced understanding of psychosocial adaptation to genetic susceptibility testing will serve to recognize individuals who need additional psychosocial support and to make recommendations for counseling interventions.

Study design

The main study is a prospective study including individuals from families with a known mutation in *BRCA1/2* or one of the HNPCC-related genes. In the second study, we report on a group of women who opted for *BRCA1/2* genetic testing who were followed prospectively from pretest

** 'Protective buffering' is defined as sparing each other from distress by ignoring a subject.

to 5 years after receiving the genetic test result (see Chapter 3, no further information provided here).

Participants

Applicants for genetic susceptibility testing for a known familial gene mutation in *BRCA1*, *BRCA2*, *MSH2*, *MLH1* or *MSH6* at three Dutch centers were asked to participate in a psychological follow-up study. Accrual took place at the Rotterdam Family Cancer Clinic of the Erasmus MC from January 2003 to October 2004, at the Centre of Human and Clinical Genetics of the Leiden University Medical Centre from February 2003 to October 2004 and at the Department of Medical Genetics of the University of Groningen from February 2004 to September 2004 (only HNPCC). Applicants were aged 18 years and older, were mainly unaffected by cancer and generally elected to have genetic testing. Also applicants affected by cancer and applicants who decided not to opt for genetic testing were included in the study. We excluded individuals with insufficient proficiency in Dutch, and males from *BRCA1/2* families because they were not at high risk of cancer themselves.

Procedure

The first questionnaire was mailed to all participants 1 week after the first counseling session. Participants who elected to have genetic testing received a second questionnaire 1 week and a third questionnaire 6 months after genetic result disclosure. Participants who did not want genetic testing received a second questionnaire 8 months after the first consultation. Semi-structured interviews were conducted with twenty 50% risk carriers (data not reported). The study and its procedures were approved by the institutional review board at the Erasmus MC (Rotterdam), Leiden University Medical Center and Groningen University Hospital.

Measures

The first questionnaire contained the predictive measures, including *illness representations* (IPQ-R), *coping* with hereditary cancer (UCL), illness and loss *experiences* in relatives and *family system characteristics* (communication, support, nuclear family functioning, differentiation in parental relationship). The second and the third questionnaire contained the outcome measures, including *hereditary cancer related distress* (IES), *cancer worry* (CWS), *general distress* (HADS) and the impact of genetic testing on *family relationships*. The questionnaire contents and their psychometric properties are described in more detail in the following chapters, especially in Chapter 4.

Outline of this thesis

In the first part of the thesis, the psychosocial impact of genetic susceptibility testing is explored. **Chapter 2** comprises a review of the literature on the short-term psychological impact of genetic susceptibility testing for a *BRCA1/2* mutation. Specifically, conclusions will be drawn on the consequences of the findings for genetic testing counseling protocols and a counseling model

will be described. **Chapter 3** describes a prospective study on the long-term consequences of carrying a *BRCA1/2* mutation. The psychosocial impact of prophylactic surgery and predictors of long-term psychological adjustment are also investigated in this chapter. Before undertaking studies with individuals from *BRCA1/2* and HNPCC mutation families, we have studied differences between the two groups with regard to the variables that were assessed in this study. In **Chapter 4** we compare psychological adjustment, illness representations, coping behavior, experiences with cancer in relatives and family system characteristics between the two groups. All baseline information and mean scores on the measures are also described in Chapter 4. **Chapter 5** describes the character of the impact of genetic cancer susceptibility testing on family relationships. Furthermore, the family system characteristics of individuals reporting negative consequences are explored.

In the second part of the thesis, we explore characteristics and mechanisms that predict maladjustment using the theoretical perspective of the common sense model of self-regulation of health and illness. The contribution of illness representations and coping, of family system characteristics and of age at the time of parental cancer diagnosis or death are explored in the **Chapters 6, 7 and 8**, respectively. **Chapter 9** is an attempt to explore the relative contribution of all factors and characteristics studied in this thesis. The contribution of experiences with cancer in the family are also evaluated. In **Chapter 10**, the main findings of the study are summarized and discussed. Consequences for genetic counseling are mentioned and suggestions for further research are made.

Part I

Genetic counseling and the psychosocial impact of genetic cancer susceptibility testing

CHAPTER 2

A counseling model for *BRCA1/2* genetic susceptibility testing

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Abstract
When *BRCA1/2* genetic susceptibility testing was introduced in the clinic in the mid-nineties, the 'Huntington protocol' was used in the counseling of individuals applying for genetic testing. This protocol includes at least three sessions with a certain reflection period before blood sampling. Evidence on the psychological impact of *BRCA1/2* genetic susceptibility testing has been accumulating the last years. We will give a short overview of these psychological studies in order to reflect on the need of using the extensive Huntington protocol in the counseling of individuals applying for *BRCA1/2* genetic susceptibility testing. A shortened and more flexible *BRCA1/2* counseling protocol is delineated, in which the attention is focused on the needs and strengths of the individual.

Introduction

When genetic susceptibility testing for hereditary breast and/or ovarian cancer was introduced in the nineties, professionals were concerned about the psychological consequences of learning one's genetic status. Women carrying a *BRCA1/2* mutation have to deal with considerable health risks[1-3] and are confronted with difficult choices concerning risk management. Mutation carriers can opt for regular surveillance, for prophylactic mastectomy and/or prophylactic bilateral salpingo oophorectomy, and/or for chemoprevention trials. Besides important health risks and the far-reaching impact of risk management options, these women may be psychologically vulnerable due to unresolved loss experiences[4, 5]. Many have witnessed the disease in relatives and have lost a mother or sister, possibly leaving young children behind. Furthermore mutation carriers risk to pass or to have passed the mutation on to their children with all the above-mentioned consequences for them.

The Huntington-protocol

Because of the potentially far-reaching implications of *BRCA1/2* susceptibility testing, the 'Huntington protocol' was adopted for the counseling of unaffected individuals who wanted to know if they had inherited a familial *BRCA1/2* mutation. This 'Huntington protocol' has a long history. As the availability of DNA analysis for the HD gene was set to become a reality, the Committee of International Huntington Association and the Working Group on Huntington's disease of the World Federation of Neurology gave consideration to the manner in which these tests should be carried out (IHA/WFN 1994). In general, the guidelines recommend that individuals at risk who participate in predictive testing programmes are seen for two to four counseling sessions, spread over a 3-month period, before disclosure of the test results. Predictive testing requires informed consent by the individual at risk, and the provision of psychological support. If the test is abnormal, counseling must be available for the family and others involved. The starting point is that predictive tests should be offered only to individuals at risk who have had the appropriate counseling, are fully informed, and wish to proceed. Genetic centers providing the predictive test have been committed to the use of the international guidelines. Admittedly, after 15 years, testing centers have developed their own local protocols and guidelines, based on experience and local or national rules, but they have in common the requirement for multiple interviews before a test result is disclosed. The number and complexity varies, partly due to the number of associated psychological and other evaluations, but the basic structure involves at least the series shown in Table 1.

The expectation of an increase of test requests for a great variety of hereditary disorders in the near future leads us to reconsider the need of such an extensive, time-consuming protocol in the counseling of individuals at risk, amongst them those who may carry a familial *BRCA1/2* mutation. What have the lessons of clinical experience and research provided so far?

Table 1. Predictive testing for Huntington's disease

Session One
• Sociodemographic details
• Confirmation of family and clinical data
• Assessment of impact of HD and test results
• Assessment of knowledge of HD and presymptomatic testing
• Reasons for requesting prediction
• Neurological examination*
Session Two
• Assessment of psychological, personality and social resources (using standardized instruments*)
• Further counseling and discussion of disclosure session
• Nomination of professional support
• Signing of consent form
• Final blood sample
Session three
• Disclosure of test results
Formal follow-up
• 2 days-1week (telephone)
• 3 months
• 12 months

*Genetic centres differ in the application of neurological examination and psychological assessment

The psychological impact of genetic testing

Several psychological studies have now been conducted to determine the psychological impact of genetic susceptibility testing for *BRCA1/2*. In most studies groups of tested individuals were followed prospectively. Generally, an assessment took place before result disclosure and several weeks or months after result disclosure. Results from these studies suggest that participants generally cope well with genetic susceptibility testing. Non-mutation carriers reported a decline in psychological distress several weeks and months after result disclosure. Mutation carriers showed a stable or decreasing level of distress shortly after result disclosure[6-8] and up to 12 months after result disclosure[9-11]. Five years after result disclosure the level of distress increased again in both mutation carriers and non-mutation carriers[12]. On the whole the mean level of psychological distress remained underneath the clinical threshold, indicating little need for intervention[6-12]. In women affected by cancer also no adverse psychological reactions have been observed following genetic testing. They reported a decrease in anxiety and no change in depression rates one month after result disclosure[13]. Remarkably, the prospect of undergoing genetic testing was rated as less distressing than the high risk status or the diagnosis of cancer by women at risk and women with a personal and familial history of breast and/or ovarian cancer[14].

The occurrence of mental health problems was low. No unusually high levels of psychiatric disorder were detected in a group of 315 unaffected individuals from families with a known mutation in *BRCA1/2*[15]. In another study[16] it was concluded that from 211 women with a previous history of breast and/or ovarian cancer and 253 unaffected women at risk remarkably few women reported psychological distress and met criteria for psychiatric disorder like depression, anxiety disorder, or alcohol abuse. Compared to women from primary care and community settings, they had lower rates of psychiatric disorder.

In summary, no elevated distress levels and a low prevalence of mental health problems have been observed both before and after *BRCA1/2* genetic susceptibility testing. The participants of the studies described here wanted to know their genetic risk status and may therefore consist of a self-selected and psychologically stable subgroup of at risk individuals. Despite the psychological stability of the majority of the group, we emphasize that a subset of women undergoing genetic susceptibility testing for *BRCA1/2* reports a level of distress that warrants clinical attention.

Need for help?

The request for psychological support proved to be rare in the short term[8]. Counselees who were referred for psychosocial help generally had more problems with issues like loss and family or partner relationships than with the concern of developing breast cancer[17]. In the five years following testing about half of the mutation carriers and a third of the non-carriers were found to have asked for professional support for psychological problems[12].

Several efforts have been made to identify counselees who risk suffering from psychological adverse reactions. An important precursor is pre-test psychological distress. Women reporting more psychological distress at the time of blood sampling generally continue to report higher distress levels after receiving the result[7, 8]. In the main these women are younger[5, 15, 18] and interested in prophylactic surgery[5].

Another factor was having an intimate relationship. Unmarried women seeking genetic counseling for a family history of breast/ovarian cancer reported more distress than married women in one study[18]. However another study[19] found equal levels of distress in married and unmarried women, but more distress in women with unhappy marriages. A study by Wylie *et al.*[20] evaluated the effects of the support and distress of spouses on *BRCA1/2* mutation carriers. Carriers who perceived their spouse to be anxious and non-supportive had higher distress levels one week after result disclosure than carriers who perceived their spouse to be supportive and anxious or low anxious and non-supportive. Carriers who perceived their spouse to be both supportive and low anxious had the lowest distress levels. In carriers with a non-supportive, anxious spouse at the time of testing, distress remained elevated up to two years after testing. The familial context may also be of importance. *BRCA1/2* mutation carriers who were the first to be tested experienced more distress[21]. Non-carrier men reported more distress when they had carrier siblings and carrier women reported more distress when tested siblings had mixed results.

Several other studies have concentrated on coping, like the anticipation of the feelings following a positive result. Women who underestimated their feelings of distress following a

positive test result, reported more psychological distress six months after having received the result[22]. A monitoring coping style, i.e. being very vigilant to threatening information, resulted in more psychological distress while waiting for the genetic test result[23], but not after receiving results[11, 23].

Decliners of genetic testing also may be more vulnerable to psychological distress. Women with high levels of baseline distress who declined genetic testing reported an important increase in depression rates[24]. Another study however did not find any psychological vulnerability in a (small) clinical sample of women at risk who did not opt for genetic testing[25].

A *BRCA1/2* counseling protocol

Genetic counseling should be tailored to the needs and capacities of its target group. If the target group generally has enough psychological resources to cope with genetic testing, our energy should be directed to the individuals who risk being unable to cope with it. Therefore we suggest adapting the Huntington-protocol to the needs and strengths of our *BRCA1/2* counselees. The shortened *BRCA1/*2 protocol we propose is depicted in Table 2. It comprises at least two sessions with a genetic counselor and additional counseling suited to the needs of the counselee. This *BRCA1/2* protocol could serve as a model for genetic susceptibility testing of other hereditary cancers such as HNPCC.

In the first session, careful exploration of the possible impact of testing upon the individual at risk and others involved enables the counselees and their partners to recognize the potential risk factors for inadequate coping. If there are any such factors, additional professional attention from a psychologist or social worker may be of help to anticipate untoward experiences after disclosure of test results. A second session with the counselor can be offered when unanticipated information or facts emerge in the first session. This enables the counselee to reflect somewhat longer upon the possible consequences and to be more certain to make a thorough decision. Also after the session in which the test result is disclosed, follow-up support by a psychologist or social worker can be offered if needed. Otherwise a follow-up interview by phone and mentioning the possibilities of additional counseling may be sufficient. It is mandatory for the genetic counselor to master specific communication skills and knowledge about the psychological risk factors, which enables him to identify those individuals who need additional support.

Table 2. Genetic susceptibility testing for *BRCA1/2*

First counseling session with genetic counselor
• Assessment of a priori knowledge concerning *BRCA1/2* mutations and genetic testing and provision of risk information
• Assessment of impact of test result
• Assessment of need to refer to psychosocial worker
• Decision counseling
• Blood sampling
No blood sampling but a second counseling session with genetic counselor or psychosocial worker if:
• counselee experiences provided information as very unfamiliar or shocking or decision making was not thorough
• other 'unfinished business' comes up such as relational conflicts, communication problems with relatives, worries about (future) children
• anticipation of inadequate coping with the test result
• the counselee is younger than 25
Disclosure session
• Disclosure of test result by the genetic counselor
• Assessment of need to refer to psychosocial worker
• Referral to specialist (for carriers)
Formal follow-up for mutation carriers:
• Follow-up interview by phone after 2-3 weeks
• Optional information seminar with experts (geneticist, oncologist, surgeon, gynaecologist) once a year
• Optional mutation carrier support group

Current practice and future research

Several centres have already adopted a shortened protocol for counselees who apply for *BRCA1/2* genetic susceptibility testing and in the United Kingdom certain centers have shortened the protocol for HNPCC pre-test counseling[26]. Aktan-Collan *et al.*[27] evaluated a shortened protocol for predictive testing for HNPCC, that consisted of two sessions and no provision of additional psychological support. The majority (88%) of counselees were satisfied with the procedure and suggested no changes. The counselees who suggested changes generally asked for more written material, not for more counseling sessions. However half of the counselees indicated that they might have used psychological support if it had been offered to them.

Given these results, we think it is unlikely that the proposed counseling protocol for *BRCA1/2* genetic susceptibility testing results in an increase of adverse psychological reactions, but more research is necessary to evaluate which aspects of genetic counseling contribute to thorough decision making[28] and to the emotional well-being of counselees and their partners. Future research should also aim at determining the characteristics of individuals who might benefit from additional psychological support and at disentangling the psychological processes

resulting in ineffective coping. This knowledge will enable us to identify these individuals as precisely as possible and to adjust our counseling further to the individual needs of the counselees.

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CHAPTER 3

Long-term psychological impact of carrying a *BRCA1/2* mutation and prophylactic surgery: a 5-year follow-up study

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Abstract

Purpose: To explore long-term psychosocial consequences of carrying a *BRCA1/2* mutation and to identify possible risk factors for long-term psychological distress.
Patients and Methods: 5 years after genetic test disclosure 65 female participants (23 carriers, 42 non-carriers) of our psychological follow-up study completed a questionnaire and 51 participants were interviewed. We assessed general and hereditary cancer related distress, risk perception, openness to discuss the test result with relatives, body image and sexual functioning.
Results: Carriers did not differ from non-carriers on several distress measures and both groups showed a significant increase in anxiety and depression from 1 to 5 years follow-up. Carriers having undergone prophylactic surgery (21 of 23 carriers) had a less favorable body image than non-carriers and 70% reported changes in the sexual relationship. A major psychological benefit of prophylactic surgery was a reduction in the fear to develop cancer. Predictors of long-term distress were hereditary cancer related distress at blood sampling, having young children and having lost a relative to breast/ovarian cancer. Long-term distress was also associated with less open communication about the test result within the family, changes in relationships with relatives, doubting about the validity of the test result and higher risk perception.
Conclusion: Our findings support the emerging consensus that genetic predisposition testing for *BRCA1/2* does not pose major mental health risks, but our findings also show that the impact of prophylactic surgery on aspects such as body image and sexuality should not be underestimated, and that some women are at risk for high distress, and as a result, need more attentive care.

INTRODUCTION

Women identified with a *BRCA1/2* mutation have a cumulative lifetime risk for breast cancer of 39-85%, and for ovarian cancer the risk is 11-63% at age 70 years[1-3]. The cancer incidence rates are of clinical relevance from 25 years of age onwards. Women from families with a *BRCA1/2* mutation often have witnessed the disease in their close relatives. The identification as a carrier further implies that they themselves may pass or may have passed the mutation on to their own children. Several risk-reducing interventions are currently available for carriers: regular breast surveillance; prophylactic bilateral mastectomy (PM) with or without reconstruction; regular gynecological surveillance; prophylactic bilateral salpingo oophorectomy (PBSO); and chemoprevention. In a large cohort of unaffected women undergoing genetic predisposition testing at the Rotterdam Family Cancer Clinic, about 50% percent of female *BRCA1/2* mutation carriers opted for PM, and more than 60% percent opted for PBSO[4].

Psychological consequences of learning one's genetic status have been studied since genetic predisposition testing for a *BRCA1/2* mutation became available in the nineties, and until now no serious adverse psychological consequences have been observed[5-12]. Most studies, however, followed participants only for a relatively short period of time (a maximum of 1 year after genetic test disclosure). To our knowledge, this is the first study to examine the long-term psychological implications of genetic predisposition testing for *BRCA1/2* in women without a personal history of cancer. The first aim of this study was to learn more about the long-term psychosocial impact of carrying a *BRCA1/2* mutation and its sequels, like PM and PBSO. The second aim was to identify risk factors for psychological distress 5 years after cancer genetic predisposition testing.

PATIENTS AND METHODS

Study population and procedure

From 1995 to 1998, 118 unaffected women with a 25% or 50% risk of carrying a *BRCA1/2* mutation applying for genetic predisposition testing at the Rotterdam Family Cancer Clinic were asked to participate in a psychological follow-up study. Of these 118 women 85 consented to the study (72%). A baseline assessment that embodied a questionnaire and interview took place shortly after blood sampling for genetic testing but before test disclosure. Follow-up assessments were completed at 1-3 weeks and at 6 and 12 months after disclosure of the test result. The procedure and results of these prior studies have been described in detail elsewhere[10, 11, 13].

In 2002, 79 participants (6 of 85 women dropped out in the '95-'98 study) were requested by letter to consent to a follow-up assessment consisting of a questionnaire and an optional semi-structured interview at home (conducted by the first author). Sixty-five women (82%; 42 non-carriers, 23 carriers) consented and filled in the questionnaire and 51 of these 65 women (31 non-carriers, 20 carriers) also agreed to be interviewed. Of the non-participants, 9 women (7 non-carriers, 2 carriers) did not want to participate, 4 (3 non-carriers, 1 carrier) had changed address and could not be traced and 1 carrier had deceased. Of the 4 carriers who were lost for this assessment, 1 opted for PM and PBSO and 3 for regular breast surveillance (1 of them opted for PBSO).

The original study and the procedure of the assessment 5 years after disclosure of test results were approved by the institutional review board at the Erasmus MC, Rotterdam. The range of time of follow-up was 4 to 6 years.

Measures

Sociodemographics

Data were obtained on age, marital status, offspring and educational level.

Psychological distress and help-seeking behavior

To compare the level of general anxiety and depression to that in earlier assessments, participants completed the Hospital Anxiety and Depression Scale (HADS)[14, 15]. This questionnaire consists of two scales assessing feelings of anxiety and depression. To assess hereditary breast/ovarian cancer related distress, the Impact of Event Scale (IES) was used. This questionnaire measures intrusive feelings and thoughts about breast/ovarian cancer and avoidance of these feelings and thoughts[16]. We did not compare the five-year level of cancer related distress with that measured in earlier assessments, because we used the original response categories of the IES (in contrast to earlier assessments). Breast cancer related worries were measured with 5 items of the Cancer Worry Scale (CWS)[17, 18]. Studies have demonstrated that the HADS, IES and CWS have acceptable psychometric qualities[15, 19-22]. Furthermore, participants indicated whether they had consulted a professional for psychological support and whether they used psychopharmacological medication since genetic test disclosure. Participants who opted for PM and/or PBSO reported on a 5-point scale whether they agreed or disagreed with: "PM and/or PBSO made me less anxious about developing cancer" and "PM and/or PBSO was worth the adverse effects".

Body image and sexual functioning

Body image and general sexual functioning were assessed by the Body Image/ Sexuality Scale[11], which was constructed following recommendations made by Cull[23] and Hopwood[24]. The instrument comprises three scales: body image (range 5-25), breast related body image (range 2-10) and general sexual functioning (range 15-17). A higher score indicates more problems. Reliability was adequate for the three scales (Cronbach's alpha = .86, .84 and .92 respectively).

Family related issues

Openness of communication about the test result in the nuclear family (i.e., partner, children) and the family of origin (i.e., parents, siblings) was assessed by an adaptation of the Openness to Discuss Cancer in the Family Scale[25]. Reliability of the adapted scale was adequate in the nuclear family and in the family of origin (Cronbach's alpha = .78 and .92 respectively). In the analysis the sum of z-scores of openness in the nuclear family and in the family of origin was used. In order to explore the impact of testing on relationships with family members, participants reported on a 5-point scale whether they agreed or disagreed with "Genetic predisposition testing and its sequels have changed the relationship with my 1) partner 2) relatives 3) children." A sum of z-scores of these three items loaded on one component in principal components analysis for nonmetric data and was used in the analyses.

Risk and test perceptions

Risk perception (" I feel like my chance of breast cancer is…") was rated on a 7-point scale varying from 'very low' to 'very high'. Perceived seriousness of carrying a mutation predisposing for breast/ovarian cancer and having doubts on the validity of the personal genetic test result were assessed with 5-point scale items.

Interview data

Consequences of prophylactic surgery on body image, like satisfaction with naked appearance, were explored in the interview. Also, participants were asked whether genetic predisposition testing and its consequences (i.e., prophylactic surgery) had affected the sexual relationship with their partner. Indicated changes were explored. When participants indicated that nothing had changed, we concentrated on how they had adapted to the reconstructed breasts. In the baseline interview shortly after blood sampling, plans for risk management and experiences with breast/ovarian cancer in relatives had been explored in order to predict distress (i.e., onset age of cancer, personal involvement, being bereaved)[13].

Statistical Methods

We used the SPSS 10.0 statistical package to analyze the data. Categorical data and the data of the interview were analyzed by χ^2 tests and results of the Fisher's exact test (2-sided) were reported. In order to assess whether carriers differed from non-carriers 5 years after test disclosure, we applied the method of logistic regression analysis with the following variables: the sub-scores of the HADS, IES and with the CWS; psychological help-seeking behavior; and body image and sexual functioning. In the logistic regression analyses we controlled for age and marital status. We performed analyses of variance (ANOVA) for repeated measurements to test for differences in levels of anxiety and depression at 1 and 5 years follow-up and in body image and sexuality at baseline and 5 years follow-up. The results of analyses of the other time-points have been described elsewhere[10, 11, 13].

To understand whether cancer related distress (IES) and cancer worry measured 5 years post-test disclosure were associated with variables measured at baseline, the method of linear regression analysis was conducted with the following variables: having young children; being younger than 40 years; considering prophylactic mastectomy if carrier; hereditary cancer related distress; and experiences with cancer in the family. In all analyses age, marital and carrier status were adjusted for. The variables that contributed significantly to predicting long-term distress were entered in a multiple regression analysis (method backward), adjusted for age and carrier status. To investigate which variables measured 5 years post-test disclosure were related to cancer related distress and cancer worry, we followed a similar strategy with openness of family communication, risk perception, seriousness of carriership, having doubts about the validity of the test, and changes in relationships due to testing.

RESULTS

Sample characteristics

No differences were found between carriers and non-carriers on several sociodemographic characteristics (Table 1). Of the 23 carriers, 19 had PM and 12 PBSO; all but 2 underwent PM at the Rotterdam Family Cancer Clinic and 17 had a reconstruction. Two carriers were diagnosed with breast cancer during the follow-up period: in one participant breast cancer was detected by magnetic resonance imaging and one participant was found to have an axillary lymph node metastasis seven months after prophylactic mastectomy. Also, two non-carriers were diagnosed with breast cancer at age 47 and 58.

Table 1. General characteristics of the study sample 5 years after genetic predisposition testing

	Carriers				Non-carriers		Dropouts	
	Prophylactic mastectomy (n=19)		Regular examinations (n=4)		(n=42)		(n=19)*	
	n	%	n	%	n	%	n	%
Mean age in years (SD)	42.4 (9.6)		41.5 (9.3)		42.9 (9.9)		47.8 (13.1)	
Married/living together	15	78.9	4	100.0	39	92.9	15	78.9
Divorced, widowed or single	4	21.1	0	0.0	3	7.1	4	21.1
Having children	14	73.7	3	75.0	36	85.7	14	73.7
Had a child since genetic testing	3	15.8	1	25.0	11	26.2	NA	
Education > high school	5	26.3	0	0.0	11	26.2	2	10.5
Opted for BSO	12	63.1	2	50.0	-	-	NA	

Abbreviations: BSO, bilateral salpingo oophorectomy; NA, not available.

*Information is available on 19 of 20 women who dropped out

Long term psychological distress and help-seeking for psychological distress

Logistic regression analysis with distress scores measured 5 years after test disclosure revealed no differences between carriers and non-carriers with respect to cancer worry (P = .5; 95.0% confidence interval [CI], 0.9 to 1.3), hereditary cancer related intrusions and avoidance (P = .5; 95.0% CI, 0.9 to 1.1; P = .8; 95.0% CI, 0.9 to 1.1), and on general anxiety and depression (P = .9; 95.0% CI, 0.9 to 1.1; P = .5; 95.0% CI, 0.9 to 1.2). Compared to assessments 1 year after disclosure however, both carriers and non-carriers showed a significant increase in anxiety and depression (P = .009 and P = .005 respectively). The increase in depression tended to be higher for carriers than for non-carriers, but this interaction did not reach significance. The course of anxiety and depression for carriers and non-carriers for whom data were complete on every assessment are depicted in Figure 1 and 2 respectively.

All the women who opted for PM and/or PBSO indicated that their fear of developing breast/ovarian cancer had decreased after surgery and most women felt that PM and/or PBSO was worth the adverse consequences (79% and 80%, respectively).

During the 5 years since genetic test disclosure, 44% of the carriers and 33% of the non-carriers consulted a psychologist, psychiatrist, social worker or a family doctor for psychological support (P = .4; 95.0% CI, 0.6 to 4.7). The reason for consulting was related to hereditary cancer for 50% (5/10) of the carriers and 29% (4/14) of the non-carriers. Carriers did not report to use more psychopharmacological medication since test disclosure than non-carriers (30% and 17% respectively) (P = .2; 95.0% CI, 0.7 to 8.0).

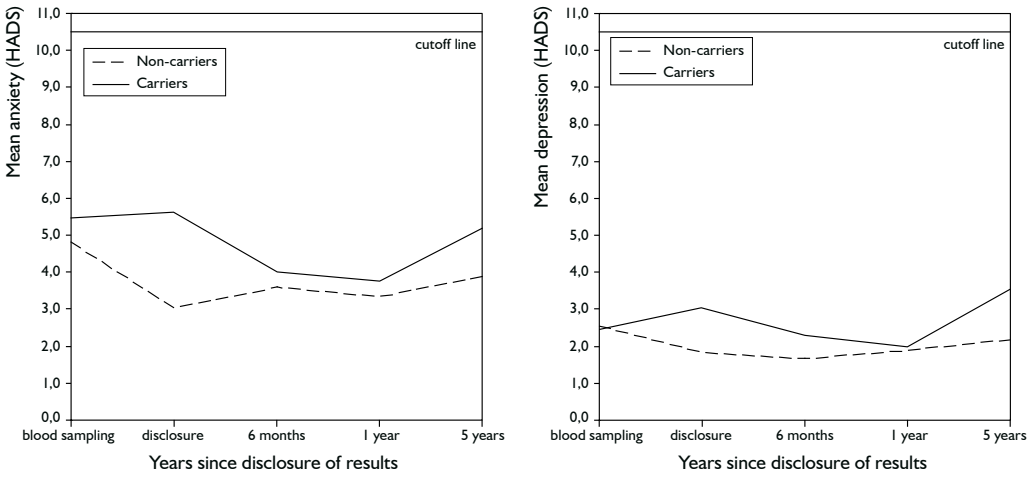

Figure 1 and 2. The course of anxiety and depression (HADS) in carriers (n = 21) and non-carriers (n = 29) (range 0-21)

Body image and sexual functioning

Five years after genetic test disclosure carriers reported less satisfaction than non-carriers on the general and on the breast related body image scale (P = .05; 95.0% CI, 1.0 to 1.3; $P \leq .001$; 95.0% CI, 1.5 to 3.9). Participants reported a change in breast related body image from baseline to 5 years follow-up (P = .02), with a decreasing satisfaction in carriers (P = .001) (see Figure 3). Also, satisfaction in general body image changed between baseline and 5 years follow-up (P = .04), with a tendency of a decreasing satisfaction in carriers (see Figure 4). Carriers did not differ significantly from non-carriers on general sexual functioning. No significant changes throughout time were found, but this may be a result of the low response rate on this scale.
In the interviews however, carriers reported more changes in their sexual relationship since genetic test disclosure (χ^2 = 16.32, $P \leq .001$) than non-carriers. Of the 16 carriers who had

undergone PM and/or PBSO and who were sexually active, 11 (70%) reported changes in their sexual relationship. The interviewed carriers opting for neither PM nor PBSO (aged 33 and 34) did not report changes in the sexual relationship. The reported changes are indicated in Table 2.

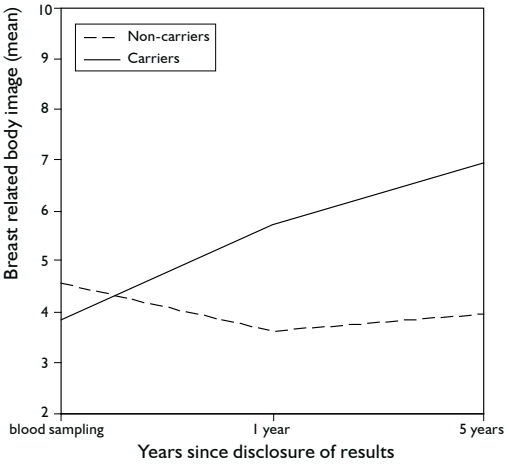

Figure 3. Satisfaction with breast related body image for carriers (blood sampling: n = 22, 1 year: n = 19, 5 years: n = 20) and non-carriers (n = 21, n = 19, n = 34)

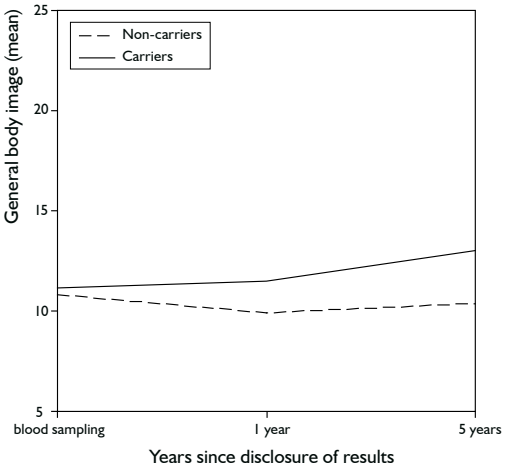

Figure 4. Satisfaction with general body image for carriers (blood sampling: n = 23, 1 year: n = 21, 5 years n = 22) and non-carriers (n = 22, n = 19, n = 34)

Table 2. Reported changes in the interview in body image and intimate relationship by carriers who had prophylactic mastectomy and oophorectomy (n = 13), mastectomy (n = 4) and oophorectomy (n = 1)

	n	%
Body image* (n = 17)		
Limitation of movements	2	12
Frequently feels pain	2	12
Does not show naked breasts to partner	4	24
Dresses differently than before surgery	5	29
Sense of shame for body	4	24
Feels less attractive	1	6
Feels less feminine	3	18
Feels PM was a mutilation	2	12
Intimate relationship† (n = 16)		
Lacks sensibility in breasts	9	56
Feels unnatural/uncomfortable when breasts are touched	6	38
Breasts are ignored during sexual intercourse	5	31
Always wears T-shirt during sexual intercourse	5	31
Less libido	5	31
Less lubrication	8	50
More difficult to have orgasm	3	19
Less pleasure from coitus	5	31
Reports long-term changes in sexual relationship	11	69
Feels reserved of being intimate with new partner (n = 4)‡	3	

Abbreviations: PM, prophylactic mastectomy; BSO, bilateral salpingo oophorectomy
* carriers who had PM
† carriers who had PM and/or BSO and were sexually active since testing (10 PM and BSO, 5 PM, 1 BSO)
‡ carriers who had PM and were single, divorced or widowed since testing

Predictive factors for long-term psychological distress

Results of the backward regression analyses are indicated in Table 3. Participants with more hereditary cancer related distress at baseline reported significantly more hereditary cancer related distress and more cancer worry 5 years later. Moreover, participants with children younger than 15 at baseline showed significantly more hereditary cancer related distress 5 years later. Participants with one or more relatives who died from breast/ovarian cancer reported more cancer worry 5 years later.

Women who communicated in a less open manner about genetic testing with relatives and who expressed more doubts about the validity of their personal test result, had significantly higher levels of hereditary cancer related distress and cancer worry 5 years following test disclosure. Also, participants who indicated more changes in the relationship with relatives

showed significantly more hereditary cancer related distress, and participants who perceived their risk of breast cancer to be higher reported significantly more cancer worry.

Table 3. Predictive factors for IES and CWS five years after genetic test disclosure for carriers (n = 23) and non-carriers (n = 42)

Predictive factors	β*	SE	*P*
IES			
Baseline			
Hereditary cancer related distress	.53	0.19	<.0001
Having young children (<15 years old)	.27	4.02	.021
Five years postdisclosure			
Openness to discuss the test-result in the family	-.33	1.36	.011
Reporting changes in relationship with loved ones as a result of testing	.31	0.69	.019
Doubts about validity of test result	.32	1.46	.009
CWS			
Baseline			
Hereditary cancer related distress	.32	0.03	.020
Knowing one or more family members who died of cancer	.25	0.83	.66
Five years postdisclosure			
Openness to discuss the test result in the family	-.42	0.18	.001
Risk perception	.30	0.25	.014
Doubts about validity of test result	.32	0.20	.011

Abbreviations: IES, Impact of Event Scale; CWS, Cancer Worry Scale
*Standardized regression coefficients for associations from backward multiple regression analysis

DISCUSSION

We found that also on the long term, most women were able to cope with their *BRCA1/2* carrier status and with subsequent risk reducing interventions. Carriers did not differ significantly from non-carriers regarding psychological distress levels, cancer worry and psychological help-seeking behavior. In carriers and non-carriers the mean general and hereditary cancer related distress levels were below the clinical cut-points[14, 16]. However, both carriers and non-carriers showed an increase in anxiety and depression from 1 to 5 years after genetic test disclosure, whereas carriers almost reached the level of anxiety and depression reported at the time of blood sampling. In addition to this, the utilization of the health care system for psychological support and psychopharmacological medication was considerable.

Our results suggest that genetic predisposition testing and prophylactic surgery alter the level of distress temporarily, but that other characteristics determine the intensity of psychological

distress on the long-term. One of the most powerful predictors of long-term hereditary cancer related distress and cancer worry was the level of hereditary cancer related distress at baseline, a finding that concurs with results of other studies on genetic predisposition testing for late onset diseases[10, 11, 26, 27]. The experience with affected relatives was another determinant of cancer worry. We found that women who lost a family member to breast/ovarian cancer tended to be more worried to develop cancer. This finding adds to the emerging evidence on the association between loss experiences and distress levels[22, 28]. Furthermore, women with young children at baseline reported more distress 5 years later. This may be related to fear of leaving young children behind and to difficulties with informing children on their cancer risks[29-31].

Perceptions of cancer risk and the genetic test also affected distress levels. In line with other studies, women who perceived themselves at higher risk to develop breast cancer were more worried[22, 32, 33]. We also found that having doubts on the validity of the personal test result was associated with more distress and cancer worry. This finding was partly due to the non-carriers who tended to doubt more often than carriers and whose overestimation of the risk of breast cancer was impressive (60% of the unaffected non-carriers overestimated their risk by more than 10%, compared to 29% of the carriers). These results imply that also non-carriers of a *BRCA1/2* mutation may have difficulties with adapting to a life without an increased risk of breast/ovarian cancer. This phenomenon has also been described in non-carriers from families with the dominant inherited late onset neurological disease Huntington's Chorea[34].

Less openness to discuss the test result with family members was associated with more cancer worry and more distress. Women might experience a lack of social support when the communication on this subject is limited. Studies have shown that support of the partner or relatives is important when coping with an elevated cancer risk[35-37]. Also, women who reported an impact of testing on relationships with relatives (both positive and negative) experienced more distress. It is, however, unclear how changes in relationships are related to the observed distress. To gain more insight into this aspect, more research is needed on family dynamics and communication about hereditary cancer.

Most women in this study expressed their satisfaction with prophylactic surgery, which is consistent with findings from other studies[38-42]. A major psychological advantage of prophylactic surgery was the diminished fear of developing cancer, although carriers who opted for prophylactic surgery were less satisfied with their bodies and breasts and reported (in the interview) more problems with sexual functioning than non-carriers. Another point to note is that the carriers who opted for PM while having no partner were very reluctant to start a new relationship after having PM.

Our findings should be viewed with the perspective that the reported changes in sexual functioning were not problematic for most women. They frequently stated that it was the price to pay for not dying of cancer at a young age, that sexuality was less important for them than for other people, or that sexuality would become less worthwhile anyway because they were getting older. Life was more valuable for them than breasts, ovaries and sexuality. The sense of perspective that the women in this study demonstrated can in part result from an attempt to escape from cognitive dissonance[43]. Cognitive dissonance theory suggests that an autonomously made decision will be positively evaluated, especially when the decision is difficult to change. Worldwide large variation exists in the appreciation of PM by at risk women and their doctors[44].

In the Netherlands and the UK the demand for this procedure is high, whereas in France and other countries the procedure is rarely performed. This difference is likely related to a more general negative attitude towards PM in these countries.

The issue of sexual functioning after prophylactic surgery has received little attention until now. In studies that used questionnaires to address the issue of sexuality, no[41] or some[40, 42] detrimental effects on women's sexual relationship were found. However, sexual problems and diminished sexual satisfaction have been reported in two interview studies[45, 46]. Since sexual functioning is an intimate issue, aspects of sexual functioning might be easier expressed in the private atmosphere of an interview than in a questionnaire. We therefore recommend including interviews in future research on the effects of prophylactic surgery.

To our knowledge, this is the first long-term psychological follow-up study of women who opted for genetic predisposition testing for BRCA1/2. For a longitudinal study, the dropout was modest (24% dropped out between informed consent and the last assessment) and dropouts were equally distributed among participants with respect to marital status, educational level, having children and baseline hereditary cancer related distress. Carriers who opted for PM were, however, overrepresented in our group when compared to the group of identified carriers at our center[4]. Furthermore, the groups of women opting for PM or PBSO were too small to determine whether PM or PBSO had more detrimental effects on sexual functioning. Our impression is that PM has more detrimental effects on body image and PBSO on sexual functioning. Future research on the long-term impact of cancer genetic predisposition testing in larger and more representative groups is needed to identify the impact of PM and PBSO on sexual functioning separately. Finally, this study exclusively assessed a group of self-selected women who all wanted genetic predisposition testing. In order to learn more about women declining genetic predisposition testing, we asked declining women eligible for testing in our surveillance program to participate in our study[47]. This resulted in a group that was too small to be compared with the test acceptors. Consequently, we cannot generalize the results of this study to all women eligible for cancer genetic predisposition testing.

Our results have several clinical and practical implications. We recommend that genetic counselors pay additional attention to women with high event-related distress, women who lost one or more family member to breast/ovarian cancer and women having young children. The issue of how the test-applicant discusses hereditary cancer related issues with relatives also merits standard evaluation. At genetic test disclosure it might be helpful to provide a copy of the test result to some non-carriers who have difficulties believing the test result and to inform them more extensively on the molecular genetic test procedures used. Before performing prophylactic surgery, it is essential to address the issues of sexuality and body image thoroughly. The way the woman experiences her sexuality and body image should be explored and the possibilities of coping with the consequences of surgery should be discussed. Additional attention is mandatory for single women, because for them, starting a new (sexual) relationship may be problematic. In the follow-up contacts with the specialist after PM and PBSO, sexual functioning should be one of the standard issues explored to ensure that women are referred to a sexologist or a psychotherapist when necessary. For the carriers opting for surveillance, no standard psychological follow-up seems mandatory, but future research needs to confirm this.

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CHAPTER 4

Comparison of individuals opting for *BRCA1/2* or HNPCC genetic susceptibility testing with regard to coping, illness perceptions, illness experiences, family system characteristics and hereditary cancer distress

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Abstract

Objective: To study differences between individuals opting for genetic cancer susceptibility testing of a known familial *BRCA1/2* and HNPCC related germline mutation.

Methods: Coping, illness perceptions, experiences with cancer in relatives and family system characteristics were assessed in 271 applicants for genetic testing before test result disclosure. Hereditary cancer distress, worry and cancer risk perception were assessed before, one week after, and six months after disclosure.

Results: Individuals from *BRCA1/2* and HNPCC mutation families did not differ with regard to the number of experiences with cancer in relatives, grief symptoms, the course of cancer distress, worry and risk perception through time and most illness perceptions, coping responses and family characteristics. Individuals from *BRCA1/2* families perceived hereditary cancer as more serious. They reported more frequently a passive coping style, cancer worry and a less open communication with their partner and children.

Conclusion: Besides subtle differences, psychological mechanisms may be mainly identical in individuals opting for *BRCA1/2* and HNPCC susceptibility testing.

Practice implications: Based on our findings, using a similar counseling approach for individuals opting for *BRCA1/2* or HNPCC genetic susceptibility testing is justified. In this approach, attention should be directed more to individual aspects than to the type of disorder.

INTRODUCTION

Genetic testing for a cancer predisposition has become a usual component of clinical practice over the last years. Hereditary Nonpolyposis Colorectal Cancer (HNPCC) and hereditary breast and ovarian cancer due to a *BRCA1/2* mutation are the most prevalent hereditary cancer syndromes. Several similarities exist between these two cancer syndromes. Both imply a high risk of developing cancer after the age of 25 years, that may cause fear of intense physical suffering, death and of leaving children and loved ones behind far before the time that would be appropriate in the family life cycle[1, 2]. The mode of inheritance of both predispositions is autosomal dominant, meaning that a carrier has a 50% risk to pass the mutation on to his children. Furthermore, early detection or prevention strategies are available for both cancer syndromes. The uptake of genetic susceptibility testing of individuals from *BRCA1/2* and HNPCC mutation families at 50% risk of carrying the familial mutation is moreover identical, i.e. 57% in our clinic[3, 4]. Motivations to opt for genetic testing were also found to be similar, including obtaining certainty about the own risk, the necessity of risk management and the risk for offspring[5, 6]. With regard to psychological well-being, adjustment to both HNPCC and *BRCA1/2* genetic testing has been shown to be adequate. Non-carriers from families with a *BRCA1/2* or HNPCC mutation generally show improvements in well-being after result disclosure, while mutation carriers report stable levels or a temporary decrease in well-being[7].

Besides these similarities, important differences also exist between the two cancer syndromes. First, a predisposition for HNPCC implies a high risk to develop colorectal and/or endometrial cancer, while a *BRCA1/2* mutation implies a high risk of breast and ovarian cancer. A *BRCA1/2* gene mutation thus mainly affects women, while HNPCC confers risks to both men and women. A *BRCA1/2* mutation moreover may affect parts of the body involved in femininity and sexuality. Second, the nature of the prevention strategies is different. Unique for *BRCA1/2* mutation carriers is the choice between screening, that cannot prevent the development of cancer, and prophylactic mastectomy with or without breast reconstruction, which is a drastic decision. Screening for HNPCC consists of colonoscopy and removal of detected polyps at a premalignant stage, that is very unpleasant but has proved to reduce the risk of developing colorectal cancer[8].

Genetic cancer susceptibility testing can be conceived as a way of coping with the threat of familial cancer[9]. Several psychological characteristics are important in this coping process. According to the self-regulation model of Leventhal et al.[10], patients create their own understanding or representations of the illness, which determine coping responses, health behavior and finally psychological well-being. Cognitive representations of the illness may have been formed by earlier experiences with the illness in close relatives, for example in parents[11-14]. Furthermore, family system characteristics may affect illness representations, coping and psychological well-being[15], since genetic testing is a family matter[1, 16, 17]. All these psychological issues are of importance for the counseling of individuals at risk of hereditary cancer.

Recently we have described a counseling model for individuals opting for *BRCA1/2* and HNPCC genetic testing [18], that is currently used in several family cancer clinics in the world[19]. Individuals opting for genetic testing of an identified *BRCA1/2* or HNPCC related family mutation are seen for an intake session where medical, psychological and social consequences

of genetic testing are discussed, the need for psychological support is assessed and blood sampling may be performed upon request. In a second session, the test result is disclosed and its implications are discussed. To our knowledge, it is not known whether a similar counseling approach for individuals from families with a *BRCA1/2* or HNPCC mutation is fully justified, since no empirical studies have evaluated the psychological differences between individuals opting for HNPCC or *BRCA1/2* genetic testing.

The present study reports findings from a prospective multi-center research project that studied the role of experiences with cancer and family characteristics on psychological adjustment to genetic susceptibility testing for a *BRCA1/2* or HNPCC related pathogenic mutation. The objective of this study was to compare counselees from families with an identified mutation in *BRCA1/2* or in one of the HNPCC related genes, in order to make recommendations to further adjust the counseling to the specific needs of patients. We focused upon differences with regard to 1) experiences with hereditary cancer in the family, 2) illness representations 3) coping 4) family system characteristics and 5) the level and course of hereditary cancer distress, cancer worry and risk perception.

METHODS

Participants

Applicants for genetic susceptibility testing for a known familial pathogenic *BRCA1/2* mutation or a mutation predisposing to HNPCC (*MSH2, MLH1 or MSH6*) aged 18 years or older were asked to participate in a psychological follow-up study. Applicants were eligible for the study if they had a relative with an identified gene mutation (e.g. were at 50, 25 or 12.5% risk of the mutation), irrespective of cancer status and of the decision to proceed with genetic testing. We excluded individuals with insufficient proficiency in the Dutch language. Males from *BRCA1/2* mutation positive families were excluded because they are not at high risk of developing cancer themselves and the research project aimed at studying coping with an increased risk to develop cancer. Recruitment took place from January 2003 to October 2004 at the Rotterdam Family Cancer Clinic of the Erasmus MC, the Center of Human and Clinical Genetics of the Leiden University Medical Center and the Department of Medical Genetics of the University Medical Center Groningen (only individuals at risk of HNPCC).

Procedure

Genetic counseling

Individuals from families with a *BRCA1/2* and a HNPCC mutation who applied for genetic testing were counseled following a similar procedure[18]. Applicants received at least two counseling sessions. Blood sampling generally took place at the end of the first counseling session if the applicant proceeded with genetic testing. The test result was disclosed during a counseling session six to ten weeks after blood sampling. Thereupon, applicants received a letter with the test result and screening recommendations. The three participating institutions adhered to the national guidelines on genetic counseling and therefore communicated the same cancer risks for the respective mutations and used the same counseling model. Psychosocial support was available for all patients on the patient's request.

Study procedure

Written consent was obtained from participants at the first counseling session. The first questionnaire was mailed one week after the first counseling session. Participants who proceeded with genetic testing received a second and a third questionnaire one week and six months, respectively, after result disclosure. Participants who refrained from genetic testing received no second questionnaire, but filled in the third questionnaire eight months after the first counseling session. The study was approved by the medical ethics committees of the participating institutions.

Measures

Demographic and medical history information

Data were obtained on age, gender, marital status, having children, educational level, cancer status, familial mutation and pretest genetic risk.

Experiences with cancer in the family and grief symptoms

At the first measurement, information was gathered on the number and relationship with relatives who developed cancer and died of cancer. Perceived closeness to affected relatives and involvement in the care of relatives were assessed by Likert type five-point scale items. Information was gathered on the age at which participants were informed about the identification of the mutation and if one of their parents was a mutation carrier.

Grief symptoms were assessed with the inventory of complicated grief[20], that was designed to pick up problematic grief reactions and has been validated in a Dutch population[21].

Illness perceptions

Illness perceptions were assessed at the first measurement by the IPQ-R[22]. The illness identity scale was excluded. The items on illness representations and causal attributions were anchored on hereditary cancer (Table 1). Principal Component Analysis with Varimax rotation was used to define the structure of the causal attributions items and resulted in four factors. Heredity was treated as a single item on theoretical grounds. The reliability of the illness representations and causal attributions subscales was evaluated by Cronbach's alpha. The chance and immune system scales had reliabilities lower than 0.70 and could not be improved by item reduction. The immune system scale was for that reason excluded from the analyses, while the items from the chance subscale were used separately. The reliabilities of the timeline, timecycle and consequences scales could be increased by removing items to 0.68, 0.67 and 0.72, respectively.

Coping

Coping was assessed at the first measurement by the Utrecht Coping List-29[23, 24] that was anchored to coping with hereditary cancer (Table 1). Principal Component Analysis with Varimax rotation resulted in eight factors. Reliabilities of the comforting thoughts and avoidance scales could not be improved by deleting items and these scales were therefore excluded from the analyses.

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

Scale	Examples of items	Number of items	α*
Cognitive representations (IPQ-R)			
Timeline	It is likely to be permanent rather than temporary, it will last for a long time	6	0.65 #
Timecycle	The symptoms change a great deal from day to day, it is very unpredictable	4	0.61 #
Consequences	It is a serious condition, it has major consequences on my life	6	0.66 #
Personal control	There is a lot which I can do to control it, I have the power to influence it	6	0.73
Treatment control	Treatment will be effective in curing my illness, there is little to be done to improve it (r)	5	0.72
Illness coherence	The symptoms are puzzling to me (r), it doesn't make any sense to me (r)	5	0.70
Emotional representations	When I think about it I get upset, I get depressed when I think about it	6	0.85
Causal attributions (IPQ-R)			
Heredity	Hereditary - it runs in the family	1	-
Chance	Chance or bad luck, ageing	2	0.35 ~
Risk factors	Diet or eating habits, smoking, alcohol, pollution, own behavior	5	0.82
Psychological functioning	Stress, emotional state, mental attitude, family problems or worries, personality, overwork	6	0.89
Immune system	Germ or virus, altered immunity, accident or injury	3	0.59 ~
Coping (UCL-29)			
Social support seeking	Sharing worries, showing feelings, looking for understanding	5	0.84
Distraction seeking	Seeking distraction, meeting happy company, thinking about other things	4	0.77
Active coping	Observe the problem, think of different options, make directed action plans	4	0.79
Passive coping	Pessimistic view, feeling overwhelmed, feeling incapable of dealing with it	3	0.70
Religious coping	Praying, seeking comfort in religion, thinking it has a meaning	3	0.82
Adapting expectations	Changing expectations, needs, priorities	3	0.75
Comforting thoughts	Thinking worse things can happen, saying it will be alright, thinking about problems of others	3	0.56 ~
Avoidance	Accepting the situation, not undertaking action	2	0.62 ~

* Cronbach's alpha
(r) reverse scored; # coefficient was improved after item reduction; ~ scale excluded from the analyses

Family system characteristics

Several family system characteristics were assessed at the first measurement. *Cohesion and adaptability with partner and children* were measured with the Dutch validated version of the Family Adaptability and Cohesion Evaluation Scales[25, 26]. Cohesion was defined as a continuum from disengaged to enmeshed, adaptation as a continuum from rigid to chaotic. Reliability (Cronbach's α) of the Cohesion and Adaptation subscales was 0.87 and 0.81[26]. Participants were assigned to a maladjusted group (n=14) if their score on cohesion and adaptability was lower than the 30th percentile (disengaged-rigid) or higher than the 60th percentile (enmeshed-chaotic) and an adjusted family functioning group having moderate scores, according to the Circumplex model[27].

The extent to which individuals felt *differentiated to their mother and father* was assessed with the Differentiation in the Family System Scale[28]. Differentiation was defined as both a sense of emotional connectedness (support, involvement) and a sense of separateness (autonomy, uniqueness, freedom of personal expression). Participants were assigned to a low differentiated group (n=27) if they scored lower than the mean on differentiation to mother and to father. Reliability (Cronbach's α) of differentiation to mother and father in our sample was 0.85 and 0.88, respectively.

Familial communication style concerning hereditary cancer was measured at the first assessment by the Openness to Discuss Hereditary Cancer in the Family Scale[16, 29]. The scale was validated in a group of women from families with a *BRCA1/2* mutation and provides an assessment of communication in the nuclear family (Cronbach's α = 0.78) and in the family of origin (Cronbach's α =0.82).

Perceived social support from partner, parents and siblings was measured at the first assessment by 5-point scale items like "I feel supported by my partner/parents/siblings in this phase of the genetic susceptibility testing process". Reliability (Cronbach's α) was 0.83.

Cancer related psychological distress

At each measurement, participants completed the Impact of Event Scale Revised[30, 31] measuring *hereditary cancer related distress* and four items of the Cancer Worry Scale[32] to measure *cancer worry*. Both measures have good psychometric properties[33, 34].

Cancer risk perception

Cancer risk perception was assessed at each measurement, using an item that was used in similar studies[35], i.e. "Independent of my actual risk, I feel my risk of developing cancer is 'not likely' (1) to 'very likely'" (7).

Data analysis

The data were analyzed using Statistical Package for Social Sciences (version 11.0) and Proc Mixed (SAS System, version 8.2). Demographic and clinical characteristics of the study sample

were analyzed using exact tests for categorical variables and T-tests for continuous variables. The probability level for statistical significance testing was set at 0.05 (two-tailed). The method of logistic regression was used to analyze differences in experiences with cancer in the family, illness representations, coping with genetic cancer risk and family system characteristics between participants from *BRCA1/2* and HNPCC mutation families. In these analyses we adjusted for sex, age, having children, educational level, cancer status and pretest genetic risk.

In order to determine the course of hereditary cancer distress, cancer worry and risk perception over time in mutation carriers and non-carriers from *BRCA1/2* and HNPCC mutation families, SAS Proc Mixed random effects modelling was used. The method of estimation was REML (residual maximum likelihood) and the error structure was defined as unstructured. For each outcome variable, the model building strategy started with the intercept, time and time squared in the random part, and time and time squared in the fixed part. To test whether a simpler random model was allowed, the difference between the two –2 log likelihoods was compared with the $X^2_{3:2}$-distribution. This means that the *P*-value equaled the average of the *P*-value taken from the X^2-distribution with two and three degrees of freedom, respectively. Releasing time squared from the random part resulted in a simpler model without losing substantial information. Subsequently, we entered confounding variables (sex, age, cancer status), predictor variables (hereditary cancer syndrome, genetic test result) and interaction effects in the fixed part of the model.

RESULTS

Study population

Figure 1 shows detailed numbers of accrual and received questionnaires. 271 patients participated in the study. Non-participants (23%) and participants who were lost to follow-up (3%) did not differ from participants with regard to age, gender, having children, cancer syndrome, pre-test genetic risk and cancer status.

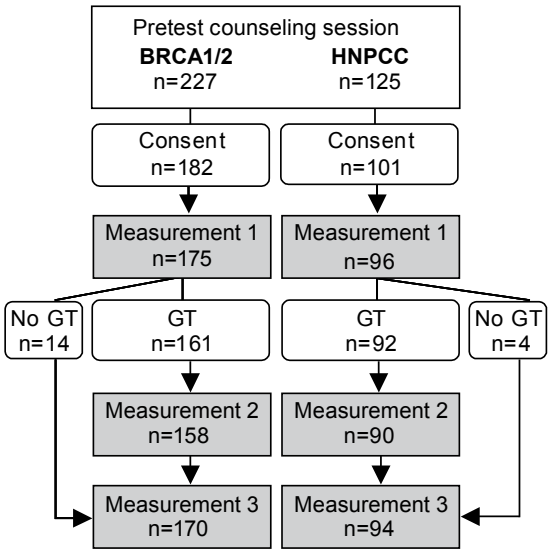


Figure 1. Uptake en response to questionnaires of participants. GT, genetic testing

Non-participants however more often refrained from genetic testing than participants ($\chi^2 = 9.4$; $P < 0.01$). Participants belonged to 96 different *BRCA1/2* and 45 different HNPCC mutation families (1.9 individuals per family, range 1-12). The majority was unaffected by cancer and willing to proceed with genetic testing and receive results (Table 2). Twenty-one patients were affected by cancer: nineteen had finished treatment 6 months to 28 years ago; two were diagnosed after having completed the second measurement and were excluded from the third measurement.

Experiences with cancer in relatives

Except for the difference in the gender of affected relatives, no significant differences were found between participants from families with a *BRCA1/2* or HNPCC mutation with regard to time since learning that the specific mutation runs in the family, number of affected or deceased relatives, closeness to affected relatives and grief symptoms (Table 3).

Illness perceptions

No significant differences were found in causal attributions of hereditary cancer between participants from *BRCA1/2* and HNPCC mutation families (Table 4). Participants indicated that HNPCC or *BRCA1/2* was caused by heredity and to a lesser extent by chance and ageing.
With regard to cognitive representations of the hereditary cancer syndrome, participants from *BRCA1/2* mutation families perceived the consequences of hereditary cancer as more serious ($P < 0.05$) and tended to perceive less personal control over the development of the illness ($P = 0.06$) than participants from families with a HNPCC related mutation. No other significant differences were reported.

Coping

BRCA1/2 participants significantly more frequently felt overwhelmed by and unable to cope with the genetic risk (i.e. passive reaction, $P < 0.05$). No significant differences were found in other coping responses with the genetic risk between *BRCA1/2* and HNPCC participants (Table 5).

Family system characteristics

Mean values of cohesion and adaptability fell within the normal range (Table 6). Participants from HNPCC mutation families reported that the communication about hereditary cancer with partner and children was significantly more open than participants from *BRCA1/2* mutation families ($P < 0.01$). No other significant differences in family system characteristics were found.

Table 2. General and demographic characteristics of the study population, and mean values of distress before test result disclosure

	BRCA1/2 n=175		**HNPCC** n=175		
	n	%	*n*	%	*P*
Age					
Mean (*S.D.*)	42.5 (12.1)		41.0 (13.3)		.40
Gender					
Women	175	100.0	64	66.7	
Men	0	0.0	32	33.3	
Marital status					
Married or cohabiting	135	77.1	78	81.3	.55
Single, divorced, widowed	40	22.9	18	18.8	
Having children					
Yes	121	69.1	65	67.7	.89
No	54	30.9	31	32.3	
Education					
<high school	46	26.3	18	18.8	.28
some college	84	48.0	53	55.2	
>college	45	25.7	25	26.0	
Cancer status					
Unaffected	159	90.9	91	94.8	.34
Affected	16	9.1	5	5.2	
Pretest genetic risk					
≥50%	123	70.3	73	76.0	.34
25%	41	23.4	19	19.8	
<25%	11	6.3	4	4.2	
DNA-test					
Yes	161	92.0	92	95.8	.31
No	14	8.0	4	4.2	
Carrier status					
Mutation carrier	61	37.9	27	29.3	.17
Non-carrier	100	62.1	65	70.7	
Familial mutation					
BRCA1	135	77.1			
BRCA2	40	22.9			
MLH1			21	21.9	
MSH2			35	36.5	
MSH6			40	41.7	
Hereditary cancer distress predisclosure					
Mean (*S.D.*)	24.3 (18.1)		16.8 (16.7)		<.05*
Cancer worry predisclosure					
Mean (*S.D.*)	7.4 (2.3)		6.4 (1.7)		<.01*

* p-value adjusted for gender, age, having children, cancer status and pretest genetic risk

Table 3. Experiences with cancer in relatives of participants from *BRCA1/2* and HNPCC mutation families

		BRCA1/2		**HNPCC**		
		n=175		n=96		
	range	mean	S.D.	mean	S.D.	*P*
Age learning cancer is hereditary	4-73	38.4	14.1	36.4	15.0	0.27
Years since learning cancer is hereditary	0-45	3.8	7.2	4.7	6.4	0.35
Mother carrier	0-1	0.2	0.43	0.3	0.44	0.86
Father carrier	0-1	0.1	0.3	0.1	0.26	0.50
Parent(s) affected by cancer	0-1	0.6	0.5	0.6	0.5	0.27
Mother affected	0-1	0.5	0.5	0.3	0.5	<0.01
Father affected	0-1	0.2	0.4	0.4	0.5	<0.01
Sibling(s) affected by cancer	0-1	0.3	0.5	0.2	0.4	0.10
Number of sisters affected	0-4	0.5	0.9	0.2	0.5	<0.01
Number of brothers affected	0-3	0.1	0.2	0.2	0.5	<0.01
Parent(s) deceased due to cancer	0-1	0.4	0.5	0.5	0.5	0.34
Mother deceased	0-1	0.3	0.5	0.2	0.4	<0.01
Father deceased	0-1	0.1	0.3	0.3	0.5	<0.01
Sibling(s) deceased due to cancer	0-1	0.2	0.4	0.1	0.3	0.20
Number of sisters deceased	0-3	0.2	0.6	0.1	0.3	<0.05
Number of brothers deceased	0-2	0.1	0.3	0.0	0.2	0.53
Mean involvement in care affected relatives	1-6	4.0	0.9	3.8	1.1	0.65[#]
Mean closeness to affected relatives	1-7	3.3	1.3	3.1	1.1	0.81[#]
Grief symptoms	1-91	20.1	18.1	19.2	17.7	0.76[#]

[#] P-value adjusted for sex, age, having children, educational level and pretest genetic risk

Table 4. Illness representations and causal attributions of hereditary cancer reported by participants from *BRCA1/2* and HNPCC mutation families

		BRCA1/2		**HNPCC**		
		n=175		n=96		
	range of scale	mean	S.D.	mean	S.D.	*P*
Illness representations						
Timeline	5-25	17.8	3.9	16.7	4.2	0.67
Timecycle	3-15	9.1	2.0	8.7	2.3	0.23
Consequences	4-20	17.4	2.5	16.2	3.3	<0.05
Personal control	6-30	16.4	3.8	18.7	3.8	0.06
Treatment control	5-25	16.0	3.0	17.5	2.9	0.16
Illness coherence	5-25	14.4	3.0	13.2	3.3	0.42
Emotional representations	5-25	16.8	3.9	15.0	3.8	0.75
Causal attributions						
Attribution to heredity	1-5	4.6	0.6	4.5	0.6	0.19
Attribution to chance	1-5	3.4	1.2	3.5	1.2	0.10
Attribution to ageing	1-5	3.0	1.0	3.3	1.2	0.55
Risk factor attributions	1-5	2.8	0.8	2.9	0.8	0.61
Psychological attributions	1-5	2.5	0.8	2.5	0.9	0.76

[#] P-value adjusted for sex, age, having children, educational level, cancer status and pretest genetic risk

Table 5. Coping with the genetic risk as reported by participants from *BRCA1/2* and HNPCC mutation families

		BRCA1/2		**HNPCC**		
		n=175		n=96		
	range of scale	mean	S.D.	mean	S.D.	*P*
Social support seeking	5-20	11.3	3.0	10.2	2.7	0.43
Distraction seeking	4-16	7.8	2.4	7.0	2.6	0.80
Active coping	4-16	9.7	2.7	9.4	2.9	0.89
Passive coping	3-12	4.4	1.6	3.9	1.3	<0.05
Religious coping	3-12	4.5	2.1	4.4	2.0	0.52
Adapting expectations	3-12	5.1	1.8	4.6	1.9	0.75

[#] P-value adjusted for sex, age, having children, educational level, cancer status and pretest genetic risk

Table 6. Family system characteristics of participants from *BRCA1/2* and HNPCC mutation families

		BRCA1/2 n=175		**HNPCC** n=96		
	range of scale	mean	S.D.	mean	S.D.	*P*#
Cohesion	23-92	71.3	7.5	69.8	7.3	0.22
Adaptability	13-52	20.6	4.3	20.4	4.1	0.99
Maladaptive family functioning	0-1	0.06	0.2	0.04	0.2	0.21
Support partner	2-10	8.9	1.9	8.8	2.1	0.15
Open communication partner, children	7-35	29.2	5.4	31.3	4.5	<0.01
Differentiation mother	11-55	44.6	8.2	43.2	7.8	0.32
Differentiation father	11-55	43.7	8.0	39.7	9.5	0.06
Low differentiation to mother and father	0-1	0.10	0.3	0.10	0.3	0.47
Support parents, siblings	2-10	7.6	2.5	6.9	2.2	0.52
Open communication parents, siblings	7-35	28.7	6.4	29.7	5.7	0.97

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

Level and course of hereditary cancer distress and perceived risk

Figures 2 to 4 display the course of hereditary cancer related distress, cancer worry and risk perception in *BRCA1/2* and HNPCC carriers and non-carriers. Generally, distress and worry increased slightly in carriers after result disclosure and decreased 6 months after result disclosure. Non-carriers remained at the same level of distress shortly after result disclosure but their scores decreased 6 months after result disclosure. With regard to perceived risk, mutation carriers generally perceived an increased risk shortly after result disclosure while non-carriers reported a substantial decrease in risk perception.

Differences between carriers and non-carriers from *BRCA1/2* and HNPCC mutation families in level and course of hereditary cancer distress, cancer worry and risk perception are displayed in Table 7. Participants from *BRCA1/2* mutation families did not differ significantly from participants from HNPCC mutation families with regard to the level ($P = 0.42$) and course ($P = 0.16$) of perceived risk. The level of distress ($P < 0.05$) and worry ($P < 0.001$) differed significantly between participants from *BRCA1/2* and HNPCC mutation families over the study period, but no significant differences in the course of distress ($P = 0.21$) and worry ($P = 0.36$) were observed.

Regression analyses of distress levels at each measurement separately resulted in a significant difference between participants from *BRCA1/2* and HNPCC mutation families in the level of hereditary cancer distress and cancer worry at the time of blood sampling ($\beta = 0.16$, $P < 0.05$ and $\beta = 0.22$, $P < 0.01$, respectively) and in more cancer worry in non-carriers from *BRCA1/2* mutation families as compared to non-carriers from HNPCC mutation families after result disclosure ($\beta = 0.20$, $P < 0.05$) and six months after result disclosure ($\beta = 0.21$, $P < 0.05$).

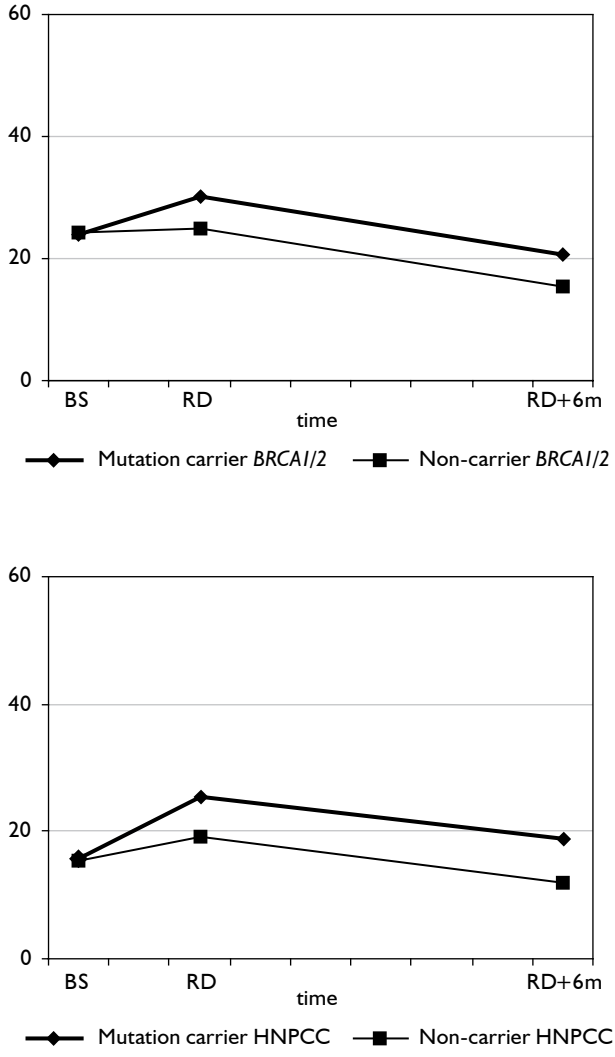
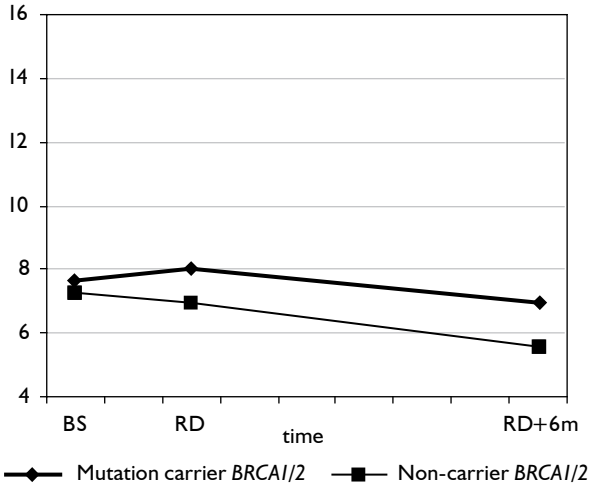


Figure 2. Course of hereditary cancer distress in mutation carriers and non-carriers from *BRCA1/2* and HNPCC mutation families
BS, blood sampling; RD, result disclosure; RD+6m, six months after result disclosure



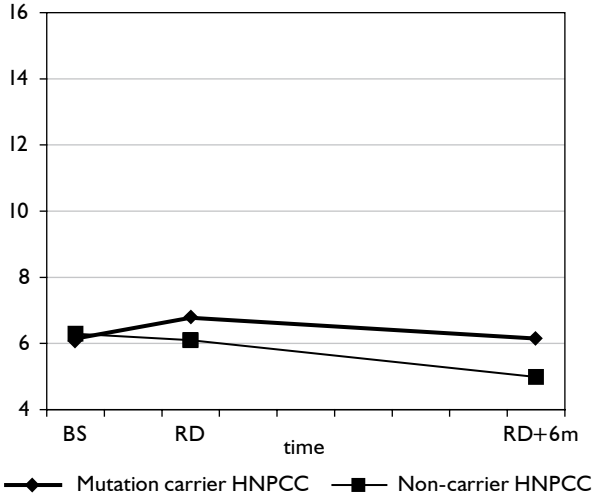
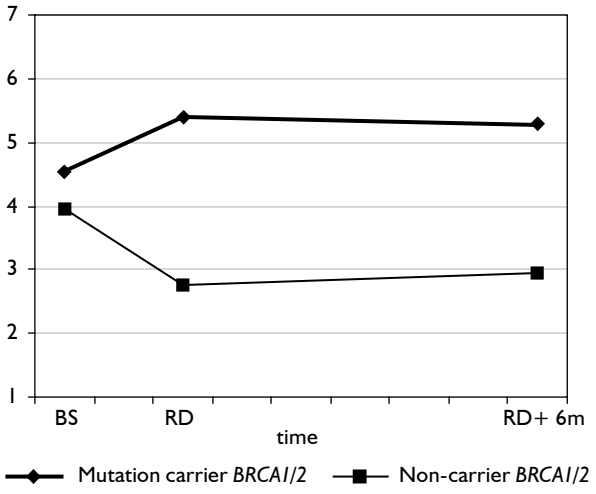


Figure 3. Course of cancer worry in mutation carriers and non-carriers from *BRCA1/2* and HNPCC mutation families
BS, blood sampling; RD, result disclosure; RD+6m, six months after result disclosure



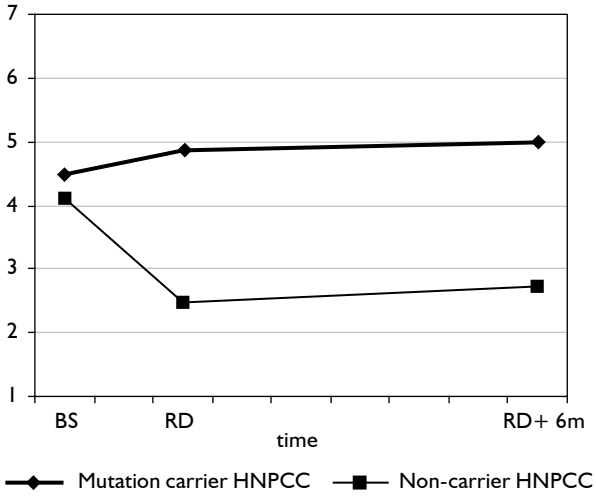


Figure 4. Course of risk perception in mutation carriers and non-carriers from *BRCA1/2* and HNPCC mutation families
BS, blood sampling; RD, result disclosure; RD+6m, six months after result disclosure

Table 7. Estimates of hereditary cancer distress, cancer worry and risk perception for mutation carriers and non-carriers from *BRCA1/2* and HNPCC mutation families, adjusted for age, gender and cancer status.

	Hereditary cancer distress			Cancer worry			Risk perception		
Effect	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*
Intercept	10.29	4.44	<0.05	6.8	0.47	<0.001	4.41	0.33	<0.001
Linear time trend	5.07	1.36	<0.001	0.05	0.15	0.73	-0.95	0.14	<0.001
Quadratic time trend	-1.22	0.24	<0.001	-0.06	0.03	<0.05	0.14	0.03	<0.001
Carrier status	2.08	2.43	0.39	0.32	0.28	0.25	1.16	0.19	<0.001
Cancer syndrome	6.51	2.56	<0.05	1.12	0.30	<0.001	0.16	0.20	0.42
Time*carrier status	1.42	0.75	0.06	0.23	0.09	<0.01	0.34	0.07	<0.001
Time*cancer syndrome	-0.72	0.57	0.21	-0.06	0.07	0.36	0.07	0.05	0.16
Time*carrier status *cancer syndrome	-0.12	0.17	0.47	-0.01	0.02	0.43	-0.03	0.02	0.09

Estimates adjusted for age, gender and cancer status

DISCUSSION AND CONCLUSION

Discussion

Striking similarities were observed between individuals from families with a *BRCA1/2* and HNPCC related mutation opting for genetic susceptibility testing. No differences were observed in time since learning about hereditary cancer, number of affected or deceased relatives, involvement and closeness with affected relatives or grief symptoms. Cognitive representations and causal attributions of the illness were almost identical, as were coping responses. In addition, the family system characteristics of individuals from *BRCA1/2* and HNPCC mutation families were almost similar, as were the courses of hereditary cancer distress, cancer worry and risk perception through time. Probably, individual characteristics determine the adjustment to genetic testing more than the type of disorder, as was found in a similar study from our group on genetic testing for several autosomal dominant inheritable late onset disorders[36].

The observed psychological differences between individuals from *BRCA1/2* and HNPCC mutation families were subtle and should be interpreted with caution in view of the many variables tested. The most important differences included perceptions of the consequences of hereditary cancer, resulting in a more positive outlook for individuals from families with a HNPCC related mutation. One of the coping responses and the level of distress differed accordingly. Individuals from *BRCA1/2* positive families more frequently felt incapable of doing something about the risk

than individuals from HNPCC mutation families, and reported more hereditary cancer related distress before result disclosure and more cancer worry at each measurement. These differences in representations, coping and distress may be due to the availability of colonoscopy to HNPCC mutation carriers, that has proven to be effective in preventing the development of cancer, and has not the mutilating consequences of prophylactic mastectomy, nor the more unsure efficacy of breast cancer screening. The differences might also be attributed to the fact that *BRCA1/2* affects women, and that losing a mother may have a greater impact than losing a father, especially to female relatives[37]. It is unlikely that the reported differences between the two groups were due to gender differences, since we have adjusted for gender in the analyses and gender was only marginally related to some measures.

Another difference between the two cancer syndromes was that individuals from HNPCC mutation families felt it was easier to talk about hereditary cancer with the partner and children as compared to individuals from *BRCA1/2* mutation families. In view of the more threatening perception of *BRCA1/2*, individuals from *BRCA1/2* mutation families might be more reluctant to communicate about hereditary cancer in order to protect the partner and children from psychological suffering, also called 'protective buffering'[38]. Finally, non-carriers from *BRCA1/2* mutation families were more worried about developing breast/ovarian cancer than non-carriers from HNPCC mutation families about developing colorectal cancer, while no significant differences were found in cancer worry between the carriers from both groups. This difference may be due to the fact that non-carriers of a *BRCA1/2* mutation continue to have a population lifetime risk of 1 in 8 to develop breast cancer, while the non-carriers of a HNPCC related mutation have a population lifetime risk of colorectal cancer of 1 in 17.

The psychological similarities between the two cancer syndromes may explain the consistent uptake of genetic testing in both populations. Besides individual characteristics like having children[3], risk perception[39, 40] and distress levels[40, 41], the uptake of genetic testing also depends on the perceived seriousness of disease and the availability of preventive options. The uptake of genetic testing in The Netherlands varied from about 24% for Huntington's disease [42] up to almost 100% for familial hypercholesterolaemia[43]. Individuals from *BRCA1/2* mutation families might be more motivated to opt for genetic testing because they perceive hereditary cancer as more serious than individuals from HNPCC mutation families, while individuals from HNPCC mutation families might be more motivated to opt for the test because they may perceive a higher preventability than individuals from *BRCA1/2* mutation families. The higher perceived seriousness of *BRCA1/2* might thus be compensated by the higher perceived preventability of HNPCC, equaling out the possible differences in genetic test uptake.

The course of distress in our population was identical to that found in other studies on the psychological impact of genetic susceptibility testing[44] and the effect of the genetic test result on the perceived risk of developing cancer was comparable to other studies[45]. With regard to illness representations, our participants perceived the consequences of a *BRCA1/2* and HNPCC related mutation as highly serious and the controllability in preventing the illness as intermediate, while Claes et al. found an intermediate perceived seriousness and a too optimistic perceived controllability of the illness in HNPCC[46] and *BRCA1/2*[47] test-applicants. The differences between this study and ours may be due to different instruments used and to cultural differences.

To our knowledge, this is the first empirical study to have analyzed differences in psychological functioning of individuals from *BRCA1/2* and HNPCC identified gene mutation families

undergoing genetic testing. Strengths of our study were the prospective study design, large sample size, low drop out rate and method of statistical analyses in which we adjusted for confounding variables. However, we cannot exclude the possibility that the instruments used may have failed to detect subtle differences. Furthermore, it may not be justified to generalize our findings to individuals who do not opt for genetic testing, even more so since they participated less often in our study than individuals who opted for the test. Finally, comparing psychological characteristics of individuals opting for *BRCA1/2* and HNPCC genetic testing to those of individuals opting for genetic testing for disorders with different implications like Li-Fraumeni, Huntington's disease or familial hypercholesterolaemia, would be necessary to draw more firm conclusions with regard to the similarities between these two most common cancer syndromes.

Conclusion

Despite several differences, like the more positive outlook for individuals from HNPCC mutation families, we found mainly identical psychological functioning characteristics in individuals from *BRCA1/2* and HNPCC mutation families who presented for genetic susceptibility testing. These important psychological similarities suggest that there may be psychological mechanisms at work that are common to individuals who decide to undergo cancer genetic susceptibility testing for these adult onset cancer syndromes for which early detection or prevention options are available.

Practice implications

In view of the important psychological similarities between the two cancer syndromes, a similar counseling model for individuals from *BRCA1/2* and HNPCC mutation families is justified. Individual aspects are more important to take into account in the counseling than the type of disorder. Counselors may help their counselees by exploring individual experiences, perceptions of risk, control and curability, and coping efforts. Especially, fostering feelings of control by informing mutation carriers in a realistic manner about improved early detection or prevention methods and improved curability of cancer may be important. In our clinical experience, we have encountered mutation carriers who never have considered the fact that medical possibilities in care and cure of cancer have improved over the last years and that they will not necessarily have to suffer or die from cancer like their relatives did many years ago.

Our findings furthermore may have implications for future research on psychological aspects of genetic cancer susceptibility testing. Based on our findings, studying individuals from *BRCA1/2* and HNPCC mutation families together could be justified, if statistical analyses are adjusted for the subtle differences of each cancer syndrome.

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CHAPTER 5

A prospective study of the impact of genetic susceptibility testing for *BRCA1/2* or HNPCC on family relationships

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Abstract

This study assessed the impact of genetic testing for cancer susceptibility on family relationships and determinants of adverse consequences for family relationships. Applicants for genetic testing of a known familial pathogenic mutation in *BRCA1/2* or a HNPCC related gene (*N*=271) rated the prevalence and nature of changes in family relationships, familial difficulties and conflicts due to genetic testing 6 months after receiving the test result. The level of family functioning, differentiation from parents, support and familial communication style regarding hereditary cancer were assessed before receiving the test result. Genetic testing affected some family relationships in a positive way (37%), i.e. by feeling closer, improved communication and support, more appreciation of the relative and relief of negative test result. A minority reported unwanted changes in relationships (19%), problematic situations (13%) or conflicts (4%). Adverse effects comprised feelings of guilt towards children and carrier siblings, imposed secrecy and communication problems. Predictors of adverse consequences on family relationships were reluctance to communicate about hereditary cancer with relatives and disengaged-rigid or enmeshed-chaotic family functioning. Open communication between relatives should be stimulated because a lack of open communication may be an important determinant of familial adverse effects.

INTRODUCTION

The impact of genetic susceptibility testing for a cancer predisposition like a *BRCA1/2* mutation (high risk of breast/ovarian cancer) or HNPCC (Hereditary Nonpolyposis Colorectal Cancer, high risk of colon/endometrial cancer) related mutation on psychological well-being is well known by now. Unaffected non-carriers show improvements in well-being after disclosure of the test result, while mutation carriers report stable levels or a temporary decrease in well-being[1]. The psychological impact of genetic testing depends partly on the familial context. The genetic test results of other family members[2, 3], support provided by the partner[4] and changed family relationships due to genetic testing[5] have been reported to affect psychological well-being. Cancer genetic susceptibility testing can furthermore have far reaching consequences for family relationships. Information from and collaboration with other relatives is often necessary in order to identify the familial gene mutation, implying communication about painful experiences with the family disease and loss, or asking help from relatives with whom the relationship may be distant or conflicted. A subsequent positive test result implies communicating to family members that they have an increased probability to develop cancer, with all the emotional consequences[6].

Although many studies have focused upon the dissemination of information from genetic susceptibility testing[7], empirical studies investigating the impact of cancer genetic susceptibility testing on family relationships are scarce. One recent study evaluated changes in cohesion, expressiveness and conflict in close family relationships of 212 individuals from families with a known *BRCA1/2* gene mutation[8]. Participants reported feeling closer to family members as a result of genetic testing. Two Belgian studies[9, 10] assessed the impact of genetic testing on family relationships in 68 individuals opting for *BRCA1/2* genetic susceptibility testing and 72 individuals opting for genetic testing of a HNPCC related mutation. The frequency of changes in relationships varied between 6% of non-carriers reporting on the relationship with their partner to 40% of mutation carriers reporting on changes in relation to their children. Participants reported mainly positive changes, but unfavorable changes may have been overlooked due to small sample sizes of these studies.

It is unknown which family system characteristics predispose to adverse consequences in family relationships and relational adjustment problems due to cancer susceptibility genetic testing[11]. From a family systems perspective, several characteristics might contribute to dysfunctional relational adjustment. Family cohesion and adaptability have been identified as key characteristics of nuclear family functioning[12, 13]. Cohesion is defined as a sense of togetherness or emotional bonding. Adaptability reflects the degree to which a family can change its power structure, rules and role relationships to meet situational demands. Families with a balanced level of cohesion and adaptability have been found to adjust better to situational and developmental stress[13]. Another predisposing characteristic may be differentiation from parents, defined as the extent to which an individual feels separated from emotional attachments to their parents without damaging these important relationships[14]. Interpersonal differentiation is essential for relational and psychological adjustment[15]. Furthermore, supportive interactions are often expected from family members and partners[16] and the inability of them to provide support could result in relational problems. Finally, communicating in an open manner about painful issues like hereditary cancer is expected to be a prerequisite for good relational adjustment[17].

The present study reports findings from a prospective multi-center research project that studied the effect of experiences with cancer and family characteristics on psychological adjustment to genetic susceptibility testing for hereditary cancer. Objectives of this paper were to investigate 1) whether genetic testing for cancer susceptibility affects family relationships, 2) the nature of this effect on family relationships and 3) whether nuclear family functioning, differentiation from parents, communication style regarding hereditary cancer within the family and perceived familial support are predictive of adverse consequences on family relationships after genetic testing. Awareness of risk factors for familial difficulties is necessary to develop interventions preventing familial difficulties and to identify those who need referral for psychosocial support.

METHOD

Participants and counseling procedure

See Chapter 4.

Study procedure

The first questionnaire, containing all predictive measures, was mailed 1 week after the first counseling session. The questionnaire containing the outcome measures was filled in 6 months after result disclosure. For more details see Chapter 4.

Measures

Outcome measures

Changes in family relationships. Six months after receiving the test result, participants were asked to indicate on a 5-point Likert type scale whether they had experienced changes in their relationship with partner, children, siblings, parents or other relatives due to genetic testing (1-5). If they indicated an impact on one or more relationships (2-5), they were asked to appraise this as positive or negative and to write down a comment on the nature of these changes.

Familial difficulties due to genetic testing. Participants also indicated 6 months after receiving results whether difficult situations or conflicts had arisen between other family members due to genetic testing over the last years (yes, a little, no). If any emerged, they were asked to write down a comment on the type of situation(s) or conflict(s).

Predictive measures

Demographic and medical history information. Data were obtained on age, gender, having children, marital status, educational level, cancer status, familial mutation and pretest genetic risk.

Nuclear family functioning (partner, children). Cohesion and adaptability were measured with the Dutch validated version of the Family Adaptability and Cohesion Evaluation Scales[19, 20]. Cohesion was defined as a continuum from disengaged to enmeshed, adaptation as a continuum

from rigid to chaotic. Reliability (Cronbach's alpha) of the Cohesion and Adaptation subscales was .87 and .81[20]. Participants were assigned to a maladjusted group if their score on cohesion and adaptability was lower than the 30th percentile (disengaged-rigid) or higher than the 60th percentile (enmeshed-chaotic), and an adjusted family functioning group having moderate scores, according to the circumplex model[12].

Differentiation from parents. The extent to which individuals felt differentiated from their mother and father were assessed with the Differentiation in the Family System Scale[21]. Differentiation was defined as both a sense of emotional connectedness (support, involvement) and a sense of separateness (autonomy, uniqueness, freedom of personal expression). Reliabilities (Cronbach's alpha) of differentiation from mother and father were .85 and .88.

Familial communication style concerning hereditary cancer. Familial communication style concerning hereditary cancer was assessed by the Openness to Discuss Hereditary Cancer in the Family Scale[5], an adaptation of the validated measure developed by Mesters *et al.*[22]. The adapted scale was validated in a group of women from *BRCA1/2* families and provides an assessment of communication in the nuclear family (Cronbach's alpha .78) and in the family of origin (Cronbach's alpha .82).

Perceived social support. 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 ranging from 5, 'yes!' to 1, 'no!'. Reliability (Cronbach's alpha) was .83.

Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (version 11.0). The significance level for statistical testing was set at .05 (two-tailed). Demographic and clinical characteristics of participants from *BRCA1/2* vs. HNPCC families were analyzed using exact tests for categorical variables. Percentages were calculated in order to evaluate the number of participants reporting consequences for family relationships (first objective). Exact tests were used to compare demographic and clinical characteristics of participants reporting consequences and participants reporting no consequences.

In order to describe the nature of the reported changes (second objective), two psychologists (IO & AT) created 12 categories for the written comments on the nature of changes in relationships and familial difficulties due to genetic susceptibility testing. After finalizing the categories, four psychologists (IO, AT, SR & SD) independently categorized each comment. Besides the most salient theme, the comments could also be categorized by a second theme. The non-accordant comments were assigned to the most frequently scored category. 67.1% of the comments was rated identically by all; 88.1% was rated identically by three or more and 98.8% was rated identically by two or more psychologists. Inter-rater accordance between the judges varied between 75% and 91%. Two coding themes were deleted due to low frequencies; comments

were assigned to the second theme. Eleven similar comments on changes in relationships and familial difficulties were deleted in order to avoid overlap. In the analysis, we included only the most salient theme in order not to overreport changes in relationships. The final coding themes are summarized in Tables 2 and 3.

The method of logistic regression analysis was used to evaluate whether family system characteristics were predictive of adverse effects on family relationships after genetic testing, adjusted for age and gender (third objective). The sample size with regard to the three outcome variables (negative changes in nuclear family, family of origin and familial difficulties) equaled 168, 188, and 260, respectively. The missing values of the predictive and outcome variables resulted mainly from the fact that some participants had no partner, children, siblings or parent(s) at the time of the study. Missing values were therefore not estimated. First, characteristics from the nuclear family (maladaptive family functioning, hereditary cancer communication style, support from partner) were analyzed as predictive variables and reporting negative changes in one or more nuclear family relationships as outcome variable. Second, characteristics from the family of origin (differentiation from mother, father, hereditary cancer communication style, support from parents and siblings) were analyzed as predictive variables and reporting negative changes in one or more family of origin relationships as outcome variable. Third, characteristics from the nuclear family and family of origin were analyzed as independent variables and reporting familial difficulties and conflicts as outcome variable. Finally, all three models were analyzed by a stepwise selection procedure (backward elimination P_{in}<.05 and P_{out}>.10), in order to evaluate which family characteristic had the most predictive qualities. To give an indication of the predictive power of the final models, the percentage of the explained variance (Nagelkerke's R^2) is presented. The Hosmer and Lemeshow test was used[23] in order to check whether the model assumptions were violated. It was investigated whether the independent variables were highly inter-correlated by Variance Inflation Factors (VIFs). Models having a VIF ≥ 4 were modified in the sense that the variables causing multicollinearity were eliminated.

RESULTS

Study population

See Chapter 4.

Frequency of changes and difficulties in family relationships

About a third of participants (36.7%) reported positive changes in one or more relationships with family members (see Figure 1). A minority of 18.8% reported negative changes in one or more relationships (see Figure 2). Furthermore, 3.5% reported one or more familial conflicts and 13.1% reported one or more difficult situations in the family due to genetic testing. Gene mutation carriers reported significantly more positive changes in relation to their parents ($\chi^2 = 11.9$; $P < .01$) and second-degree family members ($\chi^2 = 15.9$; $P < .01$) than non-carriers. Participants from *BRCA1/2* families reported significantly more frequently negative ($\chi^2 = 4.2$; $P < .05$) or positive changes ($\chi^2 = 6.1$; $P < .05$) in the relationship with their partner and

more negative changes in the relationship with their parents ($\chi^2 = 5.4$; $P < .05$) than participants from HNPCC families. Women did not report significantly more changes or familial difficulties than men.

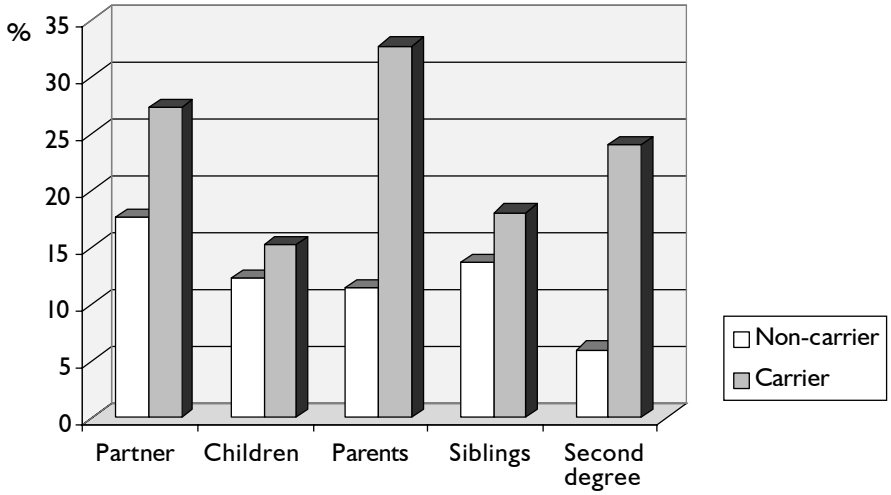

Figure 1. Percentage of mutation carriers and non-carriers reporting positive changes in relationships with family members due to genetic testing.

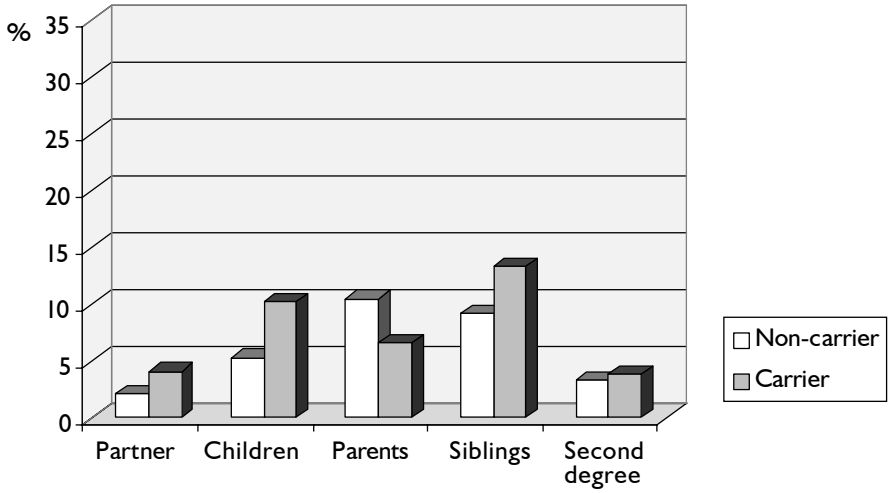

Figure 2. Percentage of mutation carriers and non-carriers reporting negative changes in relationships with family members due to genetic testing.

Comments on nature of changes and difficulties in family relationships

Of the changes and difficulties in relationships that were indicated in the questionnaire, 74% was followed by a written comment; varying between 56% on changes in relationships with children to 84% on changes with second-degree relatives. Participants who wrote down

comments (n = 109) did not differ significantly from the participants refraining from comments (n = 24) with regard to hereditary cancer syndrome, cancer status, genetic test result, age, having children and gender, but they tended to be more often cohabiting ($\chi^2 = 4.2$; $P = .06$) and have more education ($\chi^2 = 5.4$, $P = .07$).

Comments on positive changes are summarized in Table 1. Participants reported feeling closer to their partner and siblings, improved relationships with children after receiving a negative test result, more understanding and support from parents and improved communication towards second-degree relatives. Comments on negative changes in relationships, difficulties and conflicts are summarized in Table 2. The comments on negative changes in the partner relationship comprised keeping more emotional distance because of the fear of becoming ill or misunderstanding each others' coping style. Comments on adverse changes in relation to the children mainly consisted of feelings of guilt about having (possibly) passed the mutation on to children. The comments on adverse changes in relation to parents comprised parents having difficulties in talking about hereditary cancer or genetic testing, perceived guilt feelings and more emotional distance due to a lack of support. The comments on unfavorable changes in relation to brothers and sisters consisted of more distance due to differences in coping style with regard to hereditary cancer, guilt feelings towards mutation carrier siblings and difficulties talking about hereditary cancer or genetic testing. The participants who commented on adverse relational consequences with regard to aunts, uncles, nieces, nephews and grandparents, reported difficulties talking about hereditary cancer and more emotional distance. The comments on difficult situations or conflicts in the family due to genetic testing comprised reports on different attitudes between relatives concerning wanting or not wanting genetic testing to be performed in the family and on difficulties with relatives imposing secrecy in the family and beyond. Differences in expectations regarding support resulted in more emotional distance while also guilt feelings between non-carriers and carrier relatives were reported.

Table 1. Positive changes in family relationships due to genetic testing

	Partner		Children		Parents		Siblings		2nd degree	
	n	%	n	%	n	%	n	%	n	%
Feeling closer	15	43	2	15	4	17	13	41	8	36
Improved communication	6	17	0	0	4	17	9	28	10	45
More understanding, support	3	9	2	15	6	26	5	16	4	18
More appreciation of the other	6	17	3	23	4	17	2	6	0	0
Relief of negative test result	5	14	6	46	5	22	3	9	0	0
Total	35	100	13	100	23	100	32	100	22	100

Table 2. Negative changes in family relationships and familial difficulties due to genetic testing

	Changes in relationships										Familial difficulties, conflicts	
	Partner		Children		Parents		Siblings		2nd degree			
	n	%	n	%	n	%	n	%	n	%	n	%
More emotional distance	3	60	0	0	3	19	7	35	3	43	7	25
Guilt feelings	0	0	6	86	4	25	7	35	1	14	2	7
Secrecy	0	0	1	14	9	56	6	30	3	43	7	25
Does not want GT	0	0	0	0	0	0	0	0	0	0	12	43
Other relational problems	2	40	0	0	0	0	0	0	0	0	0	0
Total	5	100	7	100	16	100	20	100	7	100	28	100

GT = genetic testing

Family characteristics predisposing to adverse effects on family relationships

Results of logistic regression analysis are reported in Table 3. The analyses were adjusted for age and gender. Participants describing their families as enmeshed-chaotic or disengaged-rigid at baseline, reported more adverse consequences in relationships with their partner and/or children ($P = .03$). Participants who felt less free to communicate about hereditary cancer related issues within the nuclear family at baseline also reported more frequently adverse effects on these relationships ($P = .02$) and tended to report more familial difficulties ($P = .07$). Participants who felt less free to talk about hereditary cancer with siblings and parents reported more adverse consequences in these relationships ($P = .001$) and also more familial difficulties ($P = .01$). Participants reporting less support from their partner tended to report more adverse effects on the relationship with partner or children ($P = .06$). Participants who described the relationship with their mothers as less differentiated, reported non-significantly more negative changes in relationships with parents and/or siblings ($P = .06$) and difficult situations ($P = .09$) due to genetic testing. In the subsequent stepwise regression analysis, having an enmeshed-chaotic or disengaged-rigid family structure was selected for adverse consequences in the nuclear family ($R^2 = .07$). Familial communication style regarding hereditary cancer was selected to predict adverse consequences in the family of origin and difficult situations or conflicts ($R^2 = .11$ and .06, respectively).

Table 3. Predictors of three categorical outcome variables: reporting negative changes in the nuclear family (partner, children), in the family of origin (parents, siblings) and reporting familial difficulties or conflicts due to genetic testing (whole family), adjusted for age and gender.

	Outcome variables								
	Negative changes in nuclear family			Negative changes in family of origin			Familial difficulties, conflicts		
Predictive variables	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Characteristics of nuclear family									
Enmeshed-chaotic or disengaged-rigid functioning	5.5	1.2 to 25.3	.03				1.0	0.2 to 4.6	.97
Support partner	0.8	07 to 1.0	.06				1.0	0.8 to 1.2	.63
Open communication partner, children	0.9	0.8 to 1.0	.02				0.9	0.9 to 1.0	.07
Characteristics of family of origin									
Differentiation from mother				1.0	0.9 to 1.0	.06	1.0	0.9 to 1.0	.09
Differentiation from father				1.0	0.9 to 1.0	.20	1.0	1.0 to 1.1	.41
Support parents, siblings				0.9	0.7 to 1.0	.10	0.9	0.8 to 1.1	.19
Open communication parents, siblings				0.9	0.9 to 1.0	.001	0.9	0.9 to 1.0	.01

OR = odds ratio.

DISCUSSION

This study demonstrates that genetic testing for cancer susceptibility affects family relationships. The impact on family relationships was perceived much more frequently as positive than negative. Feeling closer to relatives was a frequently mentioned positive effect on relationships. Our finding is in line with the results from McInerney-Leo *et al*[8]. Apparently, the threat of cancer requires a family to pull together, a reaction similar to that upon chronic illness[24]. Improvements in communication were also reported quite frequently. Improved communication might be attributed to genetic counseling[25, 26], which aims at facilitating the individual's adjustment in his particular family system. Another positive consequence of genetic testing was a heightened appreciation of relationships, mainly reported by mutation carriers. Mutation carriers generally reported more positive changes in relationships than non-carriers. Finding benefits in and giving positive meaning to medical problems or threats could be an expression of resilience and adaptive coping[27].

Nineteen percent of participants reported that genetic testing negatively affected one or more family relationships, and 17% reported difficult situations or conflicts in the family. Adverse effects mainly comprised the relationship with siblings and parents. Parents reported guilt feelings about (possibly) passing the gene mutation on to children and also children noticed

this sense of guilt in their parents. Also a great sense of relief towards children was reported after a negative test result. Parental guilt has been reported earlier[28] and resulted in some cases to deteriorated and more distant relationships, especially if combined with secrecy about hereditary cancer. Feelings with a similar dynamic as survivor's guilt[29] towards a relatives' positive test result were reported by non-carriers, although infrequently. Another encountered adverse effect on family relationships appeared to be the creation of a conspiracy of silence about hereditary cancer, often in order to protect each other. Furthermore, more emotional distance between relatives was reported when support and understanding were unexpectedly lacking. The ability of relatives to provide social support is of importance for the relationship, since relatives are perceived as key social support providers to facilitate adjustment to genetic testing[16].

We found several familial characteristics predisposing to adverse consequences for family relationships following genetic testing. Not surprisingly, individuals feeling more reluctant to talk about hereditary cancer with relatives reported more familial difficulties and unwanted changes in relationships. Open communication has not only been demonstrated to be essential for families that have to cope with genetic testing but also for families coping with cancer[30]. In addition, families characterized by a rigid family structure in combination with unconnected family bonds were found to be more susceptible to negative changes in nuclear family relationships. Also, families characterized by a very loose and flexible family structure in combination with very close relationships were less well equipped to cope with the stress of genetic testing. This finding is congruent with the theory, that more extreme levels of both cohesion and adaptability are less functional[12]. It stresses the need for a balance between too much and too little cohesion and between too much and too little adaptability within families.

To our knowledge, this is the first empirical study to investigate determinants of adverse consequences on family relationships due to cancer susceptibility genetic testing. Strengths of the study are the prospective study design, low drop out rate and method of analysis in which we adjusted for potential confounding variables. Because of the small number of individuals reporting negative changes in the nuclear family, we should be ware of a lack of stability and of power to detect statistical differences. However, even in small groups we found clinically meaningful factors predicting negative changes. Furthermore, we did not take into account the differences between *BRCA1/2* and HNPCC in our analyses. On the whole, individuals from families with an identified *BRCA1/2* mutation tended to report more consequences for familial relationships than individuals from HNPCC families, especially more changes in the partner relationship. This might be related to the different implications of both cancer syndromes. A *BRCA1/2* mutation may affect parts of the body involved in femininity and sexuality. Moreover, the nature of the prevention strategies is different. Unique for *BRCA1/2* mutation carriers is the choice between screening that cannot prevent the development of cancer, and prophylactic mastectomy, which is a drastic decision. Screening for HNPCC consists of colonoscopy, that is very unpleasant but has proved to reduce the risk of developing colorectal cancer[31]. Finally, it should be noted that the perception of participants was reported and that other factors than changed family relationships themselves may have affected the reporting of changes. In future studies, the perception and experiences of other family members should be assessed as well.

We recommend that health care professionals pay special attention to the familial communication regarding hereditary cancer. Open familial communication may be essential

for adequate relational and individual[5] adjustment, and may also result in a higher uptake of genetic testing[32]. If an individual feels reluctant to talk about hereditary cancer with relatives, we suggest to underline the need of open communication and to discuss referral to a specialized psychosocial professional. We also suggest offering psychosocial education on how to communicate test results to relatives and especially children, for example in form of a leaflet. In a leaflet directed towards the communication with children, separate sections should address the communication with pre-school, school-aged, adolescent and adult children. A leaflet directed towards the dissemination of information about the genetic nature of cancer could be based upon strategies identified previously, like the six-step skills-building strategy[33].

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Part II

Predictive factors of psychological well-being of individuals opting for genetic cancer susceptibility testing

CHAPTER 6

The common sense model of self-regulation and psychological adjustment to genetic cancer susceptibility testing: a prospective study

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Abstract

This study explored the contribution of illness representations and coping to cancer related distress in individuals undergoing genetic testing for an identified mutation in *BRCA1/2* (BReast CAncer) or an HNPCC (Hereditary Nonpolyposis Colorectal Cancer) related gene, based on the common sense model of self-regulation.

Coping with hereditary cancer (UCL), illness representations (IPQ-R) and risk perception were assessed in 271 applicants for genetic testing before test result disclosure. Hereditary cancer distress (IES) and cancer worry (CWS) were assessed before, two weeks after and six months after result disclosure.

Cognitive and emotional illness representations, risk perception and causal attributions were significantly related to several coping behaviours. Cognitive and emotional illness representations and coping contributed significantly to hereditary cancer distress and cancer worry over the study period. Especially passive coping and emotional representations were significant and consistent predictors of hereditary cancer distress and cancer worry.

The self-regulatory model may be useful to understand the cognitive and emotional reactions to genetic cancer susceptibility testing. Identifying unhelpful representations, cognitive restructuring and stimulating active coping may be appropriate interventions to help distressed individuals undergoing genetic susceptibility testing for a *BRCA1/2* or a HNPCC related mutation.

INTRODUCTION

Individuals carrying a cancer susceptibility gene mutation in *BRCA1/2* or one of the HNPCC related genes are at high risk of developing cancer from the age of 25 years onwards. A predisposition for HNPCC implies a high risk to develop colorectal and endometrial cancer, while a *BRCA1/2* mutation implies a high risk of developing breast and ovarian cancer. The predisposition may cause fear of physical suffering, death and of leaving children and loved ones behind far before the time that would be appropriate in the family life cycle[1, 2]. Early detection or prevention strategies are available for both cancer predispositions. *BRCA1/2* mutation carriers can either opt for screening, which cannot prevent the development of cancer, or prophylactic surgery, which is a drastic decision. Screening for HNPCC consists of regular colonoscopy and removal of detected polyps at an early stage. Undergoing colonoscopy can be experienced as very cumbersome, but has been shown to reduce the risk of developing colorectal cancer[3]. Gynaecological examination is recommended to female carriers, but its effectiveness may be limited. The mode of inheritance of both predispositions is autosomal dominant, so a carrier has a 50% risk to pass the mutation on to a child. Most mutation carriers have been shown to cope well with the knowledge of their genetic status, in spite of increased cancer risks for themselves and their children, difficult choices concerning risk management and a potential psychological vulnerability due to earlier losses of relatives to cancer[4-6]. Nevertheless a considerable proportion of about 10-20% of individuals undergoing genetic cancer susceptibility testing reports clinically elevated distress levels[6-10].

Leventhal's common sense model of self-regulation of health and illness[11] may be a useful framework to understand the cognitive, emotional and behavioral reactions to genetic cancer susceptibility testing[12-14]. This model posits that individuals create their own understanding of an illness or health threat (i.e. illness representations), which determines coping responses, health behavior and finally psychological well-being. Cognitive processes evaluate the health threat and try to regulate it by problem-focused coping, for example by seeking information, opting for genetic testing or other types of behavior attempting to reduce the threat. Simultaneously, emotion-focused processes regulate the emotional consequences of the health threat, for example by unconscious processes like minimization or by more conscious processes like seeking social support. The simultaneous cognitive and emotion-focused processes are dynamic and mutually affect each other.

Insight into the basic elements of the self-regulatory model and their mutual relationships in individuals from families with hereditary cancer could provide more understanding of how individuals cope with increased cancer risks. This understanding will be relevant for the future, as knowledge on cancer susceptibility genes will likely increase and become more widely available. A few empirical studies have examined the relationship between illness representations and psychological well-being in individuals undergoing genetic cancer susceptibility testing. A low perceived control over developing cancer[15], more seriously perceived consequences of the condition[16-18] and less perceived curability[18] were found to be related to psychological well-being. One study has examined the relationship between illness representations and risk perception[19]. These studies have however not concentrated on all basic elements of the model simultaneously. Furthermore, they have studied individuals from *BRCA1/2* mutation families or HNPCC mutation families separately instead of studying two cancer syndromes simultaneously.

We previously have studied differences between individuals from *BRCA1/2* and HNPCC mutation families with respect to illness representations and coping styles[20]. The most important observation was that the perceptions of the consequences of hereditary cancer differed in the two groups, resulting in a more positive outlook in individuals from families with a HNPCC related mutation. One of the coping responses and the level of distress differed accordingly. Individuals from *BRCA1/2* mutation families more frequently felt incapable of doing something about the cancer risks than individuals from HNPCC mutation families, and reported more hereditary cancer related distress and worry. These differences in representations, coping and distress may partly be explained by the fact that surveillance by colonoscopy in HNPCC mutation carriers has proven to be effective with respect to early detection of colorectal cancer, and has not the mutilating consequences of prophylactic mastectomy, nor the more unsure efficacy of breast cancer screening.

The present paper reports findings from a prospective multi-center research project that studied psychological adjustment to genetic testing for a known familial predisposition, that imparts an increased risk to develop cancer at a relatively young age in adulthood and for which prevention or early detection strategies are available (i.e. a *BRCA1/2* or HNPCC related mutation). The objectives of the present paper were 1) to explore the relationships between cognitive and emotional illness representations and coping, 2) to explore the contribution of illness representations and coping styles to genetic susceptibility testing associated psychological distress and 3) to identify which illness representations and coping styles are risk factors for genetic testing associated psychological distress.

METHOD

Participants and counseling procedure

See Chapter 4.

Study procedure

The first questionnaire, containing all predictive measures and the outcome measures, was mailed 1 week after the first counseling session. Participants received a second and a third questionnaire, containing the outcome measures, 1 week and 6 months after result disclosure. For more details see Chapter 4.

Measures

Outcome measures

At each measurement, participants completed the Impact of Event Scale Revised[22, 23] measuring *hereditary cancer related distress* and the Cancer Worry Scale[24] to measure *cancer worry*. Both measures have good psychometric properties[25-27].

Predictive measures

Demographic and medical history information. Data were obtained on age, gender, marital status, having children, educational level, cancer status, pretest genetic risk and familial mutation.

Illness representations (cognitive representations, emotional representations) and *causal attributions* were assessed by the IPQ-R[28]. The items were anchored on hereditary cancer (Table 1). The illness identity scale was not appropriate for the study population and was therefore excluded. Subscales with satisfactory reliability (Cronbach's alpha ≥ .67) were used in the analyses.

Cancer risk perception was assessed using an item that was used in similar studies[29], i.e. "Independent of my actual risk, I feel my risk of developing cancer is 'not likely' (1) to 'very likely'" (7).

Coping was assessed by the Utrecht Coping List-29[30, 31] that was adapted and anchored to coping with hereditary cancer. Subscales with satisfactory reliability (Cronbach's alpha ≥ .67) were used in the analyses (Table 1).

Statistical analysis

Demographic and clinical characteristics of the study sample were analyzed using exact tests for categorical variables and independent T-tests for continuous variables. To explore the relationships between illness representations and coping, Pearson correlation coefficients were calculated between coping, cognitive representations, emotional representation, risk perception and causal attributions (objective 1). The method of multiple regression analysis was used to examine the independent contribution of coping, cognitive representations, emotional representation, risk perception and causal attributions to hereditary cancer distress and cancer worry at each measurement separately (objective 2). The demographic and clinical history variables (age, gender, hereditary cancer syndrome, pretest genetic risk, cancer status) were entered in the regression model (block 1), then genetic test result (block 2) and finally coping (block 3). This procedure was repeated with cognitive representations instead of coping, and subsequently with emotional representation, risk perception and causal attributions (each in block 3). To identify illness representations and coping styles being risk factors for genetic testing associated psychological distress, multiple regression analysis with a procedure backward elimination was used (objective 3). Variables entered in block 3 in the earlier analyses (coping, cognitive representations, emotional representation, risk perception and causal attributions) having potential predictive qualities (P<.10), were entered in the regression model, adjusted for age, gender, hereditary cancer syndrome, pretest genetic risk and cancer status and followed by the procedure backward elimination (P_{in}<.50 and P_{out}>.51). The standardized regression coefficients of the individual predictive variables were presented as a measure of performance. To evaluate the predictive capacity of the models, the increase in explained variance (R^2 change) or the percentage of explained variance (adjusted R^2) were presented. The data were analyzed using Statistical Package for Social Sciences (version 11.0). The probability level for statistical significance testing was set at .05 (two-tailed).

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

Scale	Examples of items	α*
Cognitive representations (IPQ-R)		
Timeline	It is likely to be permanent rather than temporary, it will last for a long time	.68
Timecycle	The symptoms change a great deal from day to day, it is very unpredictable	.67
Consequences	It is a serious condition, it has major consequences on my life	.72
Personal control	There is a lot which I can do to control it, I have the power to influence it	.73
Treatment control	Treatment will be effective in curing it, there is little to be done to improve it (r)	.72
Illness coherence	The symptoms are puzzling to me, it doesn't make any sense to me	.70
Emotional representation (IPQ-R)		.85
	When I think about it I get upset, I get depressed when I think about it	
Causal attributions (IPQ-R)		
Heredity	Hereditary - it runs in the family	-
Chance	Chance or bad luck	-
Ageing	Ageing	-
Risk factors	Diet or eating habits, smoking, alcohol, pollution, own behavior	.82
Psychological functioning	Stress, emotional state, mental attitude, family problems or worries, personality, overwork	.89
Coping with hereditary cancer (UCL-29)		
Social support seeking	Sharing worries, showing feelings, looking for understanding	.84
Distraction seeking	Seeking distraction, meeting happy company, thinking about other things	.77
Active coping	Observe the problem, think of different options, make directed action plans	.79
Religious coping	Praying, seeking comfort in religion, thinking it has a meaning	.82
Passive coping	Pessimistic view, feeling overwhelmed, feeling incapable of dealing with it	.70
Moderate demands	Changing demands, needs, priorities	.75

* Cronbach's alpha

RESULTS

Study population

See Chapter 4.

Intercorrelations of coping, illness perceptions and causal attributions

Correlations between coping, cognitive representations, emotional representation, risk perception and causal attributions are displayed in Table 2. Perceptions of a long duration (timeline) and more serious consequences of the cancer type were significantly related to all coping behaviors, except religious coping. Participants who perceived less treatment control reported more frequently a passive coping style and to moderate their demands and priorities in order to cope with hereditary cancer. Participants perceiving less illness coherence reported more frequently a passive and distraction seeking coping style. A more intense negative emotional representation was related to all coping behaviors, except religious and active coping, and to all cognitive representations, except timecycle. A higher perceived cancer risk was related to more social support seeking, passive coping, moderating demands and less religious coping. Participants who perceived heredity as a more important determinant of hereditary cancer, reported more social support seeking, more active coping, less religious coping and less illness coherence. Participants who perceived chance as a more important cause of hereditary cancer reported less religious coping. Participants who perceived risk factors and psychological functioning as a more important cause of hereditary cancer perceived more personal control and more frequently moderated their demands and priorities.

Contribution of coping and illness representations to hereditary cancer distress and cancer worry

The independent contribution of coping, cognitive representations, emotional representation, risk perception, causal attributions to hereditary cancer distress and cancer worry were analyzed by the method of regression analysis, adjusted for age, gender, cancer syndrome, cancer status, pretest genetic risk and genetic test result (Table 3). Coping predicted a substantial amount of variance of hereditary cancer distress and cancer worries at all assessments, although the amount of explained variance decreased through time. Participants having a more passive coping style, who distracted themselves, who modified their demands and priorities or who coped with hereditary cancer by mobilizing social support reported more distress and/or worry. Cognitive representations explained a significant proportion of variance of the outcome variables, but contributed less than coping. Participants who perceived the consequences of hereditary cancer as more serious, who perceived hereditary cancer as less coherent and who perceived hereditary cancer as more chronic reported more distress and worry. Emotional representation contributed significantly to hereditary cancer distress and cancer worry, too. Participants having more intense negative emotional representations reported more hereditary cancer distress and cancer worry at each assessment. Risk perception accounted for a significant proportion of the variance of worry before and shortly after result disclosure, and of distress shortly after result disclosure. Causal attributions did not make a significant contribution to hereditary cancer distress and cancer

worry, except for worry shortly after result disclosure. Participants who perceived heredity as a more important cause of hereditary cancer, were more worried before and shortly after result disclosure.

Table 2. Intercorrelations of study variables.
Correlations printed in bold were significant at $P < .05$ (two-tailed).

	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.
Coping																				
1. Social support	**.38**	**.51**	**.29**	.11	**.38**	**.19**	.05	**.29**	-.03	-.03	.01	**.24**	**.18**	**.18**	.03	.08	-.05	-.02	**.15**	**.36**
2. Distraction		**.46**	**.44**	.10	**.47**	**.17**	**.13**	**.26**	-.06	-.11	**.19**	**.41**	.06	.01	-.06	.01	-.06	.03	**.48**	**.37**
3. Active			**.20**	.08	**.49**	**.19**	-.05	**.24**	.03	-.10	-.12	.10	.11	**.21**	.00	.07	.07	.04	**.17**	**.19**
4. Passive				**.14**	**.31**	**.24**	.10	**.29**	-.08	**-.14**	**.20**	**.54**	**.16**	.10	-.01	.09	-.04	.02	**.62**	**.60**
5. Religious coping					**.14**	-.03	.04	.05	-.01	.04	.08	.06	**-.13**	**-.13**	**-.23**	-.08	.01	.12	.09	.01
6. Moderate demands						**.17**	.04	**.20**	-.06	**-.18**	.11	**.21**	**.13**	.08	-.07	.11	**.14**	**.14**	**.26**	**.21**
Cognitive representations																				
7. Timeline							**.23**	**.50**	**-.15**	**-.27**	-.03	**.29**	**.15**	.11	.08	.11	-.07	-.05	**.16**	**.23**
8. Timecycle								**.26**	**.12**	.01	**.25**	.02	-.02	-.09	-.03	.03	**.22**	**.15**	.01	-.03
9. Consequences									**-.31**	**-.28**	.12	**.38**	**.17**	**.17**	.05	.01	-.09	-.06	**.28**	**.32**
10. Personal control										**.53**	**-.13**	**-.20**	.00	-.09	.08	**.19**	**.28**	**.22**	-.09	**-.13**
11. Treatment control											**-.23**	**-.19**	-.05	-.07	-.09	.10	.07	.11	**-.18**	**-.15**
12. Illness coherence												**.30**	**-.14**	**-.15**	.03	-.05	.02	.05	**.26**	**.15**
13. *Emotional representation*													**.14**	**.13**	.04	-.01	-.04	.03	**.58**	**.66**
14. *Risk perception*														**.17**	**.23**	**.23**	-.05	-.06	.11	**.33**
Causal attributions																				
15. Heredity															.03	.03	**-.13**	**-.16**	.05	**.22**
16. Chance																**.21**	.03	-.04	-.03	.08
17. Ageing																	**.32**	**.24**	-.02	.06
18. Risk factors																		**.60**	-.03	-.04
19. Psychological functioning																			-.03	-.04
Psychological distress pretest																				
20. Hereditary cancer distress																				**.68**
21. Cancer worry																				

Table 3. Summaries of regression analyses testing the significance of change in explained variance on hereditary cancer distress (IES) and cancer worry (CWS)

	Outcome variables									
	Pretest counseling				**Result disclosure**				**6 months postresult**			
	IES		CWS		IES		CWS		IES		CWS	
Predictive variables	β	Δ R^2	β	Δ R^2	β	Δ R^2	β	Δ R^2	β	Δ R^2	β	Δ R^2
Block 1												
Demographic and medical variables		.05*		.12***		.04		.11***		.03		.05**
Block2												
Genetic test result						.01		.02*		.02*		.08***
Block3												
Coping		.42***		.34***		.31***		.22***		.16***		.08**
Social support seeking	-.11		.16**		.01		.12		-.04		-.08	
Distraction seeking	.28***		.12*		.25**		.10		.14		.10	
Active coping	.00		-.01		-.13		-.09		-.08		-.14	
Passive coping	.51***		.51***		.37***		.38***		.29***		.17**	
Religious coping	.01		-.07		.05		-.02		.05		.00	
Moderate demands	.03		-.05		.15*		.08		.13		.14*	
Cognitive representations		.13***		.13***		.08**		.09***		.12***		.06**
Timeline	.09		.16**		.07		.15*		-.00		.03	
Timecycle	-.08		-.07		-.06		-.09		-.10		-.06	
Consequences	.21**		.25***		.11		.20**		.09		.13	
Personal control	.11		.02		-.04		-.06		.01		-.06	
Treatment control	-.09		-.01		-.00		.04		-.11		-.02	
Illness coherence	.26***		.16**		.24**		.08		.31***		.16*	
Emotional representation		.29***		.37***		.20***		.22***		.14***		.10***
	.56***		.64***		.46***		.49***		.39***		.33***	
Risk perception		.01		.08***		.03**		.06***		.01		.01
	.10		.30***		.18**		.25***		.12		.11	
Causal attributions		.01		.04		.03		.07**		.01		.03
Heredity	.08		.17**		.08		.24***		.05		.09	
Chance	-.05		.02		-.13		-.10		-.05		-.11	
Ageing	.04		.10		.03		.05		-.00		.05	
Risk factors	.06		-.01		.11		-.02		.12		.05	
Psychological functioning	-.07		-.04		-.10		.03		-.09		.05	

* $P < .05$; ** $P < .01$; *** $P < .001$ (two-tailed)

Predictors of hereditary cancer distress and cancer worry

A backward elimination procedure was used to identify variables with predictive qualities within each set of variables, adjusted for age, gender, cancer syndrome, cancer status, pretest genetic risk and genetic test result (Table 4). Passive coping and emotional representation were included in the final models of hereditary cancer distress and worry at almost all measurements.

Table 4. Predictors of hereditary cancer related distress and cancer worry, adjusted for age, gender, cancer syndrome, cancer status, pretest genetic risk and genetic test result.

	Pretest counseling			**Result disclosure**			**6 months postresult**		
	β	*P*	R^2	β	*P*	R^2	β	*P*	R^2
Hereditary cancer distress			.50			.38			.24
Coping									
Passive coping	.38	.000		.30	.000		.22	.002	
Distraction seeking	.22	.000		.19	.002				
Cognitive representations									
Illness coherence				.13	.031		.20	.003	
Emotional representation	.27	.000		.18	.008		.24	.005	
Risk perception				.13	.026				
Causal attributions									
Chance				-.12	.039				
Cancer worry			.60			.43			.22
Coping									
Passive coping	.30	.000		.27	.000				
Social support seeking	.10	.02							
Emotional representation	.41	.000		.29	.000		.33	.000	
Risk perception	.16	.000		.14	.010				
Causal attributions									
Heredity	.09	.023		.16	.002				

R^2: R^2 adjusted for shrinkage

DISCUSSION

This study demonstrates that Leventhal's self-regulatory model[11] can be a helpful tool to understand the psychological adjustment of individuals opting for genetic susceptibility testing for an identified pathogenic familial *BRCA1/2* or HNPCC related mutation. In accordance with the self-regulatory model, we found that illness representations were significantly and meaningfully related to coping behaviours and that they significantly contributed to hereditary cancer distress and cancer worry. Individuals perceiving more serious consequences, a longer disease duration and less illness coherence displayed more coping behaviours and were more distressed and

worried, findings that are in accordance with those from other studies using the self-regulatory model[28, 32]. Illness coherence may be especially predictive of distress on the long-term. Emotional representations were related to several coping behaviours too, especially to coping strategies aiming at fear control like seeking social support, distraction and moderating demands. Our findings furthermore support the assumption of the self-regulatory model that cognitive and emotional representations were significantly related and intermingled. Another finding consistent with other studies using the self-regulatory model[33], was that causal attributions were related to several illness representations. Specifically, individuals who perceived controllable risk factors like diet, smoking and psychological functioning as more important cause of hereditary cancer perceived more personal control.

The self-regulatory model furthermore posits that coping behaviours will relate to psychological well-being. Indeed, we found that coping behaviours contributed significantly to distress and worry. Especially passive coping was a significant and consistent predictor of more hereditary cancer distress and cancer worry. A passive coping style may reflect the inability to cope with the threat of hereditary cancer and has been found to predict distress in similar studies too[17, 18, 34]. Besides passive coping, distraction seeking was positively related to distress. Religious coping was unrelated to distress, coping and most illness representations, yet individuals who coped with hereditary cancer by turning to religion and by praying had a lower risk perception and believed that hereditary cancer was less often caused by heredity and chance.

Although risk perception was not conceived as an illness representation in the original self-regulatory model, we have studied risk perception in relation to illness representations as was proposed by others[12-14]. Similar to findings from Kelly *et al.*[19], several causal attributions were related to risk perception, like heredity, chance and ageing. A higher perceived risk to develop cancer was furthermore related to several illness representations, coping behaviours and particularly to cancer worry. Other studies in women at increased risk of breast cancer have found a similar relationship between risk perception and worry[27, 35-39].

Some of our findings were not in line with the self-regulatory model. In contrast with previous reports[18], stronger beliefs about treatment control (curability) and personal control were not significantly related to distress or worry. This may be explained by the fact that the majority of participants did not have a personal history of cancer, and that perception of being able to prevent cancer may be more important to individuals at increased cancer risk than treatment control. Another unexpected finding was that we did not find a protective effect of coping styles considered as adaptive like active coping or seeking social support. Individuals having a low distress-score may have felt no need to 'cope' with the problem and may have answered that all coping questions were not applicable to them. This may have inversed the relationship between adaptive coping and distress. Indeed, individuals who perceived hereditary cancer as less chronic and as having less severe consequences, scored lower on almost all coping styles. Furthermore, social support seeking and active coping may be protective mechanisms on the long-term and their adaptive effect may be concealed on the short-term. Temporary feelings of distress, worry and despair shortly before and after receiving the genetic test result may reflect the adaptive process of working through a stressful life event. The negative correlations between active coping, social support seeking and distress on the longer term, although not statistically significant, also point in that direction.

To our knowledge, this is the first study to analyse the interdependency of the basic elements of the self-regulatory model and their role in the well-being of individuals from gene mutation families undergoing genetic cancer susceptibility testing. Strengths of our study are the prospective study design, the large study sample, the low drop out rate and the inclusion of risk perception into the self-regulatory model. The study can be criticized for failing to have included perceived preventability. This may be important to individuals at increased risk of developing cancer. In future studies, repeated measurements of illness representations and coping may provide more insight into interaction between illness perceptions and coping through time, since illness representations are rather dynamic than static. Also coping styles may not be stable traits, especially situational-specific coping as assessed in this study. Indeed, the contribution of coping to distress and worry was impressive on the short-term, but dramatically on the long-term.

In practical terms, we would suggest to identify those individuals having a more passive coping style, and to discuss referral to a mental health professional for further evaluation and potentially counseling. These individuals can be expected to perceive a longer duration, more severe consequences, less treatment control, less illness coherence, more intense negative emotional representations and a higher risk to develop cancer. A cognitive approach might help to identify unrealistic illness representations and to obtain more helpful and realistic illness representations. Especially perceptions of illness coherence need to be attended to, since they were related to long-term psychological well-being. Finally, encouraging these individuals to take up more adaptive, active coping strategies may help them to adjust better to the threat of hereditary cancer as well as other potential difficulties they might encounter in the future.

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CHAPTER 7

Family system characteristics and psychological adjustment to cancer susceptibility genetic testing: a prospective study

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Abstract

This study examined prospectively the contribution of family functioning, differentiation to parents, family communication and support from relatives to psychological distress in individuals undergoing genetic susceptibility testing for a known familial pathogenic *BRCA1/2* or HNPCC related mutation. Family functioning, differentiation to parents, hereditary cancer related family communication and perceived support from relatives were assessed in 271 applicants for genetic testing before test result disclosure. Hereditary cancer distress (IES) and cancer worry (CWS) were assessed before, one week after, and six months after test result disclosure. Participants reporting more cancer related distress over the study period more frequently perceived the communication about hereditary cancer with relatives as inhibited, the nuclear family functioning as disengaged-rigid or enmeshed-chaotic, the support from partner as less adequate and the relationship to mother as less differentiated. Especially, open communication regarding hereditary cancer and partner support may be important buffers against hereditary cancer distress. Identifying individuals with insufficient sources of support and addressing the family communication concerning hereditary cancer in genetic counseling may help the counselee to adjust better to genetic testing.

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. HNPCC (Hereditary Nonpolyposis Colorectal Cancer) 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]. The psychological impact of genetic susceptibility testing for hereditary cancer has been well documented over the last years. Despite quite favorable outcomes on the group level, about 10-20% of individuals undergoing genetic testing for a *BRCA1/2* or a HNPCC associated mutation is highly distressed[2-6].

Genetic testing and hereditary cancer are family matters[1, 7, 8]. Therefore, family system characteristics may influence the way the individual and the family as a whole copes with hereditary cancer[9]. If a mutation is identified, this not only affects the mutation carrier but also his or her relatives. Besides worries for the future health of the mutation carrier, relatives may become aware that they themselves are at risk to develop cancer at a relatively young age and have to make decisions for risk reduction, that can be burdensome in case of screening and irreversible and possibly mutilating in case of prophylactic surgery. Relatives identified as non-carriers may feel responsible for the future care of relatives with the mutation, or guilty about having a future without the threat of cancer[10]. Communicating about experiences with cancer in the family can be an emotional burden[11]. The way a family copes with earlier cancer experiences, different test results and the threat of cancer likely affects the individual perception and experience of genetic testing.

To our knowledge, no study has systematically documented the influence of family system characteristics on psychological adjustment to genetic susceptibility testing for hereditary cancer. From a family systems perspective, several characteristics are potential predictors of psychological distress resulting from genetic susceptibility testing. Family cohesion and adaptability have been identified as key characteristics of nuclear family functioning[12, 13]. Cohesion is defined as a sense of togetherness or emotional bonding. Adaptability reflects the degree to which a family can change its power structure, rules and role relationships to meet situational needs. Families with a balanced level of cohesion and adaptability have been found to adjust better to situational and developmental stress[13]. Another potential predictive characteristic may be the level of differentiation to parents, defined as the extent to which an individual feels separated from emotional attachments to their parents without damaging these important relationships[14]. Interpersonal differentiation is essential for psychological adjustment[15]. Furthermore, family members are an important source of social support[16]. If family members are unable to provide support, this could result in more adjustment problems[17]. Finally, families able to act openly and express feelings directly can be expected to experience less psychologically distress, as was found in families of cancer patients[18].

This paper reports findings from a prospective multi-center research project that examined the effect of family system characteristics on psychological adjustment to genetic

susceptibility testing for hereditary cancer. The objective was to explore the contribution of several family system characteristics to hereditary cancer distress, cancer worry and general distress.

MATERIALS AND METHODS

Participants and procedure

See Chapter 4.

Study procedure

The first questionnaire, containing all predictive measures and the outcome measures, was mailed 1 week after the first counseling session. Participants received a second and a third questionnaire, containing the outcome measures, 1 week and 6 months after result disclosure. For more details see Chapter 4.

Measures

Predictive measures

Demographic and medical history information. Data were obtained on age, gender, having children, cancer status, familial mutation and pretest genetic risk.

Nuclear family functioning (partner, children). Cohesion and adaptability were measured with the Dutch validated version of the Family Adaptability and Cohesion Evaluation Scales[19, 20]. Cohesion was defined as a continuum from disengaged to enmeshed, adaptation as a continuum from rigid to chaotic. Reliabilities (Cronbach's alpha) of the Cohesion and Adaptation subscales were .87 and .81[20]. Participants were assigned to a maladjusted group (n=14) if their score on cohesion and adaptability was lower than the 30th percentile (disengaged-rigid) or higher than the 60th percentile (enmeshed-chaotic), in order to take the curvilinear nature of the measure into account[12].

Differentiation to parents. The extent to which individuals felt differentiated to their mother and father were assessed with the Differentiation in the Family System Scale[21]. Differentiation was defined as both a sense of emotional connectedness (support, involvement) and a sense of separateness (autonomy, uniqueness, freedom of personal expression). Reliabilities (Cronbach's alpha) of differentiation to mother and father were .85 and .88, respectively. Participants were assigned to a low differentiated group (n=27) if they scored lower than the mean on differentiation to mother and to father.

Familial communication style concerning hereditary cancer was assessed by the Openness to Discuss Hereditary Cancer in the Family Scale[7, 22]. The scale was validated in women from BRCA1/2 families and provides an assessment of communication in the nuclear family (Cronbach's alpha .78) and in the family of origin (Cronbach's alpha .82). Participants were

assigned to an inhibited communication group (n=61), comprising individuals scoring lower than the mean regarding both nuclear and family of origin communication.
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 ranging from 5, 'yes!' to 1, 'no!'. Reliability (Cronbach's alpha) was .83. Participants were assigned to a low support group (n=34) if they scored lower than the mean regarding both partner and family of origin support.

Outcome measures

At each measurement, participants completed the Impact of Event Scale Revised[23, 24] measuring *hereditary cancer distress,* the Cancer Worry Scale[25] to measure *cancer worry.* Both measures have good psychometric properties[26-28].
General distress was assessed with the Hospital Anxiety and Depression Scale six months after genetic test result disclosure[29, 30]. The Dutch version of the scale has good psychometric properties[30].

Data analysis

Demographic and clinical characteristics of the study sample were analyzed using exact tests for categorical variables and T-tests for continuous variables. The method of logistic regression was used to analyze differences in family system characteristics between participants from *BRCA1/2* and HNPCC mutation families, adjusted for gender, age and cancer status. Pearson correlation coefficients were calculated to explore the relationships between family system characteristics.

Because hereditary cancer distress and cancer worry were assessed three times (before, two weeks and six months after result disclosure) and general distress was assessed once (six months), we used two different approaches to explore the effect of family system characteristics on distress. We used SAS Proc Mixed (version 8.2) to explore the effects of family system characteristics on hereditary cancer distress and worry over the three assessments. The method of estimation was REML (residual maximum likelihood) and the error structure was defined as unstructured. For each outcome variable, the model building strategy started with the intercept, time and time squared in the random part, and time and time squared in the fixed part. To test whether a simpler random model was allowed, the difference between the two –2 log likelihoods was compared with the $X^2_{3:2}$-distribution. The *P*-value thus equaled the average of the *P*-value taken from the X^2-distribution with two and three degrees of freedom, respectively. Releasing time squared from the random part resulted in a simpler model without losing substantial information. Subsequently, we entered the confounding variables (gender, age, having children, cancer syndrome, cancer status, genetic test result) and one of the predictor variables (either family functioning, differentiation to parents, family communication style regarding hereditary cancer or support from family members) in the fixed part of the model. The effects of family system characteristics on general distress six months after result disclosure were analyzed with the method of multiple linear regression analysis, adjusted for the confounding variables.

Finally, the method backward elimination (P_{in} < .050 and P_{out} > .10) was used to select familial characteristics having predictive qualities for hereditary cancer distress, worry and general distress, adjusted for the confounders. All terms with a P-value of < .10 in the above-mentioned analyses were entered into the equation.

RESULTS

Sample characteristics

See Chapter 4.

Family system characteristics

Intercorrelations and mean values of family system characteristics of participants from *BRCA1/2* and HNPCC mutation families are summarized in Table 1. Mean values of cohesion and adaptability fell within the normal range[20]. Participants from HNPCC mutation families reported more open communication about hereditary cancer with the partner and children than participants from *BRCA1/2* mutation families.

Table 1. Intercorrelations of family system characteristics measures, ranges, and means of family system characteristics for participants from *BRCA1/2* (n=175) and HNPCC (n=96) mutation families.

										BRCA1/2		**HNPCC**	
	1	2	3	4	5	6	7	8	scale range	*M*	*SD*	*M*	*SD*
Nuclear family functioning													
1. Cohesion		-.57**	.23**	.15	.25	.09	.23	.08	23-92	71.3	7.5	69.8	7.3
2. Adaptability			-.28**	-.21	-.33	-.15	-.28	-.11	13-52	2.6	4.3	2.4	4.1
Differentiation to parents													
3. Mother				.53	.22	.29	.21	.50	11-55	44.6	8.2	43.2	7.8
4. Father					-.01	.07	.30	.32	11-55	43.7	8.0	39.7	9.5
Open communication													
5. Nuclear family						.57	.46	.19	7-35	29.2 #	5.4	31.3	4.5
6. Parents, sibs							.33	.55	7-35	28.7	6.4	29.7	5.7
Support													
7. Partner								.37	2-10	8.9	1.9	8.8	2.1
8. Parents, sibs									2-10	7.6	2.5	6.9	2.2

* p<.05;** p<.01, # p<.01 *BRCA1/2* vs HNPCC (two-tailed)

The impact of separate family system characteristics on psychological distress

Results of the univariate analyses exploring the effect of family system characteristics on distress

are summarized in Table 2. Participants who perceived family functioning as maladaptive (disengaged-rigid, enmeshed-chaotic) at baseline, reported more hereditary cancer distress over the study period than participants perceiving their families as moderately cohesive and adaptive. Perceiving the relationship with mother as less differentiated was related to more hereditary cancer distress, worry and general distress. Feeling less differentiated to both parents was related to more cancer worry. Participants perceiving the communication about hereditary cancer in the family as less open reported more hereditary cancer distress and cancer worry over the study period and also more general distress six months after result disclosure. Less support from the partner was related to more hereditary cancer distress and worry over the study period and more general distress six months after result disclosure. Less support from siblings and parents resulted in more general distress six months after result disclosure.

Table 2. Contribution of separate family system characteristics to psychological distress over the study period; results from univariate analyses using SAS Proc Mixed (hereditary cancer distress, cancer worry, measurement 1 to 3) and linear regression (general distress, measurement 3), adjusted for gender, age, having children, cancer syndrome, cancer status and genetic test result.

	Hereditary cancer distress M1-3		Cancer worry M1-3		General distress M3	
Fixed effect	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*
Cohesion	-.02	.06	-.05	.05	-.19**	.06
Adaptability	.09	.05	.05	.05	.26***	.06
Maladaptive family functioning	.04*	.20	.15	.17	-.01	.28
Differentiation mother	-.15*	.07	-.13*	.06	-.19*	.01
Differentiation father	-.11	.08	-.17*	.08	-.15	.01
Low differentiation-mother and father	.23	.13	.23*	.11	.01	.22
Open communication partner, children	-.38***	.06	-.28***	.05	-.31***	.07
Open communication parents, siblings	-.30***	.05	-.23***	.04	-.27***	.06
Inhibited family communication	.69***	.12	.49***	.11	.58***	.15
Support partner	-.18**	.06	-.11*	.05	-.22**	.07
Support parents, sibs	-.04	.07	-.06	.06	-.20*	.08
Low family support	.47**	.16	.19	.14	.37*	.18

$N = 271$. Analysis was conducted using SAS Proc Mixed; z-scores were used.
* $P < .05$. ** $P < .01$. *** $P < .001$.

The method backward elimination was used to select the familial characteristics having predictive qualities for distress (Table 3). The final models included communication about hereditary cancer in the nuclear family and/or in the family of origin. No significant differences in all outcome measures were observed with regard to the test result. Participants from *BRCA1/2*

mutation families reported more cancer worry than participants from HNPCC families, but no significant differences were found in distress levels.

Table 3. Final model from SAS Proc Mixed (hereditary cancer distress, cancer worry, measurement 1 to 3) and linear regression (general distress, measurement 3), method backward elimination, of family system variables predicting psychological distress.

	Hereditary cancer distress T1-T3		Cancer worry T1-T3		General distress T3	
Fixed effect	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*
Intercept	-.31	.30	.09	.27	-.30	.25
Time	.28***	.07	.03	.07	n.a.	
Time squared	-.07***	.01	-.03*	.01	n.a.	
Age	-.14*	.06	-.21**	.06	-.10	.07
Gender	.24	.19	-.02	.17	.02	.22
Having children	.07	.13	.05	.12	.34*	.15
Cancer status	.48*	.23	.19	.19	.26	.26
Hereditary cancer syndrome	-.11	.13	-.31**	.11	-.12	.15
Test result	.01	.24	.14	.22	.13	.11
Open communication partner, children	-.28***	.07	-.28***	.05	n.s.	
Open communication parents, siblings	-.15*	.06	n.s.		-.27***	.06

$N = 271$. Analysis was conducted using SAS Proc Mixed; z-scores were used.
* $P < .05$. ** $P < .01$. *** $P < .001$

As illustration, the course of hereditary cancer distress is displayed in Figure 1 for participants reporting a less open communication style about hereditary cancer both within the nuclear family and the family of origin and participants with a more open communication style within the nuclear family or the family of origin.

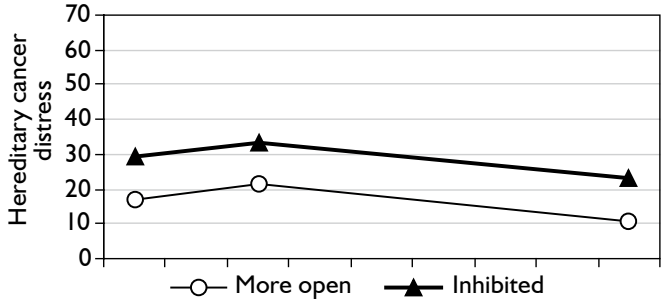

Figure 1. The course of hereditary cancer distress for participants with a less open communication style within the nuclear family and the family of origin (n=61) vs. participants with a more open communication style within the nuclear family or family of origin (n=187), adjusted for age, gender, having children, cancer status, hereditary cancer syndrome and test result.

DISCUSSION

Our findings suggest that family system characteristics are noteworthy during and after genetic cancer susceptibility testing. Especially, the quality of communication regarding hereditary cancer within the family is of paramount importance. Individuals hesitant to talk about hereditary cancer with relatives reported more psychological distress up to six months after genetic test result disclosure. The effect of a less open communication style on psychological distress may maintain for years, since it has also been demonstrated in women from BRCA1/2 mutation families five years after test result disclosure[7]. Individuals perceiving the communication as less open furthermore have been found to encounter more relational difficulties due to genetic testing[31]. The underlying motive of avoiding family communication about hereditary cancer might be avoidance of psychological distress[32] and questions about death[33], or a desire for mutual protection, also called 'protective buffering'[34]. If these processes inhibit family communication, each family member may remain alone with his own worries and preoccupations. Moreover, the healing effect of expressing emotions and concerns on mental health has been demonstrated in several controlled studies[35-37].

Besides family communication, we demonstrated that other family system characteristics are of importance for psychological adjustment as well. Support of the family during genetic testing, especially from the partner, was an important buffer against distress. This finding is congruent with other studies[17, 38, 39]. Noteworthy, hereditary cancer related family communication and support in the nuclear family contributed somewhat more to hereditary cancer distress and worry than communication and support in the family of origin. This underlines the need to take nuclear family communication and support into account in genetic counseling and stresses the importance of the partner. Differentiation to the parents, especially the mother, was important for adjustment too. Individuals who were more separated from their mother while remaining connected with her, reported less cancer related and general distress. This finding is in accordance with the Bowen theory[15].

Better family functioning and differentiation may help to adjust to all stressors including hereditary cancer and genetic testing. However, family functioning contributed less to hereditary cancer distress and worry than hereditary cancer specific characteristics like communication and support. Family functioning and differentiation may be more important for general distress independent of genetic testing and hereditary cancer. Family communication regarding hereditary cancer and family support during genetic testing may be more essential for hereditary cancer distress and worry. Indeed, in two studies that addressed family functioning in genetic counseling, family functioning was only related to satisfaction with hereditary cancer genetic counseling[40] and general distress[41].

All findings were independent of age, gender, having children, genetic test result and cancer syndrome. No significant differences in distress were observed between individuals who tested positive or negative for the familial mutation. Individuals from BRCA1/2 positive families were more worried about cancer than individuals from HNPCC families. This may be due to the different nature of prevention strategies. Surveillance by colonoscopy has proved to be effective with respect to early detection of colorectal cancer, and has not the mutilating consequences of prophylactic mastectomy, nor the more uncertain efficacy of breast cancer screening.

To our knowledge, this is the first empirical study to explore the contribution of family system characteristics predisposing to hereditary cancer related and general distress in a clinical sample. Strengths of our study are the prospective study design, large sample size and low drop out rate. A limitation is that only the patients' perception of family system characteristics was assessed and that the perception of other family members in this analysis was lacking. This is however in accordance with clinical practice, since clinicians often depart from the perception of the individual patient. Finally, our findings may not be representative for all individuals from gene mutation positives families, because individuals who did not elect to have genetic testing were underrepresented in our study.

We recommend genetic counselors to pay more attention to communication patterns and family support within families affected with hereditary cancer. Our results stress the need to stimulate open and supportive communication regarding hereditary cancer and genetic testing within the family, if individuals are withholding their concerns. Especially the ability of the partner to provide support throughout the genetic testing process and the communication within the nuclear family needs to be addressed. If distress levels are high, the patient feels reluctant to talk about hereditary cancer with relatives and feels unsupported, especially by the partner, additional support of a mental health professional may be needed and should be offered.

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CHAPTER 8

Experience of parental cancer in childhood is a risk factor for psychological distress during genetic cancer susceptibility testing

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Abstract

Background: This study explores the effect of age at the time of parental cancer diagnosis or death on psychological distress and cancer risk perception in individuals undergoing genetic testing for a specific cancer susceptibility.
Patients and methods: Cancer related distress, worry and risk perception were assessed in 271 applicants for genetic testing of an identified mutation in *BRCA1/2* (BReast CAncer) or a HNPCC (Hereditary Nonpolyposis Colorectal Cancer) related gene before, 1 week after, and 6 months after genetic test disclosure. The course of distress and risk perception were compared between individuals having witnessed parental cancer or loss due to cancer in childhood, adolescence, adulthood and having unaffected parents.
Results: Individuals with parental cancer in childhood (under age 13) reported the highest level of cancer related distress, worry and risk perception. Women having their mother affected by breast cancer in puberty (aged 10-13 years) perceived higher breast cancer risks than women with an affected mother in adulthood or without an affected mother. Individuals with an affected parent perceived cancer risks as higher than individuals without an affected parent, but were not more distressed.
Conclusions: Experience of parental cancer in childhood is a risk factor for psychological distress during the genetic testing process.

INTRODUCTION

Genetic testing for a cancer predisposition has become a usual component of clinical practice over the last years. The impact of genetic testing on mental health has been well documented. Despite quite favourable outcomes on the group level, about 10-20% of individuals undergoing genetic testing for a *BRCA1/2* mutation (high risk of breast/ovarian cancer) or an HNPCC associated mutation (high risk of colon/endometrial cancer) are highly distressed[1-5] and about 20-85% continue to have incorrect risk perceptions after genetic counselling[6]. Interestingly, mutation carrier status has only rarely been found to be related to distress levels more than one month after result disclosure[7]. Other individual characteristics may contribute more to psychological distress and cancer risk perceptions than mutation carrier status. To date there is only limited knowledge about these specific individual characteristics[8].

It has been suggested that risk perception and distress levels are influenced by experiences with cancer in the family[9, 10]. Indeed, studies assessing the psychological impact of parental cancer experiences have found a greater feeling of vulnerability to cancer[11] and more anxiety[12] in women with mothers affected by breast cancer. Women having lost their mothers to cancer reported more cancer specific distress[13, 14]. The impact of parental loss would depend more precisely on the developmentally determined attachment to the affected parent. Loss of a parent in childhood has been shown to result in a more insecure attachment style[15], more complicated grief to subsequent losses[16] and an increased risk to develop depressive disorders[17, 18] in adulthood.

Two papers have explored the impact of parental cancer and loss due to cancer in childhood on adult individuals. Adult women who were teenagers at the time of their mothers breast cancer diagnosis felt more uncomfortable about involvement in their mothers' illness as compared to women who were adults at the time of their mothers' breast cancer[19]. Adult women at familial risk of breast cancer who were teenagers when they lost their mothers to cancer perceived a higher risk of developing breast cancer, compared to women with an affected mother at another age[20].

From a developmental point of view, several factors could explain the vulnerability of children and adolescents after the confrontation with parental cancer and loss due to cancer. Young children may be vulnerable because they are still dependent on the care of their parents and may have less affective and cognitive resources to cope with stressful life events[21]. Adolescents may be vulnerable because the illness or loss of a parent may interfere with the developmental task to change the parent-child relationship in order to reach independence[22, 23]. Girls having a mother affected with breast cancer at the time they are developing breasts themselves, may become more anxious and ambivalent towards their own breasts[19].

To date, no study has documented the impact of age at the time of parental cancer and loss on individuals from hereditary cancer families undergoing genetic testing. The objective of the present study was to explore the impact of parental cancer and loss at several developmental phases on psychological distress and cancer risk perception during the genetic testing process. Developmental phases focused upon were childhood and adolescence and specifically the time of breast development (puberty) in women with breast cancer affected mothers.

METHODS

Participants

See Chapter 4.

Procedure

The first questionnaire, containing the predictive measure and the outcome measures, was mailed 1 week after the first counseling session. Participants received a second and a third questionnaire, containing the outcome measures, 1 week and 6 months after result disclosure. For more details see Chapter 4.

Measures

At the first assessment, data were obtained on age, gender, having children, cancer status, pre-test genetic risk, cancer status of parents and age at the time of the parental cancer diagnosis or death.

We categorized participants according to three developmental phases[22] at the time of the parental cancer diagnosis or death due to cancer: children (participant was younger than 13 years), adolescents (between 13 and 20 years) and adults (older than 20 years).

In addition, we categorized participants having a mother affected with breast cancer according to the following developmental phases[22] at the time of mother's diagnosis: children (participant was younger than 10 years), puberty or the time of breast development (between 10 and 13 years) and adolescents/adults (14 years or older).

At each assessment, participants completed the Impact of Event Scale Revised[25, 26] measuring hereditary cancer related distress, the Cancer Worry Scale[27] and their feelings about their lifetime risk of developing cancer (risk perception) on a 7-point scale from not likely (1) to very likely (7).

Data analysis

The data were analysed using Statistical Package for Social Sciences (version 11.0) and PROC MIXED (SAS System, version 8.2). Demographic and clinical characteristics of the study sample were analysed using exact tests for categorical variables and T-tests for continuous variables.

In order to determine differences over time between several developmental phases of parental cancer occurrence, the method of random effects models (REM) was used for hereditary cancer related distress, cancer worry and risk perception as outcome variables. In this study, the method of estimation was REML (Residual Maximum Likelihood) and the error structure was defined as unstructured. For each outcome variable, we started with a model with the intercept, time and time squared in the random part, and time and time squared in the fixed part. To test whether a simpler random model was allowed, the difference between the –2 log likelihood goodness of fit between the reduced and the saturated model was evaluated. Releasing time squared from the random part resulted in a simpler model without losing substantial information. Subsequently, we entered the predictor variables (developmental phase

of parental cancer occurrence) and confounding variables (gender, age, having children, cancer syndrome, pre-test genetic risk, cancer status, genetic test result, time since experience) in the fixed part of the model.

RESULTS

Study population

See Chapter 4.

Effect of parental cancer or loss to cancer in childhood, adolescence or adulthood

Table 1 shows the number of participants with parental cancer experiences at several developmental phases. The courses of the outcome variables for participants having an affected parent at several developmental phases are displayed in Figure 1. The analyses were controlled for age, gender, having children, cancer status, hereditary cancer syndrome, genetic test result and time since parent's cancer diagnosis or death. Explained variances of the final models for cancer related distress, cancer worry and risk perception were 65.0%, 7.5% and 36.4%, respectively. The course of distress, worry and risk perception over the study period was not different for the four subgroups. Participants having an affected parent in childhood reported significantly more cancer related distress (t=2.38; $P < .05$) a tendency towards more worry (t=1.91; $P = .06$) and significantly higher perceived cancer risk (t=2.13; $P <.05$) over the study period than the other three subgroups. Participants with an affected parent perceived the risk of developing cancer as higher over the study period than participants with no affected parent (t=-2.13; $P < .05$). The above-described differences were also found in individuals having lost a parent at one of the three developmental phases, but without reaching statistical significance.

Effect of a mother's breast cancer in puberty (age 10-13)

The analyses were controlled for age, gender, having children, cancer status, hereditary cancer syndrome, genetic test result and time since parent's cancer diagnosis (Figure 2). Explained variances of the final models for cancer related distress, cancer worry and risk perception were 66.9%, 68.8% and 37.3%, respectively. Participants having a mother affected by breast cancer during puberty (n=12) perceived their risk of developing breast cancer as higher (t=2.21; $P < .05$) and tended to report more cancer worry (t=1.93; $P = .06$) over the study period, than women with an affected mother after puberty (n=60) or without an affected mother (n=92). Women who had a mother affected by breast cancer before puberty (n=11) reported the highest level of hereditary cancer related distress (t=3.28; $P < .01$) and cancer worry (t=2.12; $P < .05$).

Table 1. Frequencies of having a parent diagnosed with cancer or losing a parent due to cancer at several developmental phases and raw means of outcome variables at first measurement

	BRCA1/2		HNPCC		Total		First measurement			
	%	*n*	%	*n*	%	*n*	Age *m (SD)*	Hereditary cancer distress *m (SD)*	Cancer worry *m (SD)*	Risk perception *m (SD)*
Parent diagnosis cancer										
Childhood (<13 y)	12.6	22	5.2	5	10.0	27	7.0 (4.3)	29.6 (19.5)	7.8 (2.2)	4.7 (1.8)
Adolescence (13-20 y)	18.3	32	17.7	17	18.1	49	16.5 (2.5)	20.6 (16.7)	7.5 (2.2)	4.7 (1.5)
Adults (>20 y)	25.1	44	35.4	34	28.8	78	32.4 (7.8)	21.0 (17.4)	6.7 (1.8)	4.2 (1.7)
No cancer	44.0	77	41.7	40	43.2	117	-	21.0 (18.4)	7.0 (2.3)	3.9 (1.7)
Parent died from cancer										
Childhood (<13 y)	4.0	7	4.2	4	4.1	11	6.0 (4.2)	30.9 (23.1)	7.9 (1.7)	4.6 (1.7)
Adolescence (13-20 y)	9.7	17	8.3	8	9.2	25	17.1 (2.6)	18.8 (14.4)	7.0 (2.3)	4.2 (1.6)
Adults (>20 y)	25.1	44	28.1	27	26.2	71	34.8 (8.4)	22.9 (18.5)	6.8 (2.0)	4.3 (1.8)
No loss	61.1	107	59.4	57	60.5	164	-	21.1 17.8)	7.1 (2.3)	4.1 (1.7)

M, mean; SD, standard deviation

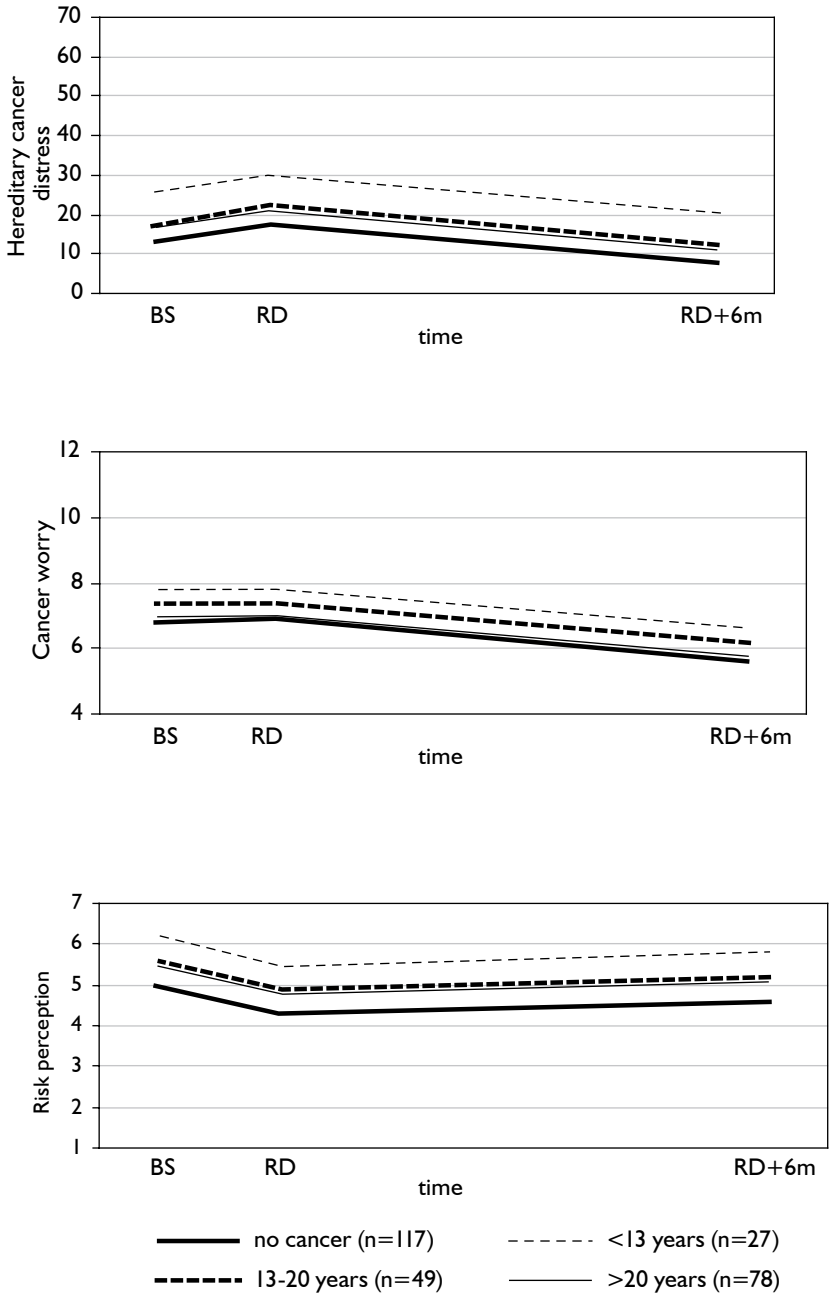

Figure 1. The course of hereditary cancer related distress, cancer worry and risk perception for individuals with an affected parent during several developmental phases (adjusted for age, gender, having children, cancer status, hereditary cancer syndrome, test result and time since cancer experience).
BS, blood sampling; RD, result disclosure; RD+6m, six months after result disclosure

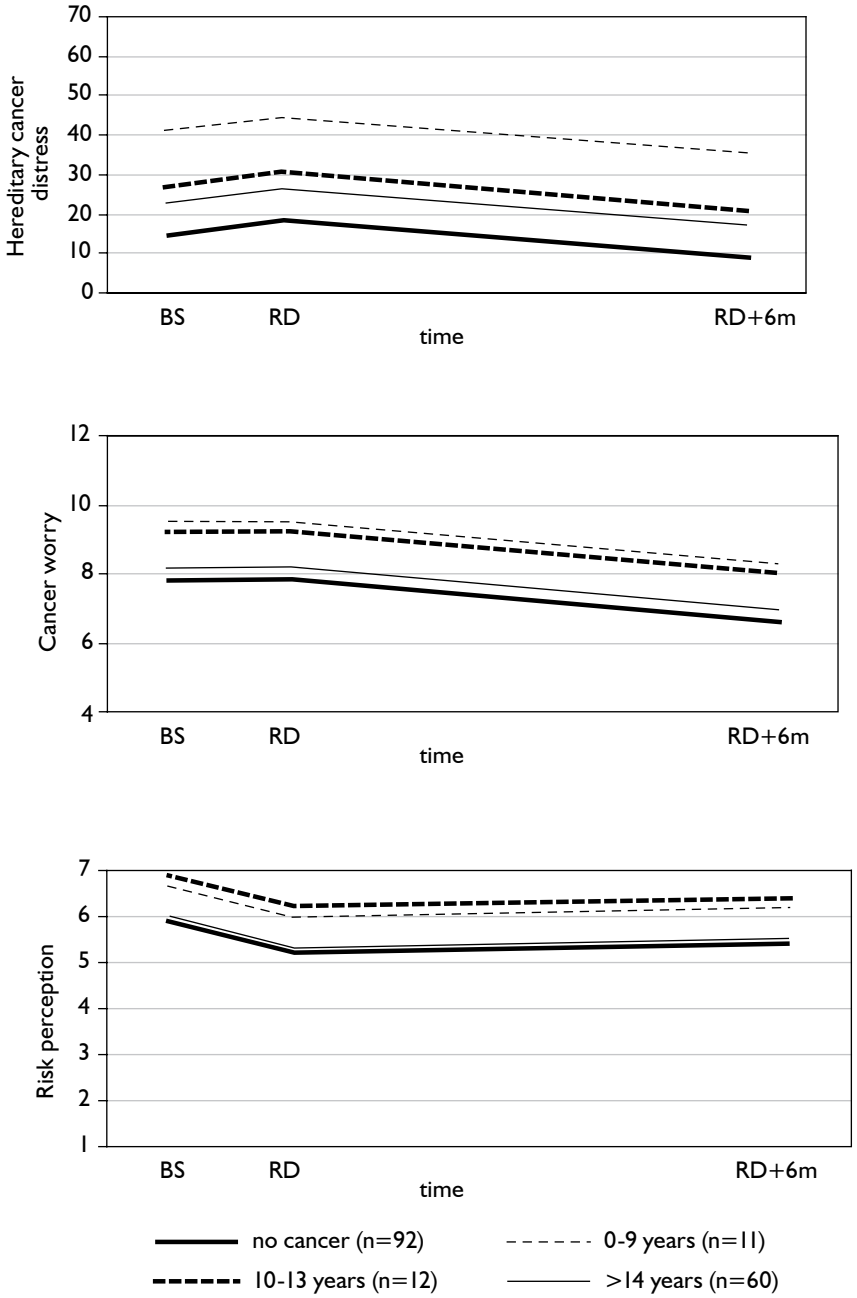

Figure 2. The course of hereditary cancer related distress, cancer worry and risk perception for women having their mothers affected with breast cancer before, during and after puberty (adjusted for age, gender, having children, cancer status, hereditary cancer syndrome, test result and time since cancer experience).
BS, blood sampling; RD, result disclosure; RD+6m, six months after result disclosure

DISCUSSION

This study demonstrates that the confrontation with parental cancer in childhood is a risk factor for psychological distress when coping with genetic testing for a cancer predisposition in adulthood. We found that those having an affected parent or having lost a parent to cancer before adolescence were psychologically most vulnerable. They reported the highest levels of hereditary cancer related distress, cancer worry and cancer risk perception several years later when going through the process of genetic testing for a hereditary cancer susceptibility. Interestingly, the courses of distress, worry and risk perception through time were similar in all groups. This might suggest that distress levels are continuously increased in individuals having an affected parent or having lost a parent to cancer before adolescence, also far before and after they opt for genetic testing. The finding of increased distress in individuals having an affected parent or having lost a parent to cancer before adolescence is, however, not in line with the study from Hopwood *et al*.[20], who reported low levels of cancer worry in women at risk of breast cancer having lost their mothers before age ten years outside the setting of genetic testing. Because they did not control for relevant confounding variables, the reported low level of cancer worry may be due to other underlying factors like age at the time of genetic counselling.

As expected, having a parent affected by cancer resulted in a higher perceived risk of developing cancer, irrespective of risk and gene mutation status. Psychological distress was not more frequent in this group. These findings are in line with studies in grown up daughters of breast cancer patients outside the genetic testing setting[19, 20]. We also confirmed our expectation that women having a mother affected with breast cancer at the time of breast development (i.e. in puberty) perceived their risk of developing cancer as higher and were more distressed. But again, women who were under age 10 at the time of their mothers' diagnosis reported the highest levels of distress over time.

Despite the vulnerability of adolescents due to the stress of adjusting family boundaries to their independence in a period of illness[28], adolescents may be more apt in finding support from others outside the family, may have more mature coping mechanisms and may be better informed about the illness of the parent as compared to younger children[29]. This may enable the adolescent to cope with and work through the illness or loss experience, which can be of help several years later when confronted with increased cancer risks. Since younger children are more dependent on their parents, their fear of the loss of an important caregiver may be more threatening[21]. Furthermore, younger children may not have the cognitive and emotional abilities to fully understand and cope with the intense emotional and physical suffering from the parent. Parents may have informed younger children less completely about the illness[30] and may have avoided communicating about cancer more frequently in order to protect them[31, 32]. Younger children consequently might be less able to correctly integrate the experience into the autobiographical knowledge base. When these children have grown up, poorly integrated representations of the illness might influence the perceived meaning of the cancer risk.

Individuals with an affected parent felt more vulnerable to cancer than individuals without affected parents, irrespective of pre-test genetic risk. Moreover, participants with an affected parent continued to feel more at risk after result disclosure, irrespective of genetic risk status. It has been suggested that individuals develop an image of their future lives through identification with their parents[9, 21].

Identifications may be more prominent in young and adolescent children, resulting in a higher cancer risk perception in these groups.

To our knowledge, this is the first study to analyse the impact of parental cancer on individuals from identified gene mutation families undergoing genetic testing. Strengths of our study are the prospective study design, low drop out rate and method of statistical analyses. Furthermore we controlled for confounding variables and used psychologically meaningful age categories. Limitations were the small sample of individuals having lost a parent before adolescence and the lesser participation of individuals not opting for genetic testing. For the future, it is warranted to study a larger sample of children of parents with hereditary cancer, in order to validate and refine our results. Another unanswered question is if having a mother affected with cancer has a more profound impact than having an affected father on the long term.

We recommend that health care professionals pay attention to the psychological impact of experiences with parental cancer. Especially, monitoring the psychological resilience of those having witnessed parental cancer as a child is necessary in case of increased cancer risks.

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CHAPTER 9

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.

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. HNPCC (Hereditary Nonpolyposis Colorectal Cancer) 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 cancer 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 specialized 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 counseling 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 counseling 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 determine coping responses, health behavior and finally psychological well-being. Illness representations, coping behaviors and emotional adjustment may be influenced by earlier experiences with cancer in the family and by the familial and social environtment[7, 9].

This paper reports findings from a prospective multi-center 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.

PATIENTS AND METHODS

Participants and counseling procedure

See Chapter 4.

Study procedure

The first questionnaire, containing all predictive measures and the outcome measures, was mailed 1 week after the first counseling session. Participants received a second and a third questionnaire, containing the outcome measures, 1 week and 6 months after result disclosure. For more details see Chapter 4.

Measures

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 categorized 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 that a gene mutation was identified in the family and which 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*
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 doesn't 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

* Cronbach's alpha
(r) reverse scored

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, involvement) and a sense of separateness (autonomy, uniqueness, freedom of personal expression).

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 cut off (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].

Statistical methods

Demographic and clinical characteristics of the study sample were analyzed 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 $\geq$ 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 procedure backward elimination ($P_{in} < 0.050$ 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 $\geq$ 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.

RESULTS

Study population

See Chapter 4.

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 Chapter 4).

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.

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

Table 2 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 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, center 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.

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 procedure backward elimination. 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 3). Explained variance of the final model was 41%; the AUC in predicting clinically elevated levels of hereditary cancer distress was 87%.

Table 2. 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*	$R^{2\#}$	β	*P*	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 yrs 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	

[#] not adjusted for age, gender, test result and cancer syndrome
β, standardized regression coefficient; R^2, R^2 adjusted for shrinkage

Table 3. Final model for hereditary cancer distress six months after genetic test result disclosure.
β - standardized regression coefficient

	β	*P*	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		

R^2 - R^2 adjusted for shrinkage; AUC - area under the curve predicting *clinically elevated* levels of hereditary cancer distress.

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 6 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 relatives' 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 cut off 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.

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CHAPTER 10

Summary and discussion

Our understanding of human genes and of the genetic basis of disease has grown dramatically over the past decade. Hundreds of genes causally related to hereditary diseases have been identified. Their identification has led to an increase in the number of available genetic tests that can detect an individual's risk of disease. With the increase in the number of available genetic tests, interest has grown in how individuals cope with the tests and the information they generate. The psychological studies conducted in our center over the past decades have closely followed the developments in clinical genetics. First, the focus was mainly on the prevention of untreatable, severe conditions by prenatal and postnatal diagnosis[131]. Later, attention switched to presymptomatic genetic testing for late-onset hereditary diseases like Huntington's disease[132-134], followed by genetic susceptibility testing for hereditary cancer syndromes[133, 135, 136].

When genetic susceptibility testing for hereditary cancer syndromes like *BRCA1/2* and HNPCC was introduced in the clinic in the mid-nineties, the 'Huntington protocol' was adopted for the counseling of unaffected individuals. This consists of at least two pre-test sessions, standard provision of psychological support and a disclosure session. Abroad, some centers still use this approach for genetic cancer susceptibility testing[137]. The current approach in The Netherlands is to provide at least two sessions with a genetic counselor and additional counseling suited to the needs of the counselee. The subset of psychologically more vulnerable counselees can be referred to a specialized psychologist or social worker. Therefore, it has become more important for genetic counselors to learn about psychological mechanisms and risk factors for psychosocial maladjustment (Chapter 2). This will help counselors to evaluate individual strengths and weaknesses and to identify the subset of individuals who may benefit from additional support by a psychologist or social worker. Consequently, more knowledge is needed on psychological mechanisms related to adjustment.

Aims of this thesis are to understand the psychosocial consequences of genetic susceptibility testing for a *BRCA1/2* or an HNPCC related mutation and to explore risk factors for maladjustment. Based on our findings, recommendations will be made for the improvement of early identification of those at risk for adjustment problems and for interventions in genetic counseling.

PSYCHOSOCIAL IMPACT OF GENETIC SUSCEPTIBILITY TESTING FOR BRCA1/2 OR HNPCC

Remarkable psychological resiliency on the short-term

We reviewed the literature on the psychosocial impact of genetic susceptibility testing for *BRCA1/2* in order to reflect on the appropriate approach for genetic counseling (Chapter 2). Evidence has been accumulating that individuals generally cope well with genetic susceptibility

testing for *BRCA1/2*. Levels of distress and worry are somewhat increased shortly before and after result disclosure, especially in mutation carriers, and decrease over the following weeks and months. The request for psychological support proved to be rare in the short term. However, a subset of women undergoing genetic testing reports a level of distress that warrants clinical attention.

It has been suggested that genetic susceptibility testing is not very distressing for each individual[82]. Our study shows that individuals who apply for genetic testing perceive already considerably high risks to develop cancer at the time of blood sampling (Chapter 4). Perceived risk decreases significantly in non-carriers after result disclosure. It increases only slightly in mutation carriers. This suggests that non-carriers win a lot and mutation carriers only lose a little. For genetic counselors it is important to perceive genetic testing not only as a burden for counselees, but to see its potential to help them cope with an increased risk to develop cancer, too.

Adequate long-term adjustment to BRCA1/2 genetic testing

Most studies on the psychological implications of genetic cancer susceptibility testing have followed participants only for a short period of time, i.e. up to one year after result disclosure. We have examined the long-term implications of genetic susceptibility testing for *BRCA1/2* in unaffected women that were followed prospectively from pretest to five years after result disclosure (Chapter 3). Five years after testing, mutation carriers were not significantly more distressed than non-carriers. However, both groups had shown a significant increase in anxiety and depression from one to five years follow-up. The number of individuals having contacted a professional for psychosocial support had increased too. A third of non-carriers and 44% of mutation carriers had contacted a professional for psychological support during the five years after genetic testing. These substantial numbers may be due to selective drop out of participants faring well, in view of the loss to follow-up of individuals who opt for regular surveillance and who are generally less distressed[61].

Another explanation to consider is that living in a *BRCA1/2* mutation family can be a burden, even if the individual test result is negative or if prophylactic surgery was successful. The relief after having done everything to diminish the risk may be short-lived or limited to the individual level. Next, another relative may develop breast cancer. Earlier losses still may have to be mourned. Or one realizes that the next generation is growing up with the burden of complicated decisions about having genetic testing, prophylactic surgery and children. Indeed, in the retrospective study[138], women who tested positive or negative for a familial *BRCA1/2* mutation one month to five years ago indicated that the initial emotional turmoil was short-lived, but went beyond the individual to the familial context. These findings support the view that professionals should pay attention to the impact of hereditary cancer on the whole family system instead of focusing on the individual and his genetic test result only[139].

We (Chapter 3) and others[19, 20, 25, 140] showed that prophylactic mastectomy (PM) and prophylactic bilateral salpingo oophorectomy (PBSO) resulted in a relief of the fear of developing cancer. The large majority would opt for a similar treatment again[21]. Prophylactic surgery can thus be an effective strategy to cope with the fear aroused by the threat of cancer. The medical

and psychological benefits have to be weighted against the risk of complications, potential adverse effects on body image and changes in the sexual relationship.

In our study, adverse effects on sexual functioning were reported, but it was impossible to disentangle the effects of PM and PBSO because the majority of women underwent both PM and PBSO. Some[19, 61, 141], but not all[20] studies have found that PM can have negative consequences for perceived body appearance and sexual functioning. Women and their partners have to adjust to the loss of the old breasts and the new proportions of their body. Moreover, some women have to adjust to the loss of sensibility in the reconstructed breasts. Not all couples may be capable to adjust their sexual life to these drastic changes. A recent study that compared large groups of women at high risk of ovarian cancer opting for PBSO or for periodic gynecological screening has found that PBSO resulted in worse sexual functioning, irrespective of hormone replacement therapy[25]. Women who had undergone PBSO reported less pleasure and satisfaction and more discomfort during sexual intercourse. The issue whether PBSO has more consequences for sexual functioning than PM merits further exploration.

A mild impact of genetic cancer susceptibility testing on family relationships

Few studies on the impact of genetic cancer susceptibility testing have focused on other outcomes than psychological distress. The impact of genetic testing for a cancer predisposition on family relationships has been studied rarely despite its clinical relevance. In our study on individuals from *BRCA1/2* and HNPCC related mutation families, the impact of genetic susceptibility testing on family relationships was generally mild (Chapter 5). Genetic testing affected some family relationships in a positive way, i.e. by feeling closer, improved communication and support and increased appreciation of relatives. A minority reported unwanted changes in relationships, problematic situations or conflicts due to genetic testing. Adverse effects comprised feelings of guilt towards children and carrier siblings, imposed secrecy and communication problems. Our findings are in line with two recent studies that have reported on the topic[39, 67, 90].

The effect of genetic susceptibility testing for *BRCA1/2* and HNPCC resembles the effect on psychological distress. In a minority of families genetic testing affects family relationships in a negative way. Individuals from these families were characterized by more reluctance to talk about hereditary cancer with relatives and also by maladaptive nuclear family functioning. They may also be more distressed, as was reported in our group of women five years after *BRCA1/2* genetic testing (Chapter 3).

Mainly comparable psychological processes in individuals from BRCA1/2 and HNPCC mutation positive families

Before undertaking studies with individuals from both *BRCA1/2* and HNPCC mutation positive families, we wanted to know whether the two groups were comparable with regard to the variables that were assessed in this study (Chapter 4). Others have suggested that each cancer syndrome is unique and should be studied separately[52]. Based on Rolland[1], we expected however to find mainly similar psychological processes in the two groups. The conditions are comparable with regard to the likelihood of developing cancer, the timing of clinical onset in the life cycle, overall clinical severity, and the availability of prevention and treatment options. Indeed, in

our study no significant differences were found between the two groups in the majority of the psychological variables assessed. The two groups reported equal numbers of experiences with cancer in relatives, grief symptoms, the course of cancer distress, worry and risk perception through time and most illness perceptions, coping responses and family characteristics. However, individuals from *BRCA1/2* families perceived hereditary cancer as more serious. They reported more frequently a passive coping style, more cancer worry and a less open communication with their partner and children. These differences in representations, coping and worry may be due to the availability of colonoscopy to HNPCC mutation carriers, that has proven to be effective in preventing the development of cancer, and has not the mutilating consequences of prophylactic mastectomy, nor the more unsure efficacy of breast cancer screening. The differences might also be attributed to the fact that *BRCA1/2* affects women, and that losing a mother may have a greater impact than losing a father, especially for women[142]. In view of the relatively small differences between individuals from *BRCA1/2* and HNPCC mutation families, it can be justified to include the two groups together in psychological studies, if the statistical analyses are adjusted for the cancer predisposition.

Predictive factors of psychosocial adjustment

In current practice, genetic counselors refer a subset of their counselees for additional support to a specialized psychologist or social worker. It is unknown what criteria are used for referral and whether these are effective. Furthermore, our understanding of factors and psychological mechanisms that contribute to psychological distress is in its infancy. To study these factors and psychological mechanisms, we have used an extended version of Leventhal's Model of Self-Regulation[94] as theoretical background. This model posits that individuals create their own understanding of an illness or health threat (illness representations), which determines coping responses, health behavior and finally psychological well-being. Besides illness representations and coping, earlier experiences with cancer in the family and the familial environment might influence emotional adjustment.

The contribution of illness representations and coping

In our prospective study on individuals from *BRCA1/2* and HNPCC mutation families, several interesting relationships were identified between illness representations, risk perception, causal attributions, coping behaviors and psychological adjustment (Chapters 6, 9). Some illness representations were clearly less adaptive: illness coherence and emotional representations. Perceiving less illness coherence results in less adaptive coping strategies and more distress and worry, especially on the long term. Individuals perceiving less illness coherence feel they don't understand the condition, that it does not make sense. Illness coherence may express insufficient cognitive processing and mastery, but also a feeling of helplessness and loss of cognitive control. More intense negative representations were also strongly related to less adaptive coping strategies and more distress and worry. For the interpretation of this result, we should however question whether emotional representations are not solely an expression of distress.

Other illness representations were related to distress and worry but may be less alarming. Perceiving more serious consequences and a more chronic duration results in more

coping behaviors in general, and more distress or worry only on the short term. Perceiving heredity as an important cause of the condition results in more adaptive coping behaviors but also in more worry shortly before and after result disclosure. These findings are in accordance with the self-regulatory model and have been confirmed by other studies[39, 67, 95].

Coping contributed also significantly to hereditary cancer distress and cancer worry. On the short term, social support seeking and distraction seeking were related to distress and worry. These coping behaviors may be observed more frequently in distressed individuals, but may engender adjustment in the long-term. Passive coping was clearly maladaptive on the long-term. Like illness coherence, passive coping may reflect a feeling of helplessness, but more on the emotional and behavioral level. Passive coping is one of the most important coping styles to attend to in genetic counseling, as it has been found to predict distress in similar studies too[39, 67, 109, 136].

The family matters

We have investigated prospectively the contribution of several family system characteristics to psychological distress in individuals applying for genetic susceptibility testing for *BRCA1/2* or HNPCC. Family system characteristics could be of importance because genetic testing can have consequences for the whole family. We found that family characteristics linked to hereditary cancer were important factors for hereditary cancer distress and worry. Especially, the quality of communication regarding hereditary cancer within the family is of paramount importance. This factor has been demonstrated in our group of individuals from *BRCA1/2* and HNPCC related mutation families during and after genetic testing (Chapters 7, 9), in our group of women from *BRCA1/2* mutation families five years after genetic testing (Chapter 3). The quality of communication is also of importance for relational adjustment (Chapter 5). Open and sensitive communication about thoughts, feelings and worries concerning hereditary cancer may promote individual psychological adjustment. It may even be beneficial to physical health and immune function, as was reported in studies on the effects of emotional expression[143]. Furthermore, family support during genetic testing was an important buffer against distress. Support from the partner was especially consequential. This finding is congruent with other studies[123, 124, 144]. More general family system characteristics like family functioning (cohesion, adaptation) and differentiation contributed less. Adequate family functioning and relationships may help to adjust to all stressors, and could be more important for general distress independent of genetic testing and hereditary cancer.

The importance of earlier experiences with family illness and grief symptoms

It has been suggested that experiences with cancer in the family may result in an increased psychological vulnerability when confronted with genetic cancer susceptibility testing[103, 110]. We showed in our group that individuals with parental cancer in childhood (under age 13) reported more cancer related distress, worry and a higher risk perception than individuals with parental cancer after age 13 or with no affected parent (Chapter 8, 9). Young children may be psychologically more vulnerable because they are still dependent on the care of their parents[112]. Moreover, they may have less affective and cognitive resources to cope with stressful

life events[145]. Another finding was that women having their mother affected by breast cancer in puberty (aged 10-13 years) perceived higher breast cancer risks than women with an affected mother in adulthood or with an unaffected mother. Individuals with an affected parent perceived higher cancer risks than individuals without an affected parent. Probably, individuals develop an image of their future health through identification with their parents[110, 145].

A recent study by Watson *et al.*[146] suggests that communication in the family is an important factor for emotional and behavioral problems in school-aged children of cancer patients. Problems in children were linked with low affective responsiveness, poor family communication and maternal depression, rather than by the mother's treatment status or time since diagnosis. Indeed, parents find it difficult to talk about cancer to children and to inform them about hereditary cancer. About two third of families experience difficulties in communicating about cancer[147]. Underlying thought processes are avoidance of psychological distress, a desire for "mutual protection" and belief in positive thinking. Especially talking to children has been experienced as difficult[148]. In order to protect them, information is frequently withheld from them. This can have devastating consequences. If children are involved to the level they want to be involved, family communication is open and family coping is adequate, children may be less vulnerable for psychological distress as adults when confronted with their own cancer risks. Based on our findings, we have developed a leaflet on informing the children about hereditary illness in the family.

Other risk factors for distress were symptoms of unresolved grief, the number of affected close relatives (Chapter 9) and the number of close relatives who died of cancer (Chapter 3). These findings contribute to the emerging evidence that individuals at increased risk of cancer who have been involved in a relatives' cancer process[114], were exposed to cancer more frequently[10, 116] and at a younger age[115], who have lost a parent to cancer[101, 113] or experience unresolved loss[76] may become psychologically more vulnerable.

From our clinical experience, we know that parental illness like cancer can compromise the developmental task of differentiation and individuation. Furthermore, it has been shown that differentiation in adolescence affects mid-life well-being[129]. In this study, differentiation at the time of parental illness was not assessed. In future studies, it would be relevant to study the relationship between parental illness in childhood, individuation in childhood and psychological adjustment in childhood and adulthood.

LIMITATIONS AND FUTURE DIRECTIONS

This study relied on self-report instruments assessing levels of psychological distress. Distress was assumed to indicate maladjustment. Although the instruments used in this study were frequently used and their psychometric values have been well-established[149-154], we should question if we have actually measured maladjustment. 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. Moreover, the number of individuals presenting for genetic testing and having clinical levels of distress is relatively low as compared to populations in a primary care setting[79]. If individuals adapt well to genetic testing with adequate counseling, we could question if more studies on psychological adjustment in individuals from *BRCA1/2*

or HNPCC related families and likewise cancer predispositions are worthwhile. Several issues have now been well-documented and do not need further investigations. For example, no more studies are needed to investigate the motivations to opt for genetic testing and the impact of genetic testing on well-being. Other questions need more future investigations.

In this study the relationships between illness representations, coping, experiences with cancer in the family and family characteristics were explored. Leventhal's Model of Self-Regulation was useful to understand the cognitive and emotional reactions to genetic susceptibility testing. Our study however did not provide insight into the mutual relationships between illness representations, coping, experiences with cancer in the family and family characteristics. More research is needed to disentangle these relationships and to study them in unaffected individuals across different genetic predispositions. Furthermore, the impact of genetic information, illness representations and coping on health behaviors should be studied in more detail. Compliance to screening recommendations for colonoscopy or mammography may not be suitable for these studies, because compliance is high[32, 33, 155] and largely depends on external variables (like scheduled appointments). An outcome measure like making lifestyle changes after genetic testing for familial hypercholesterolemia would be more suitable to study.

Future developments will furthermore engender the need for psychological studies. In the future, more genetic knowledge will likely become available on the multiple genes involved in complex and common diseases like heart disease, cancer, diabetes and mental illness. It may become possible to screen individuals for many genetic-based risks at the same time[156]. Individual risk assessments could be created for each individual based on the set of genes. Individuals could be stimulated to make lifestyle changes based on their personal genetic make-up. For mental illness, preventive programs could be developed. In view of these future potential developments in genetics, more studies evaluating the impact of genetic health risks on individual representations, coping and health behavior are needed[91, 157].

Another recent development will engender the need for more psychological studies. In the near future, the genetic diagnosis of *BRCA1/2* and HNPCC will be made more frequently at the time of the cancer diagnosis. This new development may bring several medical advantages: more effective detection of hereditary cancer syndromes, better-adjusted medical management and treatment. Although the psychological consequences can be expected to be rather benign[158], the psychological implications of these two accumulating stressful experiences need to be explored and vulnerable individuals need to be identified.

CLINICAL IMPLICATIONS

The remarkable psychological resiliency of the majority of individuals opting for genetic testing has consequences for genetic testing counseling protocols. Based on the findings in the literature (Chapter 2), it can be assumed that an approach of at least two counseling sessions with optional psychological support for the subset of vulnerable counselees provides sufficient support to adjust to genetic testing for *BRCA1/2*, HNPCC and likewise cancer syndromes. A similar counseling approach for *BRCA1/2* and HNPCC seems justified in view of the similarities between the groups (Chapter 4). This is in accordance with the current counseling approach in The Netherlands and many centers abroad[137].

The subset of counselees that is in need for additional psychological counseling has to be identified correctly. Currently it is however uncertain whether vulnerable individuals are correctly identified and receive additional psychological counseling (Chapter 3). The current approach may be improved by using a tool to identify psychologically vulnerable counselees. Such a tool is currently developed by the working group familial cancer of the Dutch Society of Psycho-Oncology (NVPO). Another way to improve the current approach is to intensify psychological training of genetic counselors. The genetic counselor has to master specific communication skills and knowledge about risk factors for psychological maladjustment, in order to identify individuals in need of additional support. Genetic counselors need to acquire sensitivity and basic knowledge of family system characteristics and communication (Chapter 3, 5, 7, 9). Currently these subjects are addressed in advanced courses. Other topics to be addressed are coping and illness representations (Chapter 6, 9); and handling of earlier experiences with cancer and grief reactions (Chapter 8, 9). Of note, we should not put too high demands on the psychological competencies of genetic counselors, who are already confronted with the increasing complexity of genetics.

Several psychological processes and risk factors need attention in genetic counseling. In Table 1, a summary of important factors is given with suggestions to handle them. With regard to coping and illness representations (Chapter 6), counselors may help patients who feel unable to deal with hereditary cancer by stimulating active coping behaviors, and by mobilizing social support. Furthermore, we should realize that illness representations and beliefs are not stable. Besides the influence of the social environment, media and internet, they can be influenced by medical professionals. When counselors identify incorrect perceptions and maladaptive beliefs, they can help the counselee to gain more realistic and adaptive perceptions by understanding the origin of the beliefs, by explaining the correct information and by using 'the full force of their professional role'[159]. For example, breast cancer is frequently perceived to equal dying. Yet, the improvements in medical treatment make breast cancer a very serious condition that is frequently survived. Such a statement can serve as a cognitive reference when inadequate perceptions emerge.

Exploration of family communication and family support may furthermore provide valuable information for the determination of strengths and weaknesses (Chapter 7). Communicating in an open and sensitive manner about hereditary cancer with relatives should be stimulated. If family support is not available to an individual, the provision of alternative resources may be beneficial. More follow-ups by the counselor or the referral to a specialized psychologist or social worker may be needed. Finally, we recommend monitoring the impact on family relationships and to stimulate respect for differences in decision making and coping (Chapter 5).

When drawing the family tree, genetic counselors need to pay attention to the illness experiences that may have resulted in more psychological vulnerability, for example having an affected parent or having lost a parent during childhood, unresolved loss and the number of affected relatives and losses (Chapter 8, 9). Evaluation of the personal experience, coping and current well-being may provide valuable information for the determination of strengths and weaknesses and of the need to refer the counselee to a psychologist or social worker.

The findings from our five-year follow-up study suggest that the potential effect on

sexual functioning should be discussed with women and partners before prophylactic surgery takes place (Chapter 3). The issue of sexual functioning should furthermore be discussed with all sexual active women after PBSO and PM. If sexual functioning is less satisfactory, women should be referred to a medical sexologist or psychotherapist for adequate evaluation and treatment.

Table 1. Psychological processes and risk factors for psychological vulnerability

Psychological process to attend to in genetic counseling	Actions
Illness incoherence	Stimulate cognitive processing, stimulate cognitive mastery and control (filling in lacks of information, providing realistic cognitions that provide feelings of control), consider referral to a SPS when help is needed to resolve past experiences
Passive coping	Reinforce mobilization of social support, stimulate active coping, consider referral to a SPS
Inhibited family communication regarding hereditary cancer	Explore family communication patterns, provide information about the consequences of protective buffering and inhibited communication, monitor the impact of genetic testing on family relationships and consider referral to a SPS
Insufficient partner and/or family support	Engage the partner in the procedure, provide additional support/ counseling sessions, identify barriers for the provision of support and consider referral to a SPS
Affected parent in childhood <13 years	Explore psychological resilience and risk perception, consider referral to a SPS
Complicated grief	Explore unresolved loss, consider referral to a SPS
High distress	Referral to SPS

SPS= specialized psychologist or social worker

MAIN CONCLUSIONS

1. A very consistent finding in the literature is that the majority of individuals who apply for genetic susceptibility testing shows a remarkable psychological resiliency and that only a minority of individuals reports a level of distress that warrants clinical evaluation.

2. A minority of individuals reports adverse effects on family relationships and needs additional attention in genetic counseling.

3. Findings on the long-term suggest that living in a family affected by hereditary cancer may be more burdensome than genetic susceptibility testing.

4. Findings on the long-term suggest that living in a family affected by hereditary cancer may be more burdensome than genetic susceptibility testing.

5. Factors that need to be attended to in genetic counseling are illness coherence, emotional representations, passive coping, family communication, family support, age at the time of parental cancer or death, the impact of having multiple family members affected by cancer and complicated grief.

6. Illness representations and beliefs are not stable. Maladaptive and incorrect beliefs can be adjusted (to some extent) by interventions of a genetic counselor.

7. Adequate and repeated psychological training is mandatory for genetic counselors. Besides communication skills, counselors need to be trained in recognizing psychological strengths and weaknesses including family influences.

8. The potential effect on sexual functioning should be discussed with female *BRCA1/2* mutation carriers and their partners before and after prophylactic surgery takes place.

9. More studies are needed to disentangle relationships between illness representations, coping and health behavior in individuals at genetically increased risk of developing an illness.

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Samenvatting

De kennis van onze genen en de genetische basis van ziekte is de laatste jaren enorm gegroeid. Honderden genen die samenhangen met erfelijke ziekten zijn ontdekt. Hun ontdekking heeft geleid tot een toename van voorspellend DNA-onderzoek, waarmee het risico van een individu op ziekte kan worden vastgesteld. Met de toename in het aantal beschikbare genetische tests, is ook de belangstelling gegroeid voor de vraag hoe individuen omgaan met het onderzoek en de informatie die eruit voortkomt. De psychologische studies die de laatste jaren in ons centrum zijn uitgevoerd hebben de ontwikkelingen in de klinische genetica nauw gevolgd. Eerst lag de nadruk voornamelijk op het voorkomen van onbehandelbare, ernstige aandoeningen door middel van prenatale en postnatale diagnostiek[1]. Daarna ging de aandacht uit naar het presymptomatisch DNA-onderzoek naar erfelijke ziekten die zich op volwassen leeftijd openbaren, zoals de ziekte van Huntington[2-4], gevolgd door voorspellend DNA-onderzoek naar een aanleg voor kanker[3, 5, 6].

Toen voorspellend DNA-onderzoek naar een aanleg voor kanker, zoals *BRCA1/2** of HNPCC** mogelijk werd in de jaren negentig, werd het 'Huntington-protocol' toegepast in de counseling voor voorspellend DNA-onderzoek. Dit protocol bestaat uit ten minste twee sessies vóór de bloedafname, een gesprek met een psycholoog of maatschappelijk werker en een sessie waarin de uitslag wordt gegeven. In het buitenland gebruiken sommige centra dit protocol nog steeds bij voorspellend DNA-onderzoek naar een aanleg voor kanker[7]. In Nederland is het nu gebruikelijk om ten minste twee sessies te hebben met een genetisch counselor. De meer kwetsbare adviesvragers kunnen doorverwezen worden naar een psycholoog of maatschappelijk werker. Omdat adviesvragers niet meer standaard door een psycholoog of maatschappelijk werker worden gezien, is het nu belangrijker geworden dat genetisch counselors kennis hebben van psychologische mechanismen en risicofactoren voor aanpassingsproblemen na een testuitslag.

Doel van dit proefschrift is het begrijpen van de psychosociale gevolgen van voorspellend DNA-onderzoek voor een *BRCA1/2*- of een HNPCC-gerelateerde mutatie en het exploreren van risicofactoren voor aanpassingsproblemen. Op basis van de bevindingen worden aanbevelingen gedaan voor de verbetering van de vroege opsporing van individuen die risico lopen op aanpassingsproblemen en voor interventies in de counseling.

*Vrouwelijke *BRCA1*/2-mutatiedragers hebben een sterk verhoogd risico op het ontwikkelen van borst- en eierstokkanker. Vrouwelijke *BRCA1*/2-mutatiedragers kunnen vanaf het 25ste levensjaar hun borsten twee keer per jaar laten controleren. Vanaf hun 35ste jaar komen zij in aanmerking voor gynaecologische controle. Omdat de controles de kans niet uitsluiten dat kanker ontstaat en dat een tumor ontdekt wordt die al is uitgezaaid, kiest een aantal vrouwen ervoor preventief de borsten en/of de eierstokken te laten verwijderen.

**Mannelijke en vrouwelijke dragers van een mutatie in één van de HNPCC-gerelateerde genen hebben een sterk verhoogde kans op het ontwikkelen van poliepen in de dikke darm, die zich uiteindelijk kunnen ontwikkelen tot een kwaadaardige tumor. Vrouwelijke dragers hebben daarnaast een sterk verhoogde kans op het ontwikkelen van tumoren in de bekleding van de baarmoeder (endometrium). Mutatiedragers komen vanaf het 25ste levensjaar in aanmerking voor een kijkonderzoek van de dikke darm, een colonoscopie. Daarbij kunnen poliepen opgespoord en verwijderd worden voordat ze zich ontwikkelen tot tumoren. Vrouwelijke mutatiedragers komen daarnaast in aanmerking voor gynaecologische controle en/of preventieve verwijdering van de baarmoeder.

PSYCHOSOCIALE IMPACT VAN VOORSPELLEND DNA-ONDERZOEK NAAR *BRCA1/2* EN HNPCC

Opvallende psychologische weerbaarheid op de korte termijn

We hebben de literatuur over de psychosociale impact van voorspellend DNA-onderzoek naar *BRCA1/2* op een rij gezet (Hoofdstuk 2). Over het algemeen kunnen individuen goed omgaan met voorspellend DNA-onderzoek naar *BRCA1/2* en de uitkomsten ervan. Stressverwerkingsklachten*** en zorgen om kanker zijn wat verhoogd kort vóór en na de uitslag, vooral bij mutatiedragers, maar nemen vervolgens af. Er is weinig vraag naar psychosociale ondersteuning. Toch rapporteert een kleine subgroep zoveel stressverwerkingsklachten dat aandacht van een psycholoog of psychiater nodig is.

Er is wel gesuggereerd dat voorspellend DNA-onderzoek naar *BRCA1/2* geen stress veroorzaakt[8]. Onze studie laat zien dat individuen die ervoor kiezen zich te laten testen al het gevoel hebben een erg hoog risico te hebben op kanker ten tijde van de bloedafname (Hoofdstuk 4). Bij niet-dragers daalt het ervaren risico sterk; bij mutatiedragers stijgt het ervaren risico licht. Het lijkt erop dat niet-dragers veel te winnen hebben en dat mutatiedragers slechts een beetje te verliezen hebben. Voor counselors is het van belang te beseffen dat het voorspellend DNA-onderzoek niet alleen een last is voor de adviesvrager, maar ook juist een mogelijkheid biedt om het verhoogde risico op kanker te kunnen hanteren.

Adequate aanpassing op de lange termijn

De meeste studies naar de psychologische implicaties van voorspellend DNA-onderzoek naar een aanleg voor kanker hebben mensen slechts gedurende een korte tijd gevolgd, maximaal tot een jaar na de uitslag. Wij hebben de lange termijneffecten van DNA-onderzoek naar een *BRCA1/2*-mutatie onderzocht in niet-aangedane vrouwen, die prospectief werden gevolgd vanaf de bloedafname tot vijf jaar na de uitslag (Hoofdstuk 3). Vijf jaar na de uitslag vertoonden mutatiedragers een vergelijkbaar niveau van psychisch welbevinden als niet-dragers. Beide groepen vertoonden wel een significante afname in psychisch welbevinden tussen de één en de vijf jaar na de uitslag. Het aantal vrouwen dat contact had gezocht met een hulpverlener voor steun was ook toegenomen. Eenderde van de niet-dragers en 44% van de dragers had contact gehad met een hulpverlener gedurende de vijf jaar na de uitslag. Het is mogelijk dat deze aantallen veroorzaakt zijn door een selectieve uitval van deelnemers aan de studie. Gezien de hogere uitval onder mutatiedragers die hebben gekozen voor regelmatige screening van de borsten en de lagere niveaus van stressverwerkingsklachten bij deze groep[9], zouden vrouwen met meer problemen in de studie kunnen zijn gebleven.

Een andere verklaring zou kunnen zijn dat het leven in een *BRCA1/2*-mutatiefamilie een last is, zelfs als het eigen testresultaat gunstig is of als de preventieve operatie succesvol was. De opluchting dat alles gedaan is om het risico te verminderen zou kortdurend kunnen zijn of beperkt tot het individuele niveau. Echter, kanker geconstateerd bij een familielid of eerdere onverwerkte verliezen kunnen ook de aanpassingsproblemen verklaren. Of men moet toezien hoe de volgende generatie opgroeit met de last van ingewikkelde beslissingen over DNA-onderzoek,

***Stressverwerkingsklachten en zorgen om kanker zijn een vertaling van 'hereditary cancer distress' en 'cancer worry'. Vaak wordt gesproken van 'psychological distress'. Dit hebben wij vertaald als aanpassingsproblemen.

preventieve operaties en het krijgen van kinderen. In een retrospectieve studie[10] bleek inderdaad dat vrouwen uit *BRCA1/2*-mutatiefamilies één tot vijf jaar na voorspellend DNA-onderzoek aangaven dat de eerste emotionele onrust aanvankelijk kortdurend was en henzelf betrof. Later had de onrust meer betrekking op de familiaire context. Deze bevindingen ondersteunen het gezichtspunt dat hulpverleners aandacht dienen te besteden aan de impact van erfelijke kanker op de familie in zijn geheel in plaats van enkel het individu en zijn uitslag[11].

Wij (Hoofdstuk 3) en anderen[12-15] hebben aangetoond dat preventieve mastectomie (PM) en preventieve bilaterale salpingo oophorectomie (PBSO) leidt tot een vermindering van de angst om kanker te krijgen. De meerderheid van de vrouwen zou weer voor een zelfde operatie kiezen[16]. Preventieve chirurgie kan dus een effectieve strategie zijn om om te gaan met de angst die wordt veroorzaakt door het verhoogde risico op kanker. De medische en psychologische voordelen moeten afgewogen worden tegen de kans op complicaties, en mogelijke effecten op het lichaamsbeeld en veranderingen in de seksuele relatie.

In onze studie werden negatieve veranderingen in de seksuele relatie gerapporteerd, maar het is onmogelijk om de effecten van PM en PBSO uit elkaar te halen, omdat de meerderheid van de deelnemers beide operaties had ondergaan. Sommige[9, 12, 17], maar niet alle[13] studies vonden een negatieve impact van PM op lichaamsbeeld en de seksuele relatie. Vrouwen en hun partners moeten zich aanpassen aan het verlies van de oude borsten en de nieuwe verhoudingen van hun lichaam. Sommige vrouwen moeten ook nog wennen aan het verlies van het gevoel in hun borsten. Niet iedereen zal in staat zijn om het seksuele leven hieraan aan te passen. In een recente studie werden grote groepen vrouwen vergeleken die kozen voor PBSO of voor regelmatige gynaecologische screening[15]. Vrouwen die hadden gekozen voor PBSO rapporteerden minder plezier en meer pijn bij het vrijen. De vraag of PM of PBSO leidt tot meer gevolgen voor de seksuele relatie dient verder te worden onderzocht.

De gevolgen van voorspellend DNA-onderzoek voor familierelaties

Weinig studies over de impact van voorspellend DNA-onderzoek naar een aanleg voor kanker hebben aandacht gehad voor de gevolgen ervan voor familierelaties. In onze studie waren ongewenste effecten over de gehele groep beperkt (Hoofdstuk 5). Het DNA-onderzoek beïnvloedde bij een aantal individuen familierelaties op positieve wijze, namelijk doordat men zich meer verbonden voelde, de communicatie verbeterde en door toegenomen steun en waardering van elkaar. Een minderheid rapporteerde ongewenste veranderingen in familierelaties, problemen of conflicten door het DNA-onderzoek. Deze ongewenste veranderingen omvatten schuldgevoelens ten opzichte van kinderen en familieleden met een ongunstige uitslag, geheimhouding en communicatieproblemen. Onze bevindingen komen overeen met de bevindingen uit twee andere recente studies over dit onderwerp[18-20].

Concluderend kan gesteld worden dat het effect van voorspellend DNA-onderzoek naar *BRCA1/2* en HNPCC op familierelaties vergelijkbaar is met het effect op het psychisch welbevinden. Slechts bij een minderheid werden negatieve gevolgen gevonden. Individuen die negatieve gevolgen voor familierelaties rapporteerden, werden gekenmerkt door minder openheid om over erfelijke kanker te spreken met familieleden en door minder adequaat familiefunctioneren. Ze vertonen gemiddeld ook meer aanpassingsproblemen, zoals werd gevonden in onze groep vrouwen vijf jaar na DNA-onderzoek naar een *BRCA1/2*-mutatie (Hoofdstuk 3).

Over het algemeen vergelijkbare psychologische processen bij individuen uit *BRCA1/2* en HNPCC mutatiefamilies

Voordat individuen uit *BRCA1/2* en HNPCC families gezamenlijk worden bestudeerd, is het van belang na te gaan of de twee groepen vergelijkbaar zijn (Hoofdstuk 4). Anderen hebben gesuggereerd dat voorspellend DNA-onderzoek naar elke kankerpredispositie uniek is en apart bestudeerd dient te worden[21]. Gebaseerd op Rolland[22], verwachtten wij daarentegen over het algemeen vergelijkbare psychologische processen te vinden in deze twee groepen. Beide groepen zijn vergelijkbaar met betrekking tot de kans op het ontwikkelen van kanker, de leeftijd van optreden, ernst, de beschikbaarheid van risicoreducerende strategieën en mogelijkheden tot behandeling. In onze studie werden inderdaad geen significante verschillen gevonden met betrekking tot het merendeel van de gemeten variabelen. Zo waren het aantal ervaringen met kanker in de familie, rouwsymptomen, het beloop van stressverwerkingsklachten, zorgen om kanker en risicoperceptie door de tijd, en de meeste ziektepercepties, copingstijlen en familiekenmerken gelijk in beide groepen. Individuen uit *BRCA1/2*-mutatiefamilies zagen erfelijke kanker wel als ernstiger. Ze rapporteerden vaker passief copinggedrag, hadden meer zorgen om kanker en een minder open communicatie met partner en kinderen. Deze verschillen kunnen veroorzaakt worden door de beschikbaarheid van colonoscopie voor dragers van een mutatie in een HNPCC-gerelateerd gen. Colonoscopie is bewezen effectief in het voorkomen van kanker en heeft niet de mutilerende gevolgen van PM, noch de meer onzekere effectiviteit van borstkankerscreening. De verschillen zouden ook kunnen worden toegeschreven aan het feit dat *BRCA1/2* alleen gezondheidsrisico's voor vrouwen geeft, en dat het verliezen van een moeder een grotere impact kan hebben dan een vader, vooral voor vrouwen[23]. Omdat er slechts enkele verschillen werden gevonden tussen beide groepen, kan geconcludeerd worden dat de groepen gezamenlijk kunnen worden geanalyseerd, mits de analyses gecontroleerd worden op kankerpredispositie.

Voorspellende factoren voor aanpassingsproblemen

In de huidige praktijk verwijzen genetisch counselors een deel van hun adviesvragers naar een gespecialiseerde psycholoog of maatschappelijk werker voor aanvullende diagnostiek en ondersteuning. Het is onbekend welke criteria worden gebruikt voor de verwijzing en of deze effectief zijn. Bovendien staat onze kennis over risicofactoren voor aanpassingsproblemen nog in de kinderschoenen. Om meer te begrijpen van de risicofactoren voor aanpassingsproblemen, hebben we een uitgebreide versie van Leventhals model van Zelfregulatie[24] gebruikt als theoretische achtergrond. Volgens dit model creëren wij ons eigen begrip van een ziekte of gezondheidsrisico (ziektepercepties), die copinggedrag, gezondheidsgedrag en aanpassingsproblemen beïnvloeden. Naast ziekteperceptie en coping, beïnvloeden eerdere ervaringen met kanker in de familie en de familiaire omgeving ook het ontstaan van aanpassingsproblemen.

Het aandeel van ziektepercepties en coping

In onze prospectieve studie naar individuen uit *BRCA1/2* en HNPCC mutatiefamilies werden verschillende interessante relaties gevonden tussen ziektepercepties, risicoperceptie, oorzakelijke percepties, copinggedrag en aanpassingsproblemen (Hoofdstuk 6, 9). Sommige

ziektepercepties waren duidelijk minder adequaat: ziektecoherentie en emotionele percepties. Het zien van de ziekte als minder coherent hing samen met minder adequaat copinggedrag en meer aanpassingsproblemen, met name op de lange termijn. Individuen die de ziekte als minder coherent zien geven aan dat ze de aandoening niet kunnen begrijpen en bevatten. Het zou een uiting kunnen zijn van onvoldoende cognitieve verwerking, maar ook van gevoelens van hulpeloosheid en een verlies van cognitieve controle. Intense negatieve emotionele percepties waren ook sterk gerelateerd aan minder adequaat copinggedrag en meer aanpassingsproblemen. Bij de interpretatie van dit resultaat moeten we ons echter afvragen in hoeverre emotionele percepties niet meer een uiting zijn van aanpassingsproblemen in plaats van een onderliggende factor.

Andere ziektepercepties waren ook gerelateerd aan aanpassingsproblemen, maar lijken minder verontrustend te zijn. Het zien van de ziekte als ernstiger en chronischer hing samen met meer ziektegerelateerd copinggedrag in het algemeen en meer aanpassingsproblemen op de korte termijn. Het zien van erfelijkheid als belangrijke oorzaak van kanker hing samen met meer adequate vormen van coping en meer zorgen om kanker op de korte termijn. Deze bevindingen komen overeen met Leventhals model en bevindingen uit andere studies[25].

Coping droeg ook in belangrijke mate bij aan de aanpassingsproblemen. Op de korte termijn waren vooral het zoeken van sociale steun en afleiding voorspellend voor aanpassingsproblemen. Op de langere termijn zou dit copinggedrag aanpassing juist kunnen bevorderen. Passieve coping was wel duidelijk inadequaat op de lange termijn. Net als ziektecoherentie, kan passieve coping duiden op een gevoel van hulpeloosheid, maar dan meer op het emotionele en gedragsmatige niveau. Passieve coping is een van de belangrijkste copingstijlen waarop gelet moet worden in de counseling, omdat ook anderen hebben gevonden dat dit copinggedrag samenhangt met aanpassingsproblemen[6, 19, 20, 26].

De familie doet ertoe

We hebben prospectief de bijdrage van verschillende familiekenmerken onderzocht op stressverwerkingsklachten bij individuen die zich aanmelden voor voorspellend DNA-onderzoek naar *BRCA1/2*- of een HNPCC-gerelateerde mutatie. Deze zouden van belang kunnen zijn, omdat DNA-onderzoek gevolgen kan hebben voor de hele familie. Familiekenmerken die gerelateerd waren aan erfelijke kanker, zoals communicatie over erfelijke kanker en steun, waren belangrijke voorspellers voor aanpassingsproblemen rondom het DNA-onderzoek. De kwaliteit van de familiecommunicatie over erfelijke kanker is in het bijzonder van belang. Deze factor is aangetoond in onze groep deelnemers uit *BRCA1/2* en HNPCC mutatiefamilies tijdens en na voorspellend DNA-onderzoek (Hoofdstuk 7, 9) en in de groep vrouwen uit *BRCA1/2*-mutatiefamilies vijf jaar na de uitslag (Hoofdstuk 3). Familiecommunicatie is ook van belang voor de kwaliteit van familierelaties (Hoofdstuk 5). Open communicatie over gedachten, gevoelens en zorgen omtrent erfelijke kanker kan het individuele en relationele welbevinden ten tijde van het DNA-onderzoek bevorderen. Het zou zelfs de fysieke gezondheid kunnen verbeteren, zoals is gevonden in studies over emotionele expressie[27]. Ook sociale steun tijdens het DNA-onderzoek was een belangrijke buffer tegen stressverwerkingsklachten. Steun van de partner was met name van belang. Deze bevinding komt overeen met bevindingen uit andere studies[28-30]. Meer algemene

familiekenmerken, zoals het familiefunctioneren (cohesie, flexibiliteit) en differentiatie droegen minder bij. Adequaat familiefunctioneren en goede familierelaties kunnen helpen bij het omgaan met allerlei stressoren, en kunnen van belang zijn voor het algemene psychische welbevinden onafhankelijk van erfelijke kanker en het DNA-onderzoek.

De bijdrage van eerdere ervaringen met de familieziekte en rouwsymptomen

Ervaringen met kanker in de familie zouden een psychische kwetsbaarheid kunnen veroorzaken, die vooral tot uiting komt onder druk van het DNA-onderzoek[31, 32]. Wij toonden in onze onderzochte groep aan dat individuen die in hun jeugd (onder de 13 jaar) kanker bij een ouder hadden meegemaakt meer aanpassingsproblemen en een hogere risicoperceptie rapporteerden dan individuen die op latere leeftijd een ouder hadden met kanker, of die geen ouder met kanker hadden (Hoofdstuk 8, 9). Jongere kinderen zouden psychisch meer kwetsbaar kunnen zijn omdat ze afhankelijker zijn van hun ouders dan oudere kinderen [33]. Bovendien beschikken ze over minder affectieve en cognitieve vermogens om met stressoren om te gaan[34]. Een andere bevinding was dat vrouwen die als puber (10-13 jaar) een moeder hadden met kanker, hun risico om kanker te krijgen als hoger inschatten dan vrouwen met een aangedane moeder na de puberteit of zonder aangedane moeder. Ook individuen met een aangedane ouder ervaarden een hoger risico om kanker te krijgen dan individuen zonder aangedane ouder. Mogelijk ontwikkelen individuen een beeld van hun toekomstige gezondheid mede op basis van identificatie met de gezondheid van hun ouders[31, 34].

Een recente studie van Watson *et al.*[35] suggereert dat familiecommunicatie een belangrijke factor is voor emotionele en gedragsproblemen in schoolgaande kinderen van kankerpatiënten. Problemen van kinderen hingen samen met weinig affectieve aandacht, weinig familiecommunicatie en depressie. Behandelstatus of tijd sinds de diagnose waren minder van belang. Ouders vinden het vaak moeilijk om over kanker te praten met kinderen en om hen te informeren over erfelijke kanker. Ongeveer tweederde van de families ervaren moeilijkheden bij het communiceren over kanker[36]. Onderliggende gedachteprocessen zijn vermijding van angstgevoelens, een verlangen naar 'tweezijdige bescherming' en het geloof in positief denken. Met name het praten met kinderen wordt als moeilijk ervaren[37]. Informatie wordt kinderen onthouden met als doel hen te beschermen. Dit kan echter juist ongunstige gevolgen hebben. Wanneer kinderen betrokken worden, de familiecommunicatie open is en familiecoping adequaat is, zullen kinderen psychisch weerbaarder worden wanneer ze als volwassenen geconfronteerd worden met hun eigen risico op kanker. Op basis van onze bevindingen is een voorlichtingsfolder geschreven over het informeren van kinderen over een erfelijke aandoening in de familie.

Andere risicofactoren voor stressverwerkingsklachten waren onverwerkte rouw, het aantal aangedane familieleden met wie de band hecht was (Hoofdstuk 9) en het aantal overleden familieleden met wie de band hecht was (Hoofdstuk 3). Deze bevindingen dragen bij aan het toenemende bewijs dat individuen met een verhoogd risico op kanker die nauw betrokken waren bij het ziekteproces[38], meer[39, 40] en op jongere leeftijd[41] aan kanker waren blootgesteld, die een ouder hebben verloren aan kanker[42, 43] of die onverwerkte rouw ervaren[44] psychisch kwetsbaarder kunnen worden.

Vanuit onze eigen klinische ervaring is gebleken dat kanker in een ouder de

ontwikkelingstaken van differentiatie en individuatie kunnen beïnvloeden. Differentiatie in de adolescentie hangt samen met het psychische welbevinden op volwassen leeftijd[45]. In onze studie was differentiatie ten tijde van de ziekte van de ouder niet gemeten. In toekomstige studies zou de relatie tussen kanker bij een ouder, differentiatie en het psychisch welbevinden bij het kind op volwassen leeftijd verder bekeken moeten worden.

BEPERKINGEN VAN DE STUDIE EN TOEKOMSTIGE ONDERZOEKSVRAGEN

Deze studie is uitgevoerd met behulp van instrumenten die stressverwerkingsklachten, zorgen om kanker en het algemeen psychisch welbevinden moesten meten. Aangenomen werd dat deze een maat vormden voor aanpassingsproblemen. Hoewel de instrumenten die gebruikt werden in deze studie regelmatig zijn gebruikt en hun psychometrische kwaliteiten goed zijn[46-51], moeten we ons afvragen of we hiermee werkelijk aanpassingsproblemen hebben gemeten. Tijdelijke gevoelens van angst, zorgen en wanhoop kort vóór en na de uitslag kunnen een uiting zijn van een gezonde verwerking van een stressvolle gebeurtenis. Bovendien is het aantal individuen dat zich aanmeldt voor DNA-onderzoek en dat verhoogde angst- en depressieve klachten heeft relatief laag in vergelijking met de populatie bij de huisarts[52]. Als nu gebleken is dat individuen zich met behulp van adequate counseling goed aanpassen aan de uitkomsten van het voorspellend DNA-onderzoek, kunnen we ons afvragen of meer studies naar de psychische aanpassing van individuen uit *BRCA1/2* en HNPCC-gerelateerde mutatiefamilies en vergelijkbare kankerpredisposities nodig zijn. Verschillende onderwerpen zijn nu goed uitgezocht en behoeven geen verder onderzoek. De motivatie om te kiezen voor DNA-onderzoek en het effect van het DNA-onderzoek op het psychisch welbevinden hoeven bijvoorbeeld niet meer onderzocht te worden. In toekomstig onderzoek dienen andere vragen beantwoord te worden.

In deze studie zijn de relaties tussen ziektepercepties, coping, ervaringen met kanker in de familie en familiekenmerken geëxploreerd. Leventhals model van Zelfregulatie was zinvol om de cognitieve en emotionele reacties op het DNA-onderzoek te begrijpen. Onze studie gaf echter geen inzicht in de onderlinge relaties tussen ziektepercepties, coping, ervaringen met kanker in de familie en familiekenmerken. Meer onderzoek is nodig om deze relaties te ontwarren en om hen te bestuderen in niet-aangedane individuen die risico lopen op andere genetische aandoeningen. Een ander onderwerp dat nog onderzocht moet worden, is het effect van genetische informatie, ziektepercepties en coping op gezondheidsgedrag. Onderzoek naar het meedoen aan screening, zoals colonoscopie en mammografie, is niet geschikt omdat deze screeningsadviezen over het algemeen goed worden opgevolgd[53-55] en afhangen van externe variabelen zoals de invloed van de arts of vergoedingen van de verzekering. Een voorbeeld van gezondheidsgedrag dat zinvoller is om te bestuderen, is het aanpassen van eetgedrag na voorspellend DNA-onderzoek voor familiaire hypercholesterolemie.

Toekomstige ontwikkelingen in de genetica zullen ook vragen om meer psychologische studies. In de toekomst zal meer genetische kennis beschikbaar komen over de genen die betrokken zijn bij complexe en veelvoorkomende ziekten zoals hart- en vaatziekten, kanker, diabetes en psychische aandoeningen. Het zou mogelijk kunnen worden om individuen te screenen voor verschillende genetische risico's[56]. Voor elk individu zouden risicoanalyses

gemaakt kunnen worden. Individuen zouden kunnen worden aangemoedigd hun levensstijl aan te passen gebaseerd op hun persoonlijke genetische kenmerken. Gezien deze toekomstige ontwikkelingen, zijn meer studies nodig die het effect van genetische gezondheidsrisico's evalueren op ziektepercepties, coping en gezondheidsgedrag[57, 58].

Een andere recente ontwikkeling vraagt ook om meer studies. In de nabije toekomst zal de genetische diagnose van *BRCA1/2* en HNPCC steeds vaker ten tijde van de diagnose kanker gemaakt worden. Deze nieuwe ontwikkeling levert verschillende medische voordelen op: meer effectieve opsporing van erfelijke kanker en een beter aangepaste behandeling. Hoewel verwacht kan worden dat de ongewenste psychosociale consequenties beperkt zullen zijn[59], zullen de psychosociale gevolgen van deze 'dubbele diagnose' wel onderzocht moeten worden en zullen kwetsbare individuen opgespoord moeten worden.

Klinische implicaties

De opmerkelijke psychologische weerbaarheid van de meerderheid van de individuen die kiezen voor DNA-onderzoek heeft consequenties voor de genetische counseling. Gebaseerd op de bevindingen in de literatuur (Hoofdstuk 2), kan aangenomen worden dat een aanpak van tenminste twee counselingsessies met de mogelijkheid de kwetsbare groep door te sturen voor psychologische ondersteuning, voldoende steun biedt om adequaat om te gaan met voorspellend DNA-onderzoek naar *BRCA1/2*, HNPCC en vergelijkbare kankerpredisposities. Individuen uit *BRCA1/2* en HNPCC-gerelateerde mutatiefamilies kunnen op dezelfde manier gecounseld worden, gezien de overeenkomsten (Hoofdstuk 4). Dit komt overeen met de huidige aanpak.

Daarentegen is het in de huidige aanpak onduidelijk of kwetsbare individuen correct worden geïdentificeerd en verwezen worden voor extra begeleiding. De huidige aanpak kan verbeterd worden door een instrument te gebruiken om kwetsbare individuen op te sporen. Een dergelijk instrument wordt momenteel ontwikkeld door de Werkgroep Familiaire Tumoren van de Nederlandse Vereniging voor Psychosociale Oncologie. Een andere verbetering zou zijn om de psychologische training van genetisch counselors te intensiveren. De counselor moet verschillende communicatievaardigheden beheersen en kennis hebben over risicofactoren voor psychische aanpassing, zodat individuen die extra steun nodig hebben vroegtijdig geïdentificeerd kunnen worden. Genetisch counselors dienen ook gevoeligheid voor en basale kennis van familiesystemen en communicatie te ontwikkelen (Hoofdstuk 3, 5, 7, 9). Momenteel worden deze onderwerpen behandeld in het (interne) nascholingsonderwijs voor klinisch genetici. Andere onderwerpen die in het onderwijs aan bod moeten komen zijn coping en ziektepercepties (Hoofdstuk 6, 9) en het omgaan met eerdere ervaringen en rouwreacties (Hoofdstuk 8, 9). We moeten er echter rekening mee houden genetisch counselors al te maken hebben met de toenemende complexiteit van hun vak, waardoor de ruimte om zich te bekwamen in psychologische processen beperkt is.

Verschillende psychologische processen en risicofactoren vragen om aandacht in de counseling. In Tabel 1 is een samenvatting opgenomen van belangrijke factoren en suggesties voor interventies. Met betrekking tot coping en ziektepercepties (Hoofdstuk 6), kunnen counselors hun patiënten die moeite hebben om om te gaan met erfelijke kanker helpen door meer actief copinggedrag te stimuleren en sociale steun te bevorderen. Daarnaast is het van belang te realiseren dat ziektepercepties niet stabiel zijn. Naast de invloed van de sociale omgeving, de

media en internet, kunnen professionals er invloed op uitoefenen. Wanneer counselors incorrecte percepties identificeren, kunnen ze de adviesvrager helpen meer reële en adequate percepties te krijgen door de herkomst van de perceptie te erkennen en door de correcte informatie te verstrekken met gebruikmaking van 'de kracht van hun professionele rol'[60].

De exploratie van familiecommunicatie en steun kan ook waardevolle informatie leveren bij het inschatten van de psychische kwetsbaarheid en weerbaarheid (Hoofdstuk 7). Een open en sensitieve familiecommunicatie over erfelijke kanker zou gestimuleerd moeten worden. Als sociale steun niet geboden kan worden vanuit de familie, kunnen andere bronnen van steun gezocht worden. In dat geval zouden meer follow-up gesprekken nodig kunnen zijn, of verwijzing naar een gespecialiseerde psycholoog of maatschappelijk werker. Ten slotte raden we aan om het effect op familierelaties nauwlettend in het oog te houden en om onderling respect voor verschillen in coping en beslissingen te stimuleren (hoofdstuk 5).

Tabel 1. Psychologische processen en risicofactoren voor psychische kwetsbaarheid

Psychische processen van belang voor de counseling	**Interventies**
Ziektecoherentie	Stimuleer cognitieve verwerking en controle (leemtes in kennis verhelpen, realistische cognities die het gevoel van controle versterken aanbieden), overweeg doorverwijzing naar een gespecialiseerde hulpverlener wanneer hulp nodig is bij het verwerken van verlieservaringen
Passieve coping	Versterk mobilisatie van sociale steun, stimuleer actieve coping, overweeg doorverwijzing naar gespecialiseerde hulpverlener
Gebrekkige familiecommunicatie betreffende erfelijke kanker	Exploreer aard van de familiecommunicatie, geef informatie over de gevolgen van een gebrek aan open communicatie, monitor de gevolgen van DNA-onderzoek voor familierelaties en overweeg doorverwijzing naar gespecialiseerde hulpverlener
Onvoldoende steun van partner en familie	Betrek de partner in de procedure, biedt extra steun of counseling sessies, identificeer blokkades in het mobiliseren van steun en overweeg doorverwijzing naar gespecialiseerde hulpverlener
Diagnose kanker in een ouder tijdens de jeugd (kind was <13 jaar)	Exploreer psychologische weerbaarheid en risicoperceptie, overweeg doorverwijzing naar gespecialiseerde hulpverlener
Gecompliceerde rouw	Exploreer gecompliceerde rouw, overweeg doorverwijzing naar gespecialiseerde hulpverlener

Bij het tekenen van de stamboom zouden genetisch counselors hun aandacht erop moeten richten of de ervaringen met de ziekte hebben geleid tot meer psychologische kwetsbaarheid. Daarbij zouden zij kunnen letten op het hebben van een ouder die aangedaan is of overleden is in de jeugd, onverwerkte rouw en het aantal aangedane familieleden en verliezen (Hoofdstuk 8, 9). Evaluatie van de individuele ervaring, coping en de aanwezigheid van aanpassingsproblemen

kan inzicht bieden voor de inschatting van de individuele kwetsbaarheid en de noodzaak om door te verwijzen naar een psycholoog of maatschappelijk werker.

De bevindingen uit onze prospectieve studie vijf jaar na de uitslag tonen dat het potentiële effect op het seksuele functioneren besproken dient te worden met vrouwen en hun partners voordat een preventieve operatie plaatsvindt. Het onderwerp dient weer ter sprake te komen na PBSO en PM. Als het seksuele functioneren minder bevredigend is dan vóór de operatie, zouden de vrouwen doorverwezen moeten worden naar een medisch seksuoloog of psychotherapeut voor adequaat onderzoek en behandeling.

BELANGRIJKSTE CONCLUSIES

1. Een consistente bevinding in de literatuur is dat de meerderheid van de individuen die zich aanmeldt voor voorspellend DNA-onderzoek een opvallende psychologische weerbaarheid kent en dat slechts een minderheid zo veel psychische klachten heeft dat klinische evaluatie en behandeling nodig is.
2. Bij een minderheid heeft DNA-onderzoek ongewenste effecten op familierelaties en is aanvullende counseling nodig.
3. Bevindingen op de lange termijn suggereren dat het leven in een familie waarin erfelijke kanker voorkomt belastender is dan het DNA-onderzoek naar een aanleg voor erfelijke kanker.
4. Open familiecommunicatie over erfelijke kanker kan het individuele en relationele welbevinden bevorderen. Het zou met name belangrijk kunnen zijn om jonge kinderen te helpen om te gaan met een ouder met kanker.
5. Kenmerken waarop in de counseling gelet moet worden zijn ziektecoherentie, emotionele representaties, passieve coping, familiecommunicatie, steun van de familie, leeftijd ten tijde van de diagnose kanker of het overlijden van een ouder, het cumulatieve effect van het herhaaldelijk meemaken van kanker bij familieleden, en gecompliceerde rouw.
6. Ziektepercepties zijn niet stabiel. Incorrecte percepties kunnen (tot op zekere hoogte) aangepast worden door interventies van een genetisch counselor.
7. Specifieke en regelmatige training in psychologische onderwerpen is nodig voor genetisch counselors. Naast communicatievaardigheden moeten counselors leren om de psychische kwetsbaarheid en potentie van het individu te herkennen, en de invloed van de familie.
8. Het potentiële effect op het seksuele functioneren dient besproken te worden met vrouwelijke *BRCA1/2*-mutatiedraagsters en hun partners voor en na de preventieve operaties.
9. Meer studies zijn nodig om de relaties tussen ziektepercepties, coping en gezondheidsgedrag in kaart te brengen bij individuen met een verhoogd risico op ziekte vanwege een genetische aanleg.

Literatuur

Zie References pagina 137.

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CURRICULUM VITAE

Iris van Oostrom was born on August 13, 1973 in Utrecht, the Netherlands. She graduated from secondary school in 1991 (Vrije School) and 1992 (VWO, Craneveld Scholengemeenschap) in Nijmegen. She worked for a year with mentally retarded individuals at the Foyer Occupationel pour Adultes in Graye-sur-Mer, France. She obtained a degree in history (propedeuse) at the Erasmus University in Rotterdam in 1994. Then, she switched her interest to psychology. For her specialisation in clinical psychology at the University of Utrecht, she worked in a psychiatric hospital in Caen, France, where she learned to perform group- and individual therapy. She also took up a master's degree in psychopathology and neurobiology at the 'Hôpital de la Salpetrière' in Paris, France. She conducted a research project on memory dysfunction in people diagnosed with schizophrenia and Parkinson's disease. She obtained her master degree in Utrecht and in Paris in 1999.

After graduation, she worked as a lecturer in psychology at the University of Utrecht. Subsequently she worked as a psychologist at the 'Institute for Psychotrauma', Zaltbommel. In that function she worked, among others, on a research project on the psychological consequences of the firework disaster in Enschede. Since 2001 she has been working as a psychologist at the department of Clinical Genetics, Erasmus MC in Rotterdam. Part of her work was to set up a PhD-study, in collaboration with the Department of Medical Psychology and Psychotherapy.

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