DEALING WITH THE RISK FOR HEREDITARY BREAST AND OVARIAN CANCER

A prospective study on psychological consequences of choices on genetic testing, surveillance and prophylactic surgery

DEALING WITH THE RISK FOR HEREDITARY BREAST AND OVARIAN CANCER

A prospective study on psychological consequences of choices on genetic testing, surveillance and prophylactic surgery

OMGAAN MET DE KANS
OP ERFELIJKE BORST- EN EIERSTOKKANKER
Een prospectief onderzoek naar de psychische gevolgen van beslissingen omtrent genetisch testen, regelmatige controles en preventieve chirurgie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam op gezag van de
Rector Magnificus

Prof.dr.ir. J.H. van Bemmel

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 7 november 2001 om 15.45 uur

door

Lidewij Nathanja Lodder
geboren te Amstelveen

Promotiecommissie

Promotoren:	Prof.dr. R.W. Trijsburg
	Prof.dr. M.F. Niermeijer
Overige leden:	Prof.dr. A. Tibben
	Prof.dr. J.G.M. Klijn
	Prof.dr. C.J. Cornelisse
Copromotor:	Dr. P.G. Frets

L'état d' équilibre n'est attrayant que pour celui qui balance sur la corde.
Pour celui qui ce trouve assis parterre cet état n'a rien de phénoménal.
André Gide (1869-1951)

Voor mijn ouders

The study presented in this thesis was performed at the Department of Medical Psychology and Psychotherapy, Erasmus University Rotterdam (Netherlands Institute for Health Sciences) and the Department of Clinical Genetics, University Hospital Dijkzigt/Erasmus University Rotterdam, in close collaboration with the Daniel den Hoed Cancer Clinic/Erasmus University Medical Center Rotterdam and the Leiden University Medical Center.

The study was funded by a grant of the Dutch Cancer Society (grant nr. EUR 95 889).
The financial support for printing this thesis by the Dutch Cancer Society and the Erasmus Universiteit Rotterdam is gratefully acknowledged.

Cover illustration made by Katelijne Wortel, september 2001.

Drukkerij Primavera Amsterdam

CONTENTS

		Page
Chapter 1	Introduction	9
Chapter 2	Presymptomatic testing for BRCA1 and BRCA2: How distressing are the pre-test weeks? **J Med Gen 1999; 36: 906-13**	29
Chapter 3	Attitudes and psychological functioning in women at risk to carry a BRCA1/BRCA2 gene mutation, who decline genetic testing **Submitted**	45
Chapter 4	The psychological impact of receiving a BRCA1/ BRCA2 test result (1-3 weeks post-test) **Am J Med Gen 2000; 98: 15-24**	57
Chapter 5	One year follow-up of women opting for pre-symptomatic testing for BRCA1/BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery) **Abridged version accepted by Breast Canc Res Treat**	75
Chapter 6	The relationship between the ability to reflect on emotions and the level of reported distress in women undergoing presymptomatic DNA-testing for hereditary breast and ovarian cancer **Submitted**	99
Chapter 7	Men at risk of being mutation carrier for hereditary breast and ovarian cancer: Exploration of attitudes and psychological functioning during genetic testing **Eur Jrnl Hum Gen 2001; 9: 492-500**	111

		Page
Chapter 8	Attitudes towards Termination of Pregnancy in individuals who underwent presymptomatic testing for the BRCA1/BRCA2 gene mutation in the Netherlands. **J Med Gen 2000; 37: 883-4**	127
Chapter 9	Discussion	129
References		146
Summary		155
Samenvatting		163
Appendices		173
Dankwoord		190
Curriculum Vitae		195

Chapter 1

INTRODUCTION

General introduction

Since 1994 genetic testing became an option for individuals from families with a hereditary form of breast and/or ovarian cancer (HBOC), due to the identification of two breast cancer susceptibility genes (Miki et al 1994, Wooster et al 1995). Healthy women with a mutation in one of these genes have a high lifetime risk for breast cancer and/or ovarian cancer; for male mutation carriers the risk for cancer is also elevated, but very small in comparison with that of the women (Blackwood & Weber 1998, Ford et al 1998, Thorlacius et al 1998). Women with the mutation may opt for either frequent surveillance or preventive removal of breast tissue (prophylactic mastectomy) and/or the ovaries (prophylactic oophorectomy). In the Daniel den Hoed Cancer Clinic/Erasmus University Medical Center Rotterdam, prophylactic mastectomy is offered with immediate breast reconstruction, mainly using silicone implants.

The studies described in this thesis focus on female and male genetic test applicants with a risk of 50% or 25% of being a mutation carrier for HBOC, who have not developed cancer, and their partners. Psychological consequences of such presymptomatic genetic testing are investigated. Attitudes and psychological functioning in women declining genetic testing are also described. The studies in this thesis are part of a continuing evaluation in our center of clinical, genetic and psychological aspects of the possibility of genetic testing for late onset diseases with autosomal dominant inheritence. Outcomes of these studies may ultimately help families and clinicians to come at grasp with the different roles, burdens and responsibilities involved.

In the introduction firstly some medical and genetic information about HBOC is provided. The procedure to detect gene mutations associated with this disease is described. Then the protocol for genetic testing of individuals from a family with HBOC as used in our center and the medical options offered to women who are identified as a mutation carrier are explained. An overview of psychological studies in the field is given, starting with a concise summary of what is known from earlier studies on other autosomal dominant late onset hereditary diseases. Most attention is paid to studies assessing psychological implications for healthy individuals at risk to carry a mutation being a mutation for HBOC. Finally, a description of the research questions, the design and the procedure of the study are given.

Hereditary breast and/or ovarian cancer and the genetic test

Hereditary breast and/or ovarian cancer

In the Western world, approximately 1 out of 10 women develops breast cancer. The mean 10 year survival for this disease is 50-65% (Blackwood & Weber 1998). Three quarter of the cases occur in women after 50 years of age. Apart from age, genetic predisposition is a strong risk factor for breast cancer. It is the major cause in about 5% of all women affected with breast cancer, and in 25% of the patients who became affected before the age of 30 (Slattery & Kerber 1993).

The chance that breast cancer can be explained by a genetic factor in a family, is associated with factors as 1) occurrence of both breast and ovarian cancer in the same or different individuals in a family, 2) occurrence of breast cancer in different generations in a number of relatives, 3) occurrence of bilateral breast cancer in a relative and 4) a young age (< 45 years) of onset. Using these factors Claus et al. (1992) tabulated individual life time and age related risk estimates.

In 1994, the first breast/ovarian cancer susceptibility gene, BRCA1, was identified on chromosome 17q21 (Miki et al 1994) and in 1995 a second susceptibility gene, BRCA2, on chromosome 13q12-13 (Wooster et al 1995). These two genes are explanatory for 33% of the families with four or five women with breast cancer (Nathanson et al. 2001), but for 81% of the families with more than five women with breast cancer (Blackwood & Weber 1998, Ford et al 1998, Thorlacius et al 1998). In this type of dominant inheritance, a gene mutation is very likely to cause symptoms of a disease, irrespective of a normal second allele from the other parent. The inheritance is autosomal dominant, implying that each child of a mutation carrier has a risk of 50% to inherit the mutation. Women with a BRCA1 or BRCA2 gene mutation have a lifetime risk for breast cancer of 56% to 87% and for ovarian cancer of 10% to 60% (Blackwood & Weber 1998, Ford et al 1998, Thorlacius et al 1998). The disease may develop from the age of 20 years. A BRCA1 gene mutation is associated with a higher risk for ovarian cancer than the BRCA2 gene mutation. Male mutation carriers, especially those carrying a BRCA2 gene mutation, have a lifetime risk of 6% to develop breast cancer and a slightly increased risk for some other types of cancer (like prostatic carcinoma) (The Breast Cancer Linkage Consortium 1999, Blackwood & Weber 1998, Ford et al 1998, Thorlacius et al 1998).

The search for a family specific gene mutation

One of the major benefits of genetic testing is the possibility of a more tailored application of risk management strategies in women from at-risk families: intensive surveillance or radical prophylactic surgical interventions (bilateral mastectomy

and/or oophorectomy) are options for BRCA1/BRCA2 gene mutation carriers, whereas non-mutation carriers have no need to consider these options.

Because mutations may occur in any part of the BRCA1/BRCA2 genes, DNA analysis in blood samples of one or more affected relatives is essential to establish a family-specific mutation. If affected relatives have died or do not wish to have their DNA tested, a mutation study may be done in 3 relatives or more with a 50% risk to be mutation carrier (i.e. the children or sister of a patient). Some mutations are specific for certain ethnic origins (like the Ashkenazi Jewish population) or become identified as regional mutations. In the first 517 families with a history of HBOC screened in our centre, in 19% a BRCA1 was detected and in 4% a BRCA2 gene mutation (Verhoog et al 2001). The time involved for such an analysis depends on the level of technological advancement and availability of staff/funding and may range from months to years.

In the absence of the availability of a family-specific genetic test, the family history will enable individual risk counseling and adaptation of surveillance protocols. In this thesis, we did not address the potential stresses of the waiting period before the DNA-test becomes possible. In other studies carried out before BRCA1/BRCA2 testing became available and in studies including subjects at risk for whom no genetic test was available, higher than 'general population distress levels' were found (Baider et al 1999, Kash et al 1992, Lerman et al 1993, 1996b, Lerman & Schwartz 1993, McCaul et al 1998, Ritvo et al 1999, Zakowski et al 1998).

Upon detection of a BRCA1/BRCA2 mutation, the index patients involved (or the associated relatives at 50% risk) become informed by the clinical geneticists about the implications: the cancer risks for mutation carriers and the options for either frequent surveillance for breast/ovarian cancer or prophylactic mastectomy/oophorectomy are explained. Possible positive and negative implications of informing other relatives about the possibility of testing, and the different ways to do so are discussed. Letters with concise information on inheritance of cancer in the family and the possibility of genetic testing or obtaining further information at a regional centre of clinical genetics are handed out to facilitate informing relatives.

The procedure of presymptomatic DNA testing in our center

The majority of men and women interested in further information or genetic testing are first and second degree relatives of the index patients. First, they are informed by the geneticist/genetic nurse/oncologist about their genetic risk (50%, 25% or 12,5%) depending on whether a first, a second or a third degree relative was known to have breast or ovarian cancer and/or to be a mutation carrier). A recent study from our center on the uptake of individuals from families in which a

BRCA1 or a BRCA2 mutation was identified at least 6 months before analysis of the data, showed that 57% of the women at 50% risk of carrying the mutation and 29% of the women at a lower risk (12.5% or 25%), applied for testing (Meijers-Heijboer et al 2000). The lifetime risk for women with a BRCA1/BRCA2 mutation to develop breast and ovarian cancer (as compared to the general population risks) is explained as well as the risk for offspring. Information is provided on the possibilities and limitations of regular breast surveillance (from age 25 years), ovarian surveillance (from age 30 years) and prophylactic mastectomy/oophorectomy. Possible psychosocial sequelae are discussed and test applicants are informed about the availability of psychological support. Social aspects (problems in obtaining life/health insurance) are emphasised. The counselling takes one or more sessions, depending on prior knowledge and the extent of expressed questions and doubts about genetic testing. If the test-applicant decides for testing, a blood sample is obtained and an appointment with the clinical geneticist/genetic nurse is made for disclosure of the test result, 6 to 8 weeks later. The test-result is disclosed in a face-to-face contact to the test-applicant and the partner.

Risk management options in women who carry a mutation

Women who carry a BRCA1/BRCA2 mutation are offered either intensive surveillance or prophylactic surgery (mastectomy and/or oophorectomy). Identified BRCA1/BRCA2 mutation carriers are referred to the Family Cancer Clinic of the Daniel den Hoed Cancer Center/University Hospital Rotterdam, for oncological/surgical/gynaecological information on the cancer risks and the risk management options.

The surveillance program for breast cancer (from the age of about 25 years) includes monthly breast self-examination, a clinical breast examination every six months, and a yearly mammogram. Since 1995 magnetic resonance imaging (MRI) has been an option at our clinic for women with mammographically very dense tissue and for BRCA1/BRCA2 mutation carriers (Meijers et al 2001). Surveillance for ovarian cancer includes yearly gynecologic examination and transvaginal ultrasound, and blood assay of CA125 twice a year. It is emphasized that this frequent surveillance can not detect all cases of carcinomas before the devolopment of (micro) metastases.

If requested, women can be informed by a surgeon about methods and consequences of bilateral mastectomy and the possibility of direct or secondary breast reconstruction. The technique usually applied in the centre is regular simple mastectomy (including the nipple) by vertical incision, with immediate implantation of a subpectoral silicon prosthesis. Depending on the patient's wishes, a nipple recontruction takes place 6 months or longer after surgery.

Patients are informed about the potential remaining risk for breast cancer after bilateral mastectomy due to possible residual mammary tissue, which presumably is lower than 10% (Hartmann et al 1999). Potential adverse physical and emotional consequences of prophylactic mastectomy are also discussed. First data demonstrating that prophylactic mastectomy in BRCA1/BRCA2 mutation carriers results in a gain of life expectancy became available recently (Schrag et al 2000, Meijers et al 2001).

The gynecologist may explain the options of laparoscopic or transabdominal oophorectomy and about the possibilities/limitations of subsequent hormonal replacement therapy. The patient is informed about oophorectomy leaving a residual risk of about 5% for peritoneal carcinoma, resulting from hormone sensitive stem cells in the peritoneal cavity. Potential adverse consequences, such as a possible negative effect on lubrication and feeling feminine are also discussed.

Psychological studies on genetic testing

The special position of studies on genetic testing in the field of health psychology

Psychological studies on genetic testing for late-onset diseases with autosomal dominant inheritance have a special position in the long history of theory building and research in the psychosomatic field. To enlarge our knowledge on psychological implications of being genetically at risk for a late-onset disease, we can not simply build on existing theories and results from studies on psychological implications of having a (non-hereditary) disease. The first reason simply is that many individuals with such genetic risk are healthy people. They may have a risk to carry a gene mutation, which implies a high risk to develop a serious disease in the next decades, but it remains uncertain at which age the disease will develop and there is a small chance that it would not develop at all (non-penetrance). Secondly, genetic inheritance implies that the implications of the disease concern not only one individual, but all relatives the individual is genetically related to. Because of these differences, scientific observations from the field of genetic testing for late onset diseases will be primarily emphazised in this thesis. Of course, when appropriate, we refer to theories developed in the psychosomatic research tradition or in other research areas in psychology (i.e. social psychology).

Experiences with genetic testing for other late-onset hereditary diseases

Before the BRCA1/BRCA2 gene mutations became identified in 1994/1995, genetic testing was available since about 10 years for a number of neurological disorders such as Huntington disease, Hereditary cerebral haemorrhages and Myotonic Dystrophy and a few cancer syndromes, such as Multiple Endocrine

Neoplasia. Before addressing psychological implications of genetic testing for BRCA1/BRCA2, studies on the disorders mentioned above are shortly summarized.

Huntington disease

Psychological implications of genetic testing have been most widely assessed for Huntington disease, a disorder associated with a progressive movement and neuropsychiatric deterioration. Similarities between testing for Huntington disease and for HBOC are the onset of a lethal disease at an adult age and the option to be informed about one's risk to develop this disease. However, Huntington disease and HBOC have some important differences concerning expression, penetrance and treatment options. Huntington disease is usually fully penetrant, implying that all those having inherited the mutation will ultimately develop the disease. Those not having inherited the mutation will remain disease-free. HBOC is incompletely penetrant: the majority of the male and also a small proportion of female mutation carriers will not develop cancer. Non-mutation carriers still have the remaining population risk for breast and ovarian cancer. Finally, whereas for Huntington disease no curative or prophylactic treatment is available, women at risk for HBOC may opt for regular surveillance or prophylactic surgery to decrease their risks to die from breast and/or ovarian cancer.

The real uptake for genetic testing for HD is much lower (9% to 20% of subjects at risk in various regions) than predicted from data on attitudinal studies (40% to 79% of subjects at risk) (Adam et al 1993, Tibben et al 1993c). In some studies it was suggested that the tested group is self selected, having a higher ego-strength than those who decided against testing (Meiser & Dunn 2000). The perceived impact in individuals identified as mutation carrier, was generally less catastrophic than suggested by preliminary impressions (Brandt et al 1989, Kessler 1987, Meissen & Berchek 1988, Nance et al 1991, Tibben et al 1990). Many carriers of the gene initially tended to deny the consequences of their test result (Tibben et al 1993b). The majority had no regret of having undergone the test. However, many stated that they experienced less control over their future than they had initially expected (Codori & Brandt 1994, Tibben et al 1993a). Whereas in some studies the test-outcome was no predictive factor for high distress (Decruyenaere et al 1996, Tibben et al 1993b), most evidence suggests that mutation carriers are more psychologically distressed than non-mutation carriers shortly after the test result, but not after a longer follow-up (Meiser & Dunn 2000). However, the confrontation with first symptoms was experienced as highly distressing (Tibben 1993). Those identified as non-mutation carriers rarely felt the expected relief and happiness (Huggins et al 1992, Tibben et al 1993b, Tibben et al 1990). Many went through a period of numbed emotions, survivor guilt, and difficulties to adapt to a new life perspective without fear of the disease, but in a

new relational network with at-risk and affected relatives. Partners and children of mutation carriers experienced distress about the need to cope and give care (Huggins et al 1992, Tibben et al 1990).

An important predictive factor for high distress up to one year after genetic testing was found to be high distress levels before disclosure of the result, and low ego-strength, as measured by the Minnesota Multiphasic Personality Inventory (Decruyenaere et al 1996, Tibben et al 1993a). Also, having learned about HD and being at risk for this disease only recently, was associated with high distress at six months post-test (Tibben et al 1993a).

Non-participation in genetic testing for Huntington disease has also been studied. Motivations for non-testing most often reported were: uncertainty about the ability to cope with an unfavorable test outcome, the burden of the genetic counseling process and expecting a reduced quality of life (Decruyenaere et al 1997, Steenstraten et al 1994). Compared with those opting for genetic testing, those refraining from genetic testing were not more emotionally distressed, but they had more pessimistic ideas about themselves, about their future and about the expected implications of either test result (Decruyenaere et al 1997, Steenstraten et al 1994). Another interesting outcome was the significant association between non-testing and having learned about the genetic nature of the disease at a young age (Steenstraten et al 1994). The authors argued that, in those declining testing, the influence of the disease on personality development might have affected their attitude towards testing: i.e. being at risk for Huntington disease may have become part of their identity. Conversely, subjects becoming aware of Huntington disease at an adult age might attempt to restore the disturbed balance of their lives and may therefore feel an urge to obtain certainty from genetic testing.

Hereditary cancer syndromes

Expression of the disease and surveillance and prophylactic treatment options for HBOC differ from those of other autosomal dominant genetic cancer syndromes, such as hereditary thyroid gland cancer (Multiple Endocrine Neoplasia 2a; MEN 2a), hereditary colon cancer (Familial Adenomatous Polyposis Coli; FAP. Hereditary Non-Polyposis Colon Cancer; HNPCC), Von Hippel Lindau disease and the Li Fraumeni syndrome.

MEN2a is characterized by tumors in the thyroid, adrenal and para-thyroid glands, which usually manifest before the age of 30. Genetic testing (also in childhood) is usually proposed as normal medical management to prevent metastatic thyroid carcinoma in a mutation carrier and to prevent the burden of surveillance in all relatives from a family. In childhood already, mutation carriers for Men2a may either undergo surgical removal of the thyroid or the less secure surveillance of the thyroid. Surveillance is also needed for other tumors related to

the syndrome. Major expressed reasons for testing were to reduce uncertainty, to know if screening needed to be continued, and to know about one's children's risk (Grosfeld et al 2000a,b,c). Adult identified mutation carriers of MEN 2a report feelings of anxiety and depression, but also of relief, since the majority opted for an immediate surgical treatment, which may be experienced as the end of a period of worrying (Grosfeld et al 1996, 1997). Partners of mutation carriers showed severe distress reactions shortly after disclosure of the result, even more than the carriers themselves. They were found to be preoccupied with issues concerning the health of their children and with reproductive decisions. This might partly be explained by the observation that whereas the disease and its consequences were familiar to individuals at risk when they applied for testing, for many partners, participating in genetic counseling implied a first confrontation with these issues (Grosfeld 2000b,c). Adverse psychological effects in mutation carriers and their partners had decreased at 12 months follow up (Grosfeld 2000b,c).

There are several genetic colon cancer syndromes, for which different medical approaches exist. The Familial Adenomatous Polyposis syndrome is characterized by a high number of colonic and sometimes extracolonic polyps, which are progressing into metastatic carcinoma if not removed. From a childhood age colonoscopic surveillance is indicated, and when polyps are detected, undergoing a total colectomy is the safest course of action. Mutation testing may prevent that children are unnecessary undergoing colonoscopic surveillance, which is mostly experienced as burdensome. Extracolonic manifestations of FAP (stomach, jaw, etc.) need special surveillance. Hereditary Non-Polyposis Colon Cancer is characterized by less polyps, and manifests somewhat later than FAP, and necessitates once every two years colonoscopy from age 25, including monitoring the urinary tract and the uterus for malignant cells.

Interviews with subjects at risk for FAP showed that these subjects often described the disease as "not a problem", and "non threatening' (Michie et al 1996). The authors suggest that such answers may be a reflection of minimization.

Complex phenotypes, including cancer in multiple organs, are characteristic for both Von Hippel Lindau disease and the Li Fraumeni syndrome. Both syndromes lead to complex monitoring and limited options for prophylactic surgery. The uptake for genetic testing for Von Hippel Lindau disease and the Li Fraumeni syndrome is low and little is known about the psychological implications of predictive testing for these two complex cancer syndromes (Schneider et al 1995).

An earlier study of our group compared individuals undergoing genetic testing for either genetic cancer syndromes (Familial Adenomatous Polyposis Coli, HBOC) or genetic neurological disorders (Huntington Diseases and Hereditary

Cerebral Haemorrhages with Amyloidosis Dutch type1). Subjects tested for HBOC (n=24) were since long time familiar with the genetic nature of cancer in their family and very motivated to be the first to be tested at that time in our center. Prior to the result, distress levels in this group were lower than those of subjects tested for HD, but higher than those of subjects tested for FAP (Dudok de Wit et al 1997a). Post-test and follow-up (n=10) distress levels in subjects tested for HBOC were lower than those of subjects undergoing genetic testing for the other diseases (Dudok de Wit et al 1998c). The low distress levels after disclosure of the result in those at risk for HBOC may partly be explained by the intensive preparation and information provided by researchers and (onco)geneticists to this first tested group. This study also showed that defensive denial may have been operative in subjects reporting low distress levels on a self-report questionnaire. Low distress was associated with lowered ability to provide truthful and clear (coherent) reflections of one's emotions during the interview (Dudok de Wit et al 1998b). High distress was associated with reporting intrusive memories of the disease in relatives in a questionnaire asking about the impact of the disease on their lives (Dudok de Wit et al 1997a).

Review of psychological studies on presymptomatic genetic testing for hereditary breast and ovarian cancer

When BRCA1/BRCA2 testing became a possibility in our center the protocol for the present study was developed, partly based on the previous studies done in our group (Dudok de Wit 1997c, Tibben 1993d). Results from these previous psychological studies can not be simply generalized to the program of genetic testing for HBOC, because of the dissimilarities between HBOC and other hereditary late onset diseases. Furthermore, the sample of the first subjects tested for HBOC that Dudok de Wit included in her study, was small.

The review of previous psychological studies on genetic testing for BRCA1 and BRCA2 includes studies with healthy individuals at risk to carry this mutation, which is the group this thesis is focussed upon. Women (previously) affected with breast and/or ovarian cancer have a much higher risk to have inherited the family-specific mutation than their healthy relatives and may therefore have a different experience of the option of genetic testing (Croyle et al 1997). Besides, their post-test risk management options will be different from those of women without the disease.

In one study healthy individuals were more distressed than affected individuals after being identified as a mutation carrier (Croyle et al 1997). It was suggested that mutation carriers who had had cancer previously, may have perceived the test-result as a confirmation of their expectation. Moreover, cancer

patients already had to adapt to the distress of their diagnosis, and may, therefore, perceive an unfavorable test result as a secondary problem. A Norwegian study demonstrated that *prior* to testing, distress was higher in women with cancer than in healthy women (Reichelt et al 1999).

The review elicits major topics of concern in literature on psychological implications of being a healthy person at risk to carry a BRCA1/BRCA2 gene mutation.

Reasons for genetic testing

Individuals at risk for HBOC more often ask for genetic testing than those at risk for neurodegenerative disorders, such as Huntington Disease (Hopwood 1997, Lerman et al 1997). Main reasons for women to opt for pre-symptomatic DNA testing for HBOC, as reported in some European studies, were to obtain certainty about 1) their personal risk to develop cancer, 2) the need for future intensive surveillance and/or prophylactic interventions, and 3) the risk of having transmitted the gene to their offspring (Dudok de Wit et al 1997a, Watson et al 1995). The two major reasons to undergo testing as indicated in data from the USA were concern about the risk for children and/or family (56%) and knowing about the necessity of an increase/decrease of surveillance (30%) (Lynch et al 1999). It should be noted that the order of importance of these two options may be determined by the fact that the American study sample not only consisted of healthy women at risk to be a BRCA1/BRCA2 mutation carrier, but half of the sample were males or affected women. In a similar population, another leading American research group found the following main reasons to opt for genetic testing: to learn about the risk for my children (78%), to know if I need to increase screening (70%), to plan my future (67%), to make decisions about surgery (63% of the women), to be reassured (61%) and to make childbearing decisions (for individuals who had not completed their family: 41%) (Lerman et al 1996a).

Expected implications of being identified as a (non) mutation carrier

Pre- and post-test anxiety and depression were found to be more prominent in test-applicants expecting many adverse consequences from BRCA1/BRCA2 testing prior to disclosure of their result than in those who did not (Dudok de Wit et al 1997a, Julian-Reynier et al 1996, Lerman et al 1995). In a study on test-applicants for several cancer syndromes, most subjects had a fairly good prediction of their post-test emotional reactions during the pre-test assessment. Subjects who, at pre-test, underestimated their post-test emotional reactions had significantly higher distress levels 6 months after disclosure of the result, than those who had accurately anticipated their emotional reactions (Dorval et al 2000).

Emotional impact of genetic testing

Many studies showed that distress levels before and after genetic testing for BRCA1/BRCA2 were similar to or lower than those of a normal population, but

there was a high variability in distress levels within the study samples (Croyle et al 1997, Lerman et al 1997, 1996b, Reichelt et al 1999). Serious short-time adverse effects were not observed among subjects (with and without a history of cancer) undergoing presymptomatic BRCA1/BRCA2 testing (Lerman et al 1996b). However, mutation carriers reported more distress one month after disclosure of the test-result, than non-mutation carriers (Croyle et al 1997, Lerman et al 1996b, 1997, Reichelt et al 1999). This difference was explained by a decrease of distress in non-mutation carriers at post-test, rather than by an increase of distress in mutation carriers. Mutation carriers in these studies often had a longstanding awareness of the genetic nature of cancer in their family and had been waiting for years before the mutation was identified in the family. They therefore might, through the years, have become adjusted to the distress induced by having an increased risk for cancer (Croyle et al 1997, Lerman et al 1996b, 1998).

French investigators demonstrated that women identified as non-mutation carriers often remained anxious and desired to continue surveillance (Julian-Reynier et al 1996). In another study survivor guilt was observed in 4 out of 101 women identified as non-mutation carriers, and one woman reported regretting how her life had been dominated by her strong conviction that she would develop cancer one day (Lynch et al 1997).

Interest in prophylactic surgery in women who carry a mutation

Decisions to undergo prophylactic mastectomy or oophorectomy among BRCA1/BRCA2 gene mutation carriers largely vary between different countries and centres (Meijers-Heijboer et al 2000, Wagner et al 2000). In our clinical setting, 51% of the unaffected mutation carriers opted for prophylactic mastectomy and 68% for prophylactic oophorectomy (Meijers-Heijboer et al 2000). Utilization of prophylactic mastectomy was found to be dependent of age (<50) and having young children. Prophylactic oophorectomy was opted for by 90% of the women aged between 40 and 55 years, compared with 56% of the women below the age of 40 years or above the age of 55 years.

In a study assessing effects of a support program for women deciding for or against prophylactic surgery, a relatively small benefit from this program was found for women with strong emotional reactions to the information provided. A high benefit was found in women who wished to be actively engaged in the decision making process (Stalmeier et al 1999).

Previous observations from the US mainly concerned women with an increased risk for breast cancer based on their family history and/or a history of previous benign biopsies, who opted for prophylactic mastectomy while not knowing their genetic status. One such prospective study showed that women opting for prophylactic mastectomy (n=14) had a higher perceived risk of developing breast cancer, had more often undergone breast biopsies and

experienced more cancer worry prior to genetic counseling, than the 150 women who did not opt for prophylactic mastectomy (Stefanek et al 1995). Among Australian women who awaited an initial appointment for risk assessment and advice about prophylactic surgery options (n=333), the intention to undergo prophylactic mastectomy if identified as mutation carrier (19%) was associated with high levels of breast cancer anxiety (Meiser et al 2000a). Similarly, among 95 women at risk, those considering prophylactic oophorectomy (23%) if found to be mutation carrier, reported higher breast and ovarian cancer anxiety than those considering surveillance (Meiser et al 1999).

Psychological implications of prophylactic mastectomy

Most available data on psychological implications of prophylactic mastectomy concern women who opted for this procedure because of a high genetic risk, without knowing whether they carried the gene mutation or not. Half the women (7/14) in the earlier mentioned study (Stefanek et al 1995), reported 6 to 30 months after prophylactic mastectomy that they had experienced much discomfort post-surgery, but the majority was not dissatisfied with the time they needed to recover emotionally and physically. Dissatisfaction with results from breast reconstructive surgery was expressed by 4/11 women. The three women opting against breast reconstruction did not regret their choice.

Satisfaction with prophylactic mastectomy was described for a sample of 370 American women, enrolled by newspaper advertisements, who had undergone the procedure 0.2 to 51.5 years previously (mean: 14.8 years) (Borgen et al 1998). Three-quarters had some form of breast reconstruction. Unacceptability of the cosmetic result was expressed by 16%, regret of surgery by 5%. Of the 21 women with regrets, 19 were interviewed by a psychiatrist and a psychologist (Payne et al 2000). The reasons for regrets addressed the following topics: 1) severe emotional trauma and/or lack of psychological support in the post-surgery period, 2) complications of surgery and reconstruction, 3) dissatisfaction with the cosmetic effect, 4) residual or phantom pain, 5) fears that implants would impede the adequacy of detecting cancer in residual breast tissue, and 6) diminished self-image or sexual satisfaction.

In a recent study all high risk women known to have had bilateral prophylactic mastectomy in a large US health clinic (mutation carriership was not confirmed), were asked to answer a questionnaire (Frost et al 2000). Of the 572 participating women, 70% were satisfied with the surgery; 19% were dissatisfied. The majority reported to be less concerned about developing breast cancer after surgery. However, 23% to 36% reported negative effects regarding the sexual relationship, feelings of femininity and body image. It should be noted that each of these variables were assessed by only one question.

In a recent prospective study from the UK including women with a high genetic risk (not knowing whether they are mutation carrier), it was found that women who underwent prophylactic mastectomy (n=79), showed a decrease in distress from prior to surgery to 6 and 18 months post-surgery, whereas women who declined surgery (n=64) did not (Hatcher et al 2001). Baseline distress levels in the two groups did not differ significantly from each other, but women declining surgery were found to have higher anxiety as a personality trait than women opting for surgery. In the mean time declining women were less inclined to act on their anxiety, but tended to use 'detachment' as a coping strategy. In both groups, no adverse effects over time were found regarding body image and sexual pleasure or discomfort.

In reports on psychological adaptation after surgery in breast cancer patients, (unilateral) mastectomy is not generally experienced as emotionally more harmful than breast conserving therapy, but may result in significantly more body image related problems (Moyer et al 1997, Aaronson et al 1988). This is in line with what one might expect, that mastectomy may profoundly alter the way a woman perceives her body. Smaller overall differences in favor of women undergoing breast conserving surgery were found with respect to psychological and sexual/marital adjustment.

Psychological implications of frequent surveillance

Psychological effects of frequent surveillance in healthy mutation carriers have not yet been studied. A study assessing distress in women with a family history of breast cancer undergoing a mammography, showed that these women had higher levels of cancer related distress than a normal control group (Baider et al 1999, Kash et al 1992, Lerman et al 1993, 1996b, Lerman & Schwartz 1993, McCaul et al 1998, Ritvo et al 1999, Zakowski et al 1998). The highest level of cancer related distress and perceived risk was found in women whose parent(s) had died from cancer. In another study it was found that surveillance for breast cancer was less stressful for women with a family history of breast cancer, than for those without (Gilbert et al 1998).

Experiences with cancer in relatives

Experiences with cancer in relatives may have an important impact on the test-applicant and on decisions regarding prophylactic surgery (Dudok de Wit et al 1997b). Hopwood et al. (1998) noticed that women who underwent genetic risk counselling and were referred for psychological support, often felt more concerned about loss of relatives and unresolved grief than about their risk for cancer. In a sample of subjects from BRCA1 families with multiple affected relatives Lerman et al. (1997) found a similar level of distress as in a sample of women at risk who had only one relative with breast or ovarian cancer.

Personality Characteristics

Similar as found for genetic testing for HD, distress after disclosure of BRCA1/BRCA2 test results is often related to the pre-test level of distress (Croyle et al 1997, Lerman et al 1998). This may indicate that high levels of distress may not only be situational, but may also be personality related. Such a relation was more directly demonstrated in a study including a group of women with a family history of breast/ovarian cancer applying for genetic counselling and/or BRCA1 testing (n=256), revealing an association between high general distress levels and a lesser optimistic personality (Audrain et al 1995).

Family dynamics

Authors of a review of studies on genetic counseling and testing for cancer susceptibility emphazise the major role of family influences in the risk awareness of subjects and decisions for genetic testing (Croyle & Lerman 1999). Moreover, relatives may have different roles in the period genetic testing becoming possible, which each involve specific problems (Dudok de Wit et al 1997b). Crucial is the role of those feeling responsible for informing the family about the availability of testing (the 'messengers') and the role of the first to utilize the test (Dudok de Wit et al 1994). The importance of the order of testing and of test-results of siblings was demonstrated in a study including 125 women and 87 men tested for BRCA1: greatest adverse psychological consequences were found in those initially identified as mutation carriers in the family and in mutation carriers whose tested siblings were non-mutation carriers (Smith et al 1999).

Guilt feelings toward relatives affected with cancer and/or identified as mutation carriers do not seem to be very prominent among relatives identified as non-carriers of the BRCA1/BRCA2 mutation (Dorval et al 2000). However, a small minority of these non-mutation carriers is found to strongly experience guilt feelings (Lynch et al 1997).

Partners

Partners of test-applicants are rarely given attention in studies on genetic testing for HBOC, although they are obviously involved because of the high risk for cancer in their wives, the effects of options as surveillance or prophylactic mastectomy/oophorectomy and the risk for offspring. In one study assessing distress prior to genetic testing partners of genetic test applicants for HBOC had significantly lower distress, than partners of subjects tested for other late-onset diseases (Dudok de Wit et al 1997a). In the discussion of Dudok de Wit's thesis this finding is explained as a possibly reflecting a tendency in male partners (about 80% of the partners were male) to act as strong, because their wife is going through such a difficult period (Dudok de Wit, 1997c).

Men at risk

Whereas males from HBOC families only have a small absolute risk for cancer, they often have close female relatives affected with the disease, and (grand)daughters to whom they may have transmitted the mutation. The psychological impact of this particular position of men in HBOC families has received limited attention. In one study males at risk to be a BRCA1/BRCA2 carrier were less anxious or depressed than females at risk (Struewing et al 1995). Lower distress in males than in females is a common observation in studies on among others individuals applying for genetic testing for other late onset disorders (Dudok de Wit et al 1998a, Vernon et al 1997) and individuals awaiting being informed about the diagnosis of a possible malignancy (Risberg et al 1996).

In a study investigating the anticipated uptake for genetic testing, men at risk for BRCA1/BRCA2 were less likely to opt for testing than women and fewer men expected to become depressed or anxious if being identified as a mutation carrier (Struewing et al 1995). An interview study with 22 men from HBOC families revealed a tendency to use avoidance of the topic of hereditary cancer as a coping strategy (McAllister et al 1998). Some men were explicit about avoiding conversations on breast or ovarian cancer in the family, which often came up among female relatives in family meetings, whereas others reported they felt excluded from such conversations. In a previous small scale interview study from our group (Dudok de Wit et al 1996) men requesting genetic counseling for BRCA1/BRCA2 were found to often cancel the appointments for interviews and for genetic counseling. Eventually, only one man out of four decided to obtain his test result. The impression was obtained that these men had problems with discussing their experiences with cancer in close relatives and with reflecting on possible implications of testing for themselves and their offspring. In our center significantly fewer males than females at risk for HBOC apply for genetic testing (Meijers-Heijboer et al 2000).

Another study showed that males who were the first to be tested in the family were more distressed prior to disclosure of the test-outcome, than those whose tested siblings were all found to be non-mutation carriers. After the result, male non-mutation carriers whose siblings were all found to carry the mutation had high distress levels (Smith et al 1999).

Women opting against testing

Confirmation of a high risk for cancer is considered a threat affecting one's entire life, and having such knowledge is therefore not always seen as beneficial by women at risk of being a mutation carrier. A recent study from our center on families in which a BRCA1 or a BRCA2 mutation was identified at least 6 months previously, showed that 43% of the women at 50% risk of carrying the mutation and 71% of the women at a lower risk (12.5% or 25%), did not apply for testing

(Meijers-Heijboer et al 2000). Part of this non-tested group may be delayed responders, needing more time to decide whether to undergo testing. Non-tested persons have been less often studied than those opting for testing, partly because the former group is assumed to be less willing to participate in psychological research than the latter group. In an attitudinal study from the USA, persons at risk who were not interested in future testing possibilities, had less anxiety feelings than those who would intend to utilise this test (Lerman, 95). In another study from the USA on the actual uptake for genetic testing, a fear of insurance discrimination was found to be the main reason to decline genetic testing (Lynch et al 1999). Lerman et al. found that subjects deciding to remain uninformed about their test outcome had higher depression levels several weeks later than the group who obtained the test result (irrespective of the outcome) (Lerman & Croyle 1995, Lerman et al 1998). This difference in depression level between the two groups was not present at the start, which was after being informed about the identification of a BRCA1/BRCA2 mutation in the family and the possibility to receive the test result. Moreover, persons choosing "not to know" had fewer relatives affected with breast cancer and less knowledge about HBOC and genetic testing, than those informed about their result. Women not requesting genetic testing in our center, were found to be older and more often childless, than those who applied for testing (Meijers-Heijboer et al 2000).

Ethical issues involved in genetic testing

As is the case for genetic testing in general, genetic testing for HBOC raises many important ethical issues. Examples of questions involved are the following: a) is there an obligation to inform relatives with a genetic risk about their situation? (Visser and Bleiker, 1997, van Zuuren, 97) b) how do we deal with conflicting interests, for example if a mother does not want to know her genetic status, while her daughter does? (de Wert 1999) c) is offering prophylactic surgery justified (Fentiman 1998, Galjaard 1997b, Klijn et al 1997) d) is genetic testing for children of minor age justified? (Benkendorf et al 1997, Hamann et al 2000), e) is prenatal diagnosis and terminating a pregnancy of a female fetus with the mutation justified? (Galjaard 1997a; Lancaster et al 1996; Wagner et al 1998), f) do insurance companies have the right to deny women known with the BRCA1/BRCA2 mutation for health/life insurance or increase rates (Lynch et al 1999)? Discussions on these issues take place within clinical settings, during expert conferences, and in literature and enable us to further develop our ideas concerning important ethical dilemmas, which are difficult to resolve due to their complexity and individual differences in points of view. Whereas the above mentioned ethical topics are not directly the focus of this thesis, studying attitudes, motivations and psychological implications of individuals from HBOC families will help the discussion of these topics.

This thesis

Aim of the study

The topics described above have been further investigated in the studies reported in this thesis including healthy women and men at 50% or 25% risk to be a mutation carrier for BRCA1/BRCA2. In our center genetic testing for the different late-onset diseases have always been monitored by clinical, genetic and psychological research. The possibility of BRCA1/BRCA2 testing in our center has prompted to develop the protocol for the current study.

Studying the consequences of the availability of this test for those deciding to undergo testing and those declining is important, because only if we obtain insight into the specific problems involved, can we provide specialized counseling and psychological support. Also, investigating the proportion of subjects needing additional psychological support, and the amount of support needed, helps us to estimate the potential of mental health employees. Moreover, improving our possibilities of identifying subjects vulnerable for short term or long term high emotional distress enables more effectively focusing the available support. Sometimes we might prevent severe psychological maladaptation by offering support in an early stage.

Most of the results described above derive from research in the United States. These results can not be generalized to the Netherlands. The first reason is that participants in studies from the USA often originate from only a couple of very extended families, the majority being aware of the genetic nature of cancer in the family for a long time and having participated in longitudinal genetic studies to identify the family-specific gene mutation. These individuals at risk might, through the years, have become adjusted to the distress induced by having an increased risk for cancer, which may explain the low distress levels found in these studies. At present, an increasing number of women will become identified as being at risk for genetic cancers through family studies or increased public awareness, having only limited experience with cancer in relatives, or a short-time awareness of the genetic susceptibility in their family. In the present study the latter group is also represented. A second reason is that for individuals in the USA, fear of discrimination by insurance companies plays a far more important role than for those in the Netherlands. Besides, in contrast to the USA, in our country genetic testing and prophylactic surgery are financed.

The research questions are the following:

1. Which motives do women and men have for undergoing genetic testing for BRCA1/BRCA2? (chapter 2) Which motives do women report for opting not to undergo genetic testing? (chapter 3)

2. What are the psychological consequences of genetic testing for women and men at risk to be a BRCA1/BRCA2 mutation carrier and their partners? (chapter 4,7)

3. Can we identify subjects at risk for high distress in the period before and after disclosure of the test result on the basis of the following variables: biographical characteristics, test-result, experience with cancer, post-test decisions for risk management options, personality traits, anticipation on negative/positive implications of either test outcome? (chapter 2, 3, 4, 5, 6, 7)

4. Are one or more variables mentioned in question 3) also associated with choices female mutation carriers make regarding prophylactic mastectomy/ oophorectomy and regular surveillance? (chapter 2, 4, 5)

5. What are the psychological consequences of prophylactic surgery? What is the impact of prophylactic mastectomy on body image and on the intimate relationship for women themselves and their partners? (chapter 5)

6. Can low distress levels before and after disclosure of the result be partly explained by a tendency to deny adverse consequences of testing? (chapter 6)

7. What are the attitudes of test applicants towards prenatal diagnosis for BRCA1/BRCA2 gene mutation carriership? (chapter 8)

8. Can we improve the guidelines for genetic counselling, the need for psychological support in individuals at risk and for post-test counselling of mutation carriers? (All chapters)

Procedure

The protocol for the group undergoing genetic testing was originally modeled on the protocol of pre-symptomatic testing for Huntington disease (Tibben et al 1997), and is described in table 1. A difference between the protocol of the present study and the original protocol, is that the first assessment took place after blood sampling instead of before. We did so, because in contrast to the protocol for genetic testing for HD, in the program for HBOC blood was often sampled at the first counseling session.

If subjects agreed to participate, an introduction with the author of this thesis followed, who provided information about the psychological follow-up study and gave questionnaires to be completed at home. The pre-test interview was

scheduled, usually in the weeks following blood sampling, but sometimes, for practical reasons, directly after the genetic counseling session.

After disclosure of the test-result, the psychologist met the test-applicants and their partners to give the opportunity to discuss their feelings. One or more days later, she contacted the participants by telephone, to schedule the post-test interview. Post-test and follow-up assessments (interview and questionnaires) took place at 1 to 3 weeks, and at 6 and 12 months after disclosure of the test-result. About two thirds of the interviews were conducted at home, one quarter at the department of Clinical Genetics or at a regional hospital, and less than 10% was done by telephone, which depended on the preferences of the participants. Women who underwent prophylactic mastectomy were interviewed by telephone one week prior to and one month following surgery.

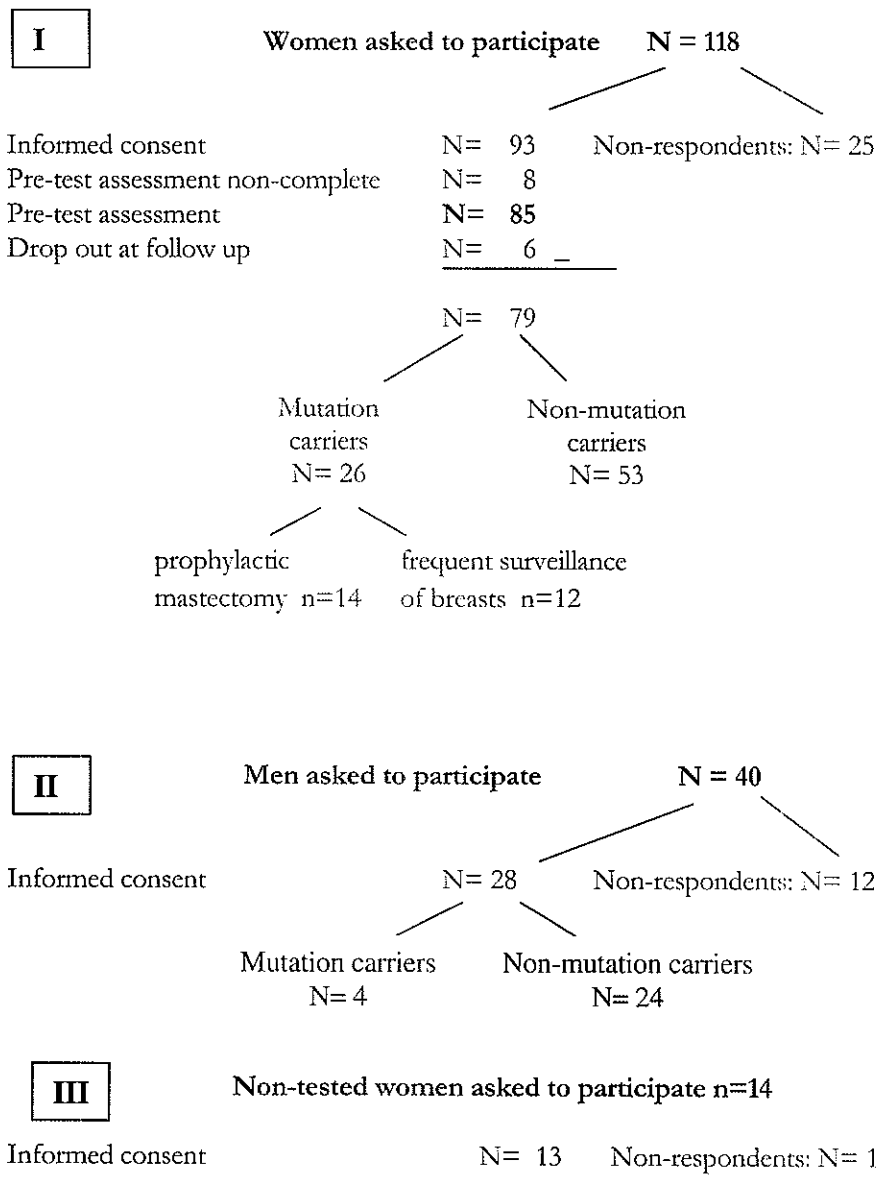
Table 1: Procedure for genetic testing and the psychological study

Genetic testing	**Psychological assessments**
Genetic counseling	
Bloodsampling	0-3 weeks after Bloodsampling: Pre-test assessment - Questionnaires - Interview
6-8 weeks later: disclosure of test-result	Short session with psychologist/researcher
	1-3 weeks, 6 & 12 months after disclosure: Post-test/follow up assessments - Questionnaires - Interview

Main factors addressed in the questionnaires were feelings of distress, personality characteristics and biographical data. A questionnaire assessing body image and satisfaction with the intimate relationship was specifically developed for this study. Attitudes toward the implications of genetic testing and one's experiences with cancer in relatives were explored both in a questionnaire and in the interview. The interview is also included to provide an in-depth perspective of the subject's experiences and feelings and may be used to illustrate results from questionnaire data. Finally, part of the interview is used to assess the extent to which subjects

talk in a coherent way about their experiences and feelings, which may be relevant to grasp whether defense mechanisms are operative (chapter 6).

Table 2: The study sample



Chapter 2

PRESYMPTOMATIC TESTING FOR BRCA1 AND BRCA2: HOW DISTRESSING ARE THE PRE-TEST WEEKS?

Lodder LN[1], Frets PG[12], Trijsburg RW[1], Meijers-Heijboer EJ[2], Klijn JGM[3], Duivenvoorden HJ[1], Tibben A[124], Wagner A[2], van der Meer CA[2], Devilee P[4], Cornelisse CJ[4], van den Ouweland AMW[2], Halley DJJ[2], Seynaeve C[3], Tilanus MMA[3], Bartels CCM [3], Verhoog LC[3], Brekelmans CTM[3], van Geel AN[3], Dukel L[3], Dudok de Wit AC[14], Niermeijer MF[2]

[1]Dept. of Medical Psychology and Psychotherapy, Erasmus University Rotterdam/ Netherlands Institute for Health Sciences; [2]Dept. of Clinical Genetics, University Hospital Dijkzigt/Erasmus University Rotterdam; [3] Daniel den Hoed Cancer Clinic/Erasmus University Medical Center Rotterdam [4]Leiden University Medical Center

Journal of Medical Genetics 1999; 36: 906-13, reprinted with permission from the BMJ Publishing Group

ABSTRACT

Pre-symptomatic DNA testing for autosomal dominant Hereditary Breast and/or Ovarian Cancer (HBOC) became an option after the identification of the BRCA1 and 2 genes, in 1994-1995. Healthy female mutation carriers have a high lifetime risk for breast cancer (56-87%) and/or ovarian cancer (10-60%) and may opt for intensive breast and ovary surveillance or prophylactic surgery (mastectomy and/or ovariectomy).

Here, we study general and cancer-related distress in 85 healthy women with a 50% or 25% risk of being carrier of a BRCA1/BRCA2 gene mutation, and 66 partners, in the 6-8 week period between genetic counseling/blood sampling and disclosure of the test result. Questionnaire and interview data are analyzed. Associations are explored between levels of distress and a) expected consequences of being identified as a mutation carrier, b) personality traits, c) sociodemographic variables, and d) experiences with cancer in relatives.

Mean pre-test anxiety and depression levels of test applicants and partners were similar to those of a normal Dutch population. In about 25% of the test applicants, and 10% of the partners, elevated to high levels of general and cancer-related distress were found. Elevated levels of distress were reported by test applicants who a) anticipated an increase of problems after an unfavourable test

outcome and/or considered prophylactic mastectomy if found to be mutation carrier, b) had a non-optimistic personality and/or tended to suppress their emotions, c) were younger than 40 years and d) were more familiar with serious consequences of HBOC. A recently obtained awareness of the genetic nature of cancer in the family was not predictive for distress.

The majority of test applicants and their partners experienced a relatively calm period prior to disclosure of the test result and seemed to postpone distressing thoughts until the week of disclosure of the result. The low distress levels may partly be explained by the use of strategies to minimize the emotional impact of a possible unfavourable test-outcome. However, a minority reported feeling very distressed. Several factors were found to be predictive for elevated distress levels.

INTRODUCTION

Because pre-symptomatic testing for HBOC is a new development with far-reaching consequences for the test applicants and their families, it is important to monitor the psychological impact of this test in the pre- and post-test period. Psychological evaluations became part of our program for pre-symptomatic testing for HBOC since its start in 1994 (Dudok de Wit et al 1997b). Main reasons for women to opt for pre-symptomatic DNA testing are to obtain certainty about 1) having an increased risk to develop cancer or not, 2) the need for future intensive surveillance and/or prophylactic interventions, and 3) the possibility of having passed on the gene to their offspring (Dudok de Wit et al 1997a). The demand for this test in persons at risk for HBOC, seems to be stronger than in those at risk for other late-onset genetic disorders (Hopwood 1997, Lerman et al 1997a).

Up till now, only few studies have analyzed psychological functioning in the weeks prior to receiving BRCA1/BRCA2 test results. These studies showed mean pre-test distress levels to be 'similar to those of a normal population'; however, the variability in distress levels was high. A first evaluation of pre-test functioning in 24 healthy test applicants applying for BRCA1/BRCA2 testing in our centre, showed that disease-related distress was lower than in test applicants for Huntington disease, but higher than in test applicants for Familial Adenomatous Polyposis Coli (a type of hereditary colon cancer) (Dudok de Wit et al 1997a). The low psychological distress in these test applicants for HBOC was explained by the intensive attention from researchers and (onco)geneticists towards this first tested group.

Test applicants in previous studies had been aware of the genetic nature of cancer in the family for a long time and had usually been involved in previous

genetic studies to identify the family-specific gene mutation (Croyle et al 1997, Dudok de Wit et al 1997a, Lerman et al 1996a, 1997). Therefore, one should be careful in generalizing the results. The long-standing adaptation to the emotional impact of belonging to a HBOC family, might explain the low distress levels (Lerman et al 1997a). At this moment, analysis of the familial BRCA1 or 2 mutation allows genetic testing of larger numbers of persons at risk, who sometimes have only limited experience with cancer in relatives, or a short-time awareness of the genetic susceptibility in their family. Our study is the first psychological study on genetic testing for HBOC, in which the latter type of persons at risk are represented.

In 1995 the present study was started, including psychological assessments from pre-test to one-year follow-up in women at 50% or 25% risk of being a BRCA1/BRCA2 mutation carrier applying for pre-symptomatic testing, and their partners. Partners were included in the study because the increased risk of developing cancer for their wives, the option for prophylactic mastectomy, and the genetic risk for offspring, are all of major concern for them as well. Women with a personal history of breast or ovarian cancer, were not included; they are likely to carry the family-specific mutation and may therefore experience the testing-period differently (Croyle et al 1997). Besides, the medical implications of the test result may be different for those with and without a history of cancer. Psychological implications of pre-symptomatic BRCA1/BRCA2 testing for males at risk for HBOC are addressed in chapter 7.

Here, we present the psychological functioning of test applicants and their partners, in the 6-8 week waiting period between genetic counseling/blood sampling and disclosure of the test result. The aim of the study is twofold. Firstly, we wanted to improve our understanding of the emotional impact of waiting for a BRCA1/BRCA2 test result. Secondly, we wanted to identify test applicants who might need additional support during the pre-test period. For this, it has been recommended to examine associations between distress levels and relevant predictive variables, such as demographic factors and personality traits (Lerman et al 1994, 1996). Beside these factors, we also assessed the expected consequences of an unfavourable test result and experiences with cancer in the family.

METHODS

Study population

Between December 1995 and April 1998, 118 healthy women, with a 50% or 25% risk of having inherited a BRCA1 or 2 gene mutation, who applied for genetic testing at the Department of Clinical Genetics Rotterdam, University Hospital

Dijkzigt, were asked to participate in the psychological study. Eighty-five of them (72%) completed the pre-test assessment, 8 (7%) declined after having completed either a questionnaire or an interview, and 25 (21%) decided not to participate. A reluctance towards discussing emotions was the reason most often mentioned for declining (further) participation in the study. Most of the declining women stated experiencing no problems, some feared the burden of discussing their feelings, and a minority did not want to complete questionnaires. Of the 76 partners of the participating test applicants, 66 (86%) joined the study. The 85 test applicants who participated, belonged to 33 different HBOC families.

Procedure

Procedures of genetic counselling and the psychological study are described in chapter 1 (page 11, 26).

Variables

OUTCOME VARIABLES

General distress

The Hospital Anxiety and Depression Scale (HAD) was administered, which consists of two subscales of seven items assessing the level of anxiety and depression (Channer et al 1985, Zigmond & Snaith 1983). Questions have four answer options, yielding scores ranging from 0 to 21 for each subscale. A score of higher than 10 is an indication of clinical anxiety or depression, scores from 8 to 10 on either subscale are indicative for 'borderline' anxiety or depression. Validity and reliability are found to be good (Spinhoven et al 1997).

To enable comparison of general distress to the normal population, the Symptom Checklist was used (Derogatis et al 1976). This questionnaire has norm tables for a Dutch female and male population (Arrindell & Ettema 1981).

Cancer-related distress

The Impact of Event Scale (IES), assessing the impact of a distressing experience, was used (Horowitz et al 1979). The 'Intrusion' (7 items) and 'Avoidance' scale (8 items), measure becoming overwhelmed by thoughts and feelings about a distressing experience and a tendency to avoid these thoughts and feelings. 'Breast/Ovarian Cancer' was taken as the distressing event. To enable comparison with results from previous studies on genetic testing in our centre, similar response categories were used (never, sometimes, often or continuously). These response categories differed from those of the original IES (Dudok de Wit et al 1997a). The score range for intrusion is 0-35, for avoidance 0-40.

PREDICTIVE VARIABLES

Sociodemographic and pedigree information

Data were obtained on age, marital status, offspring (number, gender and age), educational level and the genetic risk (50% or 25%) of being a mutation carrier.

The decision of wanting to be tested

In the interview test applicants were asked how long it took them to decide to have a genetic test and what their major reasons were to have it performed.

Expected consequences of an unfavourable test result

An attitude questionnaire (appendix A), which was adapted from previous studies from our group (Tibben et al 1993c), monitored the expected emotional consequences of either test result. Test applicants and partners could indicate whether they, after an unfavourable test result, expected their own, their partners' or children's problems to increase, to become depressed, to be able to better plan their future life and whether they expected adverse consequences for finding or keeping work. Contrasting expectations after a favourable test result were also explored. Response categories were: 'agree', 'do not know', or 'disagree'. Test applicants were also asked which test outcome they expected. Their answers were divided into 5 categories, ranging from 'I have a strong feeling of not having inherited the gene mutation' to 'I have a strong feeling of having inherited the gene mutation'. Answers such as 'I feel it as a fifty-fifty chance', or 'my feelings about it are changing every day', were scored as 'not having a particular presentiment'.

Test applicants were also asked about their plans on future risk management if identified as a mutation carrier. If women considered prophylactic surgery, it was registered how sure they felt about this option and what time schedule they had in mind to have it performed.

Personality traits

Two scales of the Self-Assessment Questionnaire-Nijmegen (SAQ-N) (Bleiker et al 1996), a questionnaire measuring different personality traits, were administered. They assess Optimism (Scheier & Carver 1985) (8 items, e.g. 'In uncertain times I usually expect the best'), and Emotional Expression (Bleiker et al 1993, Watson et al 1984) (18 items, assessing the repression, physical acting out and control over feelings of anxiety, anger and depression, e.g. 'When I feel unhappy or miserable, I let others see how I feel' and 'When I feel angry, I still have control over my behaviour'). The frequency of such feelings/behaviours could be indicated, by use of a 4-point scale, ranging from 'almost never' to 'nearly always'.

Experiences with the disease in the family

The personal experience with breast and ovarian cancer in the family was explored during the interviews with test applicants. Test applicants were asked how long they had been aware of the genetic nature of breast/ovarian cancer in their family.

Information was gathered on the number and age of relatives with breast/ovarian cancer, on the outcome of the disease, and on the personal involvement with these relatives. An affected relative was categorized as 'close', if the risk carrier was involved with her during the disease and its treatment. Thus, one could have a 'close' contact with a cousin, and a 'non-close' contact with a sister, e.g. if there had been no contact with this sister for years. Experience with serious sequelae of breast/ovarian cancer in relatives was categorized as follows: 1) women who are/were in close contact with relatives with metastatic breast/ovarian cancer, 2) women who know/knew such relatives but were not involved with them during the disease, and 3) women who knew no relative with metastatic breast/ovarian cancer.

Statistical methods

To control for a possible violation of randomness due to belonging to a same family, we used a random regression model for continuous data performed by the program Proc Mixed of the statistical package Statistical Analysis Systems (SAS/PC, release 6.12). By means of this method, family-specific effects on the outcome variables could be estimated (Gibbons et al 1993). For the further data analysis, we used Statistical Package for Social Sciences (SPSS/PC, release 8.0). Differences between subgroups, for example between test applicants and partners, were tested by t-tests for independent samples (levels of $p \leq 0.05$, 2-tailed, were regarded as statistical significant). The relation between the independent factors and the level of general and cancer-related distress, was estimated by a single linear regression model. Factors significantly related to the level of distress ($p \leq 0.05$), were included in a multiple linear regression model (backward elimination procedure). The variance explained by this regression model was described.

RESULTS

Descriptives

Sample characteristics of participants and non-respondents

For 85 women, and 66 partners, pre-test interview and questionnaire data are available. The characteristics of the women participating in the study were compared to those of the 33 women who did not want to participate in the psychological study or who dropped out during the pre-test assessment (28%), by means of a t-test for independent samples (Table 1). No differences were found between respondents and non-respondents regarding sociodemographic

characteristics, prior risk, or familiarity with metastatic breast and/or ovarian cancer in close relatives ($p \leq 0.05$, 2-tailed).

Table 1: Characteristics of the study sample (women applying for pre-symptomatic DNA testing and their partners) and non-respondents

	Women at risk (N=85)	Non-respondents (N=33)	p<0.05[1]	Partners[2] (N=66)
Mean age (years):	38.4	39,0	-	38.9
Range: 19-40	63%	67%		64%
41-68	37%	33%		36%
Education				
≤ Lower vocational school	29%	25%	-	32%
Intermediate	61%	63%		44%
> High school	10%	12%		24%
Marital status			-	
married/living together	87%	85%		
unmarried/divorced/widowed	13%	15%		
Have Children	72%	76%	-	
Mean number (range)	2,2 (1-5)	2,1 (1-4)	-	
Children < 15 years	44%	49%	-	
Girls (> 18 years)	55% (36%)	55% (39%)	-	
Boys	58%	61%	-	
Want (more) children	36%	unknown		
Prior risk 50%	78%	85%	-	
25%	19%	15%		
12.5%	3%			
Close relative(s) with metastatic breast and/or ovarian cancer	48%	42%	-	

[1]Characteristics from respondents compared to non-respondents (T-tests for independent samples)
[2]All but two male

The decision of wanting to be tested

Once a pre-symptomatic DNA test became possible in the family, it took the women in the study several weeks to one year to decide to have this test

performed. The majority (72%) decided within 2 months. A major reason for testing for almost all women was to obtain certainty about their mutation carrier status. This was closely followed (86%) by the wish to know the necessity for intensive surveillance or prophylactic surgery. Knowing the risks for their children was of major relevance for 50% of the women with children. Knowing about risks for future children was a reason for one third of the women considering future offspring (n=9).

Expected consequences after an unfavourable test result

An increase of problems after an unfavourable test outcome, was anticipated by one third of the test applicants and one fifth of the partners (Table 2). Another third of the test applicants, doubted whether an unfavourable test result would increase their problems. Unchanged levels of problems, both after an unfavourable and a favourable test outcome, were expected by 29% of the test applicants. Of the partners, only 9% thought that the test result would not affect the level of problems for their wives. This difference in percentages is statistically significant ($p \leq 0.05$, 2-tailed).

Table 2: Anticipation of the impact of the test outcome

	Women at risk (N=85)	Partners (N=66)	
After an **unfavorable** test result, I expect…	**Agree (%)**	**Agree (%)**	p<0.05
my problems to increase	35	21	*
my partner's problems to increase	30[1]	62	*
my children's problems to increase	46[2]	[2]34	
to become depressed	4	2	*
to be able to better plan future life	36	8	*
adverse effects regarding finding/ keeping work	12[3]	-	
After a **favorable** test-result, I expect…	**Agree (%)**	**Agree (%)**	
my problems to decrease	42	33	
my partner's problems to decrease	34[1]	77	*
my children's problems to decrease	50[2]	[2]56	
my mood to improve	42	33	

[1] For test-applicants having a relationship; [2] For test-applicants/partners with children; [3] For test-applicants with current or future job

Almost half of the women (43%) intended to obtain prophylactic mastectomy after becoming identified as mutation carriers. The others were still undecided (23%), or would opt for regular surveillance (34%). Ovariectomy was considered by 50% of the women and one third was still undecided or wanted to delay this intervention. A minority (17%) would not opt for prophylactic ovariectomy.

Experience with the disease in the family

Half of the participants were familiar with metastatic breast or ovarian cancer in one or more close relatives. One quarter had hardly any experience with the disease in relatives. The period of time since becoming aware of the hereditary nature of the disease in the family varied from a few weeks to 25 years. This awareness existed for less than one year in 40% of the test applicants.

Distress levels

Distress levels of test applicants

GENERAL DISTRESS

Test applicants had a mean anxiety score on the Hospital Anxiety and Depression Scale of 5.5 (0-17; SD 3.8), which is below the 'borderline value' of 8. Scores equal to or higher than 8 were found in 26% of the test applicants. The mean depression score was low (mean: 2.5; 0-14; SD 2.9), and only 7% of the test applicants had 'borderline' or higher depression levels. Mean anxiety and depression scores on the Symptom Checklist, were similar to those of a normal female population.

CANCER-RELATED DISTRESS

A large range in scores was found for both the Intrusion (0-31) and Avoidance (0-29) scales. Because of a lack of comparability with other international studies (the Impact of Event Scale is often used with different response categories and 'distressing Events'), only general conclusions are possible. Total absence of intrusive thoughts and feelings about breast/ovarian cancer in the preceding week was reported by 14%, and of avoidance of these thoughts or feelings by 22% of the test applicants. About one quarter of the test applicants reported intrusion and avoidance to occur rather frequently (their mean scores on these scales are equal to or higher than 7 and 8, respectively, which represent an average response of 'at least sometimes').

Distress levels of Partners

GENERAL DISTRESS

Partners levels on the anxiety (mean: 4.3; SD 5.6) and depression scale (mean: 3; SD 3.1) of the HAD, did not differ significantly from those of the test applicants. 'Borderline' to 'high' levels of anxiety and depression were found in 17% and 12% of the partners, respectively. On the Symptom Checklist, their mean anxiety and depression scores were similar to those of a 'normal male' population.

CANCER-RELATED DISTRESS

Partners reported significantly lower levels of intrusive thoughts and feelings about breast/ovarian cancer and avoidance of these thoughts and feelings than their wives. One quarter (28%) of the partners had experienced no intrusive thoughts or feelings about breast/ovarian cancer in the preceding week, and 42% had not experienced a tendency to avoid these thoughts or feelings. Regular experiences of intrusion or avoidance were reported by only 9% (their mean scores on these scales are equal to or higher than 7 and 8, respectively, which represent an average response of 'at least sometimes').

Single predictive factors for distress

We used a random regression model for continuous data (SAS/PC, release 6.12) in order to estimate family-specific effects on the outcome variables (Gibbons et al 1993). Seventy-three participants originated from 23 families (varying from 2 to 10 participants per family), the remaining 12 originated from different families. Because no family-specific effects were found, controlling for this variable was not necessary. For the further data analysis we used a Statistical Package for Social Sciences (SPSS/PC, release 8.0).

Table 3: Predictive factors for distress in genetic test-applicants: Beta's for associations from single and multiple regression models.

	Anxiety	Depression	Cancer-related distress
Expected consequences of an unfavourable test result			
1) Expecting increase of problems after unfavourable test result	.37**	.27*	.39**
2) Prophylactic mastectomy if mutation carrier	.40**	.28**	.42**
Personality traits			
3) Optimism	-.30**	-.36**	-.13
4) Emotional expression	-.28**	-.28*	-.25**
Sociodemographic characteristics			
5) Being younger than 40	.28**	.01	.07
6) Have children under 15	.22*	.08	.19
Experience with cancer in relatives			
7) Number of relatives with Breast/Ovarian cancer	.23*	.08	.35**
8) Familiarity with relative with metastatic Breast/Ovarian cancer	.11	.28*	.05
9) Age of onset of disease in particular family < 40	.22*	.03	.28*

*$p < 0.05$, resulting from a single regression model;

**$p < 0.05$, resulting from both a single and a multiple regression model

For the test applicants, we entered all the predictive variables included in the study in a linear regression analysis, with anxiety and depression levels (HAD) and cancer-related distress (IES) as outcome variables. Because the levels of Intrusion and Avoidance were found to be highly correlated (.58; $p< 0.01$), we decided not to distinguish between these two different aspects of cancer-related distress in this regression analysis and to use the total IES score. The variables significantly related to the level of general and/or cancer-related distress are presented in Table 3.

General Distress

More Anxiety and Depression was found in test applicants who anticipated an increase of problems after an unfavourable test result and in those who had decided to undergo prophylactic mastectomy in case of being a mutation carrier. Women who both anticipated problems and opted for mastectomy after an unfavourable test result (29%), had the highest levels of distress, those not expecting problems nor considering mastectomy after an unfavourable test-outcome (29%) the lowest. Besides, having relatively pessimistic personalities and not being inclined to express one's emotions was related to higher levels of anxiety and depression..

Anxiety (though not depression) was significantly increased in test applicants who were younger than 40 years and who had young children. Also, having many affected relatives with breast and/or ovarian cancer and an age of onset of cancer in these relatives below 40 years was related to higher levels of anxiety.

Depression (though not anxiety) was significantly related to familiarity with serious consequences of breast and/or ovarian cancer in relatives. The highest level of depression was found in women who knew/had known close relatives with metastatic breast or ovarian cancer, and the lowest level in women who had not known any of these relatives.

Cancer-related distress

Five predictive variables being related to anxiety or depression, were in the same way related to cancer-related distress. More cancer-related distress was reported by women who 1) expected their problems to increase after an unfavourable test result, 2) intended to undergo prophylactic mastectomy after becoming identified as a mutation carrier, and 3) were inclined not to express their emotions, 4) had greater numbers of relatives with breast or ovarian cancer, and 5) came from families in which the age of onset of cancer was lower than 40 years.

Joint predictors for distress

The single variables that proved to be significant predictors for general or cancer-related distress, were included in a multiple linear regression model, for the three

outcome variables seperately. As shown in Table 3, the most important variables for predicting general and/or cancer-related distress were: a) anticipating problems after an unfavourable test outcome, b) opting for prophylactic mastectomy if identified as a mutation carrier, c) being 'non'-optimistic, d) being not inclined to express one's emotions, e) being younger than 40 years, and f) having a great number of relatives with breast or ovarian cancer. These variables explain 37% of the variance for anxiety, 26% for depression and 32% for cancer-related distress.

DISCUSSION

Low distress in test applicants

For this paper we analyzed psychological functioning, expectations about post-test life and experiences with breast and ovarian cancer in the family in healthy women at risk of being a BRCA1 or 2 mutation carrier, and their partners. Assessments took place between genetic counseling/blood sampling and disclosure of the test result 6-8 weeks later.

Mean levels of anxiety and depression in test applicants were similar to those of a normal population. Similar low distress was also found in previous studies, in which all participants had been aware of the genetic nature of cancer in the family for a relatively long period of time (Croyle et al 1997, Dudok de Wit et al 1997a, Lerman et al 1996, 1997a). Participants in these latter studies may have had low distress levels due to emotional habituation (Croyle et al 1997, Lerman et al 1996, 1997a). This is the first study on psychological implications of pre-symptomatic DNA testing for BRCA1/2, including women who were only recently informed about the genetic nature of this disease in their family and/or who had little or no experience with breast or ovarian cancer in the family. It was hypothesized that these women might experience more distress than those with a longer experience with this problem. However, the length of time participants were aware of the genetic nature of cancer was not significantly related to the degree of distress. Besides, having much experience with cancer in the family was significantly associated with a high, instead of a low level of pre-test distress. This is in line with the results from a previous study at our centre (Dudok de Wit et al 1997a).

The rather low distress levels are contrary to what one would expect from individuals who, within some weeks, will hear about their risk of developing cancer. Is the period of awaiting the test result really non-threatening for many test applicants, or is there also a tendency to minimize the emotional impact of it? Our impression is that both hypotheses may be valid. On the one hand, having provided the blood sample for the DNA test may temporarily induce some rest. Test applicants then seem to have the feeling of having done everything they could and

to postpone distressing thoughts until the week in which disclosure of the result takes place. This can be illustrated by two pre-test interviews: …..'*Only sometimes it comes to my mind that I have done the test. I was much more distressed by it all when I heard about this gene in the family, some weeks ago, and I thought I would feel anxious after having the blood sample taken, but up till now, I have had no feelings of anxiety at all.*'….. And ….. '*I actually feel rather calm now. <<..>> This might be because there is so much time in-between, these five, six weeks*'....

On the other hand, because everything is still uncertain in the pre-test period, many test applicants may have used more or less conscious mechanisms to minimize the implications of an unfavourable test outcome (Dudok de Wit et al 1997a, Michie et al 1996). This is reflected in the result that only one third of the test applicants reported to expect adverse emotional consequences after being identified as a mutation carrier. Interestingly, partners acknowledged significantly more often adverse consequences for their wives. These results are strikingly similar to those described in previous studies (Dudok de Wit et al 1997a, Tibben et al 1993c). It may have been more threatening for test applicants to acknowledge adverse emotional consequences of an unfavourable test outcome for themselves, than for partners to acknowledge these consequences for their wives. Test applicants may have dismissed these threatening thoughts.

Distress in partners

Partners had general distress levels similar to their wives, but lower cancer-related distress. Only one fifth of the partners anticipated emotional consequences for themselves if their wives received an unfavourable test result. Impressions from the interviews showed a tendency of many partners of not wanting to worry in advance, 'since there is still a considerable chance of a good result': ….. '*At this moment nothing can be said about whether cancer is in the game or not, so I see no reason to worry. I mean, if there is a soccer game, and someone makes a goal, I cannot yet feel happy or sad, since nothing can be said then about the final score. I only start to react emotionally, when the game is over*'…...

Predictive factors for high distress

Elevated to high general and cancer-related distress was found in one fourth of the test applicants. Similar proportions were also reported in a study on women with first-degree relatives with breast cancer (Kash et al 1992). A number of factors were independently associated with general and/or cancer-related distress. Women who anticipated adverse emotional consequences after an unfavourable result, may have been more conscious of the threat induced by the test and, therefore, more distressed. This may be seen as 'working through' the possible impact of an unfavourable test result in advance (Dudok de Wit et al 1997a). The elevated anxiety

in women considering to undergo prophylactic mastectomy if becoming identified as a mutation carrier, may be explained by the profound physical and emotional consequences of this intervention. But it is also possible that women who are more distressed about their risk for cancer in the first place, are more likely to opt for a more radical preventive intervention.

Strong relationships were found between personality traits and distress. Many other studies on psychological functioning in burdensome conditions, report similar conclusions (Decruyenaere et al 1996, Duits et al 1998). Relatively pessimistic participants may be more distressed in uncertain times in general and, therefore, also during the testing procedure. One woman with low distress scores described herself in the interview as being always optimistic and she explained: ….. *'It would amaze me if I was found to carry the mutation, but if so, I would focus on the idea that I may very well belong to the percentage of gene carriers who never develop breast or ovarian cancer'*….. Women, who were not inclined to express their emotions, thus the more introvert types, may have been more distressed because they did not sufficiently share their feelings with others.

The age of the test applicants was also associated with the level of distress. From the interviews, the impression was obtained that many women in their thirties are very conscious of the possibility of developing cancer and, because of their young age, of the profound consequences of it. As one young woman said: ….. *'My mother was in her early thirties when she developed cancer, and not yet forty when she died from it, so that makes me anxious, the idea that life can be so short'*….. For older women the idea of developing cancer may be perceived as something more hypothetical. The fact that they have lived already a long time without having developed cancer, seems to induce a feeling of trust: Why would cancer be detected tomorrow? One woman in her sixties mentioned: ….. *'I underwent quite a lot of mammograms already, and they never showed anything suspect. This gives me the feeling that the results of future check-ups, will be all right again'*. ….. This feeling of trust in the results of surveillance seemed also to be present in women younger than 30 years. One woman in her late twenties explained: ….. *'If I am found to be a mutation carrier, this will have implications for the future, but I do not have the feeling that I could develop cancer right now'*…… Distress levels in this group of young women were somewhat lower than those in women in their thirties, but this difference was not significant.

Women with young children may experience more anxiety than women without or with grown-up children, because of the threat of leaving young children behind, in case they would develop cancer and die. For many test applicants this was a very important reason for wanting to undergo the test, as one woman said: ….. *'I feel responsible for my family, and especially for my children. I awfully regret not having a mother anymore myself, and I am over thirty, so imagine that my little children would lose their mother. I find it really terrible thinking about this'* …..

As mentioned above, women who have been more familiar with profound

consequences of breast or ovarian cancer in their families, were more distressed than those with little or no experience with affected relatives. The confrontation with burdensome consequences of HBOC may have made these women more aware of what the test is about. As one woman expressed it: ….. *'I know what I am talking about, since I've seen cancer in close relatives too often. The sickness of these relatives, and the cancer hospital, come regularly to my mind, and I do not want to end there too. That is what it is all about, you want to prevent this terrible disease'*….. Moreover, the testing procedure may reactivate sorrow and grief about cancer in relatives. This is clearly illustrated by a young woman who lost her mother from breast cancer some years ago: ….. *'This is a period that I am thinking more often about my mother than usually. I'm sometimes wondering for example what she would think and do in this situation'*…..

Strikingly, the objective and perceived prior risk of having inherited the mutation, are not related to pre-test distress. Women with a prior risk of 25% or lower, and those who expect to be non-carriers, are not less distressed than the others.

While about one fourth of the test applicants were rather distressed, only 6 (7%) received additional psychological counseling in the pre-test period. The majority of the women were able to cope without additional support. It should be noted, that the pre-test interview, and the idea that more interviews would follow in the post-test period, may have been experienced as supportive. The percentage of women requesting additional psychological counseling might have been higher if the study participants had not been interviewed for the current study. Other researchers already mentioned that special attention provided to test applicants involved in psychological studies might lead to an underestimation of the impact of testing (Lerman et al 1995).

Generalizability of the results

The study sample consisted of a relatively heterogeneous group of healthy women who wanted to know if they had inherited the BRCA1/BRCA2 gene mutation. There was a great variety with respect to age and experiences with cancer in the family. This makes the results of this study generalizable to other groups of healthy individuals undergoing BRCA1/BRCA2 testing. However, test applicants who needed more than one year to decide to undergo the test, are not represented in this study. All women applied for testing within one year after the test became available for them, and the majority even made an appointment within 2 months. This urgency for testing applied to both women who had been aware of the hereditary nature of cancer in the family for a long period of time and those having been informed about this only recently. In the interviews women often mentioned that they felt they had no choice, now that they were informed about their risk of being a

mutation carrier and about the possibility of having it tested. As one woman said: *....'I do not see it as a choice. I feel that I have to undergo the test and, after an unfavourable test result, preventive surgery <<...>> I've got a family and children and I want to stay with them as long as possible'.* ..... In the future an increasing number of individuals might apply for testing, while having been undecided for years and having doubts about the benefits of testing. Such test applicants might be more distressed than those in the present study. In this study, however, no associations were found between distress and the amount of time one took before test application.

It is unknown whether similar low distress levels would have been found in the test applicants who did not want to participate in the study. We speculate that their scores on the questionnaires might have been not so high either, since the majority of them did not see any use in participation because they perceived no adverse psychological implications of testing. However, a minority of the non-respondents found it too threatening to discuss their feelings about the issue.

Implications for clinical practice

The main aim of this study was to explore the psychological impact of awaiting a BRCA1/BRCA2 test result for healthy women and their partners. It was found that most women and partners seemed to cope well during this pre-test period, but some were rather distressed. High distress is more likely to occur in test applicants who: 1) expect their problems to increase after an unfavourable test-result, 2) consider prophylactic mastectomy if identified as a mutation carrier, 3) are non-optimistic, 4) have a tendency not to express their emotions, 5) are younger than 40 years, and 6) are familiar with serious consequences of cancer in the family.

Future analyses of post-test data may establish if test applicants with low pre-test distress and expecting no increase in problems after an unfavourable test outcome, may be at risk for severe psychological maladaptation after the result. Because at this stage it is unknown which attitudes are related to maladjustment in post-test life, it is important to respect different ways to deal with the uncertainty induced by the test and not to force test applicants to abandon possibly minimizing strategies.

Acknowledgements

This study is supported by a Dutch Cancer Society grant. We are grateful to the participants in the study. We also want to thank mrs. C. Tengnagel for her secretarial activities.

Chapter 3

ATTITUDES AND DISTRESS LEVELS IN WOMEN AT RISK TO CARRY A BRCA1/BRCA2 GENE MUTATION WHO DECLINE GENETIC TESTING

Lodder LN[1], Frets PG[1,2], Trijsburg RW[1], Klijn JGM[3], Seynaeve C[3], Tilanus MMA[3], Bartels CCM[3], Meijers-Heijboer EJ[2], Verhoog LC[3], Niermeijer MF[2].

[1]Dept. of Medical Psychology and Psychotherapy, Erasmus University Rotterdam/ Netherlands Institute for Health Sciences; [2]Dept. of Clinical Genetics, University Hospital Dijkzigt/Erasmus University Rotterdam; [3]Daniel den Hoed Cancer Clinic/Erasmus University Medical Center Rotterdam

Submitted

ABSTRACT

Genetic testing enables women at risk for Hereditary Breast and/or Ovarian Cancer to find out whether they have inherited the gene mutation, and if so, to opt for undergoing frequent surveillance and/or prophylactic surgery. However, the option to know about one's genetic status is not always seen as a benefit by women at risk.

Motives for declining genetic testing were explored in 13 women at risk to be a BRCA1/BRCA2 mutation carrier, who participated in a surveillance program for breast/ovarian cancer (the non-tested group). We investigated whether high anxiety was an important motive to decline testing and whether the non-tested group differed from a reference group of women who did undergo the test (tested group; chapter 2) with regard to factors such as biographics and experience with cancer in relatives.

Most non-tested women (10/13) were satisfied with participating in the surveillance program. Four reported to feel emotionally unprepared to cope with the consequences of testing. Compared with the tested group, the non-tested women had similar mean distress levels (which were not high), but a higher education level, they were more often childless, showed more reluctance towards prophylactic surgery, were younger when first confronted with a relative affected with breast/ovarian cancer, and were longer aware of the genetic nature of the disease.

This study showed that women were more likely to have thoroughly reflected on their decision not to undergo presymptomatic testing, than to deny the whole issue due to high anxiety. Being confronted at a relatively young age with breast/ovarian cancer in a relative, and being aware of the genetic risk for many years, may have resulted in the risk for cancer becoming an integrated part of their lives. However, generalization of these results to women who neither underwent the test nor participated in a surveillance program should be considered with caution.

INTRODUCTION

Confirmation of having a high risk for breast/ovarian cancer is considered a threat affecting one's entire life, and having such knowledge is not always seen as a benefit by women at risk of being a mutation carrier. A recent study from our center on families in which a BRCA1 or a BRCA2 mutation was identified at least 6 months before analysis of the data, showed that 43% of the women at 50% risk of carrying the mutation and 71% of the women at a lower risk (12.5% or 25%), did not apply for testing (Meijers-Heijboer et al 2000). Women in that study not requesting genetic testing were older and more were childless, than those who applied for testing.

In our experience, most women who do not request testing, neither apply for an informative discussion about the genetic disease at the department of Clinical Genetics; therefore, clinical information about this group of women is scarce. However, as indicated by clinical experience and other reports (Codori et al 1999), high anxiety may be a major reason for not undergoing testing. Therefore, a study on women declining the test might elucidate whether this is a particular anxious and psychologically vulnerable group, necessitating measures such as: 1) the offer of psychological support by departments involved with genetic disorders, and 2) structuring the routing of information about the hereditary disease to relatives who are still unaware of the genetic nature of cancer in their family. More generally, knowledge on attitudes towards genetic testing and psychological distress in subjects deciding against testing is indispensable to estimate the impact of the availability of genetic testing in HBOC families. Nevertheless, fewer studies have focussed on subjects declining genetic testing than on those undergoing the test.

One study showed that main reasons to decline testing for BRCA1/BRCA2 were a fear of insurance discrimination and fear of being identified as mutation carrier (Lynch et al 1999). A recent study in the United States found that subjects deciding not to be informed about their test outcome had higher depression levels

several weeks later, than the group who chose to obtain the test result (irrespective of the outcome) (Lerman et al 1998). This difference in depression level between the two groups was not present at the baseline assessment, which was held shortly after the initial information about the identification of a BRCA1/BRCA2 mutation in the family and the possibility to receive the test result. The same study also reported that the subjects choosing not to know about the result had fewer relatives affected with breast cancer and had less knowledge about HBOC and genetic testing, than the informed group. Because subjects in that study were invited to receive their test outcome within a few weeks after being informed about the availability of the results, some of those deciding not to know their genetic status may have made a different decision after a longer period of deliberation.

Nonparticipation in genetic testing for late onset diseases has been especially studied for Huntington disease. Compared with those opting for genetic testing, individuals declining genetic testing were not more emotionally distressed, but did have a more pessimistic outlook about themselves and their future (Decruyenaere et al 1997, Steenstraten et al 1994). This pessimistic attitude also included the expected implications of either test result. The main reasons given for declining genetic testing were: doubts about the ability to cope with an unfavorable test outcome, the burden of the genetic counseling process and/or receiving an unfavorable test outcome and expecting a reduced quality of life (Decruyenaere et al 1997, Steenstraten et al 1994).

Another interesting finding was that learning about the genetic nature of the disease at a young age was significantly related to declining testing (Steenstraten et al 1994). It was argued that, in those declining testing, the influence of the disease on the separation-individuation process and personality development might have affected their attitude towards testing: i.e. being at risk for Huntington disease may have become part of their identity. Conversely, subjects becoming informed about Huntington disease at an adult age might attempt to restore the disturbed balance of their lives and may have a great urge to obtain certainty by undergoing genetic testing.

In the present study, we explore self-reported motives for not undergoing genetic testing and factors related to this decision in women at 50% or 25% risk to be a BRCA1/BRCA2 mutation carrier. These women learned about the possibility of testing in their family more than one year before the start of the study. Expected implications of receiving the test result and one's intention to undergo testing in the future were explored. Biographical data, levels of emotional distress, experience with cancer in relatives, and personality traits were compared with those of women who did undergo genetic testing (chapter 2).

METHODS

Participants

The study sample comprised women having a 50% or 25% risk of carrying a BRCA1 or BRCA2 gene mutation, who did not demand to be tested after learning about this possibility more than one year earlier. These women did participate in a breast and/or ovarian surveillance program at the family cancer clinic of the Daniel den Hoed Cancer Clinic (Erasmus University Medical Center Rotterdam). During a follow-up visit (in the period January to December 1999), the physician invited the 14 women meeting the inclusion criteria to participate in a psychological study assessing their motivation for not undergoing the test and their emotional wellbeing. Of these, 13 women agreed to answer a questionnaire and 6 of these women also consented to be interviewed.

This sample was compared with a sample of 85 women (belonging to 33 different families) who underwent genetic testing in the period December 1995 to April 1998 (chapter 2). These latter women had completed similar questionnaires in the 6 to 8 week period between genetic counseling/blood sampling and disclosure of the result. A description of the genetic counseling procedure and information on attrition are reported in chapter 1 and 2. The present study and its procedure have been approved by the medical ethical review board of the University Hospital Rotterdam.

Procedure

Eligible women were informed about the present study by the physician who saw them in the breast surveillance program. Woman considering participation received written information about the aim and content of the study (appendix C). It was emphasized that any decision with regard to genetic testing would be respected and no attempt would be made to influence their decision. Women were asked to return a form indicating whether they agreed to the questionnaire and/or the interview part of the study and, when agreeing, to sign an informed consent form. Depending on their decision, subjects either received a questionnaire to be returned by mail or were contacted by telephone to schedule the interview; subjects participating in the interview could return their questionnaire at that time.

Variables

Questionnaire on attitudes and past experiences with HBOC

We developed a questionnaire (appendix D) dealing with the following topics:

Biographical data

Questions addressed age, marital status, offspring and educational level.

Attitudes toward the genetic test

Reasons for declining genetic testing and intentions regarding testing at a later stage were assessed by open-ended questions. Women's perception of the chance of having inherited the mutation was indicated by their choice of one of the following answers: 'I feel as if I have inherited the mutation', 'I feel as if I have not inherited the mutation', 'I perceive the chance of having or not having inherited the mutation as equally high', 'I have no particular feeling about having or not having inherited the mutation'. Moreover, participants were asked to respond to items similar to those responded to by the tested group concerning the expected emotional impact of either test result: i.e. did they expect an increase of their own problems or their children's problems, or to become depressed if identified as a mutation carrier. Contrasting expectations of becoming identified as a non-mutation carrier were explored. Women were also asked whether they expected to have more certainty, or to be better able to plan the future, if they knew whether or not they carried the mutation.

Satisfaction with being informed about the genetic nature of cancer in the family

Some questions addressed which person or institution had informed the subject about the genetic nature of cancer in the family and the possibility of genetic testing, whether one was satisfied with being informed, and whether interfamilial relationships had changed since being informed.

Attitudes toward close surveillance and prophylactic surgery

Subjects were asked how comfortable they felt with self-examination of the breasts and with following a close surveillance program. As in the tested group, subjects were asked to report their attitudes toward prophylactic mastectomy and oophorectomy.

Knowledge on risks associated with HBOC

Two questions checked irrational perceptions of 1) the risk of a woman with the mutation to develop cancer (the options were: 'no increased risk', 'an increased risk', 'a risk of about 100%' or 'other') and, 2) the frequency of cancer being detected 'in time' (before having spread out) when under close surveillance ('seldom', 'often', 'always' or 'other').

Experience with breast/ovarian cancer in relatives

Subjects were asked to report on the relatives they knew/have known to be affected with breast/ovarian cancer. Data on the number of known relatives affected with breast/ovarian cancer, their relation to these relatives (e.g. first or second degree) and whether one was confronted with profound implications from cancer (metastases, death), were compared with similar data from women who underwent genetic testing.

Psychological distress

Anxiety and Depression were measured with the two subscales of the Hospital Anxiety (7 items) and Depression (7 items) Scale (HAD) (Zigmond & Snaith, Channer et al 1983). Each question has four answer possibilities. Scores of the two subscales range from 0 to 21. Scores higher than 10 indicate clinical anxiety or depression, scores from 8 to 10 indicate 'borderline' anxiety or depression. The validity and reliability of the scale are documented (Spinhoven et al 1997).

Cancer related distress was measured using 9 of the 15 items of the Impact of Event Scale (IES, Horowitz et al 1979), assessing: 1) the occurrence of intrusive thoughts and feelings about breast/ovarian cancer and, 2) the tendency to avoid such thoughts and feelings. Response categories were: 'never', 'sometimes', 'often' or 'continuously'. Six items of the original scale were excluded to minimize the burden of completing this questionnaire, which might be distressful for women with an increased risk of developing breast/ovarian cancer. Items found to have a low discriminating value among the 85 women who underwent testing were omitted. (Included items were: 'I thought about breast/ovarian cancer (BOC) when I didn't meant to', 'I tried to remove BOC from my memory', 'I had difficulty sleeping because of thoughts about BOC', 'I had waves of strong feelings about BOC', 'I stayed away from people or situations that might remind me of BOC', 'I felt so unrealistic about it, as if nothing had happened', 'Images about BOC popped into my mind', 'I knew that I still have a lot of feelings about BOC, but I did not want to think about it' and 'I tried not to think about BOC'.)

Personality traits

Optimism was assessed with a Dutch adaptation (Bleiker et al 1995) of the Life Orientation Test (Scheier & Carver 1985), measuring the extent to which one has a positive attitude towards life (8 items, e.g. 'In uncertain times I usually expect the best'). The frequency of occurrence of such thoughts or feelings could be indicated on a four-point scale (ranging from 'almost never' to 'nearly always'). In addition, we used two of the three subscales of a Dutch-adapted Rationality scale, which was originally developed by Grossarth-Maticek (1980) and adapted by Spielberger (1988) and van der Ploeg et al. (1989). These scales assess Rationality (6 items, e.g. "I try to do what is reasonable and logical") and Anti-emotionality (4 reversed items, e.g. "In important situations, I trust my feelings").

Interview

Because only 6 women agreed to an interview, it was decided to omit analysis of transcripts for this study. However, the interview data were used to check if they corresponded with data obtained from the questionnaires; this is briefly addressed in the discussion section.

Statistical Methods

To test differences in means and proportions between the tested and the non-tested group, t–tests and χ^2 tests for dichotomized data were used (Statistical Package for Social Sciences, release 8.0). A p value of ≤ 0.05 (two-tailed) was regarded as statistically significant.

RESULTS

Sample characteristics

Table 1 gives biographical data on the 13 non-tested women and the 85 women who were tested for the BRCA1/BRCA2 gene mutation. Both groups have a similar mean age, but non-tested women were more likely to be childless (χ^2 test; $p < 0.03$) and to have a higher education level (χ^2 test; $p < 0.01$) than tested women.

Attitudes toward the genetic test

Regarding the possibility of undergoing the test in the future 8 of the 13 women did not completely rule this out whereas 3 did. Two women thought they would undergo the test within a few years. Both reported to feel satisfied with undergoing frequent surveillance at the moment, one of these two women (aged 35 years) reported not to be emotionally prepared to receive an unfavorable test outcome, while the other (aged 25 years) preferred to postpone the test until completion of her family. Satisfaction with frequent surveillance was indicated as a reason for non-testing in 8 other women. Of these 8 women, 4 emphasized that they would not undertake other risk management strategies (such as prophylactic surgery) if found to carry the mutation, 3 felt not emotionally prepared to receive an unfavorable test outcome and one other woman was too preoccupied by other psychosocial problems to worry about her cancer risk. The reasons given for not undergoing genetic testing are listed in Table 2 (women could report more than one reason).

Ten of the 13 untested women had a correct perception of their genetic risk for the mutation, whereas two overestimated and one underestimated this risk. Compared to the tested women, non-tested women were not more pessimistic about possible implications of being identified as a mutation carrier or as a non-mutation carrier. Four of the 13 non-tested women believed that confirmation of having inherited the mutation would yield a higher sense of certainty than not knowing.

Satisfaction with being informed about the genetic nature of cancer in the family

In 12 non-tested women initial information about the genetic nature of cancer in the family and the possibility of testing was provided by a relative, and one woman obtained this information from a gynecologist. All women were satisfied that they

Table 1: Characteristics of women declining presymptomatic DNA testing and compared with women who underwent the test

		Non-tested women (n= 13)	Tested women (n= 85)	p
Biographical data				
Mean age in years (SD)		40.9 (13.3)	38.4 (10.9)	
(Range)		(20-66)	(19-68)	
Education:	< High school	38.5%	69.4%	
	High school	23.0%	21.2%	***
	> High school	38.5%	9.4%	
Married/living together		77%	87%	**
Have children		38%	72%	**
Want (more) children		31%	36%	
Experience with cancer in relatives				
Familiar with close relative with metastatic breast/ovarian cancer		62%	48%	
Mean number of relatives known to have (had) breast/ovarian cancer		2.5	3.4	*
Mean age (years) when first confronted with breast/ovarian cancer in a relative		20.5	29.1	**
Mean number of years aware of the genetic nature of cancer in the family		11.5	4.0	***

* = p <.07; ** = p <.05; *** = p <.01

had been informed about the genetic nature of breast/ovarian cancer in the family. Four of the 13 women reported that being informed had influenced intra-familial relationships: two women stressed that contacts with relatives were intensified because they 'shared the same problem', one reported that cancer was more often discussed in the family, and another described that after an initial commotion everything had normalized again.

Attitudes toward close surveillance and prophylactic surgery

Ten of the 13 non-tested women felt safe with the surveillance program for breast/ovarian cancer, whereas only 3 felt satisfied with the sense of control that breast self-examination gave them. Prophylactic mastectomy was considered too far-reaching by 12/13 non-tested women, compared with 29/85 (34%) of the tested group (χ^2 test $p < 0.001$). Prophylactic oophorectomy was considered too

Table 2: Reasons for deciding against genetic testing (more than 1 reason could be given)

		Number
1	Satisfied with participation in breast/ovarian cancer surveillance program	10
2	Can emotionally cope with having increased risk	4
3	Would not change risk management (more frequent surveillance/ prophylactic surgery) if identified as mutation carrier	4
4	Emotionally not ready for receiving possible unfavorable test outcome	4
5	Does not want to worry about oneself more than necessary	2
6	Prefers postponing until after child wish is fulfilled	1
7	Too preoccupied with other psychosocial problems to focus on increased risk for breast/ovarian cancer	1
8	Partner and daughters are not ready for it	1
9	Had colon cancer probably due to carrying a HNPCC mutation, sees breast/ ovarian cancer as one of the many cancers she is at risk for. Finds surveillance very important, afraid of exclusion if identified as a non-mutation carrier.	1

far-reaching by 7/13 non-tested women, as compared to 14/85 (17%) of the tested group (χ^2 test $p < 0.05$).

Knowledge on risks associated with HBOC

All non-tested women agreed that female mutation carriers had an increased risk to develop cancer. However, 3/13 stated that this still "does not say much about the possibility that a woman would ultimately develop cancer or not". The fallibility of frequent surveillance to detect cancer at an early stage was known to all women from the non-tested group.

Experience with breast/ovarian cancer in relatives

The proportion of women being familiar with metastatic cancer in a first degree relative was similar in the non-tested and the tested group. The mean number of known cancer cases in the family was somewhat lower in the non-tested group (2.5) than in the tested group (3.4) ($p < 0.07$; t–test, two-tailed). Furthermore, the non-tested women were younger (mean 20.5 years) when first confronted with a relative affected with breast/ovarian cancer, than the tested women (mean 29.1 years) ($p < 0.03$; t-test for independent samples, two-tailed). Non-tested women also had a longer awareness of having an increased risk to develop cancer (mean 11.5 years) than tested women (mean 4.0 years) ($p < 0.01$; t-test for independent samples, two-tailed).

Levels of psychological distress

A borderline to high level of anxiety and/or depression was found in 3/13 of the non-tested women. This proportion did not differ from that of the tested women. Mean levels and standard deviations of general anxiety (6.1, SD 5.2) and depression (2.1, SD 4.6) in the non-tested group did not differ significantly from those of the tested group (5.5, SD 3.8; 2.5, SD 2.9) ($p > 0.6$; t-test for independent samples, two-tailed). On the cancer-related distress scale, 4/13 women answered on ≥ 1 item that the content of that item 'often' applied to them. The others reported lower cancer-related distress levels

Personality characteristics

There were no significant differences between the non-tested and the tested group on the scales assessing optimism and rationality ($p > 0.05$; t-test for independent samples, two-tailed).

DISCUSSION

Reasons for non-testing and discriminative characteristics of the non-tested group

In the present study, high anxiety levels were not the main reason why women declined to apply for presymptomatic testing for BRCA1/BRCA2 after it became possible in the family (more than one year previously). The mean anxiety and depression levels in this group were similar to those of the tested women, which were rather low (chapter 2). The hypothesis that women abstain from testing because they are too anxious to face the consequences seemed to apply for 4 of the 13 untested women; 3 of these women reported a high (or 'borderline') level of anxiety and 2 of them also had a high level of cancer-related distress. Seven of the women who chose not to be tested seemed to have decided so after having seriously considered the advantages and the disadvantages of testing. Two other women declined testing for 'external' reasons: one because the partner and children did not seem ready, and the other woman was too preoccupied with other emotional problems. It should be noted that half the women in this study did not completely rule out undergoing the test sometime in the future.

Thus, this study shows that women were more likely to have thoroughly reflected on their decision not to undergo presymptomatic testing, than to deny the whole issue due to high anxiety. This finding was underscored by the impression we obtained in five of the six interviews held. A relatively high proportion of the non-tested women were highly educated, which may have influenced the perception of the possibility of testing as an autonomous choice, as opposed to a decision primarily influenced by what a physician offers.

Most non-tested women were satisfied to follow the frequent surveillance program and considered the possibility of prophylactic surgery too far-reaching as a risk-reducing option against cancer. Some women explicitly stated they saw no reason to know their genetic status, since that would still not alter their risk-reduction strategies. Non-tested women were satisfied with the surveillance program without overestimating its efficacy to detect cancer at an early stage. Neither were they likely to over- or underestimate the risk of having inherited the mutation, or the risk of developing cancer after being identified as a mutation carrier. In contrast to other reports (Decruyenaere et al 1997), our non-tested group was not more pessimistic about the expected implications of either test result, than the tested group. Furthermore, scores on the personality questionnaire showed that non-tested women were not more pessimistic than tested women, neither were they more likely to behave on their ratio rather than on emotions.

For many tested women the reason for testing was that they wanted to minimize the chance of leaving young children behind (chapter 2). This might also partly explain why tested women were more likely than the non-tested group to seriously consider undergoing prophylactic surgery if found to carry the mutation. Another important reason to opt for testing was to know whether they could have transmitted the mutation to their children. Because most non-tested women were childless, one important motive for testing did not apply to these women.

Similar to the results found for Huntington disease (Steenstraten et al 1994), our non-tested group was significantly younger when first confronted with the disease in a relative, than the tested group. They also had been longer aware of the genetic nature of cancer in the family. These women may have accepted the fact of being a member of a HBOC family, and of having an increased risk to develop breast/ovarian cancer as a part of their life. They may therefore have perceived the option of undergoing genetic testing as something to seriously reflect on. The tested women were in their late twenties on the average when first confronted with an affected relative, they had become aware of the genetic nature of cancer in the family more recently than non-tested women and, similar as to reported in another study (Lerman et al 1998), they tended to have been familiar with more affected relatives. Being confronted with cancer in more than one relative and with their own increased risk for cancer in a relatively short time span may have led these women to develop some serious existential doubts. The possibility of testing may therefore have been perceived as an opportunity to regain some control over their lives. This is in accordance with a previously reported finding that tested women found obtaining certainty the most important reason for undergoing the test (chapter 2). The present study showed that only a minority of the non-tested group thought that confirmation of having inherited the mutation would yield a sense of certainty.

Concluding remarks

This study found that neither anxiety nor irrational beliefs about the test result and its consequences were the most important reasons to refrain from undergoing genetic testing. Most women decided not to undergo the test after serious deliberation about the advantages and the disadvantages of being informed about the result. For the majority of the non-tested group, one or more of the following factors seem to have influenced their decision: 1) satisfaction with participating in the surveillance program and reluctance toward prophylactic surgery, 2) having no children, and 3) becoming acquainted with breast/ovarian cancer in the family relatively early in their lives. In conclusion, this group of women was not found to be a specifically psychologically vulnerable group.

However, it should be emphasized that the non-tested women in this study were a small, selected group. All were well informed about their risk to be a mutation carrier and about the risks to develop cancer. For ethical reasons, we did not include any woman in this study who was not known at the cancer clinic; we wanted to prevent approaching women with avoidant behavior, who could perceive being asked for participation in a psychological study on motives for not taking the test as threatening. In contrast to the women in the present study, some of those women may have negative feelings about being informed about the genetic nature of cancer in the family. For these reasons, the findings from this study can not be generalized to all women who refrain from testing. Future studies need to address the important question how to recruit a more heterogeneous study sample in an ethical way; for example, via support groups for women from HBOC families. Meanwhile, as long as data of such heterogeneous sample are lacking, adequate counseling of probands or other counsellees who want to inform their relatives about the possibility of testing is of utmost importance. The possibility that some of these relatives will come to know more than they ever would have wanted to know, should be a prime consideration.

For women participating in a surveillance program who decide not to undergo the test (or to postpone it), there seems to be no direct need for psychological support in their decision-making process, or in coping with the increased risk for breast/ovarian cancer. Such support should of course be offered if requested, but including it as a standard part of the surveillance program for women at 50% or 25% risk to be a BRCA1/BRCA2 mutation carrier may be superfluous.

Acknowledgements

This study is supported by a Dutch Cancer Society grant. We are grateful to the participants in the study.

Chapter 4

THE PSYCHOLOGICAL IMPACT OF RECEIVING BRCA1/BRCA2 TEST RESULTS

Lodder LN[1], Frets PG[1], Trijsburg RW[1], Meijers-Heijboer EJ[2], Klijn JGM[3], Duivenvoorden HJ[1], Tibben A[124], Wagner A[2], van der Meer CA[2], van den Ouweland AMW[2], Niermeijer MF[2]

[1]Dept. of Medical Psychology and Psychotherapy, Erasmus University Rotterdam/Netherlands Institute for Health Sciences; [2]Dept. of Clinical Genetics, University Hospital Dijkzigt/Erasmus University Rotterdam; [3]Daniel den Hoed Cancer Clinic/Erasmus University Medical Center Rotterdam; [4]Dept. of Neuropsychology, Leiden University Medical Center; the Netherlands

American Journal of Medical Genetics 2000; 98: 15-24

ABSTRACT

Mutation analysis for autosomal dominant hereditary breast/ovarian cancer genes (BRCA1/BRCA2) became an important technique for women at risk of carrying these mutations. Healthy female mutation carriers have a high life time risk for breast and/or ovarian cancer and may opt for frequent breast and ovary surveillance or prophylactic surgery (mastectomy and/or oophorectomy).

Psychological distress was assessed in 78 healthy women at risk of having inherited a BRCA1/BRCA2 mutation opting for genetic testing, and 56 partners, several weeks prior to ('pre-test') and after ('post-test') learning about their DNA test result. Twenty-five women were found to be mutation carriers, and 53 non-mutation carriers. One goal of the study was to identify individuals at risk for high distress 1 to 3 weeks following disclosure of the test result. In mutation carriers, choices for risk management options were explored Interview transcripts were used to give a fuller picture of pre- and post-test distress.

High post-test anxiety was reported by 20% of women with the mutation and by 35% of their partners. Eleven percent of women without the mutation and 13% of their partners, reported high post-test anxiety levels. High post-test anxiety in women was significantly related to 1) a high level of pre-test anxiety and 2)

being a mutation carrier. Women without a mutation who had a sister identified as a mutation carrier recently, had higher post-test levels of depression than the other non-mutation carriers. Most mutation carriers who made up their mind about either undergoing frequent surveillance (n= 12) or prophylactic mastectomy (n= 11), had made this decision already prior to disclosure of the result.

It is suggested to consider seriously the need for psychological support in mutation carriers, who had been anxious at pre-test already. For most non-mutation carriers, psychological follow-up might be of lesser importance, but those having a sister receiving an unfavorable test result should be informed about the possibility that they might not feel relief.

INTRODUCTION

This study is part of a continuing evaluation of distress in healthy women with a risk of 50% or 25% of being a BRCA1/BRCA2 mutation carrier, who apply for genetic testing, and their partners. Main reasons for these women to opt for pre-symptomatic DNA testing are to obtain certainty about 1) having an increased risk to develop cancer or not, 2) the need for future frequent surveillance and/or prophylactic interventions, and 3) the possibility of having passed the gene to their offspring (Chapter 2, Dudok de Wit et al 1997a). Individuals at risk for HBOC, seem to ask for this test more often than those at risk for other late-onset genetic disorders (Hopwood 1997; Lerman et al 1997). Because of the far-reaching implications of pre-symptomatic BRCA1/BRCA2 mutation testing, we have monitored its psychological impact in the pre- and post-test period since 1994, when the first HBOC families applied for testing in our center (Dudok de Wit et al 1997a,b). An earlier study in 10 of these test-applicants assessed psychological distress from pre-test to 6 months follow-up (Dudok de Wit et al 1998a). Compared to subjects undergoing genetic testing for other hereditary diseases, such as Huntington disease, these subjects at risk showed relatively low pre- and post-test distress levels.

In studies from the United States on larger groups of subjects at risk for HBOC (with and without a history of cancer), no evidence was found for serious short-time adverse effects of BRCA1/BRCA2 testing (Croyle et al 1997; Lerman et al 1996a). However, mutation carriers reported more distress than non-mutation carriers one month after disclosure of the test-result. This difference was explained by a decrease of distress in non-mutation carriers at post-test, rather than by an increase of distress in mutation carriers. One study analyzed the course of distress for mutation carriers and non-mutation carriers with high and low pre-

test distress separately, and the only subgroup showing a significant change (a decrease) in depression levels were non-mutation carriers who had been distressed at pre-test (Lerman et al 1998). Mutation carriers in these studies, most of whom having participated in genetic studies on the identification of the family specific gene mutation previously, might, through the years, have become adjusted to the distress induced by having an increased risk for cancer (Croyle et al 1997; Lerman et al 1996a, 1998).

In addition to the test result, the level of pre-test distress was found to be predictive for levels of post-test distress: subjects being distressed at pre-test were more likely to be highly distressed after disclosure of the test-result (Croyle et al 1997; Lerman et al 1998). Pre-test indications for post-test distress are important, since they may enable early identification of subjects in need of psychological support after disclosure of the test result.

Participants in the studies from the United States were at risk subjects both with and without a history of cancer (Croyle et al 1997; Lerman et al 1996a, 1998). In one of these studies, examining whether the personal cancer history affected post-test distress, healthy mutation carriers (n=13) were found to be the most distressed (Croyle et al 1997). Mutation carriers who had had cancer previously, might experience less distress, because they may perceive the test-result as a confirmation of their expectation. Moreover, cancer patients already had to adapt to the distress of their diagnosis, and may, therefore, perceive genetic testing as a secondary problem. This study, in which only a small sample of healthy mutation carriers had been included (Croyle et al 1997), illustrates the need to further evaluate distress in healthy subjects receiving a BRCA1/BRCA2 test result.

The present study is the first European follow-up of a large group of healthy women at risk of being a BRCA1/BRCA2 mutation carrier with either a longstanding or a recent perception of the genetic nature of cancer in the family. The latter group is of special importance, because an increasing number of women will become identified as being at risk for genetic cancers through family studies or increased public awareness. In chapter 2 distress in the current study sample during the pre-test period is described, and such women were not found to experience more distress than women who became aware of their genetic risks years earlier. Now, we examine whether at post-test the former group does experience more distress than the latter. Because pre-test distress was found to be generally low, we expect, in contrast to findings from studies in the United States, distress levels in mutation carriers to increase from pre- to post-test. Besides, young women with the mutation and those with young children are expected to experience more distress at post-test than the older ones and those with adult children. Among non-mutation carriers, distress levels at post-test are expected to be lower than in mutation carriers, but close involvement with the disease or

mutation carriership in relatives, might reduce this difference in the level of distress. The course of distress from pre- to post-test in identified mutation and non-mutation carriers is clarified by interview transcripts. Furthermore, we describe which choices women with the mutation make regarding prophylactic mastectomy/oophorectomy and regular surveillance. Distress levels in partners are specifically addressed, because the potentially high risk for cancer in their wives, the option for prophylactic mastectomy/oophorectomy and the risk for offspring, affect them as well.

METHODS

Participants

Between December 1995 and April 1998, 118 healthy women with a 50% or 25% risk of being a BRCA1/BRCA2 mutation carrier who applied for genetic testing at the department of Clinical Genetics, Erasmus University Medical Center Rotterdam, and their partners, were asked to participate in a psychological follow-up study. Seventy percent did participate; 21% of the women decided not to take part and 9% dropped out after initial agreement. Reasons for declining (further) participation were a reluctance to discuss emotions with a psychologist or to complete questionnaires.

Procedure

The procedures of genetic counselling and the psychological study are described in chapter 1 (page 11, 26).

Dependent variables

General distress

General distress was assessed by the validated Hospital Anxiety and Depression Scale (HAD) (Channer et al 1985; Spinhoven et al 1997; Zigmond and Snaith 1983). This questionnaire consists of 2 scales of 7 items, assessing the level of anxiety and depression. Each question has 4 answer options and the scale scores vary from 0 to 21. A score of higher than 10 is an indication of clinical anxiety or depression, scores from 8 to 10 on either subscale are indicative for 'borderline' anxiety or depression.

Cancer related distress

The Impact of Event Scale (IES), assessing the impact of a particular distressing experience, was used (Horowitz et al 1979). The 'Intrusion' (7 items) and 'Avoidance' scales (8 items), measure becoming overwhelmed by thoughts and feelings about breast or ovarian cancer and a tendency to avoid these thoughts and feelings. Comparison with previous studies in this group was possible because

identical response categories were used (never, sometimes, often or continuously) (Dudok de Wit et al 1998a,c). These response categories differed from those of the original IES. The total score ranges from 0 to 75.

Descriptive and predictive variables

Sociodemographic and pedigree information

Data were obtained on age, marital status, offspring (number, gender and age), educational level and the genetic risk (50%or 25%) of being a mutation carrier.

Participation in prior genetic studies and experiences with breast/ovarian cancer in relatives

In the pre-test interview, women were asked since when they had become aware of the genetic nature of cancer in the family and whether they had been involved in genetic studies already before the mutation was found. Furthermore, they were asked about involvement with relatives identified as mutation carriers and/or with breast/ovarian cancer. The number of known affected relatives, the consequences of the diseases and the lowest age of onset were registered. An affected relative was categorized as 'close', if one was involved with her during the disease and its treatment.

Intentions concerning risk management

In pre- and post-test interviews women were asked about their plans concerning frequent surveillance or prophylactic surgery after disclosure of the test-result. In women considering prophylactic surgery after being identified as a mutation carrier, we registered how certain they felt to have it performed and what time schedule they had in mind.

The reported impact of the test-outcome

More insight into the impact of the testing procedure, was provided by verbatim transcripts of answers the open-ended question in the post-test interview: *"What does it mean to you that you are found to be a (non-) mutation carrier"?*

Statistical methods

Statistical Package for Social Sciences (SPSS/PC, release 8.0) was used for the descriptive analyses and to explore the effect of the test result on the course of distress. For the latter analyses we used analysis of variance (ANOVA) for repeated measurements, or, in case of dichotomized data, logistic regression for dichotomized data. To test differences between subgroups at one assessment point (for example between respondents and non-respondents) t-tests for independent samples were used. Levels of $p \leq 0.05$ (2-tailed) were regarded as statistically significant.

For the prediction of post-test distress levels, we controlled for a possible violation of randomness due to belonging to a same family. In the study 33

different families were involved, implying that test-applicants (n=78) could belong to the same family. This was the case for 67 test-applicants, coming from 23 different families (varying from 2 to 8 participants per family). The remaining 11 test-applicants came from different families. We used a random regression model for continuous data performed by the program Proc Mixed of the statistical package Statistical Analysis Systems (SAS/PC, release 6.12), which estimates family specific effects on the outcome variables, instead of mean effects for the study population in total (Gibbons et al 1993).

RESULTS

Descriptives

Study sample

Data were analyzed on 78 female test-applicants, originating from 33 different HBOC families, and for 56 partners. Twelve percent of the partners of the participating women preferred not to join the study (n=9), and another 7% did not complete their post-test questionnaires (n=5). Twenty-five women were found to be mutation carrier and 53 non-mutation carrier. Table 1 depicts general characteristics of the participating women (n=78) and their partners (n=56), and the non-respondents (n=40), being women who either 1) did not want to participate in the psychological study (n=25), 2) dropped out during the course of the study (n=11) or 3) failed to return their post-test questionnaires, while having participated in the post-test interview and endorsing further participation in the study (n=4; two mutation carriers and two non-mutation carriers). The only significant difference between mutation carriers and non-mutation carriers was that the latter group was more often married than the former group (p= 0.05; t-tests for independent samples, two-tailed).

No significant differences regarding sociodemographic characteristics and genetic risk to be a mutation carrier were found between the study sample and non-respondents (t-tests for independent samples, two tailed).

Eighty-eight percent of the partners of the participating women joined the study. Five partners (one partner of a mutation carrier and four partners of non-mutation carriers) failed to complete their post-test questionnaires. Their scores on pre-test questionnaires or sociodemographic variables did not seem to differ from those of partners continuing participation in the study.

Prior experiences with genetic research and with cancer in the family

The time since becoming aware of the genetic nature of cancer in the family varied from a few weeks to 25 years and was less than one year for 39% of the women.

Previous involvement in genetic studies was reported by half of the participants. The experience with breast or ovarian cancer in the family varied from being acquainted with one or more close relatives having (had) metastatic breast or ovarian cancer (51%) to no experience with cancer in relatives in this stage of the disease (22%).

Table 1: General characteristics of the study sample: BRCA1/BRCA2 mutation and non-mutation carriers

	Female study participants (n = 78)		Female non-respondents/ drop outs (n = 40)	Partners (n = 56)
	Mutation carriers (n= 25)	Non-mutation carriers (n = 53)		
Age: mean	39.0	37.8	39.3	38.7
(range)	(19-68)	(23-64)	(19-65)	(21-64)
Education				
≤ Lower vocational school	36%	28%	8%	84%
Intermediate	48%	66%	29%	11%
> High school	16%	6%	3%	25%
Married/living together	72%	92%	87%	96%
Living apart	8%	0%	0%	4%
No partner	20%	8%	13%	0%
Having children	64%	70%	80%	68%
Partners declining (further) participation	26%	20%		

Decisions regarding screening/prophylactic surgery

At post-test, intentions for risk management remained unchanged for most identified mutation carriers, in comparison with their pre-test intentions (Table 2). Ten of the 11 mutation carriers who intended to undergo prophylactic mastectomy, had made this decision before disclosure of the test-result. Similarly, the pre-test choice for frequent surveillance if mutation carrier (n=10), was doubted by only one woman at post-test.

At post-test, prophylactic oophorectomy in the near future was considered by one third of the women who were found to be mutation carriers (n=9). All these women had made this decision before disclosure of the test-result. The same was

true for women who did not want to have their ovaries removed (n=6). The remaining 10 were still undecided, or decided to postpone this intervention.

Table 2: Mutation carriers' intentions for Prophylactic mastectomy or Regular surveillance of breasts (n=25)

		POST-TEST INTENTIONS (n)			
		Mastectomy	Surveillance	Undecided	Total
PRE-TEST INTENTIONS (n)	Mastectomy	10	-	-	10
	Surveillance	-	9	1	10
	Undecided	1	3	1	5
	Total	11	12	2	25

Distress levels

Distress levels of test applicants

The course of anxiety and depression from pre-test to post-test was significantly different for mutation carriers and non-mutation carriers ($p<.05$; ANOVA for repeated measurements; Table 3). Non-mutation carriers became less anxious and depressed from pre- to post-test and mutation carriers showed a slight increase in anxiety and depression, the mean pre-test distress levels being rather similar for the two groups. Figure 1 illustrates patterns of anxiety for both mutation carriers and non-mutation carriers.

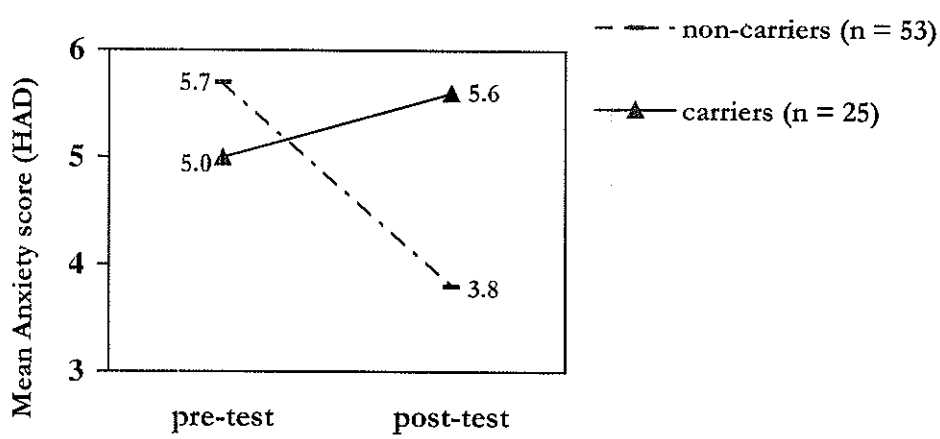
High post-test anxiety scores (equal or higher than 8) were reported by 20% of the mutation carriers and by 11% of the non-mutation carriers. High post-test depression scores were reported by 12% of the mutation carriers and by 4% of the non-mutation carriers. Analysis of these post-test percentages, while correcting for those at pre-test, showed that the difference in proportions of highly anxious and depressed mutation carriers and non-mutation carriers failed to reach significant levels (Logistic regression for dichotomized data).

Table 3: Mean distress scores in Mutation carriers and Non-mutation carriers

		MEAN *(SD)* DISTRESS SCORES		ANOVA					
				Time		Test-outcome		Time x Test-outcome	
Assessment moment		Mutation carriers (n=25)	Non-mutation carriers (n=53)	F	p	F	p	F	p
HAD									
Anxiety	*Pre*	5.0 *(4.1)*	5.7 *(3.8)*	1.89	.17	.44	.51	8.10	.01
	Post	5.6 *(3.8)*	3.8 *(3.8)*						
Depression	*Pre*	2.0 *(2.5)*	2.8 *(3.1)*	.09	.77	.00	.99	4.31	.04
	Post	2.7 *(3.5)*	1.8 *(2.4)*						
IES									
Cancer related Distress	*Pre*	8.2 *(10.3)*	10.2 *(9.3)*	.15	.70	.08	.78	5.56	.02
	Post	10.3 *(9.6)*	7.3 *(6.7)*						

The course of cancer related distress for mutation carriers and non-mutation carriers showed a pattern similar to that of anxiety and depression ($p<0.05$; ANOVA for repeated measurements; Table 3).

Figure 1: Course of anxiety for mutation carriers and non-mutation carriers



Distress levels of Partners of the test-applicants

The course of anxiety, depression and cancer related distress was significantly different for partners of mutation carriers and partners of non-mutation carriers, the former showing an increase of distress levels from pre- to post-test and the latter a decrease ($p<.05$; ANOVA for repeated measurements; Table 4), as shown in figure 2 for anxiety scores.

At post-test, significantly more partners of mutation carriers had 'borderline' to 'high' levels of anxiety (35%) than partners of non-mutation carriers (13%) ($p< 0.03$; Logistic regression for dichotomized data, pre-test percentages have been corrected for), differences in proportions of highly depressed partners of mutation carriers (18%) and non-mutation carriers (3%) failed to reach a significant level ($p<.08$).

Distress levels in partners compared to those of women at risk

Mean levels of anxiety and depression (HAD) of the partners were not significantly different from those of their wives (n=56), but their pre- and post-test levels of breast/ovarian cancer related distress were significantly lower ($p<.05$; ANOVA for repeated measurements; Table 5, first column). Differences regarding the *course* of distress from pre- to post-test, for partners of (non-) mutation carriers and (non-) mutation carriers themselves were not found to be No significant (Table 5, last column).

Table 4: Mean distress scores for partners of mutation carriers and non-carriers

		MEAN (SD) DISTRESS SCORES		ANOVA					
				Time		Test-Outcome		Time x Test outcome	
Assessment moment		Partners Mutation carriers (n=16)	Partners Non-mutation carriers (n=38)	F	p	F	p	F	p
HAD									
Anxiety	*Pre*	4.4 *(3.8)*	4.3 *(3.5)*	.03	**.86**	1.49	**.23**	6.18	**.02**
	Post	5.7 *(4.8)*	3.3 *(3.9)*						
Depression	*Pre*	3.3 *(3.5)*	2.7 *(3.0)*	.14	**.71**	3.13	**.08**	4.54	**.04**
	Post	4.4 *(4.1)*	2.1 *(2.5)*						
IES, Cancer related Distress	*Pre*	3.0 *(3.0)*	5.6 *(6.6)*	.40	**.53**	.05	**.82**	8.00	**.01**
	Post	5.8 *(7.4)*	3.9 *(5.2)*						

Figure 2: Course of anxiety for partners of mutation carriers and non-mutation carriers

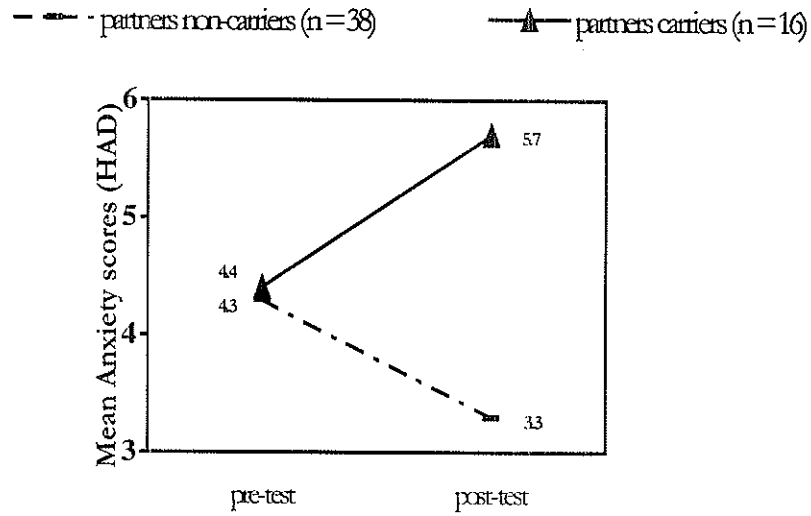


Table 5: Results from an ANOVA for repeated measurements including 3 independent variables (Woman/Partner; Pre-/Post-test; Test-outcome) for 55 women at risk and their partners

		Woman/Partner		Pre-/Post-test X Test-outcome		Pre-/Post-test X Woman/Partner X Test-outcome	
		F	p	F	p	F	p
HAD	Anxiety	2.35	.13	6.45	.01	.01	.94
	Depression	3.19	.08	5.50	.02	.06	.80
IES	Cancer Related Distress	17.32	.00	6.88	.01	.13	.72

Predictors for distress in women

For prediction of levels of post-test distress in women, the following variables were included in Random Regression Modeling, which controlled for a possible violation of randomness due to belonging to a same family: 1) pre-test distress, 2) the test result, 3) biographical data (marital status age, children, ages of children), 4) participation in genetic research in previous years, 5) experiences with breast/ovarian cancer in relatives, 6) having a sister who had been identified as a mutation carrier recently, 7) pre-test intentions concerning prophylactic mastectomy.

Factors significantly related to the levels of post-test distress, were 1) the level of pre-test distress and 2) being a mutation carrier or not. The level of post-test levels of anxiety, depression, and cancer related distress, was strongly related to the level of pre-test distress on the same scales (p varies from .0001 to .05). Being a mutation carrier was related to higher post-test anxiety (p=.004) and cancer related distress (p=.009).

An interaction effect was found for test-outcome and having a sister who had received an unfavorable test-outcome recently. Non-mutation carriers having a sister who recently obtained an unfavorable test-outcome (n=10), had higher post-test levels of depression (p=.01), than the other non-mutation carriers and the mutation carriers.

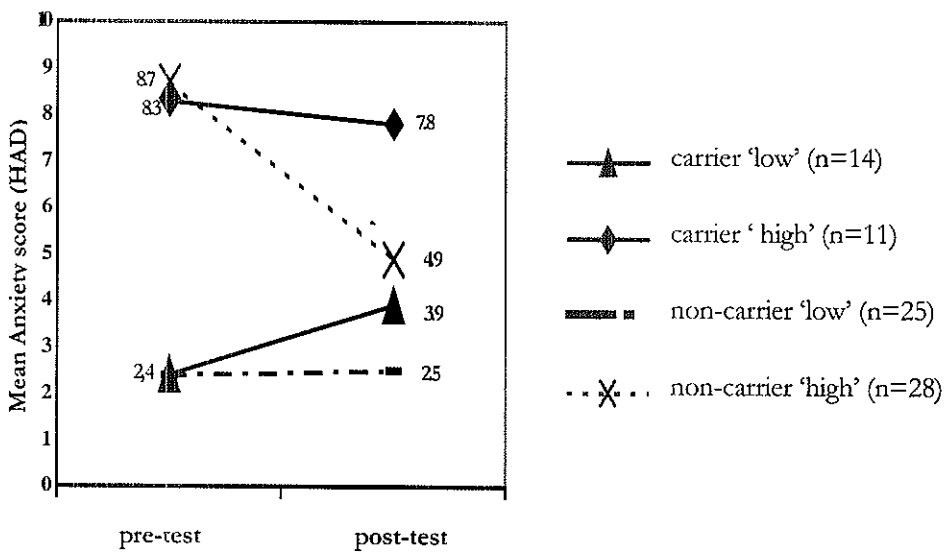
The course of distress in women with high and low pre-test anxiety

Because pre-test distress and carrier status were found to be the most important predictive factors for post-test distress, we explored the course of distress for both mutation carriers and non-mutation carriers with high and low pre-test distress. This was done for the levels of anxiety assessed with the Hospital Anxiety and Depression Scale. Figure 3 shows the course of distress for both mutation carriers and non-mutation carriers with high and low pre-test distress. In order to dichotomize anxiety levels, we opted to take the median value as a cut off score. Pre-test scores lower than 5 were considered as 'low', scores equal to or higher than 5 as 'high'. It can be seen that of the subjects with 'high' pre-test anxiety levels, those who were identified as mutation carriers still had a high mean level of anxiety at post-test, whereas those having received a favourable test-outcome revealed a clear decrease in anxiety. Besides, of the women with low pre-test anxiety an unchanged mean level of anxiety was found in those identified as non-mutation carriers, while women found to be mutation carriers showed a slight increase in anxiety.

Figure 3 represents four different patterns of mean anxiety levels at pre- and post-test, but if we take a closer look at individual changes in anxiety levels in mutation carriers and non-mutation carriers with 'high' and 'low' distress at pre-

test (dichotomized as above), eight possible patterns can be discerned. Two patterns occurred only incidentally, which were a decrease in distress in carriers with 'high' pre-test distress, and an increase in distress in non-mutation carriers with low pre-test distress. The six most frequently occurring distress patterns were illustrated by vignettes, verbatim transcripts from the interviews. They were derived from answers to the post-test question: *"What does it mean to you that you are found to be a (non) mutation carrier"?*

Figure 3: Course of anxiety for mutation carriers and non-mutation carriers, with pre-test high or low anxiety



Of the mutation carriers with 'high' pre-test anxiety, most were also highly anxious at post test (9/11). One of these mutation carriers stated: **(1)** *'It feels so threatening now that I carry this gene with me, it is as if I carry a bomb in my body that can explode at any time. I suppose that if you are found to have cancer or another serious disease, that it would feel even more burdensome, because then you know that this 'bomb' has already exploded. It may seem strange, but I have the idea that my feelings since I know about my high risk of developing cancer, do not differ that much from those of women being diagnosed as cancer patients. I never expected that it would give me so much mental pressure"*

One-third (5/14) of the mutation carriers with a low anxiety score at pre-test, show high anxiety levels at post-test. For example this woman: **(2)** *'I am disappointed about the extent to which I am affected by the test-outcome and by the idea that I am*

undergoing mastectomy in the nearby future. My feelings before and after the test result appear to differ a lot. Before I thought 'if I have to undergo surgery, than so be it'. Rationally, I am still thinking this way, but emotionally, it feels highly unnatural that my body will be mutilated, whereas I am not sure to develop cancer".

Two-third (9/14) of the mutation carriers with low pre-test anxiety, also had a low score several weeks post-test. One woman with this score pattern said: **(3)** *"It felt like a shock to me when I was informed about the unfavorable test result, which I had not expected at all, so the first days after the result I was thinking and talking a lot about it, but then I recovered quite fast, I started to make all kind of plans and I began thinking about it in a positive way, like "if I never knew about my test result things could have been much worse for me, now I can do a lot to prevent dying from cancer", so now I start making the best out of it."*

Most non-mutation carriers with low pre-test scores of anxiety, had also such low scores at post-test (19/25). One of these women said about her test result: **(4)** *"It feels unreal, it is not at all what I expected. I had anticipated that I would carry the gene with me, and I had also accepted this. I do not think that it would have been a shock for me if I had inherited the gene, but now that I have a favourable test outcome, I am slightly confused. But this does not keep me from my sleep, don't get me wrong, above all I consider it as very positive, my test-outcome".*

Of non-mutation carriers with 'high' pre-test anxiety, half had 'high' anxiety at post-test (15/28) and half had low anxiety (13/28). One non-mutation carrier with high anxiety both before and after disclosure of the test-result said: **(5)** *"I continue to feel this pain in my breasts, and this frightens me from time to time, because my mother had exactly the same complaints before she was diagnosed with breast cancer".*

One of the women showing an apparent decrease of anxiety from pre- to post-test stated **(6)** *"The pressure is finally gone. You feel free again, your life is not dominated anymore by anxiety, the test, or breast and ovarian cancer, as it was before. And, what is very important to me, I feel so much more at ease with my wish to become pregnant. We wanted to have children anyway, also if I was found to be a mutation carrier, but that would have been such a burdensome decision".*

DISCUSSION

Pre- and post-test distress and intentions for risk management

General and cancer related distress were assessed in 78 healthy women at risk to be a BRCA1/BRCA2 mutation carrier, and 56 partners, several weeks before and after disclosure of the DNA test result. Women identified as mutation carriers (n=25), generally showed no shift in attitude towards their plans for risk management (frequent surveillance or prophylactic surgery) as expressed prior to disclosure of the test-outcome.

Factors significantly related to the levels of distress 1-3 weeks after

disclosure of the test result, were the level of pre-test distress and BRCA1/BRCA2 carrier status. Women with high levels of pre-test distress were more likely to feel distressed in the post-test period, than those with low pre-test distress; mutation carriers were more distressed than non-mutation carriers. These results are similar to those found in previous studies from the United States (Croyle et al 1997; Lerman et al 1998). The profound emotional consequences for women identified as mutation carriers, may explain the important effect of the test-result on distress. Factors as the time since one is aware of the hereditary nature of disease, previous involvement in genetic research, the profoundness of one's experience with cancer in relatives, or whether one has (young) children, were not found to affect post-test distress levels in mutation carriers. The strong relation between pre- and post test distress levels however, may indicate that underlying individual differences are involved which are independent of the test outcome.

Another result similar to studies on genetic testing for BRCA1/BRCA2 from the United States, was that the difference in mean post-test anxiety levels between mutation and non-mutation carriers was due to a decrease in distress in non-mutation carriers from pre- to post-test. Those who were found to be mutation carriers had no higher distress levels than prior to their result. This study showed that this was not only, such as hypothesized in previous studies, due to these mutation carriers having become adjusted to their increased risk for cancer years before. In our study many mutation carriers had been informed about a genetic predisposition for cancer in the family only recently.

The decrease in distress in non-mutation carriers was not reported in a previous study in our group including subjects from families with Huntington disease, familial adenomatous polyposis coli (a type of hereditary colon cancer) and HBOC (Dudok de Wit et al 1998c). For the latter subjects this result should not obtain too much weight because of the small number of non-mutation carriers involved (n=6). Other studies on genetic testing for Huntington disease did not find the test-outcome to significantly affect the level of distress at short time follow up neither (Decruyenaere et al 1996, Tibben 1993c). An absence of relief in many non-mutation carriers in families with Huntington disease, due to worries for affected or at risk relatives was also reported (Tibben et al 1993b). In the present study high distress in non-mutation carriers, was found to be related to high pre-test levels of distress, but also to the test-outcome in close relatives. It was found that non-mutation carriers with a sister who had been recently diagnosed as a mutation carrier, were more depressed than the other non-mutation carriers. An absence of relief was clearly showed by this woman, having high levels of depression both prior to and following her test-outcome. (7) *'I cannot feel glad, because two of my sisters had*

unfavorable test-results. It feels as if I am not allowed to be glad, even though they insisted that I should. I imagine that I would have felt quite happy, if there was not so much going on in the family". However, high depression after disclosure of the test result was found in only 15% of all non-mutation carriers. Absence of relief due to the discrepancy between one's own favourable test outcome and unfavorable scenarios for relatives, may be more prominent in families with Huntington disease than in HBOC families. Firstly, Huntington disease is fully penetrant, and not having inherited the mutation, means that one will never have the disease, while knowing many at risk or affected relatives. HBOC is incompletely penetrant (the majority of male and also a proportion of female mutation carriers will not develop cancer) meaning that non-mutation carriers, who still have the remaining population risk for breast and ovarian cancer, may be less confronted with the disease in relatives. Secondly, Huntington Disease is characterized by a long and incurable process of mental deterioration, while BRCA1/BRCA2 mutation carriers may opt for regular surveillance or prophylactic surgery to decrease their risks to die from cancer. These differences between both diseases in penetrance, expression and treatment options may leave more opportunity for non-mutation carriers in HBOC to escape from complex feelings of survivor guilt, than for non-mutation carriers in Huntington families.

It is interesting that we found similar patterns of pre- to post-test changes in distress as in the studies from the United States (Croyle et al 1997; Lerman et al 1998), even though the timing of the pre-test assessment was not the same. In these other studies, the pre-test assessment was scheduled shortly after having informed subjects about the identification of a BRCA1/BRCA2 gene mutation in the family and the possibility of testing. Bloodsampling in these studied had either taken place years before (Lerman et al 1998), or could be scheduled after the pre-test assessment (Croyle et al 1997). In our procedure, we chose to schedule the first assessment in the 6 to 8 week period in between bloodsampling and disclosure of the test result, so that to the period of time in between this first assessment and disclosure of the result could be standardized. Consequently, our first assessment is not a real 'pre-test' assessment. More generally, in studies assessing the emotional impact of genetic testing it is hard to find a neutral moment for the pre-test assessment. Pre-test distress levels in the studies from the United States, might have been affected by being recently informed about the identification of a BRCA1/BRCA2 gene mutation in the family. However, as we take the similar results from all these studies into account, we may conclude that the different timing of the pre-test assessments does not seem to have much impact on the found levels of distress. Nevertheless, this impression can only be affirmed by a study in which distress

levels shortly after being informed about the availability of the genetic testing are compared to those shortly after bloodsampling.

Partners

Partners of mutation carriers reported apparent higher distress levels at post-test than partners of non-mutation carriers and one third of them had borderline to high anxiety levels at post-test. Levels of cancer related distress in partners of mutation carriers were low. The whole group of partners did report significantly less breast and ovarian cancer related distress than their wives (both at pre- and post-test), whereas their levels of general anxiety and depression were similar. This may be explained by the fact that partners do not have increased risks to develop cancer themselves, but they may also have difficulty empathizing with these female diseases.

Requests for psychological support

Only 2 of the 25 mutation carriers (their pre- and post-test HAD anxiety scores being 5 and 10 for one and 15 and 16 for the other) and none of the non-mutation carriers requested psychological counseling in the month following disclosure of the test result. This modest self perceived need for support, may imply that most test-applicants were able to cope with their test result. The options of regular surveillance or prophylactic surgery, which decrease the risk to die from cancer, may give mutation carriers the feeling that they are fighting against the disease and, by doing so, to keep death at a distance. The previous study of our group on a small sample of subjects at risk for BRCA1/BRCA2 came to similar conclusions (Dudok de Wit 1998c).

However, part of the potential need for support might have been fulfilled by participating in the psychological follow-up study. Three mutation carriers and one non-mutation carrier explicitly stated, that the post-test interviews sufficiently fulfilled their wish to reflect upon the impact of the test. The need for long-term psychological support needs further study, especially during and after the process of prophylactic surgery.

Implications for clinical practice

Being a mutation carrier and having high pre-test distress levels, are both strong predictors for high distress in the weeks after disclosure of the result. This finding implies a first step towards the possibility of early identification of women who, more than others, may benefit from psychological support. It may be useful to schedule a follow-up contact with either a psychologist/social worker or the genetic counselor for women who are identified as mutation carriers and who had been evaluated as being more anxious than average at pre-test. For most others,

such psychological follow-up might be of lesser importance. Furthermore, women found not to have inherited the mutation, while one or more close relatives have, may be prepared for the possibility of experiencing feelings of guilt towards these relatives. This may prevent confusion if a woman feels sad despite her favourable test result.

Acknowledgements

This study is supported by a Dutch Cancer Society grant. The authors are very thankful to the medical and scientific colleages participating in the Rotterdam/Leiden Workgroup for Hereditary Cancers, whose important work had been indispensable for the study: DJJ Halley (department of Clinical Genetics, Erasmus University Rotterdam); C Seynaeve, MMA Tilanus, CCM Bartels, LC Verhoog, CTM Brekelmans, AN van Geel, L Dukel (Daniel den Hoed Cancer Clinic/Erasmus University Medical Rotterdam); P Devilee, CJ Cornelisse, AC Dudok de wit (Leiden University Medical Center).

Chapter 5

ONE YEAR FOLLOW-UP OF WOMEN OPTING FOR PRESYMPTOMATIC TESTING FOR BRCA1 AND BRCA2: EMOTIONAL IMPACT OF THE TEST OUTCOME AND DECISIONS ON RISK MANAGEMENT (SURVEILLANCE OR PROPHYLACTIC SURGERY)

Lodder LN[1], Frets PG[1], Trijsburg RW[1], Meijers-Heijboer EJ[2], Klijn JGM[3], Seynaeve C[3], van Geel AN[3], Tilanus MMA[3], Bartels CCM[3], Verhoog LC[3], Brekelmans CTM[3], Burger CW[3], Niermeijer MF[2]

[1]Dept. of Medical Psychology and Psychotherapy, Erasmus University Rotterdam/Netherlands Institute for Health Sciences; [2]Dept. of Clinical Genetics, University Hospital Dijkzigt/Erasmus University Rotterdam; [3]Daniel den Hoed Cancer Clinic/Erasmus University Medical Center Rotterdam

abridged version of this paper accepted by Breast Cancer Research and Treatment, reprinted with permission from the journal.

ABSTRACT

Genetic testing enables women at risk for Hereditary Breast and/or Ovarian Cancer to find out whether they have inherited the gene mutation (BRCA1/BRCA2), and if so, to opt for frequent surveillance and/or prophylactic surgery (bilateral mastectomy and/or oophorectomy). Here, a follow up is described for 63 healthy women at 50% risk of being a BRCA1/BRCA2 mutation carrier who underwent genetic testing.

The course of distress and problems regarding body image and sexuality up to one year after disclosure of the test-outcome were described separately for mutation carriers undergoing mastectomy (n=14), for mutation carriers opting for surveillance (n=12) and for non-mutation carriers (n=37). Furthermore, we analyzed whether women opting for prophylactic mastectomy differed from those opting for close surveillance with respect to biographical characteristics, experiences with cancer in relatives and personality.

Women opting for prophylactic mastectomy had significantly higher distress levels than mutation carriers who opted for surveillance, and the non-mutation carriers. This difference in levels of distress had almost disappeared at one-year follow-up. Besides, mutation carriers opting for prophylactic

mastectomy were more often in their thirties, more often had young children and had a longer awareness of the genetic nature of cancer in the family than those opting for regular surveillance. Adverse effects were observed in women who underwent prophylactic mastectomy (mostly in combination with immediate breast reconstruction) regarding the perception of how their breast region looked like and felt, the intimate relationship and physical well-being.

Women opting for prophylactic mastectomy reported more distress than the other women in the study. However, their distress levels had significantly decreased 6 months or longer after surgery, possibly due to the significant risk reduction of developing breast cancer. This might explain, why most women who underwent prophylactic mastectomy were satisfied with this decision, despite a perceived negative impact on body image, the intimate relationship and physical wellbeing.

INTRODUCTION

One of the major benefits of genetic testing for BRCA1/BRCA2 is the possibility of a more individually tailored application of risk management strategies in women from at-risk families. Options of intensive surveillance or radical prophylactic surgical interventions (bilateral mastectomy and/or oophorectomy) may be discussed with BRCA1/BRCA2 gene mutation carriers, whereas surveillance can be discontinued in non-mutation carriers. Reported proportions of BRCA1/BRCA2 gene mutation carriers expressing interest in prophylactic mastectomy or oophorectomy are highly variable (Meijers-Heijboer et al 2000). In our clinical setting 51% of the identified mutation carriers opted for prophylactic mastectomy and 68% for prophylactic oophorectomy (Meijers-Heijboer et al 2000).

Since direct mutation testing only recently became possible, little is known about the psychological consequences of healthy mutation carriers undergoing prophylactic mastectomy. Previous observations from the United States concerned women with an increased risk for breast cancer based on their family history and/or a history of previous benign biopsies, who opted for prophylactic mastectomy while not knowing their genetic status. One such prospective study showed that women opting for prophylactic mastectomy (n=14) perceived their risk of developing breast cancer as higher, had more often undergone breast biopsies and experienced more cancer worry prior to genetic counseling, than the women who did not opt for prophylactic mastectomy (n=150) (Stefanek et al 1995). At the follow-up assessment (ranging from 6 to 30 months after surgery) half the women reported having experienced much discomfort post-surgery, but

the majority was not unsatisfied with the time it took to recover emotionally and physically. Since the women obtaining prophylactic mastectomy comprised only 9% of the total study sample, these women were probably a highly selected and motivated group, which may partly explain the overall satisfaction with the consequences of surgery. However, four of the eleven women who underwent breast reconstructive surgery, were dissatisfied with the reconstruction. The three women opting against breast reconstruction did not regret their decision (Stefanek et al 1995).

A large retrospective study from the United States described satisfaction with surgery in 370 women who had undergone bilateral prophylactic mastectomy 0.2 to 51.5 years previously (mean: 14.8 years). Breast reconstruction (technique unspecified) was performed in three-quarters of these women. Sixteen percent of the women in the study reported to find the cosmetic result unacceptable, and 5% regretted their decision for surgery (Borgen et al 1998). Since women in this latter study were enrolled through advertisements in lay journals, the satisfaction rate may not be representative for all women having undergone bilateral prophylactic mastectomy. Nineteen of the 21 women regretting surgery were subsequently interviewed about their experiences with surgery by a psychiatrist and a psychologist (Payne et al 2000). A global classification of the reasons for regrets revealed the following major complaints: 1) severe emotional trauma and/or lack of psychological support post-surgery, 2) complications of surgery and reconstruction, 3) dissatisfaction with the cosmetic effect, 4) residual or phantom pain, 5) fears that implants would impede the adequacy of detecting cancer in residual breast tissue, and 6) diminished self-image or sexual satisfaction.

In reports on psychological adaptation after surgery in breast cancer patients, (unilateral) mastectomy is not generally experienced as emotionally more harmful than breast conserving therapy. However, in an extensive meta-analysis, unilateral mastectomy was associated with significantly more body image related problems than breast conserving therapy (Moyer et al 1997). Smaller overall differences in favor of women undergoing breast conserving surgery were found with respect to psychological and sexual/marital adjustment. This meta-analysis is in line with impressions from clinical practice, showing that mastectomy may profoundly alter the way a woman perceives her body.

The present study is a one-year follow-up study of the psychological implications after presymptomatic testing for BRCA1/BRCA2 mutations. Decisions of mutation carriers with respect to prophylactic surgery and regular surveillance were explored. We analyzed whether women opting for prophylactic mastectomy differed from those opting for frequent surveillance with respect to biographical characteristics, experiences with cancer in relatives, personality and levels of distress. It was also examined whether non-mutation carriers could adapt

to the discontinuation of close surveillance. The course of general distress, body image and sexuality up to one year after disclosure of the test-outcome were described separately for mutation carriers undergoing mastectomy, for those opting for surveillance, and for non-mutation carriers. It was hypothesized that prophylactic surgery would lead to a reduction of anxiety, but would simultaneously induce problems regarding body image and the intimate relationship. Finally, we explored the perceptions of the partners with respect to the body change in their wives and its impact on the intimate relationship at 6 to 8 months after surgery.

METHODS

Study Population

Between December 1995 and April 1998, 118 healthy women with either a 25% or 50% risk of carrying a BRCA1/BRCA2 mutation applying for genetic testing at the University Hospital Rotterdam (Dept. of Clinical Genetics), were asked to participate in a psychological follow-up study, as well as their partners. The initial participation rate was 79%, but 14 women (12%) subsequently dropped out, either before or directly after disclosure of the test result (n= 11) or during follow-up (one mutation carrier and two non-mutation carriers), yielding a group of 79 women (26 mutation carriers and 53 non-mutation carriers). To homogenize the study sample of non-mutation carriers, we decided to exclude women having a prior risk of 25% of carrying the mutation (n=16) from the 6 and 12 months follow-up assessments. Mutation carriers in the study all had a prior risk of 50%. The women with a prior risk of 25% of carrying the mutation differed from those at 50% risk, not only because of this lower prior risk, but also because none of them had (had) a first degree relative affected with breast and/or ovarian cancer. Personal experiences with cancer in the family may influence how the testing period is perceived (Dudok de Wit et al 1997a). However, mean levels of general and cancer-related distress levels prior to and after disclosure of the result were not significantly different for non-mutation carriers with a prior risk of 25% (n=16) or 50% (n=37) ($p>0.4$, t-test for independent samples, two-tailed). The numbers of participants included in the analyses for the present paper are described in Table 1.

No significant differences regarding biographical characteristics were found between the study sample (n=63) and non-respondents/drop-outs (n=39, women with a prior risk of 25% not included) (t-tests for independent samples, two-tailed). Data from assessments up to one year after the test outcome were

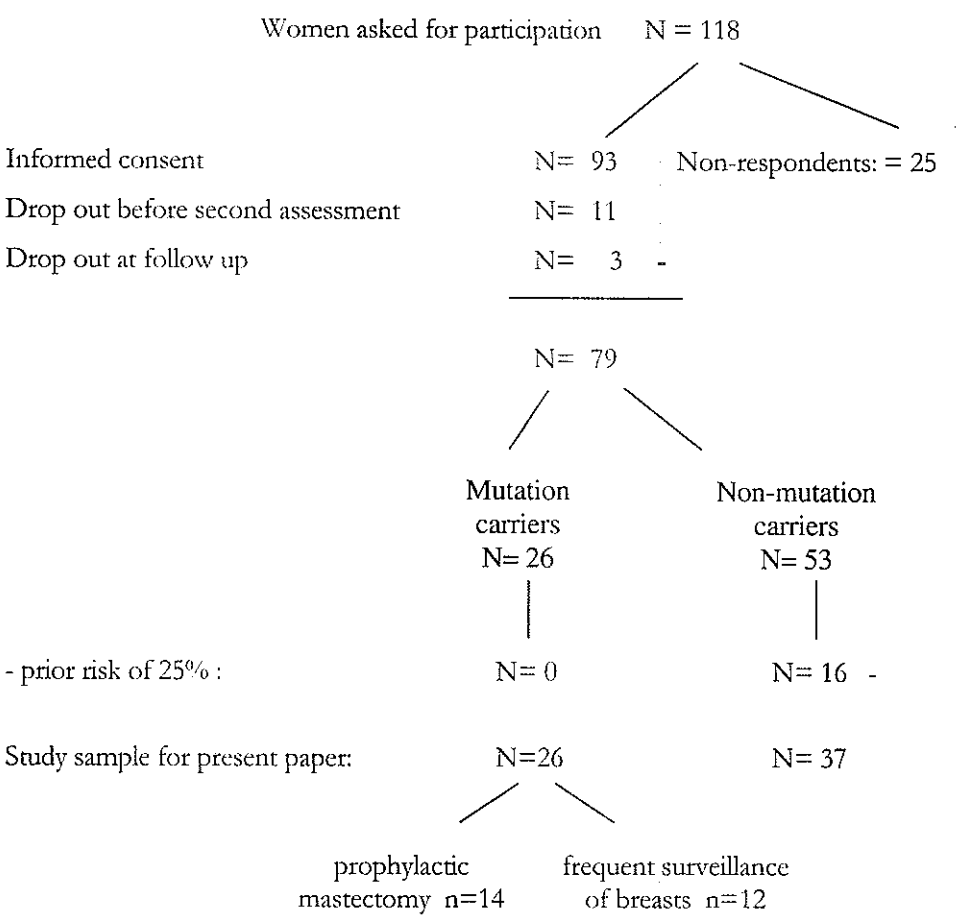
analyzed for 26 mutation carriers and 37 non-mutation carriers. These women originated from 29 different HBOC families.

The study and its procedure have been approved by the medical ethical review board of the Erasmus University Medical Center Rotterdam.

Procedures

Procedures of genetic counselling and the psychological study are described in chapter 1 (page11, 26).

Table 1: The study sample



Assessments

DESCRIPTIVE VARIABLES

Biographical and pedigree information

In a questionnaire, information was obtained about age, marital status, offspring (number, gender and age) and educational level. The pedigree was obtained and the prior genetic risk of being a mutation carrier (25% or 50%) was registered.

Experiences with cancer in relatives

In the pre-disclosure interview we explored at what age women became confronted with breast or ovarian cancer in a relative for the first time and when they became aware of the hereditary nature of this disease in the family. Women were also asked how many affected relatives they (have) had, what the outcome was of the disease in these relatives and at what age they had been diagnosed with cancer.

Optimism

A Dutch adaptation (Bleiker et al 1996) of the Life Orientation Test (Scheier & Carver 1985) is used as a measure of dispositional optimism, assessing a generally positive attitude towards life (8 items, e.g. 'In uncertain times I usually expect the best'). The frequency of occurrence of such thoughts or feelings could be indicated by use of a four-point scale, ranging from 'almost never' to 'nearly always'.

DEPENDENT VARIABLES

General distress

To assess the level of general distress, we used the Hospital Anxiety and Depression Scale (HAD) (Zigmond & Snaith 1983, Channer et al. 1985). This questionnaire consists of two scales of seven items, assessing the level of feelings of anxiety and depression. The items comprised four answer options and the score range was 0 to 21 for each scale. A score of > 10 is an indication of clinical anxiety or depression, scores from 8 to 10 on either subscale are indicative for 'borderline' anxiety or depression. The validity and reliability of this questionnaire have been described elsewhere (Spinhoven et al 1997).

To get a better impression of the anxiety and depression levels compared to a general population, we also included the Symptom Checklist, which has extensive normtables for a normal Dutch female and male population (Arrindell & Ettema 1981, Derogatis et al 1976). This questionnaire was filled out at the pre-disclosure assessment and at 6-month and 12-month follow-up.

Cancer-related distress

The Impact of Event Scale (IES), assessing the impact of a particular distressing experience, was used (Horowitz et al 1979). The 'Intrusion' (7 items) and

'Avoidance' scales (8 items) measured the extent to which subjects became overwhelmed by thoughts and feelings about breast/ovarian cancer and the tendency to avoid these thoughts and feelings. The score range for the whole scale was 0 to 75. To enable comparison with results from previous studies on genetic testing performed in our centre, similar response categories were used (never, sometimes, often or continuously) (Dudok de Wit et al 1997a). These response categories differed from those of the original IES.

Body image and sexuality

At the onset of the study, no questionnaires on body image and sexuality tailored to the current study population were available. The lack of such questionnaires for studies in the oncological field was also reported by Hopwood (1993) and by Cull (1992). We therefore developed a questionnaire (appendix E), following the recommendations of these authors, assessing: 1) general body image, 2) breast-related body image and 3) the quality of the intimate relationship.

In the body image scale we incorporated five of the seven dimensions described to be important in the assessment of body image in cancer patients (Hopwood 1993): 1) satisfaction with appearance when dressed (1 item), 2) feeling feminine (1 item), 3) satisfaction with appearance when naked (2 items), 4) feeling sexually attractive (1 item), and 5) feeling conscious about appearance (1 item). Two dimensions concerning effects on body image by the cancer treatment were excluded because they are not applicable to women not having undergone prophylactic mastectomy. Mutation carriers opting for surveillance and non-mutation carriers functioned as a reference group and therefore completed the same scales. We added three questions for a 'breast related body image scale', assessing whether women were satisfied with the way their breasts felt when touching them (2 items) and with their appearance (1 item). Finally, we included two questions on the estimated importance of physical appearance.

General sexual functioning was assessed by five of the six dimensions proposed to be incorporated by Cull (1992): 1) spontaneous sexual interest, 2) frequency of sexual intercourse, 3) adequacy of arousal, 4) influence of pain on sexual functioning, and 5) general satisfaction with sexual life. These dimensions were represented by 7 items in the questionnaire. No question was included on the experience of orgasm, firstly because the intimate character of this topic might deter participants and secondly because one may enjoy sexual contact without experiencing an orgasm. Three items were added concerning the frequency and quality of non-sexual intimacy (e.g. 'I cuddled or kissed my partner less often than usual') and five items concerning the perception of the partner's feelings (e.g. 'I had the feeling that my partner found it difficult making love to me'). These 15 items together form the scale assessing the quality of the intimate relationship. Two items were added to obtain an impression about how important one judged

cuddling or having sex with the partner, and one open-ended question giving subjects the opportunity to comment on possible changes in the intimate relationship.

In sum, this questionnaire consisted of 28 items followed by a five-point scale ranging from 'definitely disagree' to 'definitely agree', and one open-ended question. This Body Image/Sexuality scale was completed prior to disclosure and one year after disclosure of the test result. In the questionnaire, we opted for a time frame of three months, because of a possibly low frequency of sexual intercourse in some relationships. At pre-test, this long time frame may have helped to reduce the influence of the testing moment, at which women might have been more conscious of their body and sexuality.

Inspection of internal consistence of the three scales yielded low item total correlations for the general body image and the breast-related body image scale, which could be explained by a very small number of women agreeing with one item of each scale ('I felt very conscious about my appearance' and 'I had difficulty touching my breasts'). After exclusion of these items, Cronbach's alpha for the pre-test and the one-year follow-up assessment was 0.60 and 0.78, respectively, for the General Body Image scale and 0.75 and 0.91, respectively, for the Breast-Related Body image scale. Cronbach's alpha for the pre-test and the one-year follow-up assessments of the intimate relationship was 0.86 and 0.90, respectively.

For partners we developed a similar scale, using different phrasing when appropriate. The Body Image scale assessed how partners felt about the physical appearance of their wives; the scale on the quality of the intimate relationship had questions similar to those for the women on general aspects (e.g. 'I was in the mood for having sex with my partner'), but three questions were formulated differently (e.g. 'I had difficulty touching my partner' instead of 'I had the feeling my partner had difficulty touching me'). The internal consistence of the three scales was found to be low to moderate. We therefore decided not to include the mean scale scores in statistical analyses, but to describe the answers of the partners on several items of interest.

Specific physical and psychological implications of prophylactic mastectomy and oophorectomy

In the interviews with women who underwent prophylactic mastectomy we explored possible physical and psychological implications from surgery and we asked them to indicate the severity of these implications on a nine-point scale. We formulated 9 questions concerning consequences on: 1) physical well-being, 2) satisfaction with how the breast region looks like and feels, 3) self-esteem and 4) psychological consequences of oophorectomy (if performed) 5) overall satisfaction with the decision for prophylactic surgery. One month after surgery, this short questionnaire was also completed at home.

We explored whether mutation carriers had an accurate expectation prior to the result about the problems they would face after the test result. For this, subjects reported in the pre-test questionnaire (appendix A) whether they expected their problems to increase if they were found to be mutation carrier. Response categories were: 'agree', 'do not know' or 'disagree'. These answers were compared to their answers to the question in the 6-month follow-up questionnaire (appendix B), about whether they had experienced an increase, a decrease or an unchanged level of problems since the result.

Statistical methods

To test differences in means and proportions of the subgroups (mutation carriers opting for mastectomy/mutation carriers opting for frequent surveillance/non-mutation carriers), analyses of variance (ANOVA) and χ^2 tests for dichotomized data were used (Statistical Package for Social Sciences, release 8.0). A p-value of ≤ 0.05 was regarded as statistically significant. To test differences between the three subgroups on the course of distress we carried out analyses of variance (ANOVA) for repeated measurements. The four timepoints were decomposed into the orthonormalized polynomial contrasts.

We controlled for a possible violation of randomness due to belonging to a same family by means of a random regression model for continuous data performed by the program Proc Mixed of the statistical package Statistical Analysis Systems (SAS/PC, release 6.12), which can estimate family-specific effects on the outcome variables (Gibbons et al 1993). It was found that levels of distress were not associated with the family one belonged to; therefore, in further analyses, study participants were treated as 'independent' from one another.

RESULTS

Descriptives

Study sample

Data were analyzed for 63 women; 26 were identified as BRCA1/BRCA2 mutation carriers and 37 as non-mutation carriers. General characteristics of the study sample are given in Table 2. Fourteen mutation carriers underwent prophylactic mastectomy within one year (within ± 4 to 6 months) after disclosure of the test result, eight of whom also underwent prophylactic oophorectomy. Twelve mutation carriers opted for breast surveillance, while five of them underwent prophylactic oophorectomy. The mean age was similar for mutation carriers opting for prophylactic mastectomy, mutation carriers opting for surveillance and non-mutation carriers, but the standard deviation was significantly

higher in mutation carriers opting for breast surveillance than in those opting for mastectomy (Levene's test for equality of variances, $p< 0.01$). Relatively few women opting for breast surveillance were in their thirties or had young children.

Table 2: General characteristics of the study sample: BRCA1/BRCA2 Mutation carriers and Non-mutation carriers

	Mutation carriers (n=26)		Non-mutation carriers (n=37)
	prophylactic mastectomy (<1 year after test) (n=14)	intensive surveillance of breasts (n=12)	
Biographical data			
Mean age in years (SD)	35.4 (7.9)	42.3 (16.0)	37.4 (9.5)
Aged 30 to 40 years	64%	8%	46%
Education > High school	14%	8%	5%
Married/living together	86%	67%	89%
With children	79%	58%	68%
With children aged < 15 years	57%	8%	49%
Experience with cancer in relatives			
Mean age when confronted with breast/ovarian cancer in relative for the first time (years)	20.6	29.3	26.6
Years since becoming aware of the hereditary nature of cancer in the family	5.9	1.9	4.2
Mean number of relatives with Breast/Ovarian cancer	3.9	2.8	3.6
Familiarity with relative with metastatic Breast/Ovarian cancer	79%	75%	84%
Age of onset of disease in family < 40 years	79%	42%	65%
Oophorectomy			
Number	8/14	5/12	0/37
Mean age (years)	39.1	50.8	
Range	(32-54)	(43-68)	

Furthermore, there was a tendency that mutation carriers opting for breast surveillance were less longer aware of the hereditary nature of cancer in the family

than mutation carriers opting for prophylactic mastectomy and non-mutation carriers ($p<0.07$; ANOVA). There were no differences between the three groups regarding the subject's general tendency to stay optimistic in difficult times ($p=.3$; ANOVA).

Decisions on risk management after the test result

Eight of the 14 mutation carriers opting for mastectomy were between 30 and 40 years of age and had young children. Of these eight women, five also underwent oophorectomy (four during the same procedure). Two of these five women already had completed their families several years earlier and the remaining three found risk reduction more important than the fulfillment of a possibly emerging child wish in the future. Three of the eight women between 30 and 40 years of age with young children refrained from oophorectomy because they wanted to have more children or found the option for prophylactic mastectomy enough distressing to cope with. One of these women, being only recently informed about her increased risk for ovarian cancer, said that she did not worry much about this risk, because none of her relatives were yet affected by this type of cancer.

The other six women undergoing mastectomy were either aged 26 to 32 years and childless (n=3) or older than 42 years with grown-up children (n=3). None of the younger women had undergone oophorectomy, whereas all the older women had, one of them already a few years before disclosure of her test outcome. The younger women not opting for oophorectomy decided so because they were informed that the risk for ovarian cancer was not high at their age.

Direct reconstruction with silicon implants was applied in 10/14 women. Two women opted not to have a reconstruction and in two women the prosthesis would be implanted at a later stage (one of whom having a tissue expander).

Women opting for regular breast surveillance were either 30 years or younger (n=5) or older than 43 years (n=7). The younger women considered they still had time to reflect upon whether they would ultimately have their breasts removed, or reported they would never opt for such a drastic intervention. The women who were older than 43 years reported to feel sufficiently safe with the surveillance program. Five of these seven older women (and none of the five younger women) underwent prophylactic oophorectomy. Three of these women were pre-menopausal, but still considered this intervention far less invasive than a prophylactic mastectomy. The two older women opting for ovarian surveillance (> 56 years) felt reluctant about having healthy tissue removed, but did not completely rule out a future choice for prophylactic oophorectomy.

Of the 37 non-mutation carriers, eight (22%) continued some form of breast surveillance, because of an elevated risk due to either their age (> 50 years) or having relatives with breast cancer on the other side of the family. Twenty-three non-mutation carriers had no problems to discontinue surveillance, but six

women (16%) felt more secure by continuing surveillance, despite their low risk for breast cancer.

Course of distress in mutation carriers either opting for mastectomy or surveillance and in non-mutation carriers

From the 63 women who continued participation in the follow-up study, twelve did not return either the post-test questionnaire (n=3), the 6-month (n=2) or the one-year follow-up questionnaire (n=7). This resulted in 4.8% of the total number of scores missing. 'Predictive mean matching' was used to estimate the missing scores on the general and cancer-related distress scales for these women (Little & Rubin 1987). The strategy is that for the estimated value of the subject with a missing score, one looks for a 'donor' subject whose estimated value is most similar to the observed value of the subject with a missing value. Subsequently, the observed value of the 'donor' subject was imported for the missing value. The method used was regression analysis, by means of which the values for all subjects, including patients with missing values, are estimated. Terms entered into the regression model were: 1) distress scores on the previous assessment moment (scores on the first assessment were used to estimate scores on the second assessment etc.), and 2) the subgroup one belonged to (mutation carriers opting for mastectomy/mutation carriers opting frequent surveillance/non-mutation carriers).

Anxiety, depression and cancer-related distress in the period before and up to one year after the test result were found to have a significantly different course for mutation carriers opting for mastectomy, for mutation carriers opting for surveillance and for the non-mutation carriers ($p<0.05$; analysis of variance for repeated measurements). Figures 1 and 2 depict the course of anxiety and cancer-related distress for the three groups. Generally, higher levels of general and cancer-related distress were found in mutation carriers opting for mastectomy than in the other two groups. This difference was greatest shortly after disclosure of the test result and smallest at one-year follow-up. Mutation carriers opting for regular surveillance had lower anxiety levels than the other two groups, except for the post-test assessment. Their levels of cancer-related distress at post-test and follow-up, were similar to those of non-mutation carriers. Non-mutation carriers reported lower levels of general and cancer-related distress at post-test and follow-up than they had reported at pre-test.

The proportion of women with borderline to high levels of anxiety one year after the test outcome, was not significantly different for mutation carriers opting for prophylactic mastectomy (29%), mutation carriers opting for frequent surveillance (8%) or non-mutation carriers (16%) ($p=0.38$; χ^2 test). All mutation carriers with borderline to high anxiety at one-year follow-up, had also reported elevated anxiety levels on the previous two post-test assessments (mean 9.6, range

6 to 16). The same was true for four of the six non-mutation carriers with high distress at one-year follow-up (mean 10.1, range 6 to 14). Three of the women who underwent prophylactic mastectomy requested psychological support in the year following the result (all having a high distress level, two being in their thirties with young children). None of the women who opted for close surveillance requested to see the psychologist, but two of the non-mutation carriers (having high distress levels) did in the months following the result.

Mean levels of anxiety and depression prior to the result (Symptom Checklist) were higher than those of a normal female population in women who were later found to be mutation carriers who opted for mastectomy, and in non-mutation carriers. Mean distress levels prior to the result in women who were later found to be mutation carriers who opted for intensive surveillance, were similar to (anxiety) or lower than (depression) those of a normal female population. At one-year follow up, mean levels of anxiety and depression of the three groups, were all similar to or lower than those of a normal female population.

Figure 1: The course of anxiety (HAD) in mutation carriers undergoing mastectomy, mutation carriers opting for screening and non-mutation carriers.

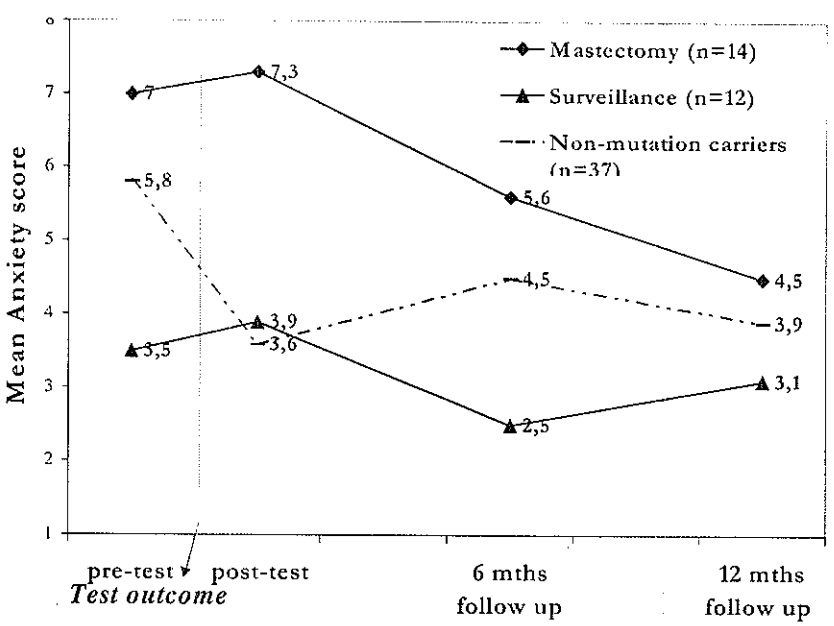
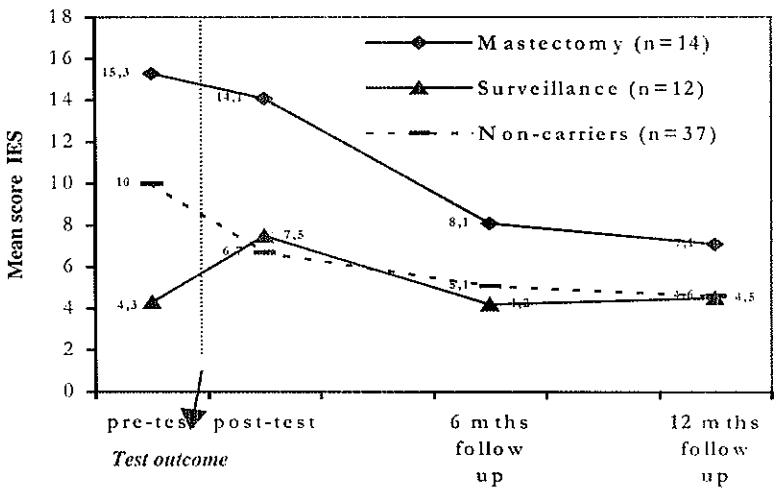


Figure 2: The course of cancer related distress (IES) in mutation carriers undergoing prophylactic mastectomy, mutation carriers opting for screening and non-mutation carriers.



Changes in Body image and Sexuality, depending on test outcome and prophylactic surgery in mutation carriers

Subjects

Because one out of five female participants indicated on an appendix of the Body image/Sexuality scale that they considered the questions involved 'too personal', we decided to stop giving this questionnaire to non-mutation carriers, after we had enough data from this subgroup to serve as a 'control group' for the mutation carriers. Of the mutation carriers opting for mastectomy, one woman decided not to fill out this scale and two did not return their follow-up questionnaires. Of the mutation carriers opting for surveillance, two (widowed) women preferred not to fill in the scale and two did not receive the pre-test questionnaire due to administrative failure. A completed pre-test and follow-up version of the body image scale was available for 11 mutation carriers opting for mastectomy, whose scores were compared with those of 8 mutation carriers opting for surveillance and 18 non-mutation carriers. The scale assessing the quality of the intimate relationship was answered by fewer subjects than the body image scale, because women without a partner did not fill out this subscale. The subscale for breast-related body image was not filled out by three women who did not have a breast reconstruction. None of the women who underwent breast reconstruction had (as

yet) undergone a nipple reconstruction at the moment of the post-surgery assessment.

The body image/sexuality questionnaire was filled in by eight partners of women who underwent prophylactic mastectomy and by 13 partners of either mutation carriers opting for surveillance or non-mutation carriers. The small number of questionnaires filled out by partners was explained by: 1) 7/40 women who filled out the follow-up body image/intimate relationship scale did not have a partner, 2) ten partners chose not to participate in the study, and 3) two partners did not answer the follow-up questionnaires.

Prior attitudes towards physical appearance and sexuality

At pre-test, BRCA1/BRCA2 mutation carriers opting for prophylactic mastectomy had a similar estimation of the importance of their physical appearance and their sexual relationship as those undergoing surveillance ($p= 0.17$ and $p= 0.6$ respectively; t-tests for independent samples, two-tailed).

Changes in body image and sexuality over time

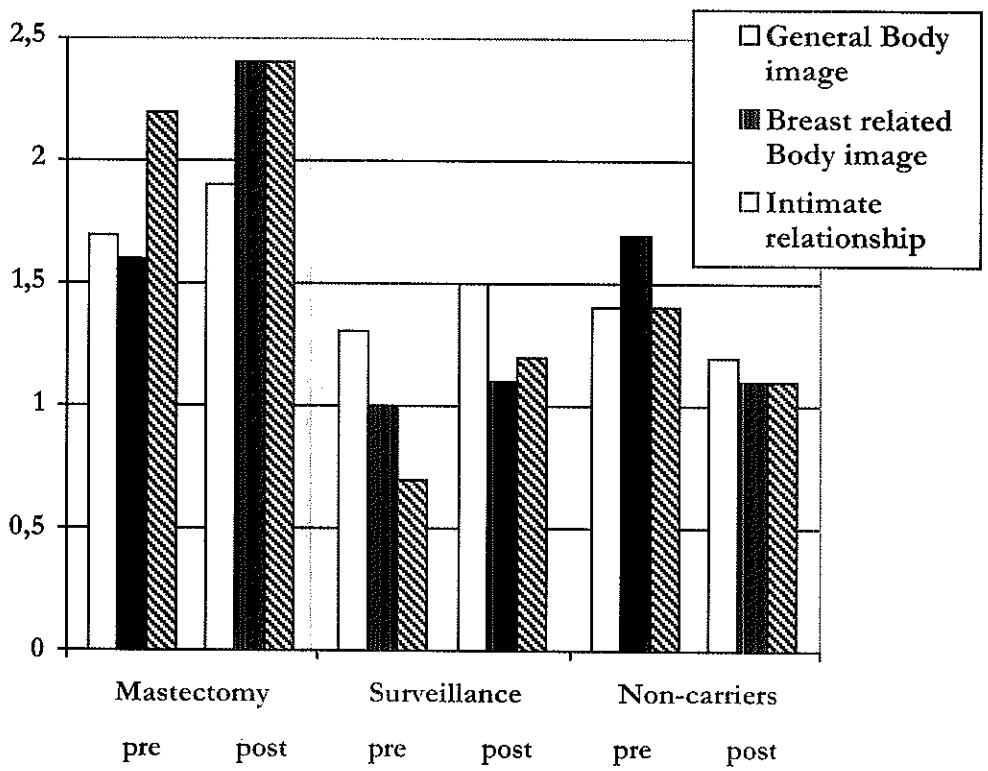
Significant differences between the three groups (mutation carriers opting for mastectomy, mutation carriers opting for frequent surveillance and non-mutation carriers) regarding changes from pre-test to one-year follow-up were found for breast related body image and the intimate relationship ($p<0.01$ and $p=0.05$, respectively; ANOVA for repeated measurements), but not for the general body image ($p=0.30$, ANOVA for repeated measurements). Figure 3 presents transformed scores, for reasons of comparability of scores on the different scales.

An apparent increase of problems regarding breast-related body image at follow-up was reported by mutation carriers who underwent prophylactic mastectomy (with reconstruction), unlike the women of the other two groups (Figure 3). An increase in problems in the intimate relationship was found for both mutation carriers undergoing mastectomy and those opting for surveillance, but the first group reported more problems than the latter both at pre-test and follow-up. Breast-related body image and the intimate relationship of non-mutation carriers improved at follow-up (Figure 3). Strikingly, at pre-test women opting for prophylactic mastectomy already reported higher levels of problems concerning general body image and the intimate relationship than the other two groups (Figure 3).

Tables 3 gives an impression of the specific problems related to body image and the sexual relationship experienced by mutation carriers undergoing prophylactic mastectomy. For this, we selected about half of the items of the one-year follow-up Body Image/Sexuality questionnaire and compared the answers from women having undergone mastectomy (6-8 months prior to the assessment) with those not opting for mastectomy together with non-mutation

carriers. For this selection we took notice of the categories described by Hopwood (1993) and Cull (1992): Each category was represented by one or two items. A similar overview is given for the partners (Table 4).

Figure 3: Changes in body image, breast related body image and the intimate relationship from pre-test to follow up, for mutation carriers opting for prophylactic mastectomy (n=11) or surveillance (n=8) and non-mutation carriers (n=18) (a higher score indicates a higher level of problems).



After prophylactic mastectomy, half of the women were not satisfied with their physical appearance when undressed, did not feel sexually attractive, and/or experienced a decreased frequency of cuddling and sexual intercourse with their partner (Table 3). More than half of the women having undergone mastectomy reported being unhappy with how their (reconstructed) breasts looked like and felt, and/or had not been in the mood to have sex. Difficulty in getting excited or feelings of shame when undressed occurred in 4/10 women who underwent prophylactic mastectomy, compared with 0/23 respectively 3/23 of the other women. (Table 3).

Table 3: Answers of mutation carriers opting for mastectomy on individual items of the body image/sexuality scale one year after genetic testing, compared to those of other mutation carriers and non-mutation carriers.

	Women opting for mastectomy (n = 12)	Non-mutation carriers / mutation carriers not opting for mastectomy (n = 28)
Items on Body Image		
Dissatisfied with body when dressed	0/12	2/28
Dissatisfied with body when undressed	6/12	5/28
Difficulty watching body when undressed	2/12	2/28
Not feeling feminine	2/12	3/28
Not feeling sexually attractive	6/12	3/28
Items on Breast-related Body Image		
Dissatisfied with appearance of breasts	6/10[1]	4/28
Breasts feel unpleasantly	7/10[1]	3/28
Items on the intimate relationship[2]		
Cuddled/kissed partner less often than usually	5/10	2/23
Had sex with partner less often than usually	4/10	2/23
Was not in the mood for having sex	7/10	2/23
Had difficulty getting excited	4/10	0/23
Afraid that having sex would be painful	3/10	1/23
Ashamed of body when undressed	4/10	3/23

[1] Women opting for mastectomy without breast reconstruction did not answer the items on breast-related body image.
2 Women without a partner did not answer the items on the intimate relationship.

Partners of women having undergone prophylactic mastectomy only rarely reported to have problems with the physical appearance of their wives, or with how her breasts looked like or felt (Table 4). However, four of the seven partners reported a decreased frequency of cuddling and/or having sex with their partners.

Specific physical and psychological implications of prophylactic mastectomy and oophorectomy

The physical and/or psychological implications reported by mutation carriers at one month and at 6 to 8 months after prophylactic mastectomy are given in Table 5. A negative influence on self-esteem and/or physical restrictions up to 6 to 8 months after mastectomy was reported by about half the women. Whereas one month post-surgery all women who had a breast reconstruction were satisfied

with that decision, three women had some doubts about this decision at a longer follow-up. The two women who opted not to have a reconstruction reported to be satisfied with this decision at the follow-up sessions. The majority did not suffer major physical or emotional adverse effects from oophorectomy, but at 6 to 8 months follow-up two women (with no actual child wish), reported having some difficulty with the idea of being infertile. Although at one-month follow-up half of the women found that prophylactic surgery had a greater impact than expected, the vast majority did not regret their decision. However, one woman continued regretting having undergone mastectomy up to 8 months after surgery.

Table 4: Answers of partners of mutation carriers opting for mastectomy on individual items of the body image/sexuality scale one year after genetic testing, compared to those of partners of other mutation carriers and non-mutation carriers.

	Partners of women opting for mastectomy (n=8)	Partners of non-mutation carriers /mutation carriers not opting for mastectomy (n=13)
Items on attitudes/feelings about wife's body		
Find partner not sexually attractive	0/8	0/13
Difficulty watching partner's body when undressed	1/8	0/13
Items on attitudes/feelings about wife's breasts		
Dissatisfied with appearance of partner's breasts	2/6[1]	0/13
Difficulty touching partner's breasts	2/6[1]	0/13
Items on the intimate relationship		
Cuddled/kissed partner less often than usually	4/8	1/12
Had sex with partner less often than usually	5/8	3/12
Did not feel like having sex	3/8	0/12
Afraid that having sex would be painful for partner	3/8	3/12

1Partners of women who did not have their breasts reconstructed did not answer the items about their wife's breasts

In the questionnaire administered six months following the result, seven of the 14 women who had opted for prophylactic mastectomy reported that they had experienced an increase of problems since disclosure of the test result; four of these seven women had not expected this to happen prior to their result. Mean distress levels at 6-month follow-up for these four women were similar to those of the three women who did not underestimate their level of problems after the result ($p>0.05$, t-test, two-tailed).

Table 5: Prophylactic mastectomy and oophorectomy in mutation carriers: Emotional and physical implications at 1 month and 6 to 8 months after surgery

	1 month follow-up (n = 13)	6-8 months follow-up (n = 12)
Prophylactic mastectomy		
Physical complaints (pain, skin feels firmly, little strength)	9/13	7/12
Breast region feels strange when sitting or walking	8/13	6/12
No reconstruction would have been fine	0/10	3/9
Negative influence on self-esteem	4/13	5/12
Prophylactic oophorectomy		
Physical complaints due to oophorectomy	0/7	1/7
Uneasy feelings about having no ovaries	1/7	2/7
Prophylactic mastectomy & oophorectomy		
Surgery and its consequences worse than expected	6/13	3/12
Regrets about having opted for prophylactic surgery	2/13	1/12

DISCUSSION

Decisions on risk management in mutation carriers and non-mutation carriers

This is the first European prospective follow-up study assessing psychological distress and decisions on risk management options (frequent surveillance and/or prophylactic surgery) in women undergoing presymptomatic BRCA1/BRCA2 mutation testing (n= 63). Within one year after disclosure of the test result 14 of the 26 mutation carriers underwent prophylactic mastectomy, eight of whom also underwent prophylactic oophorectomy. Twelve mutation carriers opted for intensive breast surveillance, and five of them underwent prophylactic oophorectomy. These proportions are similar to those reported in an earlier study by our group assessing decisions for risk management in 68 healthy female BRCA1 or BRCA2 mutation carriers (of whom 26 participated in the present study) (Meijers-Heijboer et al 2000). In the present study, six of the 37 non-mutation carriers preferred to continue undergoing breast surveillance due to a difficulty to adapt to their reduced risk status.

More than half of the mutation carriers opting for prophylactic mastectomy was aged 30 to 40 years and had young children. Of the mutation carriers opting for surveillance only one fell into this age group and one other woman had young children. In the earlier study of our group (Meijers-Heijboer et

al 2000), women opting for prophylactic mastectomy were often young mothers too. Because the age of women is obviously related to having young children, it is unknown which of these two biographical factors is most explanatory for the decision for prophylactic mastectomy. The relatively high interest for prophylactic mastectomy in mutation carriers aged 30 to 40 years may be because this group has, on the one hand, a higher risk to develop breast cancer than those younger than 30 years, and, on the other hand, a higher estimated gain in life expectancy than older mutation carriers (Meijers-Heijboer et al 2000). Interviews with young mothers opting for prophylactic mastectomy (Chapter 2) and clinical experience have shown that the fear of leaving behind young children was an important independent factor to decide for surgery. A longstanding awareness of being at risk for cancer was another factor associated with the decision for prophylactic mastectomy. One explanation for this may be that women opting for prophylactic mastectomy may have had sufficient time to prepare themselves emotionally for such a far-reaching risk management option.

Prophylactic oophorectomy was opted for by 13 of the 26 mutation carriers, of whom eight also underwent prophylactic mastectomy. The latter women generally did not report physical or emotional complaints associated with prophylactic oophorectomy, which might be because these women either were menopausal or received hormonal replacement therapy. The serious impact of prophylactic mastectomy may also have concealed possible adverse effects from oophorectomy. Main reasons given not to opt for prophylactic oophorectomy were a young age and having a child wish; the women aged over 50 years (n= 2, one pre-menopausal) explained to feel reluctant towards having healthy tissue removed and to have trust in the results from surveillance, since no malignancy had been detected at their age.

High distress in mutation carriers opting for prophylactic mastectomy

Strikingly, mutation carriers undergoing mastectomy had higher levels of general and cancer-related distress over the study period (especially at pre- and post-test), than mutation carriers undergoing regular surveillance and non-mutation carriers. A relatively high distress level in women opting for prophylactic mastectomy was also observed in other studies (Stefanek et al 95, Meiser et al 2000a). As described in chapter 4, all but one of the women who underwent prophylactic mastectomy within one year after disclosure of the test result, had already made this decision prior to disclosure of the result. The prospect of this burdensome and irreversible surgical option might have induced anxiety both prior to and following the test result (Chapter 4). A second explanation may be that the decision for mastectomy is prompted by high distress. Statements from interviewed support this second explanation. One woman in her thirties with young children said: *"the two months*

between disclosure of the test outcome and surgery were really terrible. It felt as if I already had developed breast cancer". The fact that many other women opting for prophylactic mastectomy were in their thirties and/or had young children (as discussed above), may be an important explanation for the high anxiety level in these women. Prior to disclosure of the test result, these two biographical factors were both significantly related to high distress (Chapter 2). Besides, of the three women undergoing prophylactic mastectomy and requesting psychological support in the year following the result, two were in their thirties and had young children.

Generally low distress in non-mutation carriers and mutation carriers opting for surveillance

Not surprisingly, women identified as non-mutation carriers showed a decrease in distress after receiving their test outcome, as was also reported in previous studies (Croyle et al 1997, Lerman et al 1998). Whereas the majority of non-mutation carriers reported low anxiety or depression at post-test and follow-up, ongoing sorrow about relatives with cancer or carrying the mutation are often expressed in the post-test interviews. One non-mutation carrier (with a low distress level both at post-test and follow-up) explained: *"despite my favourable test outcome, I will always be confronted with hereditary breast cancer, firstly because my sister carries the gene and secondly because of the impact of my mother dying from breast cancer when I was a little girl."* The majority of non-mutation carriers expressed no need for psychological support in the months following the result. High anxiety (HAD score > 8) at one-year follow-up was found in 6/37 non-mutation carriers. These high axiety scores had been present at at least two previous assessments in four of these non-mutation carriers, and at one previous assessment for the other two non-mutation carriers. This result leads us to hypothesize that high levels of distress may not only reflect adverse situational factors, but also high individual 'baseline' levels of distress.

The low anxiety in mutation carriers undergoing regular surveillance might reflect a basic trust in participating in the surveillance program. However, why distress in these women at the follow-up assessments was similar to or lower than that of non-mutation carriers remains puzzling.

Influence of prophylactic mastectomy on body image/sexuality

Women who underwent prophylactic mastectomy (with reconstruction) were, as expected, significantly less satisfied with the look and feel of their breasts at the end of the follow-up period, than mutation carriers who opted for surveillance and non-mutation carriers. The following quotes provide insight into how women's breast-related body image is affected after prophylactic mastectomy (with reconstruction): *"There is something in my body (i.e. silicon implant) which is not mine, something that is not meant to be there so to say, and I feel a slight aversion to touch or see that*

part of my body". Another woman said: *"I sometimes really miss my own breasts. They felt much softer and more natural than my breasts do now. I also feel that I am not ready to dispose of my bras, which are a sort of personal souvenir for me."*

With regard to both general body image and sexuality it is remarkable that not only after surgery, but already prior to disclosure of the test result, mutation carriers opting for mastectomy report less satisfaction with both their bodies and their intimate relationship than mutation carriers opting for surveillance and non-mutation carriers. Differences between the three groups at follow-up can therefore not only be attributed to the impact of prophylactic mastectomy. Post-hoc analyses on pre-test scores of non-mutation carriers, revealed that no such differences in body image and sexuality scores existed between those who would opt for and those who would opt against mastectomy if identified as mutation carriers. The intention to undergo prophylactic mastectomy is therefore unlikely to be an independent explanatory factor for the relatively negative perception of one's body and the intimate relationship prior to the test result in women opting for prophylactic mastectomy.

A limitation of our observations is that we have not applied a validation study on the body-image/sexuality questionnaire. This might exclude definite conclusions about the *level* of problems with breast-related body image and sexuality in women undergoing prophylactic mastectomy. However, an exploration of answers to specific questions revealed that at least half the women who underwent prophylactic mastectomy reported a negative influence on the look and the feel of their breasts, on feeling sexually attractive or in the mood for having sex, and on their physical well-being. Many women who underwent a direct reconstruction specified the latter with: *"my breast region feels stiff"* or *"it is an unpleasant sensation ('over-sensitive', 'numb') when my breast region is touched".* One woman said: *"I feel physically limited in a lot of things I am doing, which makes me think continuously of the surgery I have undergone".*

Because only a small number of partners participated in the study, their perceptions of the implications of prophylactic mastectomy are sparsely represented. Whereas partners of women having undergone prophylactic mastectomy did not report having more problems with their wife's appearance than partners of the other women, surgery did seem to have a negative effect on the frequency of intimate contact with their spouses up to 8 months after surgery. From the interviews the impression was obtained that the reduction in frequency of cuddling and/or making love, was rather due to the women feeling inhibited to have intimate contact, than due to the partners. One partner said: *"when I touch my wife's breasts it feels different than before, it feels more stiff, but it does not adversely effect the intimate relationship. I have become familiar with it now. The most difficult for me was the period after the test, to accept my wife's decision to undergo mastectomy. I find beautiful breasts very*

important for a woman and the breasts of my wife were gorgeous, but I was realizing more and more that we did not have much a choice." Another partner emphasized he perceived the reduced frequency of intimate contact since surgery, as a minor disadvantage in relation to the increased chance of experiencing together that their young children would grow up and leave home.

Overall satisfaction with the decision for prophylactic mastectomy

Clearly, prophylactic mastectomy may have serious adverse implications for physical well being, the perceived look and feel in the breasts, the intimate relationship and self esteem. However, the majority of the mutation carriers opting for this type of risk prevention, did not regret their decision. The major reason for the overall satisfaction with the decision may be relief due to a significant risk reduction of developing breast cancer. Analyses of distress levels revealed that mean distress levels in these women, which were high before and after genetic testing, clearly decreased at the final assessment (6 to 8 months after surgery). In the follow-up interview one woman stated that surgery had meant the end of a period "dominated by fear of developing cancer and eventually dying from it". Another woman told about intrusive memories of her deceased aunt and about how she felt happy having been given the opportunity to prevent this sad fate. One woman clearly explains how she weighs the positive and negative implications from prophylactic mastectomy: *"now that I have had prophylactic surgery, a big problem has vanished because I no longer have this high risk to develop breast cancer or die from it. A new but relatively smaller problem has taken its place, which is that I have to adapt to my new body and to learn to feel attractive and feminine again."*

One can not exclude the possibility that the few regrets after prophylactic mastectomy might, in part, be explained by the fact that regretting an autonomously made decision for an irreversible surgical intervention would lead to a state of 'cognitive dissonance' (Festinger 1957). A 'cognitive dissonance' is assumed to be smaller if one had a smaller sense of autonomy at the moment of the decision, e.g. because of external pressure affecting the decision-making process. In this perspective it is interesting to refer to the earlier cited retrospective study, in which satisfaction with prophylactic mastectomy was described in 370 women (Borgen et al 1998). The 21 women in the latter study who regretted having undergone prophylactic mastectomy significantly more often reported than women having no regrets, that the subject of prophylactic mastectomy had been initiated by their physicians (instead of by themselves). These women also stated that they had received insufficient information about surgery. Some of them even stressed that, having received more information about the consequences, they would have reconsidered their decision. A similar result was found in a retrospective study assessing satisfaction with immediate breast reconstruction

following unilateral or bilateral mastectomy: the less satisfied patients were with immediate breast reconstruction, the more often they reported having missed information about the physical implications of this surgery (Contant et al. 2000). Similarly, the woman in our study who regretted her decision for prophylactic mastectomy said she would have decided otherwise had she been more completely informed about the profound impact of surgery on her physical well-being, body image and intimate relationship. She suffered from the lack of physical contact when holding her one-year-old baby and about not being able to lift it up. It should be noted that this woman reported high levels of psychological distress and low satisfaction with her body and the sexual relationship already prior to disclosure of the result.

Implications for clinical practice

The hypothesis that satisfaction with the decision for prophylactic mastectomy is related to the perception of having been completely informed about its consequences is very important for clinical practice. Whether or not this relationship is partly explained by the theory of cognitive dissonance leaves intact the need to provide substantial information about the negative consequences of prophylactic surgery. When discussing interventions that reduce the risk of developing breast cancer with women, one should be aware of factors associated with the decision for prophylactic mastectomy, such as being 30 to 40 years old, having young children, and (probably consequently) being emotionally distressed. Ideally, it should be prevented that high anxiety would impede rationally weighing pros/cons of prophylactic mastectomy. Discussion of the adverse consequences of prophylactic mastectomy should address a possibly altered perception of the body and the sexual relationship and a negative physical impact of surgery. However, it cannot be prevented that despite adequate information, some women will suffer more than others from adverse consequences of surgery. As long as predictive factors for long term psychological maladjustment after prophylactic mastectomy are lacking, psychological support may be offered to all women with difficulties in adapting to prophylactic mastectomy.

Relatively few mutation carriers opting for close surveillance may feel a need to see the psychologist in the period of genetic testing and up to one year afterwards. This may change after a longer period of intensive breast surveillance, which may become perceived as very distressing whenever something suspect has been detected. To gain more insight into the perceived pros/cons of having decided for frequent surveillance or prophylactic surgery, our group is currently investigating satisfaction with these decisions and psychological well-being in a larger number of mutation carriers at a longer follow up.

Chapter 6

THE RELATIONSHIP BETWEEN THE CAPABILITY TO REFLECT ON EMOTIONS AND THE LEVEL OF REPORTED DISTRESS IN WOMEN UNDERGOING PRESYMPTOMATIC DNA-TESTING FOR HEREDITARY BREAST/OVARIAN CANCER

Lodder LN[1], Trijsburg RW[1], Frets PG[1], Tibben A[123], Duisterhof GMD [1], Niermeijer MF[2]

[1]Dept. of Medical Psychology and Psychotherapy, Erasmus University Rotterdam/Netherlands Institute for Health Sciences; [2]Dept. of Clinical Genetics, University Hospital Dijkzigt/Erasmus University Rotterdam; [3]Dept. of Neuropsychology, Leiden University Medical Center

submitted

ABSTRACT

The psychological impact of genetic testing for hereditary breast/ovarian cancer is generally assessed by means of self-report questionnaires. A shortcoming of such questionnaires is that low distress scores may either indicate normal health, or a state of normality maintained by (un)conscious defense strategies. This study investigated the relationship between low distress reported in a questionnaire and the inability to coherently and truthfully express current experiences and thoughts about one's genetic status (coherence score of an interview transcript).

Assesments took place before and several weeks and 6 months after genetic testing in 57 healthy women at risk of being a BRCA1/BRCA2 mutation carrier.

Mutation carriers with an incoherent score (7/22) reported significantly lower distress than those with a coherent score, but in non-mutation carriers (n=35) incoherent scores were associated with *high* anxiety.

Low distress in incoherent mutation carriers may be indicative of defensive denial. In non-mutation carriers, incoherence might reflect ambivalent feelings due to the elimination of a burden for oneself, but not for close relatives.

INTRODUCTION

Most studies on the psychological impact of genetic testing for Hereditary Breast/Ovarian Cancer show that test-applicants generally cope well prior to and several weeks after disclosure of the test result (Croyle et al 1997, Lerman et al 1996a). Similar findings were obtained in our group (Chapter 2 and 4). In these studies, psychological distress was measured with self-report questionnaires, such as the Symptom-Checklist (Arrindell & Ettema 1981, Derogatis et al 1976, Channer et al 1985), Hospital Anxiety and Depression Scale (Channer et al 1985, Spinhoven et al 1997, Zigmond & Snaith 1983), the Impact of Event Scale (Horowitz et al 1979), the State Anxiety Scale (Spielberger et al 1970, Croyle et al 1997) or the Center for Epidemiologic Studies-depression scale (Radloff 1977, Lerman et al 1996a).

However, such self-report questionnaires may lead to problems in the interpretation of low distress scores. Shedler et al. (1993) demonstrated that subjects with low distress scores on self-report questionnaires may either be mentally healthy, or may maintain an illusion of mental health, due to conscious or unconscious defense strategies. They used clinical judgement of psychological functioning and manifestations of unconscious defense strategies in order to discriminate between 'genuinely' healthy subjects and those being 'illusory' healthy. It was found that in a subgroup of subjects, the self-reported mental health seemed in fact illusory. This subgroup, judged distressed by the clinician, was found to use more defense strategies in verbal associations to threatening stimuli than the subjects who were judged healthy.

These findings were reason for our group to explore defensive denial in subjects undergoing presymptomatic DNA testing for various severe inheritable late-onset diseases (Dudok de Wit et al 1998b). The level of reported distress several weeks prior to the test outcome was found to be similar to distress in the general population (e.g. in subjects tested for the Huntington disease gene mutation) or even lower (in subjects tested for BRCA1/BRCA2 and Familial Adenomatous Polyposis Coli, a hereditary colon cancer). This is somewhat surprising considering that these subjects would learn about their genetic status in a few weeks time. To establish whether these low mean pre-test distress levels could partly be explained by a defensive way of dealing with distress, the distress levels were compared with the way in which subjects discussed the genetic disorder, the test, and its implications in an interview. For this, a manual for rating coherence of interview transcripts was used, which was based on the manual used for studies on the parent-child attachment (the Adult Attachment Interview; Main & Goldwyn 1994). Interestingly, subjects with low levels of disease-related distress

(Impact of Event scale, Horowitz et al 1979), were found to be less capable of providing truthful and clear reflections of their emotions, than those reporting moderate to high disease-related distress (Dudok de Wit et al 1998b). Dudok de Wit et al concluded that the low distress in these subjects was partly a reflection of the use of defensive denial strategies.

The potential importance of assessing defensive denial in combination with self-reported distress prompted us to extend the earlier findings in a follow-up study on psychological distress in healthy women undergoing genetic testing for BRCA1/BRCA2. The rationale was to strengthen the findings from this previous study (Dudok de Wit et al 1998b), because 1) few women at risk for HBOC had been included in that study and 2) the low distress in subjects tested for HBOC as compared to subjects tested for Huntington Disease.

We expected that a low coherence level of the interview transcript would be found more often in women reporting low than in those reporting moderate to high pre-test cancer-related distress. This analysis was repeated for the post-test and 6 months follow-up assessments, and also for reported levels of general anxiety. Finally, for the assessments after the test outcome, we analyzed associations between cancer-related/general anxiety and coherence for mutation carriers and non- mutation carriers separately.

METHODS

Study sample

Between December 1995 and April 1998 we invited 118 healthy women, who applied for genetic testing because of a 25% or a 50% risk to carry a BRCA1/BRCA2 mutation, to participate in a psychological study. Of these women, 21% declined and 9% dropped out after initial agreement. Another 14% was excluded from the follow-up assessments for reasons previously described (chapter 5), all being non-mutation carrier with a prior risk of 12.5-25% of being a mutation carrier. Biographical characteristics of the 63 study participants are described in chapter 5. Audiotaped pre-test and follow-up interview transcripts were available for 90% of these subjects (n=57), which are used for the current study. Unavailability of interview transcripts (for 6 of the 63 subjects) was due to: 1) for practical reasons three interviews had to be conducted by telephone, 2) three participants who answered questionnaires but preferred not to be interviewed. The 57 women participating in this study originate from 28 different BRCA1/BRCA2 families.

Procedure

The procedure of genetic counselling and of the psychological study are described in chapter 1 (page 11, 26).

Variables

QUESTIONNAIRES

General anxiety

We used the anxiety scale of the Hospital Anxiety and Depression Scale (HAD) (Channer et al 1985, Spinhoven et al 1997, Zigmond & Snaith 1983). This scale assesses feelings of anxiety by means of seven items, each with four answering possibilities, yielding scores ranging from 0 to 21. A score of 10 or more is an indication of clinical anxiety, scores from 8 to 10 are indicative for 'borderline' anxiety. The validity and reliability of the scale have been documented (Spinhoven et al 1997).

Cancer-related distress

The Impact of Event Scale (IES), measuring the impact of a particular distressing experience, was used (Horowitz et al 1979). The 'Intrusion' (7 items) and 'Avoidance' scales (8 items), measured overwhelming thoughts and feelings about breast/ovarian cancer and a tendency to avoid these thoughts and feelings. To enable comparison with results from previous studies on genetic testing in our centre, similar response categories were used (never, sometimes, often or continuously)(Dudok de Wit et al 1998b); these response categories differed from those of the original IES. The intrusion scale ranges from 0 to 35 and the avoidance scale from 0 to 40 for (the higher the score, the higher the level of intrusion/avoidance)

Biographical data

Questions about age, marital status, offspring (number, gender and age) and the educational level were incorporated in the questionnaire which was filled in prior to disclosure of the result (appendix A).

COHERENCE OF THE INTERVIEW TRANSCRIPTS

The interviews contained three (pre-test) or two (post-test) open-ended questions, the formulation of which was based on the Adult Attachment Interview (Dudok de Wit et al 1998, Main & Goldwyn 1994, Main 1995, Main 1996, Kobak & Sceery 1988, Kobak et al 1998). For that interview subjects are asked to describe the relationship with their father and mother by means of five adjectives and to subsequently illustrate these adjectives with examples. Similarly, in the present study subjects were asked to formulate short answers which they could illustrate with examples from everyday experiences.

In the pre-test interview they were asked to express in one or two words (1) what breast/ovarian cancer meant to them, (2) what it would mean to them if they were found to be a mutation carrier, and (3) if they were found to be a non-mutation carrier. In the post-test and follow-up interviews, the first question was repeated and then subjects were asked what the test outcome (being identified as a mutation carrier or as a non-mutation carrier) meant to them. It was emphasized that subjects could take their time to formulate their answers in one or two words. If they were not capable to illustrate their answers, they were prompted once or twice in a standardised way.

The manner of talking about breast/ovarian cancer and the implications of genetic testing was judged by a panel of 5 psychologists, who were trained in scoring the coherence of a transcript. For this, they used the manual which was translated and adapted by the second author for the previous study, on the basis of the manual used for studies on Attachment (Dudok de Wit et al 1998b, Main & Goldwyn 1994). The coherence measure described in the manual derives in part from a concept of coherence as described for linguistic research (Grice 1975). Each interview was audiotaped and transcribed following specific recommendations (Dudok de Wit et al 1998b, Main & Goldwyn 1994) including, for example, timing the duration of silences (in seconds). A score was attributed between 1 and 9, incrementing with halves; the higher the score, the more coherent the transcripts. 'Average coherence' is indicated by a score of 5. A higher score is assigned to transcripts of subjects showing a readiness to discuss and evaluate experiences, ideas and feelings about cancer and genetic testing, with a clear and consistent flow of ideas (Dudok de Wit et al 1998b, Main & Goldwyn 1994). More specifically, raters focussed on the extent to which a transcript is 1) truthful, providing evidence for what is said, 2) succinct and yet complete, 3) relevant or perspicacious, presenting what has to be said so that it is plainly understood and 4) clear and orderly (Grice 1975). Deviations from the such characteristics of a 'coherent transcript', result in lower coherence scores.

Below one example is given of an interview judged as coherent, and two examples of interviews judged as incoherent. An example of a coherent transcript:

Question: *"Can you tell me in one or two words what it means to you that you are found to be carrier of the gene for breast/ovarian cancer?"*

Answer: *<<14 sec silence>> "A feeling of relief, that you know where you stand now, and at the same time uncertainty, doubting between do I or don't I want to have children -- so in two words: you get more certainty as well as more uncertainty."*

Question: *"You said you are feeling uncertain about whether to have children or not, can you explain in what way you felt uncertain about that in the past weeks?"*

Answer: *"Well, sometimes I was thinking about my mother not knowing, at the time she was pregnant with me, that she could have transmitted the mutation to me, whereas if I choose*

to have children and if I have them, I know that I can transmit the gene. And, I am thinking that although I have to undergo surgery, life still has much to offer. But can I make such a decision for my offspring? I have not solved this dilemma yet."

This young woman shows a readiness to reveal to the interviewer the dilemma she is working through. She relates this in an orderly way, not using many words, it is clear what she means.

The following are two examples of incoherent transcripts:

Question: *"Can you tell me in one or two words what it means to you that you are found not to carry the gene for breast/ovarian cancer?"*

Answer: *"I found that rather positive."*

Question: *"Can you tell me a little more about this, something that can illustrate in what way you were rather positive about it?"*

Answer: *"Well, in fact I never worried about it, I never had the feeling that I would carry the gene with me. I can not say anything more about that, I just had that feeling, and, eh, but if you receive the test result, that makes you feel a little more positive than you already felt, in one way or the other. I cannot give an illustration of it, it is just a feeling."*

This transcript is judged incoherent, because the subject seems unready or unable to provide evidence for the short first answer she gave.

The following transcript is not judged coherent because it does not meet the requirement perspicacity (e.g. the answer breaks off in the middle of a sentence, oscillation, odd reasoning).

Question: *"Can you tell me in one or two words what breast/ovarian cancer means to you at this moment?"*

Answer: *<<8 sec.>> Insecurity – I mean that I continue to have a risk, and like I told you last time, that will feel kind of strange, because it is not at all, uhm, but I keep having this feeling that I will have breast cancer one day, even if I do not carry the mutation, but yes, okay, it is difficult, eh – to explain why I have this feeling. It is like what I sometimes say that 'all right, I do have a chance now to become 50 years old', because I keep having that strange feeling that one day I will, eh -- I do not know why, but it is just a feeling, but it is not that I, uhm, that okay that I, that I find that, eh – burdensome."*

Final scores for each transcript were the mean of the five individual scores of the raters, if these individual scores differed less than two points from each other. If these differences were larger, a consensus score was obtained during the regular scoring sessions with all raters present.

Statistical methods

To test differences in means between 2 or ≥ 2 subgroups, t-tests (two-tailed) respectively analyses of variance (ANOVA) were used (Statistical Package for

Social Sciences, release 8.0; a p value of ≤ 0.05 was considered statistically significant).

Because violation of randomness might occur due to some subjects originating from the same family, a random regression model for continuous data performed by the program Proc Mixed of the statistical package Statistical Analysis Systems (SAS/PC, release 6.12) was used to estimate family-specific effects on the outcome variables (Gibbons et al 1993). The family of origin was not found predictive for the level of distress. Therefore, in further analyses, study participants were treated as independent from one another.

RESULTS

Descriptives

The mean age of the 57 women in this study was 38.1 (range 19 to 68) years. The majority was married or living with a partner (84.2%) and 70.2% had children. Sixty-three percent had finished high-school, and 9% had an education level higher than high-school.

Distress levels

As reported in chapter 2 and 5, mean levels of anxiety on the Symptom Checklist were similar to those of normal controls at both several weeks prior to disclosure of the result and 6 months afterwards. No differences were found between levels of pre-test anxiety and cancer-related distress between women for whom no interview scores were available (n = 6) and the women included in the analyses of the present study (n = 57). A post-test interview score is missing for three of the 57 subjects, because of failed audiotaping.

Coherence scores

To categorize the level of coherence at the 3 different assessment times, we dichotomized coherence scores using a cut-off score of 5, indicating 'average coherence'. Transcripts with a score of 5 or higher were labeled coherent and those with a lower score as 'incoherent'. The percentage of transcripts having a coherent score increased from 46% at pre-test, to 59% at post-test and to 70% at six months follow-up. The test outcome (being a mutation carrier or a non-mutation carrier) had no influence on the proportions of high and low coherence scores. Examination of individual patterns of coherence scores over the three assessment times revealed that the following patterns occurred most frequently: 1) consistently coherent subjects (24%), 2) consistently incoherent subjects (17%), and 3) subjects showing incoherence at pre-test and coherence at post-test and

follow-up (26%). The remaining 33% (n=19) showed other patterns of coherence scores from pre-test to follow-up.

Interrater reliability

To determine the interrater reliability, we first examined the level of agreement between each rater's scores (n = 5) and the final score at the three assessment times. The correlations between the individual rater scores and the final score (Kappa) were all significant, but varied depending on the rater and the assessment time (ranging from .13 ($p = 0.05$) to .72; ($p < 0.01$)).

The highest mean Kappa of a rater was .49, and the lowest .16; Kappas for other raters ranged from.32 to .38. When we eliminated the scores assigned by the rater showing the lowest agreement with the final score assigned, the mean Kappa of the pre-test interview was .28, of the post-test interview .40 and of the follow-up interview .50 (all significant).

Subsequently, we examined how often raters unanimously judged a transcript as either coherent (score ≥ 5) or incoherent (score < 5). This occurred in one third of the pre-test and the post-test interviews. After exclusion of the scores of the rater with the lowest Kappa, these proportions became 40% and 46%, respectively. For the follow-up interviews an unanimous agreement in judging transcripts as either coherent or incoherent was reached for 56% of the transcripts, and for 58% after exclusion of the scores of the rater with the lowest Kappa. For the transcripts for which no unanimous agreement was reached, a consensus score was determined.

Cancer-related distress and coherence of transcript

We dichotomized pre-test scores on the intrusion and avoidance scale of the Impact of Event Scale at the median, as in the previous study (Dudok de Wit et al 1998b). This resulted in four subgroups of subjects having either 1) high intrusion/high avoidance scores (32%), 2) high intrusion/low avoidance scores (19%), 3) low intrusion/high avoidance scores (9%), or 4) low intrusion/low avoidance scores (40%). These percentages were rather similar to those of our previous study (i.e. 45%, 6%, 13% and 36% respectively) (Dudok de Wit et al 1998b). In our sample, pre-test coherence scores in women reporting low intrusion and low avoidance, were not lower than those of women in the other three groups, which reported high intrusion and/or high avoidance ($p = 0.38$, t-test for independent samples, two-tailed). This is in contrast to the findings in the previous study, in which a significantly lower level of coherence was found in the subgroup that reported low intrusion and low avoidance (Dudok de Wit et al 1998b).

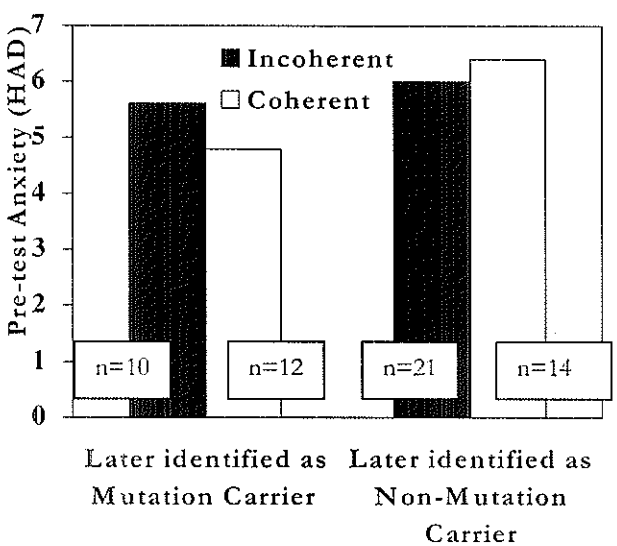
We repeated the categorization and subsequent statistical analyses of coherence levels for the post-test and the follow-up assessment. Again, coherence

scores of transcripts were not lower in women reporting low intrusion/low avoidance than in the other 3 subgroups ($p = 0.1$; $p = 0.62$; t-test for independent samples, two-tailed). Repeating this analysis of post-test and follow-up data for mutation carriers and non-mutation carriers separately, did not alter the results ($p = 0.17$; $p = 0.29$; $p = 0.46$; $p = 0.96$; t-test for independent samples, two-tailed).

Associations between coherence and general anxiety

The coherence score of transcript was not significantly related to the level of reported anxiety prior to the test outcome and several weeks and 6 months afterwards. At the post-test and follow-up assessment we found significant associations between the coherence score and reported anxiety when we included the test outcome in the analysis. At pre-test, significant associations for those later identified as mutation carriers or non-mutation carriers did not yet exist (Figure 1).

Figure 1: Differences in Pre-test Anxiety between (later identified) mutation carriers and non-mutation carriers with a high or low Coherence score (pre-test interview)



At post-test, coherent non-mutation carriers had a significantly *lower* level of anxiety than incoherent non-mutation carriers and all mutation carriers ($p = 0.04$, ANOVA; Figure 2). At the follow-up assessment the group of incoherent mutation carriers were found to have the lowest distress levels ($p = 0.02$, ANOVA; Figure 3). Again, incoherent non-mutation carriers had a *higher* anxiety level than coherent non-mutation carriers.

Figure 2: Differences in Post-test Anxiety between mutation carriers and non-mutation carriers with an (in)coherent score (post-test interview)

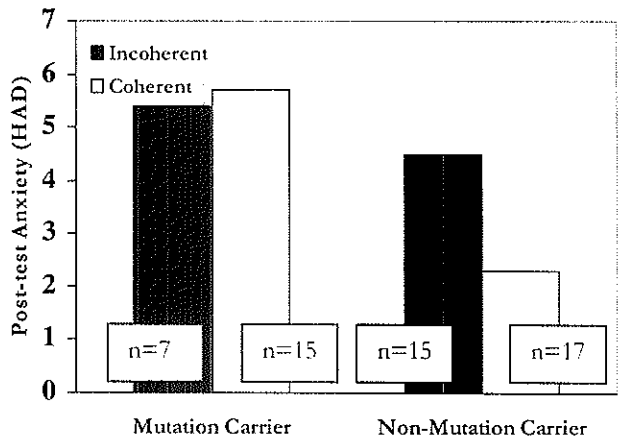
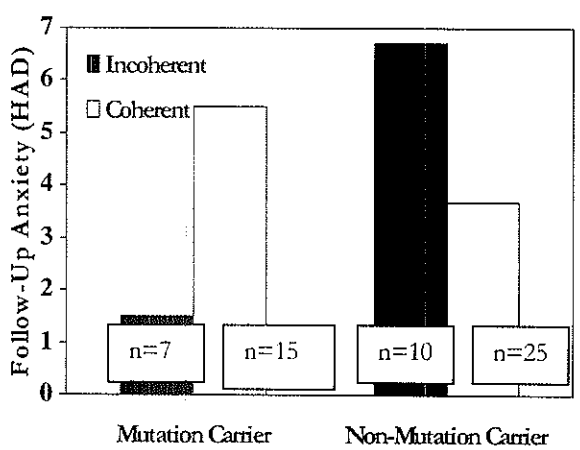


Figure 3: Differences in Anxiety at six months Follow-up between mutation carriers and non-mutation carriers with an (in)coherent score (Follow-up interview)



DISCUSSION

In this study, the test outcome significantly affected the relation between one's ability to reflect on experiences and levels of self-reported distress. Whereas for the whole study sample no association was found between an incoherent reflection on experiences and low levels of self-reported distress, such an association did exist for the group of mutation carriers at the follow-up assessment. In non-mutation carriers, incoherence of interview transcripts was found to be associated with high instead of low distress at post-test and at follow-up. Apparently, not being able to coherently reflect on experiences could mean different things depending on whether a burdensome condition continues or has ceased to exist.

The low anxiety in incoherent mutation carriers at 6 months follow-up may reflect the use of defensive denial of continuing distress due to their genetic status (e.g. having a high risk for cancer, having underwent either prophylactic surgery or frequent surveillance, having children at risk for having inherited the mutation). These incoherent mutation carriers might be emotionally unprepared to experience the impact of the existential threats they are confronted with and may, to avoid painful feelings, maintain an illusion of mental health. This would be in accordance with the interpretation presented by Shedler et al. (1993) and Dudok de Wit et al. (1998b).

The incoherent non-mutation carriers had higher levels of anxiety than coherent non-mutation carriers at both post-test and at follow-up. This finding can not be interpreted as possibly resulting from defensive denial. Instead, one could speculate that in this case the incoherence resulted from a difficulty to distance oneself from a threat that no longer exists. Or, incoherent non-mutation carriers may still harbour ambivalent, unresolved feelings towards relatives who were identified as mutation carriers or who are affected with breast or ovarian cancer or have died of it. Ambivalent feelings in non-mutation carriers have been described previously (Tibben et al 1993b). Further research is needed to address the question whether differences can be found between incoherence reflecting defensive denial and incoherence reflecting complex feelings due to difficulties in adjusting to a new situation in which a burdensome perspective has been eliminated for oneself, but not for one or more relatives.

That we did not find a positive relationship between reported low disease-related distress at pre-test and incoherence, in contrast to the study by Dudok de Wit et al. (1998b), may be due to differences in the study samples. In their sample many test applicants for Familial Adenomatous Polyposis Coli (FAP) were included, who generally reported very low distress levels and often showed an

unwillingness to reflect on implications of genetic testing or on FAP in general, which results in low coherence scores. In another study it was also concluded that subjects at risk for FAP tended to minimize the threats posed by the disease. In interviews these subjects often described the disease as "not a problem" and "non threatening" (Michie et al 1996). This group might have significantly affected the outcome of the previous study (Dudok de Wit et al 1998b). Nevertheless, in our study it remains puzzling why no association was found between self-reported disease-related/general distress and one's capability to reflect on experiences in the weeks prior to disclosure of the test outcome. Neither do we have an explanation for the finding that, when including the test-outcome significant results were found for general anxiety but not for disease-related distress.

We suggest that the finding that the inter-rater reliability became larger at each assessment time is associated with the fact that the proportion of transcripts judged as coherent became somewhat larger during the course of the study. Post-hoc analyses revealed that transcripts finally judged as coherent significantly more often yielded a consensus between the different raters than transcripts finally judged as non-coherent. However, we cannot exclude that the higher inter-rater reliability at the later assessment times may also partly be explained by raters having become more experienced in judging the coherence score of a transcript during the study. If the latter explanation holds, a more valid way of scoring the interviews might have resulted in more significant inter-group differences at the later assessments than at the pre-test assessment. Because of the ambitious task to grasp defensive denial strategies by scoring the coherence of a transcript, such as applied in this study, it is important to further investigate and adapt this method to optimise the inter-rater reliability. New findings will also elucidate the association between incoherence and defensive strategies, and how these strategies affect scores on self-report questionnaires. Whereas many questions remain, this study yielded promising results about the possibility of assessing coherence in a standardized way, and about its importance, for we found coherence and self-reported distress to be significantly associated.

Acknowledgments

This study was supported by a Dutch Cancer Society grant. We are grateful to the participants in the study and to Mrs C Tengnagel, Mrs A Brink and Mrs A vd Sijden for the preparation of interview transcripts.

Chapter 7

MEN AT RISK OF BEING MUTATION CARRIER FOR HEREDITARY BREAST/OVARIAN CANCER: AN EXPLORATION OF ATTITUDES AND PSYCHOLOGICAL FUNCTIONING DURING GENETIC TESTING

Lodder LN[1], Frets PG[1], Trijsburg RW[1], Tibben A[123], Meijers-Heijboer EJ[2], Duivenvoorden HJ[1], Wagner A[2], van der Meer CA[2], Devilee P[3], Cornelisse CJ[3], Niermeijer MF[2].

[1]Dept. of Medical Psychology and Psychotherapy, Erasmus University Rotterdam/Netherlands Institute for Health Sciences; [2]Dept. of Clinical Genetics, University Hospital Dijkzigt/Erasmus University Rotterdam; [3]Leiden University Medical Center; the Netherlands

European Journal of Human Genetics 2001; 9: 492-500, reprinted with permission from the journal

ABSTRACT

Males with a BRCA1/BRCA2 mutation are not at greatly increased risk for cancer, whereas their (grand)daughters, and other female relatives carrying the mutation, are. Males from BRCA1/BRCA2 families may opt for genetic testing to confirm whether or not they may have transmitted the mutation to their children and, if so, to inform them at an appropriate age about the genetic risk and its implications. The psychological implications of genetic testing for men at risk of being a BRCA1/BRCA2 mutation carrier have received little attention.

We report on 28 men requesting BRCA1 or BRCA2 testing, and their partners. Men were at 50% (n=24) or 25% risk (n=4) of being a mutation carrier, the majority with daughters and half of them with daughters aged over 20 years. Levels of general psychological distress were assessed several weeks before and after disclosure of the test result. In addition, we investigated the level of intrusive thoughts and feelings about breast and ovarian cancer and the tendency to avoid these thoughts and feelings. By means of interviews and a questionnaire,

participants could report on (expected) emotional implications of genetic testing for themselves and their children and on experiences with cancer in the family. Another questionnaire assessed the personality trait optimism.

Distress levels prior to the result in tested men and their partners were low. Many men and partners expected the test result to affect their children's, but not their own level of problems. Men without daughters and those with an optimistic personality had especially low distress prior to disclosure of the result. Most men reported that they did not actively avoid the issue. Only four of the 28 men were identified as mutation carriers. High distress after disclosure of the result was reported by one mutation carrier and by three non-mutation carriers. Verbatim transcripts from interviews showed a large variation of psychological reactions in male mutation carriers (e.g. regarding guilt feelings).

Low pre-test distress in males does not seem necessarily to indicate avoidance of the issue. Many at risk men and their partners think that the test outcome will affect the emotional well-being of their children, but not their own. Future studies may explore psychological reactions in male mutation carriers when the problem becomes more acute, e.g. when a daughter is found to carry the mutation and/or is diagnosed with breast or ovarian cancer.

INTRODUCTION

Whereas female BRCA1/BRCA2 mutation carriers have a lifetime risk for breast cancer of 56-87% and for ovarian cancer of 10-60%, risks for cancer in male mutation carriers are not very high. The lifetime risk for breast cancer in male BRCA2 mutation carriers is 6% and is marginally increased for some other types of cancer in male BRCA1 and BRCA2 mutation carriers (Thorlacius et al 1998, The Breast Cancer Linkage Consortium 1999, Ford et al 1994).

Thus whereas males from HBOC families are not at high risk for cancer, many of them have close female relatives who are affected with or have died from breast or ovarian cancer, and (grand)daughters for which the mutation in the family has profound consequences. The psychological impact of this particular situation for men in HBOC families has received limited attention. Struewing et al reported on the anticipated uptake and the expected consequences of genetic testing in 91 women and 49 men from families suspect for BRCA1 (Struewing et al 1995).Whereas the anticipated future uptake for genetic testing was high, men were less likely to opt for testing than women. Besides, significantly fewer men than women expected to become depressed or anxious upon being identified as a mutation carrier.

A qualitative study exploring interviews with 22 men from hereditary breast/ovarian cancer families, showed that these men tended to use avoidance of the topic of hereditary cancer as a coping strategy (McAllister et al 1998).Whereas some men stated that they avoided conversations on breast or ovarian cancer in the family, which were generally conducted among female relatives, others reported that they felt excluded from such discussions.

In a previous study from our group (Dudok de Wit et al 1996), four men requesting genetic counseling for BRCA/BRCA2 were interviewed by a psychologist. Only one of these men ultimately decided to obtain his test result, after having postponed his appointment for bloodsampling twice. Two men decided to postpone undergoing the test after their first visit, and one did so after having cancelled the appointment for bloodsampling twice. The psychologist's impression was that these men had problems discussing their experiences with cancer in close relatives, and reflecting upon possible unfavorable implications of testing for themselves and their offspring. A lower uptake for genetic testing in males than in females at risk of inheriting a BRCA1/BRCA2 mutation and a higher drop-out rate in follow up interviews was also described in a larger study from the United States (Lerman et al 1998).

The present study aims to provide a more systematic analysis of distress in males at risk of carrying a BRCA1/BRCA2 mutation who applied for genetic testing, and their partners. Symptoms of anxiety and depression in the weeks prior to and following the test result were assessed. The tendency actively to avoid thinking or talking about breast or ovarian cancer in daily life was also assessed. Prior to disclosure of the result participants reported on their expectations of the emotional impact of the test for themselves and the children. We aimed to establish whether men who reported high levels of distress in the period before disclosure of the result differed from those with low distress with regard to biographical characteristics, experiences with cancer in the family and personality. Low distress was expected to be associated with having no daughters, having no close relatives with breast and/or ovarian cancer and having a general tendency to stay optimistic in difficult times. We used both questionnaire and interview data, the latter giving an in-depth perspective of male's experiences and feelings, which might be used to illustrate some results from questionnaire data.

METHODS

Participants

Between January 1996 and April 1998, 40 men with a 25% or a 50% risk of having inherited a BRCA1 or a BRCA2 gene mutation who requested genetic testing at

the Department of Clinical Genetics of the University Hospital Rotterdam were asked to participate in the psychological study together with their partners. Of these men, 28 (70%) returned the pre-test questionnaire and participated in the interview. Twenty-five participants had children (Table 1). Ten men (25%) decided not to participate and two (5%) were excluded because they did not return the questionnaire after being interviewed. Most of the declining men reported that they felt reluctance towards participating in the interview. The 12 non-respondents/drop-outs did not differ from the study sample with regard to age, marital status, offspring, age of daughters or prior genetic risk to be mutation carrier ($p > 0.05$; t-test for independent samples, two-tailed or χ^2 test).

The 28 participating men were at risk for being a BRCA1 (n=24) or a BRCA2 (n=4) mutation carrier, and belonged to 18 different HBOC families. The maximum number of men at risk belonging to one family was 4. Twenty-seven men had a partner, 24 of whom joined the study. One of the partners was not included because she was not the mother of the children at risk, two other partners declined participation.

Table 1: Characteristics of the study sample and the non-respondents

		Men at risk (N=28)	**Partners (N=23)**	***Non-respondents (N=12)***
Mean age (years)		47	44	*52*
(range)		(29-67)	(25-65)	*(29-70)*
Marital status	Married/living together	89%		*83%*
	Unmarried/divorced	11%		*17%*
With Children		89%		*92%*
With daughters		79%		*83%*
Older than 20 years		50%		*70%*
Education	< High school	32%	36%	
	High school	36%	50%	
	> High school	32%	14%	
Prior risk	50%	86%		*100%*
	25%	14%		-

Procedures

The process of BRCA1/BRCA2 mutation analysis, enabling mutation detection for relatives at risk are described in chapter 1. Males at risk who were considering genetic testing had one or more pre-test counseling sessions with the clinical geneticist or genetic nurse. They were informed about the genetic, medical and psychosocial implications of testing for themselves and their children. In case the children were young, it was discussed that the parent may face problems if, at some point in the future, the child expresses that he/she would rather not have known about having a 50% risk of being a mutation carrier. After consideration of these implications, if the test applicant still decided for testing, a blood sample was obtained. The appointment for disclosure of the test result took place 6 to 8 weeks later. Men and their partners were informed about the availability of psychological support from a clinical psychologist.

The protocol for this study was developed on the basis of the protocol of pre-symptomatic testing for Huntington disease (Tibben et al 1997). The study was introduced by the clinical geneticist or genetic nurse during the intake/blood sampling session. After agreement to participate, the psychologist (LNL) provided more information and questionnaires to be completed at home. The pre-test interview usually took place directly after the blood sampling session, but sometimes several weeks later, at the participants' homes. The post-test assessment (including questionnaires and an interview) took place 1 to 3 weeks after the test outcome.

Variables

General distress

The Hospital Anxiety and Depression Scale was administered prior to and following disclosure of the result. The questionnaire consists of two subscales of 7 items each, assessing the level of anxiety and depression (Zigmond & Snaith 1983, Channer et al 1985). Each question has four answer possibilities and the scores for the two subscales range from 0 to 21. A score of higher than 10 on either subscale is an indication of clinical anxiety or depression, scores from 8 to 10 indicate 'borderline' anxiety or depression. The validity and reliability of the scale are good (Spinhoven et al 1997).

To enable comparison of levels of anxiety and depression with the normal population, the Symptom Checklist was used prior to disclosure of the result (Derogatis et al 1976); this questionnaire has norms for a Dutch female and male population (Arrindell & Ettema 1981). This scale was also used to register the answers to the question if one had experienced feelings of guilt in the period prior to disclosure.

Intrusion and Avoidance

The Impact of Event Scale, assessing the impact of a particular distressing experience, was used prior to and following disclosure of the test result (Horowitz et al 1979). The 'Intrusion' (7 items) and 'Avoidance' scales (8 items), measured the extent to which subjects became overwhelmed by thoughts and feelings about breast/ovarian cancer and if they had a tendency to avoid these thoughts and feelings. The score for the intrusion scale ranges from 0 to 35 and for the avoidance scale from 0 to 40. To enable comparison with results from previous studies on genetic testing of our group (Dudok de Wit et al 1997a), similar response categories were used (never, sometimes, often or continuously); these response categories differed from those of the original Impact of Event Scale.

Biographical and pedigree information

Questions on age, marital status, offspring (number, gender and age) and the educational level were included in the pre-test questionnaire. The pedigree was obtained to examine the prior genetic risk of being a mutation carrier (25% or 50%).

Experiences with the disease in the family

In the pre-test interview, men were asked about their experience with breast and ovarian cancer in relatives. The number of known affected relatives, their place in the pedigree (first, second, third degree relatives), the consequences of the disease, and the lowest age of onset were registered.

Reasons for testing and self-reported (expected) consequences of genetic testing

In the pre-test interview, men were asked about their main reasons for testing. They were also asked if they had informed their children about their genetic risk and, if not, at what point in time they expected to inform their children in case they became identified as mutation carriers.

An attitude questionnaire, adapted from previous studies from our group (Tibben et al 1993c), monitored the expected emotional consequences of either test result. Men and their partners could indicate whether they expected their own or children's problems to increase if they were found to carry the mutation. Contrasting expectations after exclusion of a mutation were also explored. Response categories were: 'agree', 'do not know', or 'disagree'.

In the interview prior to disclosure of the result, men were asked in a semi-structured way to report on the implications they expected of either test result. They were asked to initially formulate answers of a limited number of words and then to provide examples from everyday experiences to illustrate their brief answers. This part of the interview was audiotaped and literally transcribed. The post-test interview contained a similar semi-structured part, in which men were asked what it meant to them that they were found to be a (non-)mutation carrier. These transcripts were used either to find illustrations for results from

questionnaire data, or to provide additional information in case questionnaire data were not conclusive enough.

Optimism

At pre-test, a Dutch adaptation (Bleiker et al 1996) of the Life Orientation Test (Scheier & Carver 1985) was used as a measure of dispositional optimism, assessing a positive attitude towards life (8 items, e.g. 'In uncertain times I usually expect the best'). The frequency of occurrence of such thoughts or feelings could be indicated on a 4-point scale, ranging from 'almost never' to 'nearly always'.

Statistical Analyses

The Statistical Package for Social Sciences (SPSS/PC, release 8.0) was used. To test differences in means and proportions of two subgroups, t-tests for independent samples and χ^2 tests for categorical data were used. A p-value <0.05 (two-tailed) was regarded as statistically significant. The relation between predictive variables and the level of distress was estimated by a single linear regression model. Variables significantly related to the level of distress ($p<0.05$, two-tailed), were included in a multiple linear regression model (backward elimination procedure).

RESULTS

Study sample

Whereas 24 of the 28 males participating in the study had a 50% risk to inherit the BRCA1/BRCA2 gene mutation (the others had a risk of 25%), only four were identified as mutation carriers. Each of these mutation carriers had one daughter, aged between 10 and 18 years. Of the 24 non-mutation carriers, seven did not return their post-test questionnaires; three expressed reluctance towards answering questions on psychological functioning having received a favourable test outcome, and four did not specify their reasons for declining further participation. Thus, post-test results are available for 4 mutation carriers and partners (n=4) and 17 non-mutation carriers and partners (n=14). Distress levels prior to disclosure did not differ between non-mutation carriers continuing and non-mutation carriers declining further participation in the study (t-test, two-tailed; $p>0.05$).

Descriptives prior to disclosure of the result

Experiences with the disease in the family

Seventeen of the 28 men had (had) a mother and/or one or more sisters with breast or ovarian cancer; 15 of these men had also lost one or more of these close relatives due to the disease. Ten men were familiar with the disease only in second

degree relatives and one had not known any affected female relative. None of the men knew any male relative to be affected with breast cancer.

Reasons for testing

All of the 25 men with children wanted to obtain certainty about whether they could have transmitted the mutation to their offspring. Almost half of these men had children aged less than 15 years. If they became identified as mutation carriers all these men intended to postpone informing their children about their possible risks for several years. Two of the 14 men with adult daughters would opt to inform their daughters about BRCA1/2 testing after having received the test outcome. One of the three men without children, and his partner, wished to include the test outcome in their decision as to whether or not to have children. The other two wanted to undergo genetic testing since they knew that the test was available and saw no reason to postpone it.

Expected consequences of genetic testing

An increase of problems for their children was expected by 19 of the 25 men with children and half of their partners (11/21), in case they would be identified as a mutation carrier (Table 2). Only nine men and two partners expected their own problems to increase after such a test outcome.

Table 2: Expected consequences of the test outcome

	Men at risk (N=25*)	**Partners (N=23*)**
After being identified as a mutation carrier, I expect...		
My children's problems to increase	76%	52%
My own problems to increase	36%	9%
After being identified as a non-mutation carrier, I expect...		
My children's problems to decrease	83%	71%
My own problems to decrease	44%	55%
My mood to improve	33%	18%

* For men/partners with children

Distress levels prior to disclosure of the result in male participants

Anxiety and depression prior to disclosure of the result

On the Hospital Anxiety and Depression Scale men had a mean pre-disclosure score of 3.0 for anxiety (range: 0 to 9; SD: 2.8) and of 2.4 for depression (range: 0

to 7; SD: 2.3), both being far below the 'borderline value' of 8. Borderline or high scores of anxiety were found in 2/28 men (7%), and none had similar high scores for depression.

The mean pre-test anxiety and depression scores on the Symptom Checklist were slightly below those of a normal male population. The majority of men (23/26) reported that they had not experienced guilt feelings several weeks prior to disclosure of the result.

Intrusion and Avoidance prior to disclosure of the result

The mean level of intrusion of thoughts and feelings about breast/ovarian cancer was low (2.7; range: 0 to 13; SD: 3.2) and the mean level of avoidance of such thoughts/feelings was even lower (1.7; range: 0 to 12; SD: 2.9); the full range of scores on these two scales being 0 to 35 and 0 to 40 respectively. Looking closer at the answers addressing avoidance, it seems that most men not consciously avoided the topic, e.g. none reported avoiding people or situations which reminded them of breast/ovarian cancer, and only 4/28 affirmed that they 'simply did not want to think about the disease'.

Predictive factors for pre-test distress in men at risk

For the men at risk, we used a linear regression analysis to explore whether biographical characteristics, experiences with cancer in first degree relatives, and an optimistic personality were predictive for levels of pre-test anxiety and depression (Hospital Anxiety and Depression Scale). Two predictive variables were found. Men with higher scores on the optimism scale, were significantly less likely to have high levels of pre-test anxiety ($p<0.01$) and depression ($p<0.03$) than non-optimistic men. Also, men without daughters ($n=6$) had significantly lower depression levels ($p<0.03$) than those with daughters ($n=22$). The age of the daughters (>20 or ≤ 20 years of age) was not predictive for distress in men.

Descriptives after disclosure of the result

Anxiety and depression after disclosure of the result

Post-test anxiety and depression levels for each of the 4 mutation carriers and 17 non-mutation carriers are compared to their scores prior to the result (Figures 1 and 2). At post-test, one mutation carrier and three non-mutation carriers had borderline to high levels of anxiety (≥ 8); anxiety levels for these men were already elevated at the pre-test assessment. One of these non-mutation carriers and the mutation carrier also reported a borderline level of depression at post-test. The depression levels for these two men had changed little since pre-test.

Mean post-test scores for mutation carriers and non-mutation carriers were, respectively, 4.0 and 3.1 for anxiety (SD: 4.9 and 3.2) and 2.5 and 2.2 for depression (SD: 3.8 and 2.7).

Figure 1: Pre- and Post-test anxiety levels in male mutation carriers and non-mutation carriers. One dot can represent more than one subject. The regression line is drawn separately for both groups.

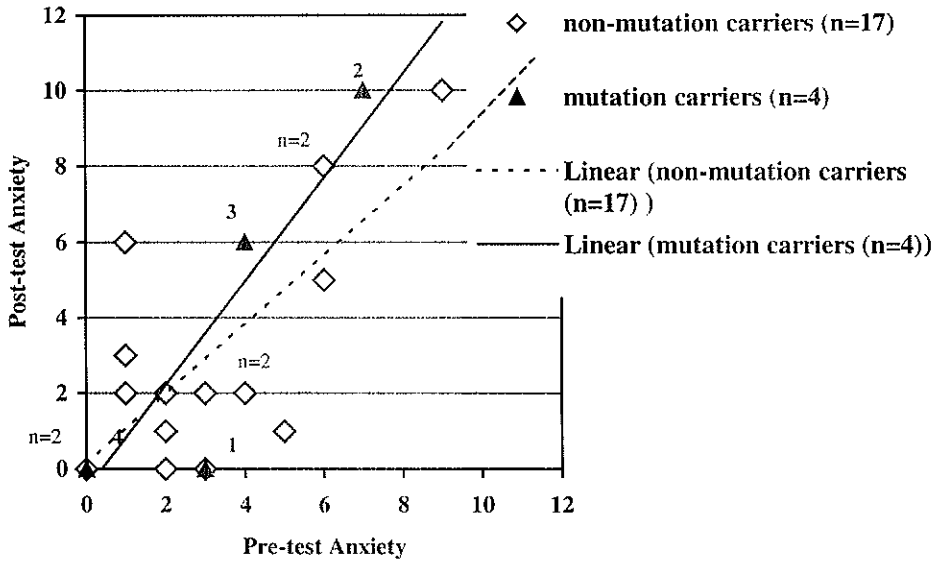
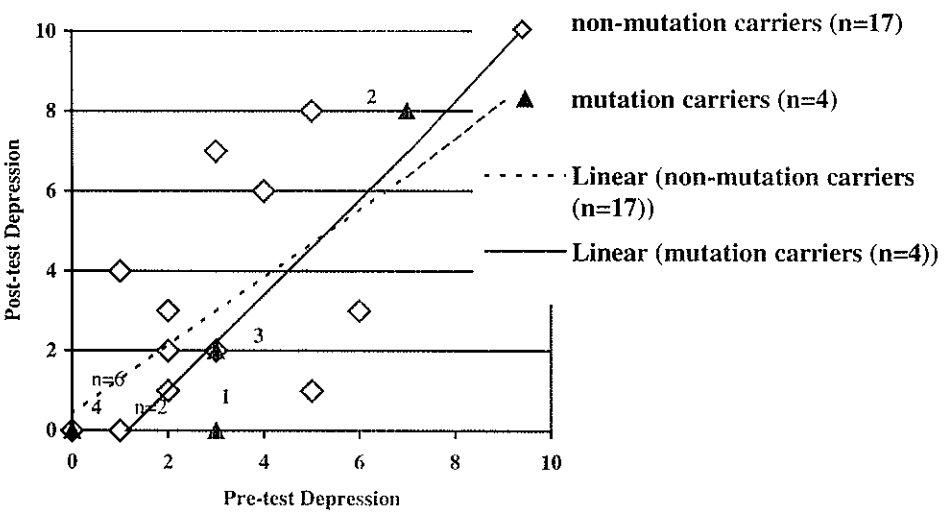


Figure 2: Pre- and Post-test depression in male mutation carriers and non-mutation carriers. One dot can represent more than one subject. The regression line is drawn seperately for both groups.



Verbatim interview transcripts of male mutation and non-mutation carriers
Because of the small number of mutation carriers in the study sample, no statistical comparison was made between their mean distress levels and those of non-mutation carriers. To obtain some insight into the men's feelings concerning the impact of being identified as a (non-)mutation carrier, we used the verbatim transcripts from the interviews held about two weeks after the test result. We describe the words these men used when asked to express in a limited number of words what it meant to them that they were found to be a (non-)mutation carrier, and their illustrations of these words while using examples from everyday experiences.

Post-test verbatim transcripts of the interview were available for the 4 mutation carriers and for 10 of the 17 non-mutation carriers. With the other 7 non-mutation carriers, interviews were held by telephone and therefore no verbatim transcripts are available. This latter group was included after the main data collection period had passed, in a (failed) attempt to increase the number of mutation carriers in the study.

Mutation carriers

One mutation carrier (with low pre- and post-test distress levels, see '1' in Figures 1 and 2), whose daughter still attends primary school, anwered: [I] *"It is a pity, but I think I am already quite far in the process of accepting the fact that I carry the mutation and that I may have transmitted it to my daughter. I cannot change anything about it, and I do not experience feelings of guilt towards my daughter, neither do I blame my mother for having passed the gene on me. But my perception of things has changed a little since the result. For example, last week my daughter was playing in the garden and I wanted to tell her to come in, but then I let her play a little longer, because she was having so much fun. While I was watching her play I was conscious of the fact that she may have to face difficult times in the future. As a father I want to give her a life as pleasant as possible of course, and now I have the feeling that something has come in between. I think I will become less conscious about this after some time, because it will take many years before my daughter may get the test. In that period of time, a lot can change in the medical world and, besides, she may have a good test result."* Feelings of guilt towards the daughter at risk were explicitly indicated by one mutation carrier (with moderate to high pre- and post-test distress levels, see '2' in Figures 1 and 2), who planned to postpone informing his adolescent daughter for several years. He and his wife wanted their daughter to live the remaining years of her adolescence without the burden of her elevated risk for cancer. [II] …. *'I feel guilty and insecure. Guilty, because if everything had been all right in my body, my children would not have had any problem. And although I know that I cannot help it, it gives me a very bad feeling. Besides, the insecurity I feel is hard to live with. In the first place the insecurity of "does she have this gene, or not". I sometimes have the fantasy of secretly taking some of her blood and having it tested. Secondly, I feel uncertain about what will happen in the future. If my child develops cancer she will be an adult person, but she is still my daughter…."*

Two mutation carriers each had one daughter who had just finished high school. One of these daughters wanted to postpone the test until her life became more settled. Her father (who had a moderately high post-test anxiety score, see '3' in Figure 1 and Figure 2) described her as a worrying type of person, and answered: [III] ...."*From now on, it will always be in my mind that my daughter may have inherited the gene, unless she undergoes the test and receives a favourable test outcome. A lot of things do remind me of it, for example something on TV or if there is a campaign by the cancer society.*" The daughter of the other mutation carrier had undergone the test herself several weeks after she was informed about her father's test outcome. In the week after his own test outcome, her father (who reported an absence of feelings of distress both at pre- and post-test, see '4' in Figures 1 and 2) said: [IV] ...."*That I am found to be a mutation carrier does not mean anything to me at this moment. This may change if my daughter is also found to be a mutation carrier. On the one hand it may come closer then but, on the other hand, she has not yet reached the age at which it becomes relevant for her. At this moment it simply is not an important issue in my life.*"

Non-Mutation carriers

Relief about the test result was reported by 9 of the 10 non-mutation carriers who were interviewed 1 to 2 weeks after disclosure of the result; one non-mutation carrier said that the result had neither positively nor negatively affected his feelings. Seven men reported that hereditary cancer continued to affect their lives, because they had relatives who were identified as mutation carriers and/or affected with or died from breast or ovarian cancer. Guilt feelings towards these relatives were not reported. The following quote is from a man who seemed to succeed to separate the grief he felt about deceased female relatives, from the gratefulness for his own favourable test outcome. [V]...."*In the past fifteen years I have seen all my female relatives, my mother, my sisters, a number of cousins and aunts die. That caused a lot of pain, depending on how close these relatives had been to me, and I feel very grateful that the test has shown that my children and my brother's children do not have to suffer from this black history in our family.*"...

Anxiety and depression in partners of male participants before and after disclosure of the test result

At pre-test, scores on the Hospital Anxiety and Depression Scale of the partners did not differ much from those of the men in the study. The mean pre-disclosure score was 3.9 for the anxiety scale (range: 0 to 10; SD: 2.9) and 1.8 for the depression scale (range: 0 to 8; SD: 2.2). Borderline anxiety was found in 2 of the 23 partners (8%), one of whom also had a borderline depression level. Mean anxiety and depression scores on the Symptom Checklist were somewhat lower than those of a normal female population.

A borderline anxiety level at post-test was reported by one of the four partners of the mutation carriers. This woman had also reported high anxiety at pre-test. Two of the 14 partners of non-mutation carriers reported similar high post-test anxiety levels, one of whom had reported high anxiety also at pre-test; the latter woman was the only partner with a high level of depression at both pre- and post-test.

DISCUSSION

Distress in men at risk and their partners prior to disclosure

Distress levels were explored in 28 men at risk of having inherited a BRCA1/2 mutation (and in their partners) wanting to undergo genetic testing primarily to know about risks for (future) offspring. The majority of the men, and their partners, had low distress levels in the weeks prior to receiving the test result. It should be noted, however, that the study sample was small and not randomly selected. Firstly, 30% of the men (n=12) resigned from participation in the study; the biographical characteristics of these non-respondents did not differ from those participating, but we do not know their levels of distress. Secondly, about half the participating men had one or more male relatives participating in the study, which implies that the sample was not 'statistically independent'. Because of these sample-related restrictions, only cautious interpretations are possible.

The majority of males not only reported low general distress at pre-test, but also low levels of intrusive thoughts/feelings about breast and/or ovarian cancer. They did not report to be actively avoiding such thoughts/feelings or situations reminding them of the disease. It might be that possible negative implications of testing are perceived as distant. Prior to disclosure of the result, it is not yet known whether one is a mutation carrier and, if so, it is not certain whether (grand)daughters are also mutation carriers. Accordingly, men without daughters had significantly less distress than those with daughters. The impression that men were postponing worrying about the issue until after the result, is also reflected in the result that men with daughters aged over 20 years, whom they would soon inform about the result, were not more distressed than those with young daughters, who could be informed about the result at a much later date.

Considering the latter findings, it is understandable that optimistic test applicants may have felt less distress prior to disclosure than less optimistic test applicants, the former being especially successful in postponing worrying until negative consequences of testing become incontrovertible. For example, one man with a low distress and a high optimism score, stated: [VI] ...*"If I carry this mutation with me I would worry about my daughters, but I am not seeing things too pessimistically, because*

in five years time they might have found a cure for cancer." Another man, with a high distress and a low optimism score said: [VII] …*"If I am found to be a mutation carrier, what future misery will my children have to face, and how much will they have to suffer? I do not assume efficient new treatments to be developed at that time, but I might be doomwatching"*…

In case they became identified as a mutation carrier, three quarter of the men at risk who had children, and half of the partners, expected an increase of problems for their children. Interestingly, half of these men and more than three quarters of these partners reported that this would have no consequences for their own emotional well-being. An explanation for this result in male participants might be two-fold. Firstly, men might wish to ignore that their own problems would increase, because they feel that the consequences of being a mutation carrier are far more severe for their daughters. They might perceive themselves as irresponsible or weak if they admit having difficulty themselves. Secondly, most males did not seem to have experienced guilt feelings about the possibility of an increase of problems for their children.

Reporting an absence of guilt feelings prior to disclosure of the result might be because at that moment, men do not yet know whether they could have transmitted the mutation. Furthermore, the impression gained from the questions in the interview about the expected impact of being found to be mutation carrier was that many men seem to be aware that they cannot be blamed for possibly having transmitted the mutation to their children. In literature about guilt (Madow 1988), guilt feelings are characterized by the perception that one is responsible for a bad situation. Individuals feeling guilty tend to use expressions starting with "had I only…" or "how could I…". Feelings of guilt are called irrational if one was not responsible for the outcome, e.g. if one survives a plane crash or if one has a child with a serious disease (Madow 1988). It is precisely this issue of responsibility, which is ambivalent for men at risk for carrying a BRCA1/BRCA2 gene mutation. On the one hand, these men already had children before they knew about the genetic nature of cancer in their family; on the other hand, they may feel responsible because if their children are found to be mutation carriers, they would be the ones who transmitted the mutation. This ambivalence is clearly illustrated by the only test applicant who expressed feeling guilty about the chance of having transmitted the mutation to his daughter: [VIII] …."*I would feel very miserable about my daughter, if I have inherited the mutation. I would not say that I can be blamed for this, it is due to coincidence, but I find it difficult to accept that this gene comes from my body. It is not that I…, yes I actually do, I do feel guilty about this."* This quote clearly shows the complexity of feelings of guilt, and the difficulty to verbalize such feelings. The difficulty to identify painful feelings of guilt may be another reason why some of those who expressed feeling sorry for their children, did not report feeling guilty towards them.

Psychological implications of the test outcome

Each of the four men who were identified as mutation carriers, seemed to have different levels of concern about their daughters. Two mutation carriers reported not having felt distressed in the weeks following the result, whereas the other two had moderate to high levels of distress. Although the latter two men appeared not to have achieved the level of certainty from testing that they had hoped for, they did not regret having undergone testing. However, the small number of mutation carriers in the present study limits generalizations about the incidence of clinical levels of psychological distress or regrets about having the test done. As long as no data on larger samples are available, genetic counseling should address the fact that feelings of uncertainty about implications for the children may remain or become even stronger if one is identified as a mutation carrier.

About one third of the non-mutation carriers declined to participate in the post-test assessment, some of whom explained to see no value in further participation because of their favourable test outcome. A previous study also reported a tendency in males from BRCA1/BRCA2 families to cancel appointments for interviews (Lerman et al 1998). The present paper does not answer the question whether subjects who withdrew did so to avoid psychological discomfort, or because of a reluctance to continue participating in a process that was no longer a major issue in their lives.

Of the non-mutation carriers who completed the post-test assessment, the majority reported relief about their test outcome. Some were still confronted with the implications of hereditary cancer for female relatives, but none reported feeling guilty about their own favourable test outcome. The explanation for this finding may be similar to the explanation we gave for the low prevalence of guilt towards children at risk. Again, there is no question of responsibility or control in case of relatives being identified as mutation carriers or developing cancer (Madow 1988). Besides, some men may have had difficulty in labeling their feelings of discomfort in terms of guilt.

Concluding remarks

We conclude that the majority of the men at risk and their partners did not have elevated levels of anxiety and depression in the weeks prior to and following the test result, nor did they report to actively use avoidance to prevent becoming distressed. Whereas participants were concerned about the implications of testing for their offspring, the majority did not need psychological support. The interviews gave the impression that many men perceived the implications from an unfavorable test outcome as distant, and felt that they are not to be blamed for the possibility of having passed the mutation to their offspring. This situation could

change drastically, however, if daughters have to undergo invasive prophylactic surgery or become diagnosed with cancer. The difference in emotional impact of such a threatening event and the situation of men in the present study, is clearly summarized by the following quote: [IX] ...*"If I had a daughter affected by cancer, this would affect me twice as badly if this was due to me carrying a gene mutation. I think that as long as things are going fine, you may very well continue to feel all right, but as soon as a daughter becomes ill, you will be overwhelmed by devastating feelings."*

Acknowledgements
The authors are indebted to Dr. DJJ Halley and Dr. AMW van den Ouweland, involved in mutation analysis at the Department of Clinical Genetics, Erasmus University Rotterdam.

Chapter 8

ATTITUDES TOWARDS TERMINATION OF PREGNANCY IN INDIVIDUALS WHO UNDERWENT PRESYMPTOMATIC TESTING FOR THE BRCA1/BRCA2 GENE MUTATION IN THE NETHERLANDS

Lodder LN; Frets PG; Trijsburg RW, Meijers-Heijboer EJ; Klijn JGM; Niermeijer MF

Journal of Medical Genetics 2000; 37: 883-4, reprinted with permission from the BMJ Publishing Group

The offspring of mutation carriers for autosomal dominant inheritable late onset disorders have a 50% chance of inheriting the gene-mutation. The possibility of prenatal genetic diagnosis for such disorders, such as Hereditary Breast/Ovarian Cancer, raises complex ethical questions (Lancaster et al 1996; Wagner et al 1998). The present paper addresses the question to which extent physicians and policy makers working in Genetics or Oncology, may expect requests for prenatal diagnosis and termination of pregnancy because of BRCA1/BRCA2 carriership.

A questionnaire assessing attitudes towards termination of pregnancy if the fetus was found to be a BRCA1/BRCA2 female or a male mutation carrier was answered by 78 subjects (67 women and 11 men) who underwent presymptomatic DNA-testing for Hereditary Breast/Ovarian Cancer, six months after receiving their test-results. Subjects were asked to indicate to which extent they found termination of pregnancy acceptable for themselves. Subjects with and without a desire of having children were included in the study. There were 26 carriers of the BRCA1/BRCA2 mutation (23 females/3 males; mean age 36,5) and 52 non-mutation carriers (44 females/8 males; mean age 38,8). The latter group served as a reference group: they cannot transmit the mutation to their offspring, but are well informed about implications of Hereditary Breast/Ovarian Cancer.

None of the 26 mutation carriers found termination of pregnancy in case of a female or a male mutation carrier fetus as acceptable for themselves. A minority of the non-mutation carriers viewed termination of pregnancy as acceptable in case of a female (14%) or a male mutation carrier fetus (10%; see table). The differences between mutation and non-mutation carriers are significant ($p<.05$; Pearson Chi-square test, SPSS/PC, release 8.0). Five of the seven non-

mutation carriers held termination of pregnancy acceptable independent of the sex of the mutation carrier child. This is surprising, since males with a BRCA1/BRCA2 mutation have no high lifetime risk to develop cancer. However, the majority of the non-mutation carriers and all the mutation carriers in the present study, rejected termination of pregnancy in case of a child which 1) has a high risk of developing breast- or ovarian cancer later in life (a girl) and/or 2) can transmit the gene to his/her offspring (boy or girl).

Attitudes of BRCA1/BRCA2 Mutation carriers and Non-Mutation carriers towards Termination of Pregnancy because of a fetus carrying a mutation

If there was a pregnancy in my family, I would find Termination of Pregnancy acceptable if the child was:	**Mutation-carriers N=26**	**Non-Mutation carriers N=52**
A female BRCA1/BRCA2 mutation carrier	0%	13,5%
A male BRCA1/BRCA2 mutation carrier	0%	9,6%

The stronger reluctance in mutation carriers than in non-mutation carriers towards terminating a pregnancy of a mutation carrier boy or girl may have several reasons. Firstly, mutation carriers may be more acutely aware of the burdensome emotional implications of terminating a pregnancy because of BRCA1/BRCA2 carriership, than non-mutation carriers. Secondly, they may perceive terminating the pregnancy of a mutation carrier child as incompatible with their own existence.

In subjects at risk for autosomal dominant Huntington Disease, the actual demand for prenatal diagnosis and termination of pregnancy is much lower than could be expected based on studies assessing attitudes towards these techniques (Tibben et al 1993c; Adam et al. 1993). Prenatal diagnosis and termination of pregnancy for late-onset diseases, with decades of healthy life before onset of the disorder, are considered as very difficult choices for parents. In our experience of 500 families at risk for Hereditary Breast/Ovarian Cancer seen during the past five years, two requests for prenatal diagnosis were made by recently identified mutation carriers, who wanted to have children in the nearby future. Considering the few actual requests for prenatal diagnosis for BRCA1/BRCA2, the emotional burden of such a decision and the general reluctance towards terminating a pregnancy of a mutation carrier child (this study), the demand for prenatal diagnosis in Hereditary Breast/Ovarian Cancer families is expected to remain low. Genetic counseling of couples considering these highly complex and burdensome options should focus on supporting parents in the decision making process. There are no general rules of wisdom or ethical desirability that could take priority in finding individual solutions and the need to support each couple.

Chapter 9

DISCUSSION

Introduction

This thesis addresses the emotional and behavioural consequences of presymptomatic DNA testing for women and men from families with hereditary breast and ovarian cancer. Moreover, emotional well-being and attitudes were also analysed in women who decided to decline genetic testing.

In the following section, the conclusions on the principal questions in this study (chapter 1) are summarized, discussed and compared with findings from other studies. In the final section, clinical implications of the results for improving genetic counseling and psychological support for women and men from HBOC families will be given, and suggestions for further research will be done.

1) Motives of women and men to opt for genetic testing for BRCA1/BRCA2 or for declining the test *(Chapter 2 and 3)*

Major reasons to opt for genetic testing reported by female and male test-applicants were generally similar to those reported in previous studies (Dudok de Wit et al 1997a, Hopwood 1997, Lerman et al 1996a, 1997, Lynch et al 1999, Watson et al 1995). Reasons most often expressed by women were to obtain certainty about 1) having an increased risk to develop cancer or not (96%), 2) the need for future intensive surveillance and/or prophylactic interventions (86%), and 3) the risk of having transmitted the gene to their offspring (36%). Knowing about risks for future offspring was a reason for 9 of the 31 women considering future offspring (29%).

In contrast to findings in the USA, in our study learning about the children's risks was not the most reported reason to apply for testing (Lerman et al 1996a, Lynch et al 1999). This difference follows from the inclusion in the American studies of male test applicants and women who had an earlier cancer diagnosis, besides healthy women at risk for a BRCA1/BRCA2 mutation. Male test applicants in our study indeed indicated to learn about their children's risks as their major motive for testing. The importance of this motive in males is also reflected in the result that only 3/28 (11%) of the male test applicants were childless, as compared to 24/85 (28%) female test applicants.

Of the women opting against testing, 8/13 (62%) were childless. This indicates that the important motive of 'knowing the test result for one's

children' did not apply to more than half of the women declining testing. Reasons to decline testing as reported by these women include 1) feeling satisfied with frequent surveillance (10/13), 2) not wanting to change risk management (more frequent screening/prophylactic surgery) if identified as mutation carrier (4/13), 3) feeling unable to cope emotionally with an increased risk for cancer (4/13), and 4) feeling emotionally unprepared for the possibility of receiving an unfavorable test outcome (4/13). Also, two thirds of the non-tested women did not expect to obtain more certainty if they knew that they were mutation carrier.

The impression was that most non-tested women had seriously weighed pros and cons of testing. They reported not more anxiety than the women who opted for testing. A fear of problems in obtaining/keeping health insurance, which was the major reason to decline testing in findings from the USA, was not reported in our study (Lynch et al 1999). This reflects the current acceptance of this type of health care by most health insurance organisations in the Netherlands. It is uncertain whether this will remain unchanged in the future. Because in the USA genetic testing and costs for prophylactic surgery often are not reimbursed (Lynch, Watson et al. 1999), individuals declining genetic testing in that country, may be a less wealthy group than the sample undergoing genetic testing.

2) Psychological consequences of genetic testing for women and men at risk to be a BRCA1/BRCA2 mutation carrier and their partners *(Chapter 4 and 7)*

Women identified as (non)mutation carriers

Women recently (1 to 3 weeks) identified as mutation carriers had a mean distress level in the normal range, and similar as prior to disclosure of the result, which is in agreement with findings from other studies (Croyle et al 1997, Lerman et al 1996a, 1998). High anxiety was reported by 20% of the mutation carriers in these post-test weeks (5/25). Non-mutation carriers less often reported high post-test distress (6/53). The mean post-test distress level in non-mutation carriers was significantly lower than in mutation carriers and was explained by the decrease in distress in non-mutation carriers from pre- to post-test. In studies from the USA similar findings were reported (Croyle et al 1997, Lerman et al 1996a, 1998). In those studies, mean distress levels in the normal range and the unchanged level of distress in mutation carriers were explained by the long anticipation and preparation period in participants, most of whom having been involved in long-term family studies. In our study, about 40% of the female test-applicants was since less than 1 year aware of the genetic nature of cancer in the family, making long-term adaptation a less likely explanation

for non-excessive mean distress levels and no increase of distress in mutation carriers. An alternative explanation might be the support experienced from participating in the psychological follow-up study, which offered a regular opportunity to talk to a professional familiar with various issues involved in BRCA1/2 testing. Other authors have already addressed that distress levels found in psychological studies might be an underestimation of distress that would be experienced, if no such special attention is paid to test-applicants (Lerman & Croyle 1995).

Another factor which may be related to the non-excessive mean pre-test distress levels and the unchanged distress level in mutation carriers is the high motivation and the urge participants seemed to have to undergo genetic testing: all applied for testing within one year, and the majority within two months after the test became available in their family. In the future, test applicants may show up who are less certain about the benefits of genetic testing and who may have needed one or more years to overcome their ambivalence. As Grosfeld et al. (2000a) wrote: 'today's decliners may become tomorrow's applicants'. Psychological reactions in such applicants if they are found to be mutation carrier need further study. Finally, the decision about risk management if identified as mutation carrier (surveillance/prophylactic surgery) is made by most women in our study already prior to disclosure of the result. Such 'early anticipation' on the post-test period, may indicate that the work of worrying process, and the distress involved, are not only present in the post-test weeks, but start already prior to disclosure of the result.

The decrease of distress from pre- to post test in women found not carrying the mutation, is in line with what one might expect, and similar to observations by others (Croyle et al 1997, Lerman et al 1996a, 1998). A small increase of distress was found at 6 months after the result, but the distress level at that assessment moment was still lower than prior to the result. If this increase of distress can be explained by 'survivor guilt', as found in non-mutation carriers for Huntington disease, is not clear. Survivor guilt is an inability to feel relief, despite the fact that a period of fear about one's life and destiny has vanished. An important factor in survivor guilt is empathy with others whose fate is less favorable than one's own. Outcomes from studies on Huntington disease in which the distress level of non-mutation carriers was found to be similar to that of mutation carriers in the weeks after disclosure of the result, leave the impression that survivor guilt may be more prominent in non-mutation carriers for Huntington disease than in non-mutation carriers in HBOC families (Decruyenaere et al 1996, Dudok de Wit et al 1998c, Tibben et al 1993b). Some non-mutation carriers in those studies explained their absence of relief by worries for affected or at risk relatives (Tibben et al 1993b). We

suggest that absence of relief due to the discrepancy between ones own favorable test outcome and unfavorable scenarios for relatives, may be more prominent in non-mutation carriers for Huntington disease than in non-mutation carriers for HBOC for the following reasons. Firstly, Huntington disease is fully penetrant, and not having inherited the mutation, means that one will not develop the disease, while knowing many at risk or affected relatives. HBOC is incompletely penetrant (the majority of male and also a proportion of female mutation carriers will not develop cancer) meaning that many non-mutation carriers (who themselves have the remaining population risk for breast and ovarian cancer), may be less intensely confronted with the disease in relatives. Secondly, Huntington Disease is characterized by a long and incurable process of mental deterioration, while BRCA1/BRCA2 mutation carriers may opt for regular surveillance or prophylactic surgery to decrease their risk to die from cancer. These differences between both diseases may explain possible differences in the degree of survivor guilt for non-mutation carriers for Huntington disease and non-mutation carriers for HBOC. However, survivor guilt may become manifest in the last group when the implications of mutation carriership in a close relative can no longer be denied, such as when a relative undergoes prophylactic surgery or when she becomes diagnosed with cancer. Psychological consequences for non-mutation carriers when their close relatives face such burdensome circumstances need to be further analysed.

Another explanation for high distress in non-mutation carriers in HD families, is the confrontation with choices they made throughout their lives, in anticipation of becoming affected with the disease, and which, retrospectively, may have been unnecessary (Huggins et al 1992). A partner choice might primarily have been made because he/she is perceived as a future caregiver, or a career is chosen offering security in case of future illness (Grosfeld 2000a). For women who apply for genetic testing for BRCA1/BRCA2, these may be less likely dilemmas, because of their options for surgery and absence of mental illness. In our study such regrets of earlier made choices were not expressed and in another study they were observed in one out of 101 non-mutation carriers for HBOC (Lynch et al 1997).

Psychological implications of obtaining a specific role in a family from the moment the family-specific gene mutation becomes identified, such as 'the messenger' of this news and/or being 'the first to utilise the test/prophylactic surgery' (Dudok de Wit et al 1994, 1997b), were not specifically addressed in this study. Observations of many different branches within a family, showed that individual roles seemed to change over time, and that multiple persons in a family assumed the responsibility to inform (often distant) relatives about the

genetic nature of cancer and the possibility of testing. Also, multiple persons who underwent the test and/or prophylactic surgery functioned as an example for other relatives. The impact of genetic testing on the family system, as demonstrated for Huntington disease, needs further study for families with HBOC (Sobel & Cowan 2000).

Partners of women and men identified as (non)mutation carriers

Distress levels of partners of female test-applicants (prior and several weeks after disclosure) and male test-applicants (prior to disclosure) were not lower than those of the test applicants themselves. Unlike female mutation carriers, their partners experienced increased distress from prior to disclosure of the result to 1 to 3 weeks post-test, one third reporting high distress. Post-hoc analyses revealed that six months after disclosure the distress level had returned to the pre-test level again. Probably, in the post-test weeks many partners became perceptive for the first time of the consequences of an unfavorable test-outcome; at pre-test most of them anticipated that their problems would not increase if their partner was identified as a mutation carrier. This may be indicative for a tendency to postpone worrying until after the test outcome (chapter 2). These findings seem to support the rationale of the protocol for genetic testing for HBOC, that partners are included in the pre-test counseling session, in which the choices and consequences after the test result are discussed.

Men at risk to be a BRCA1/BRCA2 mutation carrier

Male test-applicants were found to have lower pre-test anxiety levels than female test-applicants, but the depression levels were similar in both groups. High anxiety prior to disclosure of the result, was found in 25% of the female test-applicants and in 7% of the male test-applicants. A similar proportion of men (35%) and women (36%) expected their problems to increase after being identified as a mutation carrier, and to decrease after a favourable test-outcome (44% versus 42%). More men (76%) than women (46%) with children expected that problems of these children would increase after an unfavourable test-outcome and decrease after a favourable test-outcome (83% versus 50%). Men might be more concerned about their children since this is the major reason for them to undergo the test, whereas most women primarily apply for testing to know about the implications for their own lives. Also, men with daughters reported more distress than men with only sons, or without children; this result did not apply for women. Lower anxiety levels in male than in female test applicants might be either due to 1) the fact that unlike their female counterparts males identified as mutation carrier do not face a high cancer risk nor difficult choices on risk management and 2) the observation that men in

general tend to report lower distress levels than women (Dudok de wit et al 1998a, Risberg et al 1996, Vernon et al 1997).

3) Identifying subjects at risk for high distress ***(Chapter 2, 3, 4, 5, 6 and 7)***

At pre-test, many predictive factors for high distress were found for female test-applicants. Factors most strongly related to high distress in these women include 1) expecting an increase of problems after being identified as a mutation carrier, 2) opting to undergo prophylactic mastectomy 3) being non-optimistic and having a tendency to suppress emotions, 4) being younger than 40 and 5) having much experience with cancer in the family. Some of these results are similar to those found in other studies. In a large sample of women receiving genetic counseling for their increased risk for breast cancer, those who opted for prophylactic mastectomy (while not knowing their genetic status) had higher distress than those who did not (Stefanek et al 1995). In a similar population, a relation between high distress and not being optimistic was demonstrated (Audrain et al 1995). In contrast to our findings, Lerman et al. (1997) found in their study on individuals from BRCA1 families, who all had multiple affected relatives, a similar level of distress as in at risk women with only one relative with breast/ovarian cancer. However, contrary to our study, in these studies no distinction was made between whether the relationship with these relatives were close or distant. In our study sample we found that the relationship with a first degree relative could be distant, which illustrates the importance of addressing the degree of perceived closeness of the family relationship.

Factors related to high distress several weeks after the test result were 1) being identified as a mutation carrier and 2) having high distress levels prior to disclosure of the result. These factors were also observed in the American studies (Croyle et al 1997, 1998). The finding that high pre-test distress is related to high post-test distress, may indicate that high levels of distress not only represent adverse situational factors (such as being identified as a mutation carrier), but may also be the result of having a 'distress-prone personality'.

Within the group of mutation carriers, those opting to undergo prophylactic mastectomy were much more distressed both before and after the result, than women opting for frequent surveillance. The high distress levels in the first group may be explained by the fact that 1) many women were in their thirties and had young children, and 2) they were confronted with a threatening prospect of surgery. Of women undergoing surveillance only one was in her thirties and one other had young children. However, it remains puzzling why throughout the study distress levels in the group of women opting for

surveillance were similar to or even lower than in the group of non-mutation carriers. Experiencing a basic trust in participation in the surveillance program might be part of the explanation.

Contrary to an earlier study, we found no higher distress 6 months after being found to be a mutation carrier in women who had underestimated their post-test emotional reactions at pre-test than in those who had accurately anticipated their reactions (Dorval et al 2000, Chapter 4). Of the mutation carriers who reported having experienced an increase of problems since disclosure of the result (8/26), those who had not expected this to happen prior to the result (5/8), were not more distressed than those who had (3/8). However, the small number of women in this analysis, precludes definitive conclusion from these findings.

Interestingly, high distress in non-mutation carriers was found to be related to high pre-test levels of distress, but also to the test-outcome in close relatives: more depression was found in non-mutation carriers with a sister who had been recently identified as a mutation carrier, than in the other non-mutation carriers. A similar finding had been reported for males who underwent genetic testing for BRCA1/BRCA2 (Smith et al 1999). These results reflect that the reaction to one's own favorable test-outcome, can become overshadowed by a concern for a sister with an unlucky fate. However, such concern is not found to cause frequent depressive reactions: 15% of the non-mutation carriers reported a high level of depression in the weeks after disclosure of the test result.

4) Factors associated with choices female mutation carriers make regarding prophylactic mastectomy/oophorectomy and frequent surveillance *(Chapter 2, 4 and 5)*

Women identified as a mutation carrier who opted for prophylactic mastectomy were significantly more often in their thirties and/or had young children, and were longer aware of having an increased risk to develop breast/ovarian cancer than women who opted for frequent surveillance. Mutation carriers being aged between 30 to 40 years have a higher risk to develop breast cancer than those younger than 30 years, and, they may have a higher gain in life expectancy after surgery than older mutation carriers (Meijers-Heijboer et al 2000). Mothers of young children may be more likely to opt for prophylactic mastectomy because of the intention to maximize their chance to raise their children. A longer experience with their genetic risk might have prepared women emotionally for this far-reaching risk management option.

However, chapter 3 shows that another group, i.e. women who opted to decline genetic testing, also had a longstanding awareness of the genetic

nature of cancer in the family. Besides, as in the group opting for prophylactic mastectomy, they were relatively young when first confronted with breast/ovarian cancer in a relative. For the non-tested women we hypothesized that being confronted at a relatively young age with breast/ovarian cancer in a relative, and being aware of the genetic risk for many years, made them integrate the risk for cancer as part of their lives. Genetic testing may not be seen by these women as a means to regain control over their life. But this explanation does not apply to women who do opt genetic testing, and after being identified as mutation carrier, for prophylactic mastectomy. A difference between the two groups is that women opting for testing and prophylactic mastectomy were subsequently more often confronted with affected relatives than the non-tested women. Repeated confrontations with the disease and its consequences in relatives, may have made the first group more conscious of the possibility of becoming the next affected person in the family. From this perspective, the choice to opt for genetic testing and subsequent prophylactic mastectomy is quite understandable.

Mutation carriers who opted for frequent surveillance were less long aware of the genetic nature of cancer in the family and were older when first confronted with cancer in a relative than both the non-tested group and mutation carriers who opted for prophylactic mastectomy. Besides, this group was familiar with about the same number of affected relatives as the non-tested group, which was lower than in women opting for prophylactic mastectomy. Possibly because mutation carriers opting for surveillance had been confronted with fewer affected relatives than those opting for prophylactic mastectomy, their perceived threat of developing cancer might have been smaller, and consequently, their interest for prophylactic mastectomy lower. Accordingly, we may better understand the low distress levels in mutation carriers opting for frequent surveillance throughout the study. Moreover, being confronted with an increased risk for cancer relatively late in their lives, may have resulted in sudden existential doubt in these women, and genetic testing might have been perceived as an opportunity to regain some control over their lives. However, prophylactic mastectomy might be experienced as too far reaching, because most may need a longer time period to adapt emotionally to such a burdensome decision. More research is needed to confirm the above hypotheses.

Our study was the first to compare women refraining from testing with mutation carriers opting for prophylactic mastectomy or frequent surveillance. Analysing differences in experiences with cancer in the family between women deciding in such different ways increases our understanding of factors important for these decisions and may also help to improve the counseling of women in the decision making process. In women opting for prophylactic

mastectomy, one may explore whether they feel as if they will be the next to develop cancer in the family and in women opting for surveillance, whether their high risk for cancer is perceived as something rather abstract. Other researchers have developed a decision making program to support women finding their way with different risk management options and first reports on the implementation of this program are positive: women who utilized this program felt less decision uncertainty, less burden of the decision, and their knowledge and risk comprehension had improved (Stalmeier et al 1999).

In our study the impression was obtained that in some families there was a greater tendency among relatives to opt for mastectomy than in others, but we have no statistical evidence for this observation. It may be an incentive for future research to study whether such family tendencies do exist and, if so, which explanations for this (such as relatives conforming to each other in decision making, or families having specific values, for example regarding the perceived importance of femininity) will be valuable.

5) Psychological consequences of prophylactic surgery and the impact on body image and on the intimate relationship for women themselves and their partners *(Chapter 5)*

Mutation carriers undergoing mastectomy within one year after the test outcome, had strikingly higher levels of general and cancer-related distress during the study period (especially at pre- and post-test), than mutation carriers undergoing regular surveillance and non-mutation carriers (Chapter 4). All but one of the women of the first group, had already made the decision about this course of action prior to disclosure of the test result (Chapter 4). It might be that the decision for mastectomy might be prompted by such high distress. A second explanation for the higher levels of distress in women opting for mastectomy may be that the prospect of this burdensome and irreversible surgical option might have induced anxiety both prior to and following the test result. Statements from interviewed women are more often in line with the first explanation than with the second. The fact that many women opting for prophylactic mastectomy were in their thirties and/or had young children, may be an important explanation for the high anxiety level in these women (see the discussion under 3)). Prior to disclosure of the test result, these two biographical factors were both significantly related to high distress (Chapter 2). A relatively high distress level in women opting for prophylactic mastectomy was also observed in other studies (Stefanek et al 95, Meiser et al 2000a). However, one study including women with a high genetic risk (not knowing whether they were mutation carrier) did show that baseline distress levels in women undergoing (n=79) and declining prophylactic mastectomy (n=64) were

similar, but women declining surgery had higher anxiety as a *personality* trait than women opting for surgery (Hatcher et al 2001). In our study, this was not investigated, but no difference was found in the personality trait 'optimism' between those undergoing and those declining prophylactic mastectomy.

Similar to results from others studies, a clear decrease in distress over time was found at the follow up assessments in the study, the last of which was held 6 to 8 months after surgery (Frost et al 2000, Hatcher et al 2001). However, women who underwent prophylactic mastectomy (with reconstruction) were significantly less satisfied with the look and feel of their breasts at this last assessment moment, than mutation carriers who opted for frequent surveillance and non-mutation carriers. Other negative influences of prophylactic mastectomy reported were: not feeling sexually attractive, not feeling in the mood for having sex, having physical complaints and a lowered self-esteem. Frost et al. (2000) found among 572 high risk women who had undergone bilateral prophylactic mastectomy in a large US health clinic about 6 to 40 years earlier (mean 14,5 years; mutation carriership was not confirmed), that 23% to 36% reported negative effects regarding the sexual relationship, feelings of femininity and body image. However, Hatcher et al. (2001) did not find adverse effects for the sexual relationship.

With regard to both general body image and sexuality it is remarkable that not only after surgery, but already prior to disclosure of the test result, mutation carriers opting for mastectomy report less satisfaction with both their bodies and their intimate relationship than mutation carriers opting for surveillance and non-mutation carriers. Post-hoc analyses reveal that this is more likely to be a bias characteristic of the mastectomy group, than that the lower satisfaction rates are related to the decision for prophylactic mastectomy: within the group of non-mutation carriers (n=53), those who reported at pre-test that they would opt for prophylactic mastectomy if identified as a mutation carrier, had similar body image and sexuality scores as those who would opt against prophylactic mastectomy.

The choice for prophylactic mastectomy was not regretted by 13/14 mutation carriers. The major reason for the overall satisfaction with the decision for prophylactic mastectomy may be relief due to a significant reduction of the risk for breast cancer. We can not exclude the possibility that the low number of regrets might, in part, be explained by the fact that regretting an autonomous, far-reaching decision for an irreversible surgical intervention would lead to the undesirable state of 'cognitive dissonance' (Festinger 1957, Chapter 5). A 'cognitive dissonance' is assumed to be less distinct if the sense of autonomy in the decision-making process is reduced, e.g. because of external pressure. We did not assess such perceived autonomy in the

decision making process, but it is intriguing that the woman in this study who regretted surgery, expressed that she would have decided otherwise had she been better informed about the profound impact of surgery on her physical well-being, body image and intimate relationship. In other research evidence was found for the association between regretting the decision for prophylactic mastectomy and a lower perceived autonomy in the decision making process/dissatisfaction with the information provided about the implications of prophylactic mastectomy (Borgen et al 1998, Stefanek et al 1995).

Because only a small number of partners of women undergoing prophylactic mastectomy participated in the study, their perceptions and feelings about the implications of surgery are only sparsely represented. Whereas these partners (n= 8) reported no more problems with their wife's appearance than partners of women who did not undergo prophylactic mastectomy (n= 13), they reported to have less frequent intimate contact with their spouses up to 8 months after surgery. From the interviews the impression was obtained that the reduction in frequency of cuddling and/or making love, was more due to the women feeling inhibited and uneasy with their bodies, than due to the partners' feelings.

6) Low distress as a reflection of a tendency to deny adverse consequences of testing *(Chapter 6)*

We showed how low anxiety scores reported by mutation carriers at six months follow-up could be a reflection of defensive denial of the continuing distress due to their genetic status (e.g. having a high risk for cancer, having undergone either prophylactic surgery or frequent surveillance, having children at risk for having inherited the mutation). Mutation carriers who had difficulty to coherently and truthfully express current experiences and thoughts about their genetic status (coherence score of an interview transcript) reported less anxiety in the self-report questionnaire than the mutation carriers with no such difficulty: This may indicate that the non-coherent mutation carriers do not feel emotionally prepared to experience the impact of the threats they are confronted with, and may, in order to avoid painful feelings, maintain an illusion of mental health. This psychological mechanism was observed earlier by Shedler et al. (1993) and Dudok et al (1998b).

Interestingly, in non-mutation carriers low anxiety was associated with the capability to coherently reflect on current experiences and thoughts about their genetic status, which may indicate 'genuine mental health'. High distress in non-mutation carriers with incoherent interview transcripts cannot be interpreted as possibly resulting from defensive denial. Instead, one could speculate that the incoherence in this case resulted from difficulties to take distance from a burden

that has vanished, or from ambivalent feelings due to personal relief from a burdensome perspective, whereas relatives still live under the same threat. Such ambivalence in non-mutation carriers ('survivor guilt') was reported previously (Tibben et al 1990). More research may clarify whether 1) assessing coherence is a method to grasp the complex psychological state of 'survivor guilt' and whether 2) incoherence reflecting defensive denial is different from incoherence caused by a situation in which ambivalence and 'survivor guilt' may be experienced.

7) Attitudes of test applicants towards prenatal diagnosis for BRCA1/BRCA2 gene mutation carriership *(Chapter 8)*

Whereas professionals generally consider prenatal diagnosis and termination of pregnancy in case of a fetus with a BRCA1/BRCA2 mutation as too far reaching (Lancaster et al 1996, Wagner & Ahner 1998), attitudes of women for whom this option might be relevant have not been studied previously. Our study showed that all mutation carriers (n= 26) considered termination of pregnancy in case of a mutation in a female or a male foetus as 'unacceptable for themselves'. A minority of the non-mutation carriers viewed termination of pregnancy as acceptable in case of a female (14%) or a male mutation carrier fetus (10%). The stronger reluctance towards terminating a pregnancy in mutation carriers than in non-mutation carriers is significant and may have several reasons. Firstly, mutation carriers may be more acutely aware of the burdensome emotional implications of terminating a pregnancy because of BRCA1/BRCA2 carriership, than non-mutation carriers. Secondly, they may perceive terminating the pregnancy of a mutation carrier child as incompatible with their own existence. Finally, it may be a reflection of the natural inclination of human beings to adapt to the burdensome experiences they face in their lives, instead of judging their life in retrospect as 'not worth living'.

The finding that the majority of the non-mutation carriers and all the mutation carriers in the present study rejected termination of pregnancy in case of a child which 1) has a high risk of developing breast- or ovarian cancer later in life (a girl) and/or 2) can transmit the gene to his/her offspring (boy or girl) indicates that the subjects in this study consider a life worth living, despite burdensome implications of BRCA1/BRCA2 mutation carriership.

8) Suggestions for improving guidelines for genetic counselling, the need for psychological support in individuals at risk and for post-test counselling of mutation carriers *(Chapter 2,3,4,5,6,7 and 8)*

Guidelines for genetic counseling

Mean distress levels in healthy women and men at risk undergoing genetic testing for BRCA1/BRCA2 were not found to be higher than those of a

normal population in the period before and after disclosure of the result. This implies that with the use of the present protocol for presymptomatic genetic testing, the procedure is not psychologically distressing to the extent that additional psychological support is needed for all test-applicants. Sessions with a psychologist in the year following the result were requested by 3/14 women who underwent prophylactic mastectomy (all having a high distress level, two being in their thirties with young children). None of the women who opted for close surveillance requested to see the psychologist, but 2/53 non-mutation carriers (having high distress levels) did in the months following the result.

The majority of the test-applicants seemed to be satisfied with the protocol which was developed for the procedure of presymptomatic genetic testing for BRCA1/BRCA2 when this test was firstly offered some years ago (described in the introduction section). Whereas many were positive about the emphasis placed on pre-test preparation and discussion of implications of the test-result, and the way of disclosing the test-result in a face-to-face contact with the test-applicant and the partner, some test-applicants proposed changes in the protocol. Incidentally, test applicants expressed in the interviews, that they, contrary to the policy to disclose the result to each test-applicant personally, wished to share this session with a sister or other relative who was tested simultaneously. The motivation of this policy is to give each individual the opportunity to experience her/his first emotional reactions to the result without needing to consider feelings of a close relative who is informed about the result at the same time. Some other test applicants preferred to obtain the result by telephone or through their GP. Considering the low percentage of women reporting clinical levels of distress in the weeks following the result, there seems to be a reason to deal with the protocol in a flexible way if this is thought to be appropriate. It is important to closely follow up any negative effects this may have. In the sample described in this thesis, we once complied with the strong wish of two sisters to receive their (possibly different) result together. We offered these sisters a session with the psychotherapist, to discuss (dis)advantages of this wish. Although these sisters did not receive the same result, they were satisfied that the disclosure session was organized in accordance with their wishes.

No frequent requests for prenatal diagnosis for BRCA1/BRCA2 are to be expected

Clinical practice has shown that very few mutation carriers with a desire to have children show interest in the possibility of prenatal diagnosis for BRCA1/BRCA2. In this study we observed that none of the mutation carriers would accept for themselves to terminate a pregnancy in case the mutation is detected in a female or male fetus. Taking together the low incidence of such

requests and the overall unfavorable attitudes towards this option as found in this thesis, we may conclude that prenatal diagnosis for BRCA1/BRCA2 is not likely to become common practice. In the same vein, in subjects at risk for Huntington Disease, the actual demand for prenatal diagnosis and termination of pregnancy is much lower than could be expected based on studies assessing attitudes towards these techniques (Adam et al 1993, Tibben et al 1993c). Genetic counseling of couples considering these highly complex and burdensome options should focus on discussing the various aspects of these options and helping the couple to find the decision which is most appropriate for them.

The need for psychological support in the testing procedure

The overall low pre- and post-test distress levels found in those undergoing BRCA1/BRCA2 testing, indicate that extensive psychological support does not seem to be necessary for the majority of test applicants in the period before and after the result. However, a number of test-applicants did have high distress levels at one or more assessment moments. This thesis revealed some predictive factors for high distress: women who were found to be mutation carriers and who seemed to be highly distressed at pre-test and/or who intend to undergo prophylactic mastectomy feel more distressed upon being informed about their result than other test-applicants. Genetic counselors may take notice of these predictive factors and offer a psychological support session in the weeks following the result to female mutation carriers who seemed distressed already prior to the result and/or who intend to undergo prophylactic mastectomy. Distress could be assessed by means of the Hospital Anxiety and Depression scale, for which cut off scores are described for a 'borderline' and a 'clinical' level of anxiety and depression. During the period of surgery referral to a psychologist or social worker at the hospital is recommended.

For the other test-applicants found to be mutation carrier (male and female) it might be sufficient to emphasize during the disclosure session that receiving additional psychological support is possible and to leave the initiative to request such support by the test-applicant, except when the genetic counselor/clinical geneticist considers it important to be more directive in proposing such support. Future assessments with distress scales should closely monitor if such a support protocol is indeed sufficient. When applying this 'more selective' support strategy, the threshold to ask for support if one needs it may be decreased if a letter is given with the name and telephone number of the social worker/psychologist, or if the social worker/psychologist introduces him-/herself personally after the genetic counselling session. When distress levels in test-applicants will be significantly higher when applying this 'selective'

support strategy than in the present study, we may conclude that the repeated contacts in our study with the researcher-psychologist before and after disclosure of the result, might have had an important supportive function.

Among non-mutation carriers, those having sister(s) identified with a mutation in the same period were more likely to experience depressive feelings in the weeks after the test result than other non-mutation carriers. Explaining these women in the session of disclosure of the result that such ambivalent feelings are normal may help them to understand themselves better and explain themselves towards their environment when they are confronted with such feelings. Future research may identify non-mutation carriers who besides such psycho-education are needing psychologically support in the post-test weeks.

Not only to enable decision making about the *quantity* of support needed for men and women applying for genetic testing for BRCA1/BRCA2, but also about the methods of the interventions themselves, random control trials should be developed, in which the effects of different support strategies on distress levels will be compared. Beneficial effects of pre- and/or post sessions with a social worker or genetic nurse in which the test-applicant can discuss his/her concerns and emotions about the situation may be compared to the effects of sessions with a psychologist/psychotherapist (preferably knowing the dynamics of cancer and genetics). An earlier study has shown that a supportive group intervention was effective in decreasing levels of distress in women at increased risk for breast cancer (Esplen et al 2000).

Supporting decision making regarding risk management options in women identified as mutation carriers

This study revealed that the decision about which risk management option one would undergo after being identified as a mutation carrier, was made already prior to disclosure of the result. It is not known whether this decision was generally made after the pre-test counseling session or before, but our impression is that this decision at least becomes more solid in the period between pretest counseling and disclosure of the result. Prophylactic mastectomy may be seen as the most far-reaching preventive risk management option for female mutation carriers. Since such surgery is irreversible, it seems wise that women make their decision after seriously weighing the advantages and disadvantages. In this study, women opting for prophylactic mastectomy were found to be more anxious than women opting for surveillance, both in the weeks before and after disclosure of the result, and most of them made the decision for prophylactic mastectomy already prior to disclosure of the test result. To confirm whether high anxiety in the period of testing is the most important incentive to opt for prophylactic mastectomy, more research is needed. Furthermore, research including more women carrying the mutation

and assessments moments after a longer follow-up should also elicit whether fast decision making increases the chance of regretting one's decision post-surgery. Of the woman in our study who regretted her decision for mastectomy, we do not know whether she would have decided otherwise had she taken more time for decision making. If the amount of time taken for the decision is found to be important, it may be wise to give recently identified mutation carriers the opportunity to restore a little from the storm induced by genetic testing and its result, for example by offering the possibility to start by participating in the surveillance program.

Support for female mutation carriers undergoing prophylactic mastectomy

This thesis pointed out that prophylactic mastectomy may have adverse affects on 1) physical well being, 2) satisfaction with how the breast region feels and looks like, 3) one's sexual life and 4) self esteem. Interview data provided information on the specific complaints women may have after surgery. Such information should be used to optimally prepare women for adverse effects beforehand. After surgery it may be supportive for women with specific problems to explain that such problems also occur in other women undergoing prophylactic mastectomy. Patient support groups for HBOC, have become increasingly important to exchange experiences and share information about this type of surgery. In our centre, many women who were identified as mutation carriers showed interest in hearing from experiences of other women who had undergone prophylactic mastectomy, either individually or in a group (van der Meer 1999).

Support for women deciding not to undergo the test (while undergoing surveillance)

The women at risk to be a BRCA1/BRCA2 mutation carrier described in this thesis who decided not to undergo genetic testing, but who underwent intensive surveillance, were not found to be a specifically distressed subgroup. For these women, it seems to be sufficient if the attending physician/oncologist is attentive for the needs for psychological support their patients may have. However, because of the small study sample, we should remain cautious generalizing these results.

The relevance of systematic research for clinical practice and future studies

The prospective study described in this thesis enabled providing an integrative and systematic picture of the process individuals at risk to carry a BRCA1/BRCA2 mutation go through from prior to receiving the result until one year post-test and of the problems they may face at different moments in time. Nevertheless, the period of time chosen is restricted. We did not study distress levels in earlier stages, for example when the search for the mutation in

the family was started, or shortly after the family specific mutation was identified. These are topics worth addressing in future studies.

Another moment of interest may be some years after genetic testing, to study the long term satisfaction with the decision for frequent surveillance (including false positive outcomes followed by biopsies) or prophylactic mastectomy in female mutation carriers, and the moment that children are becoming aware of being at risk. The latter may result in a serious reactivation of what these women had lived through years before. Apart from larger observation periods, larger numbers of mutation carriers who either decided to undergo frequent surveillance or prophylactic mastectomy should be included in future studies. Studying perceived pros/cons of such decisions has become especially relevant since the effectiveness of prophylactic mastectomy to prevent cancer in women with the BRCA1/BRCA2 mutation became demonstrated. In our group two large prospective projects have been started addressing satisfaction with these decisions and psychological well-being in a larger number of women at high risk of developing breast/ovarian cancer at a longer follow up. An important merit of the studies in this thesis include that their findings have provided fundamental data for such future research.

LIST OF REFERENCES

Aaronson NK, Bartelink H, van Dongen JA, van Dam FSAM. Evaluation of breast conserving therapy: Clinical, methodological and psychological perspective. *Eur J Surg Onc* 14: 133-40

Adam S, Wiggins S, Whyte P, Bloch M, Shokeir MH, et al. 1993. Five year study of prenatal testing for Huntington's disease: demand, attitudes, and psychological assessment. *J Med Genet* 30: 549-56

Arrindell WA, Ettema H. 1981. Dimensional structure, reliability and validity of the Dutch version of the Symptom Checklist (SCL-90): Data based on a phobic and a "normal" population. *Ned Tijdschr Psychologie en Haar Grensgebieden* 36: 77-108

Audrain J, Lerman C, Rimer B, Cella D, Steffens R, et al. 1995. Awareness of heightened breast cancer risk among first-degree relatives of recently diagnosed breast cancer patients. The High Risk Breast Cancer Consortium. Adherence and psychological adjustment among women at high risk for breast cancer. *Canc Epidemiol Biomarkers Prev* 4: 561-5

Baider L, Ever-Hadani P, Kaplan De-Nour A. 1999. Psychological distress in healthy women with familial breast cancer: like mother, like daughter? *Int J Psychiatr Med* 29: 411-20

Benkendorf JL, Reutenauer JE, Hughes CA, Eads N, Willison J, et al. 1997. Patients' attitudes about autonomy and confidentiality in genetic testing for breast-ovarian cancer susceptibility. *Am J Med Genet* 73: 296-303

Blackwood MA, Weber BL. 1998. BRCA1 and BRCA2: from molecular genetics to clinical medicine. *J Clin Oncol* 16: 1969-77

Bleiker EM, Van der Ploeg HM, Hendriks JH, Leer J-WH, et al. 1993. Rationality, emotional expression and control: Psychometric characteristics of a questionnaire for research in psycho-oncology. *J of Psychosom Res* 37: 861-72

Bleiker EM, van der Ploeg HM, Ader HJ, van Daal WA, Hendriks JH. 1995. Personality traits of women with breast cancer: before and after diagnosis. *Psychol Rep* 76: 1139-46

Bleiker EM, van der Ploeg HM, Hendriks JH, Ader HJ. 1996. Personality factors and breast cancer development: a prospective longitudinal study. *J Natl Cancer Inst* 88: 1478-82

Borgen PI, Hill AD, Tran KN, Van Zee KJ, Massie MJ, et al. 1998. Patient regrets after bilateral prophylactic mastectomy. *Ann Surg Oncol* 5: 603-6

Brandt J, Quaid KA, Folstein SE, Garber P, Maestri NE, et al. 1989. Presymptomatic diagnosis of delayed-onset disease with linked DNA markers. The experience in Huntington's disease. *Jama* 261: 3108-14

Channer KS, Papouchado M, James MA, Rees JR. 1985. Anxiety and depression in patients with chest pain referred for exercise testing. *Lancet* 2: 820-3

Claus EB, Risch N, Thompson WD. 1992. Age of onset as an indicator of familial risk of breast cancer. *Cancer* 131: 961-72

Codori AM, Brandt J. 1994. Psychological costs and benefits of predictive testing for Huntington's disease. *Am J Med Genet* 54: 174-84

Codori AM, Petersen GM, Miglioretti DL, Larkin EK, Bushey MT, et al. 1999. Attitudes toward colon cancer gene testing: factors predicting test uptake. *Canc Epidemiol Biomarkers Prev* 8: 345-51

Croyle RT, Smith KR, Botkin JR, Baty B, Nash J. 1997. Psychological responses to BRCA1 mutation testing: Preliminary findings. *Health Psychol* 16: 63-72

Croyle RT, Lerman C. 1999. Risk communication in genetic testing for cancer susceptibility. *J Natl Cancer Inst Monogr*: 59-66

Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, et al. 1996. Prediction of psychological functioning one year after the predictive test for Huntington's disease and impact of the test result on reproductive decision making. *J Med Genet* 33: 737-43

Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cloostermans T, Cassiman JJ, et al. 1997. Non-participation in predictive testing for Huntington's disease: individual decision-making, personality and avoidant behaviour in the family. *Eur J Hum Genet* 5: 351-63

Derogatis LR, Rickels K, Rock AF. 1976. The SCL-90 and the MMPI: A step in the validation of a new self-report scale. *Brit J Psychiatr* 128: 280-9

Dorval M, Patenaude AF, Schneider KA, Kieffer SA, DiGianni L, et al. 2000. Anticipated versus actual emotional reactions to disclosure of results of genetic tests for cancer susceptibility: findings from p53 and BRCA1 testing programs. *J Clin Oncol* 18: 2135-42

Dudok de wit AC, Meijers-Heijboer EJ, Tibben A, Frets PG, Klijn JG, et al. 1994. Effect on a Dutch family of predictive DNA-testing for hereditary breast and ovarian cancer. *Lancet* 344: 197

Dudok de wit AC, Tibben A, Frets PG, Meijers-Heijboer EJ, Devilee P, Niermeijer MF. 1996. Males at-risk for the BRCA1-gene, the psychological impact. *Psycho-oncology* 5: 251-7

Dudok de wit AC, Tibben A, Duivenvoorden HJ, Frets PG, Zoeteweij MW, et al. 1997a. Psychological distress in applicants for predictive DNA testing for autosomal dominant, heritable, late onset disorders. The Rotterdam/Leiden Genetics Workgroup. *J Med Genet* 34: 382-90

Dudok de wit AC, Tibben A, Frets PG, Meijers-Heijboer EJ, Devilee P, et al. 1997b. BRCA1 in the family: a case description of the psychological implications. *Am J Med Genet* 71: 63-71

Dudok de wit AC. 1997c. *"To know or not to know". Psychological implications of presymptomatic DNA testing for Autosomal Dominant Inheritable Late Onset Diseases.* PhD thesis Erasmus University Rotterdam

Dudok de wit AC, Tibben A, Duivenvoorden HJ, Niermeijer MF, Passchier J. 1998a. Predicting adaptation to presymptomatic DNA testing for late onset disorders: who will experience distress? Rotterdam Leiden Genetics Workgroup. *J Med Genet* 35: 745-54

Dudok de wit AC, Tibben A, Duivenvoorden HJ, Niermeijer MF, Passchier J, Trijsburg RW. 1998b. Distress in individuals facing predictive DNA testing for autosomal dominant late-onset disorders: comparing questionnaire results with in-depth interviews. Rotterdam/Leiden Genetics Workgroup. *Am J Med Genet* 75: 62-74

Dudok de wit AC, Duivenvoorden HJ, Passchier J, Niermeijer MF, Tibben A. 1998c. Course of distress experienced by persons at risk for an autosomal dominant inheritable disorder participating in a predictive testing program: an explorative study. Rotterdam/Leiden Genetics Workgroup. *Psychosom Med* 60: 543-9

Duits AA, Duivenvoorden HJ, Boeke S, Taams MA, Mochtar B, et al. 1998. The course of anxiety and depression in patients undergoing coronary artery bypass graft surgery. *J Psychosom Res* 45: 127-38

Esplen M, Toner B, Hunter J, Glendon G, Liede A, et al. 2000. A supportive-expressive group intervention for women with a family history of breast cancer: Results of a phase II study. *Psycho-Oncology* 9: 243-52

Fentiman IS. 1998. Prophylactic mastectomy: deliverance or delusion? We don't know, so we need to start registering all cases now. *Bmj* 317: 1402-3

Festinger L. 1957. A theory of cognitive dissonance. *Stanford, CA, USA: Stanford University Press* 291

Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. 1994. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet* 343: 692-5

Ford D, Easton DF, Stratton M, Narod S, Goldgar D, et al. 1998. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 62: 676-89

Frost MH, Schaid DJ, Sellers TA, Slezak JM, Arnold PG, et al. 2000. Long-term satisfaction and psychological and social function following bilateral prophylactic mastectomy. *Jama* 284: 319-24

Galjaard H. 1997a. Clinical genetics in The Netherlands. II. Genetic counseling and prenatal diagnosis. *Ned Tijdschr Geneeskd* 141: 2386-91

Galjaard H. 1997b. Future developments in genetic research. II. Psychological and social aspects. *Ned Tijdschr Geneeskd* 141: 2438-43

Gibbons RD, Hedeker DR, Elkin I, Waternaux C, et al. 1993. Some conceptual and statistical issues in analysis of longitudinal psychiatric data: Application to the NIMH Treatment of Depression Collaborative Research Program dataset. *Arch General Psychiatr* 50: 739-50

Gilbert FJ, Cordiner CM, Affleck IR, Hood DB, Mathieson D, Walker LG. 1998. Breast screening: the psychological sequelae of false-positive recall in women with and without a family history of breast cancer. *Eur J Cancer* 34: 2010-4

Grice HP. 1975. Logic and Conversation. In Cole P, Moran JL (eds), Syntax and Semantics, New York: Academic Press, 41-58

Grosfeld FJ, Lips CJ, Ten Kroode HF, Beemer FA, Van Spijker HG, Brouwers-Smalbraak GJ. 1996. Psychosocial consequences of DNA analysis for MEN type 2. *Oncology* 10: 141-6

Grosfeld FJ, Lips CJ, Beemer FA, van Spijker HG, Brouwers-Smalbraak GJ, ten Kroode HF. 1997. Psychological risks of genetically testing children for a hereditary cancer syndrome. *Patient Educ Couns* 32: 63-7

Grosfeld FJ, Lips CJ, Beemer FA, Ten Kroode HF. 2000a. Who is at risk for psychological distress in genetic testing programs for hereditary cancer disorders? *J Gen Couns* 9: 253-266

Grosfeld FJ, Lips CJ, Beemer FA, Blijham GH, Quirijnen JM, et al. 2000b. Distress in MEN 2 family members and partners prior to DNA test disclosure. Multiple endocrine neoplasia type 2. *Am J Med Genet* 91: 1-7

Grosfeld FJ. 2000c. *"Beyond a shadow of doubt". Assessing the psychological impact of predictive genetic testing for multiple endocrine neoplasia type 2.* University Medical Center, Utrecht

Grossarth-Maticek R. 1980. Psychosocial predictors of cancer and internal diseases. An overview. *Psychother Psychosom* 33: 122-8

Hamann HA, Croyle RT, Venne VL, Baty BJ, Smith KR, Botkin JR. 2000. Attitudes toward the genetic testing of children among adults in a Utah-based kindred tested for a BRCA1 mutation. *Am J Med Genet* 92: 25-32

Hartmann LC, Schaid DJ, Woods JE, et al. 1999. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Eng J Med* 340: 77-84

Hatcher MB, Fallowfield L, A'Hern R. 2001. The psychosocial impact of bilateral prophylactic mastectomy: prospective study using questionnaires and semistructured interviews. *Bmj* 322: 76

Hopwood P. 1997. Psychological issues in cancer genetics: current research and future priorities. *Patient Educ Couns* 32: 19-31

Hopwood P, Keeling F, Long A, Pool C, Evans G, Howell A. 1998. Psychological support needs for women at high genetic risk of breast cancer: some preliminary indicators. *Psycho-oncology* 7: 402-12

Horowitz MJ, Wilner N, Alvarez W. 1979. Impact of Event Scale: A measure of subjective stress. *Psychosom Med* 41: 209-18

Huggins M, Bloch M, Wiggins S, Adam S, Suchowersky O, et al. 1992. Predictive testing for Huntington disease in Canada: adverse effects and unexpected results in those receiving a decreased risk. *Am J Med Genet* 42: 508-15

Julian-Reynier C, Eisinger F, Vennin P, Chabal F, Aurran Y, et al. 1996. Attitudes towards cancer predictive testing and transmission of information to the family. *J Med Genet* 33: 731-6

Kash KM, Holland JC, Halper MS, Miller DG. 1992. Psychological distress and surveillance behaviors of women with a family history of breast cancer. *J Natl Cancer Inst* 84: 24-30

Kessler S. 1987. The dilemma of suicide and Huntington disease. *Am J Med Genet* 26: 315-20

Klijn JG, Janin N, Cortes-Funes H, Colomer R. 1997. Should prophylactic surgery be used in women with a high risk of breast cancer? *Eur J Cancer* 33: 2149-59

Kobak R, Sceery A. 1988. Attachment in late adolescence: Working models, affect regulation, and representations of self and others. *Child Dev* 59: 135-146

Kobak R, Duemmler S, Burland A, Youngstrom E. 1998. Attachment and negative absorption states: Implications for treating distressed families. *Jrnl Syst Ther* 17: 80-92

Lancaster JM, Wiseman RW, Berchuck A. 1996. An inevitable dilemma: prenatal testing for mutations in the BRCA1 breast-ovarian cancer susceptibility gene. *Obstet Gynecol* 87: 306-9

Lerman C, Schwartz M. 1993a. Adherence and psychological adjustment among women at high risk for breast cancer. *Breast Canc Res Treat* 28: 145-55

Lerman C, Daly M, Sands C, Balshem A, Lustbader E, et al. 1993b. Mammography adherence and psychological distress among women at risk for breast cancer. *J Natl Cancer Inst* 85: 1074-80

Lerman C, Kash K, Stefanek M. 1994. Younger women at increased risk for breast cancer: perceived risk, psychological well-being, and surveillance behavior. *Monogr Natl Cancer Inst*: 171-6

Lerman C, Seay J, Balshem A, Audrain J. 1995a. Interest in genetic testing among first-degree relatives of breast cancer patients. *Am J Med Genet* 57: 385-92

Lerman C, Croyle RT. 1995b. Genetic testing for cancer predisposition: behavioral science issues. *J Natl Cancer Inst Monogr*: 63-6

Lerman C, Narod S, Schulman K, Hughes C, Gomez-Caminero A, et al. 1996a. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. *Jama* 275: 1885-92

Lerman C, Schwartz MD, Miller SM, Daly M, Sands C, Rimer BK. 1996b. A randomized trial of breast cancer risk counseling: Interacting effects of counseling, educational level, and coping style. *Health Psychol* 15: 75-83

Lerman C, Schwartz MD, Lin TH, Hughes C, et al. 1997. The influence of psychological distress on use of genetic testing for cancer risk. *J Consul Clin Psychol* 65: 414-20

Lynch HT, Lemon SJ, Durham C, Tinley ST, Connolly C, et al. 1997. A descriptive study of BRCA1 testing and reactions to disclosure of test results. *Cancer* 79: 2219-28

Lerman C, Hughes C, Lemon SJ, Main D, Snyder C, et al. 1998. What you don't know can hurt you: adverse psychologic effects in members of BRCA1-linked and BRCA2-linked families who decline genetic testing. *J Clin Oncol* 16: 1650-4

Lynch HT, Watson P, Tinley S, Snyder C, Durham C, et al. 1999. An update on DNA-based BRCA1/BRCA2 genetic counseling in hereditary breast cancer. *Cancer Genet Cytogenet* 109: 91-8

Madow L. *Guilt: How to recognize and cope with it.* Northvale: Jason Aronson inc., 1988

Main M, Goldwyn R. 1994. Adult Attachment Scoring and Classification system. London: University College (Draft, version 6.0)

Main M. 1996. Introduction to the special section on attachment and psychopathology: 2. Overview of the field of attachment. *J Cons Clin Psychol* 64: 237-243

Main M. 1995. Recent studies in attachment: Overview, with selected implications for clinical work. Goldberg, Susan

McAllister MF, Evans DG, Ormiston W, Daly P. 1998. Men in breast cancer families: a preliminary qualitative study of awareness and experience. *J Med Genet* 35: 739-44

McCaul KD, Branstetter AD, O'Donnell SM, Jacobson K, Quinlan KB. 1998. A descriptive study of breast cancer worry. *J Behav Med* 21: 565-79

Meer CA van der 1999. *Behoeftepeiling lotgenotencontact onder dra(a)g(st)ers van een borstkankergenmutatie "mede-weten is mede-delen".* Dept. Clinical Genetics, Erasmus University, Rotterdam

Meijers-Heijboer EJ, Verhoog LC, Brekelmans CTM, Seynaeve C, Tilanus-Linthorst MMA, et al. 2000. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. *Lancet* 355: 2015-20

Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MBE, Bartels CCM, Verhoog LC, van den Ouweland AMW, Niermeijer MF, Brekelmans CTM, Klijn JGM. 2001. Efficacy of prophylactic bilateral mastectomy in women with a BRCA1/BRCA2 mutation. *N Engl J Med* 345: 159-64

Meiser B, Butow P, Barratt A, Friedlander M, Gattas M, et al. 1999. Attitudes toward prophylactic oophorectomy and screening utilization in women at increased risk of developing hereditary breast/ovarian cancer. *Gyneco/ Onco/* 75: 122-9

Meiser B, Butow P, Friedlander M, Schnieden V, Gattas M, et al. 2000a. Intention to undergo prophylactic bilateral mastectomy in women at increased risk of developing hereditary breast cancer. *J Clin Onco/* 18: 2250-7

Meiser B, Dunn S. 2000b. Psychological impact of genetic testing for Huntington's disease: an update of the literature. *J Neuro/ Neurosurg Psychiatr* 69: 574-8

Meissen GJ, Berchek RL. 1988. Intentions to use predictive testing by those at risk for Huntington's disease: implications for prevention. *Am J Community Psychol* 16: 261-77

Michie S, McDonald V, Marteau T. 1996. Understanding responses to predictive genetic testing: A grounded theory approach. *Psychol & Health* 11: 455-70

Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, et al. 1994. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 266: 66-71

Moyer A, Verhovsek H, Wilson VL. 1997. Facilitating the shift to population-based public health programs: innovation through the use of framework and logic model tools. *Can J Public Health* 88: 95-8

Nance MA, Leroy BS, Orr HT, Parker T, Rich SS, Heston LL. 1991. Protocol for genetic testing in Huntington disease: three years of experience in Minnesota. *Am J Med Genet* 40: 518-22

Nathanson KL, Weber, BL. 2001. 'Other' breast cancer susceptibility genes: searching for more holy grail. *Hum Mol Gen* 10: 715-20

Payne DK, Biggs C, Tran KN, Borgen PI, Massie MJ. 2000. Women's regrets after bilateral prophylactic mastectomy. *Ann Surg Oncol* 7: 150-4

Ploeg HM vd, Kleijn WC, Mook J, van Donge M, Pieters AM, Leer JW. 1989. Rationality and antiemotionality as a risk factor for cancer: concept differentiation. *J Psychosom Res* 33: 217-25

Radloff LS. 1977. The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Meas* 1: 385-401

Reichelt JG, Dahl AA, Heimdal K, Moller P. 1999. Uptake of genetic testing and pre-test levels of mental distress in Norwegian families with known BRCA1 mutations. *Dis Markers* 15: 139-43

Risberg T, Sorbye SW, Norum J, Wist EA. 1996. Diagnostic delay causes more psychological distress in female than in male cancer patients. *Anticancer Res* 16: 995-9

Ritvo P, Robinson G, Irvine J, Brown L, Murphy KJ, et al. 1999. A longitudinal study of psychological adjustment to familial genetic risk assessment for ovarian cancer. *Gynecol Oncol* 74: 331-7

Scheier MF, Carver CS. 1985. Optimism, coping, and health: Assessment and implications of generalized outcome expectancies. *Health Psychol* 4: 219-47

Schneider KA, Patenaude AF, Garber JE. 1995. Testing for cancer genes: decisions, decisions. *Nat Med* 1: 302-3

Shedler J, Mayman M, Manis M. 1993. The illusion of mental health. *Am Psychologist* 48: 1117-31

Slattery ML, Kerber RA. 1993. A comprehensive evaluation of family history and breast cancer risk. The Utah Population Database. *Jama* 270: 1563-8

Smith KR, West JA, Croyle RT, Botkin JR. 1999. Familial context of genetic testing for cancer susceptibility: moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. *Canc Epidemiol Biomarkers Prev* 8: 385-92

Sobel SK, Cowan DB. 2000. Impact of genetic testing for Huntington disease on the family system. *Am J Med Genet* 90: 49-59

Spielberger CD, Gorsuch RL, Lushene RE. 1970. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press

Spinhoven PH, Ormel J, Sloekers PPA, Kempen GIJM. 1997. A validation study of the Hospital Anxiety and Depression scale (HADS) in different groups of Dutch subjects. *Psychol Medicine* 27: 363-70

Stalmeier PF, Unic IJ, Verhoef LC, Van Daal WA. 1999. Evaluation of a shared decision making program for women suspected to have a genetic predisposition to breast cancer: preliminary results. *Med Decis Making* 19: 230-41

Steenstraten IM vd, Tibben A, Roos RA, van de Kamp JJ, Niermeijer MF. 1994. Predictive testing for Huntington disease: nonparticipants compared with participants in the Dutch program. *Am J Hum Genet* 55: 618-25

Stefanek ME, Helzlsouer KJ, Wilcox PM, Houn F. 1995. Predictors of and satisfaction with bilateral prophylactic mastectomy. *Prev Med* 24: 412-9

Struewing JP, Lerman C, Kase RG, Giambarresi TR, Tucker MA. 1995. Anticipated uptake and impact of genetic testing in hereditary breast and ovarian cancer families. *Canc Epidemiol Biomarkers Prev* 4: 169-73

Struewing JP, Lerman C, Kase RG, Giambarresi TR, Tucker MA. 1995. Anticipated uptake and impact of genetic testing in hereditary breast and ovarian cancer families. *Canc Epidemiol Biomarkers Prev* 4: 169-73

The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. 1999. *J Natl Cancer Inst* 91: 1310-6

Thorlacius S, Struewing JP, Hartge P, Olafsdottir GH, Sigvaldason H, et al. 1998. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. *Lancet* 352: 1337-9

Tibben A, Vegter-vd Vlis M, vd Niermeijer MF, Kamp JJ, Roos RA, et al. 1990. Testing for Huntington's disease with support for all parties. *Lancet* 335: 553.

Tibben A, Duivenvoorden HJ, Vegter-van der Vlis M, Niermeijer MF, Frets PG, et al. 1993a. Presymptomatic DNA testing for Huntington disease: identifying the need for psychological intervention. *Am J Med Genet* 48: 137-44

Tibben A, Frets PG, van de Kamp JJ, Niermeijer MF, Vegtervan der Vlis M, et al. 1993b. On attitudes and appreciation 6 months after predictive DNA testing for Huntington disease in the Dutch program. *Am J Med Genet* 48: 103-11

Tibben A, Frets PG, van de Kamp JJ, Niermeijer MF, Vegter-van der Vlis M, et al. 1993c. Presymptomatic DNA-testing for Huntington disease: pretest attitudes and expectations of applicants and their partners in the Dutch program. *Am J Med Genet* 48: 10-6

Tibben A. 1993d. *"What is knowledge but grieving?" On psychological effects of presymptomatic DNA testing for Huntington's disease.* PhD thesis Erasmus University Rotterdam

Tibben A, Timman R, Bannink EC, Duivenvoorden HJ. 1997. Three-year follow-up after presymptomatic testing for Huntington's disease in tested individuals and partners. *Health Psychol* 16: 20-35

Verhoog LC, van den Ouweland AMW, Berns E, van Veghel-Plandsoen MM, van Staveren LL et al. 2001. Large regional differences in the frequency of BRCA1/BRCA2 mutations in 517 Dutch breast and/or ovarian cancer families. *Eur J Canc.* in press

Vernon SW, Gritz ER, Peterson SK, Amos CI, Perz CA, et al. 1997. Correlates of psychologic distress in colorectal cancer patients undergoing genetic testing for hereditary colon cancer. *Health Psychol* 16: 73-86

Wagner TMU, Möslinger R, Langbauer G, Ahner R, the Austrian Hereditary Breast and Ovarian Cancer Group. 2000. Attitude towards prophylactic surgery and effects of genetic counseling in families with BRCA mutations. *Brit J Canc* 82: 1249-53

Wagner TM, Ahner R. 1998. Prenatal testing for late-onset diseases such as mutations in the breast cancer gene 1 (BRCA1). Just a choice or a step in the wrong direction? *Hum Reproduction* 13: 1125-6

Watson M, Murday V, Lloyd S, Ponder B, Averill D, Eeles R. 1995. Genetic testing in breast/ovarian cancer (BRCA1) families. *Lancet* 346: 583

Watson M, Pettingale KW, Greer S. 1984. Emotional control and autonomic arousal in breast cancer patients. *J Psychosom Res* 28: 467-74

Wert GMWRd. 1999. Met het oog op de toekomst. Voortplantings technologie, erfelijkheidsonderzoek en ethiek. PhD thesis Erasmus University Rotterdam

Wooster R, Bignell G, Lancaster J, Swift S, Seal S, et al. 1995. Identification of the breast cancer susceptibility gene BRCA2. *Nature* 378: 789-92

Zakowski SG, Valdimarsdottir HB, Bovbjerg DH, Borgen P, Holland J, et al. 1998. Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer. *Ann Behav Med* 19: 362-9

Zigmond AS, Snaith RP. 1983. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 67: 361-70

SUMMARY

Since the identification of the BRCA1 and BRCA2 gene mutations, in 1994-1995, genetic testing for Hereditary Breast and/or Ovarian Cancer (HBOC) has become an important technique for persons at risk for these mutations. The inheritance is autosomal dominant, implying that each child of a mutation carrier has a risk of 50% to inherit the mutation. Female mutation carriers have a high lifetime risk for breast cancer (56-87%) and/or ovarian cancer (10-60%) and may opt for intensive breast and ovary surveillance (by which not all cases of carcinoma are detected before becoming metastatic) or preventive removal of breast tissue (prophylactic mastectomy from the age of 25 years) and/or the ovaries (prophylactic oophorectomy from the age of about 35 years). In our hospital a simple mastectomy including the nipple is mostly applied with immediate implantation of a silicone prothesis, and its effectiveness to prevent cancer was recently established. Males with a BRCA1 or BRCA2 mutation also have an increased risk to develop cancer (prostate, breast, colon cancer), but their absolute risk is low.

Because mutations may occur in any part of the BRCA1/BRCA2 genes, DNA analysis in blood samples of one or more affected relatives is essential to establish a family-specific mutation. At present in our centre, such mutation is identified in about 20% of families with a history of autosomal dominant HBOC. Members from these families may opt for genetic testing. The studies described in this thesis focus on healthy women (n=85) and men (n=28), having a risk of 50% or 25% of being a BRCA1/BRCA2 mutation carrier, and their partners, who apply for genetic testing. Attitudes and psychological functioning in women declining genetic testing are also described (n=13).

The studies in this thesis are part of a continuing evaluation of clinical, genetic and psychological aspects of the possibility of genetic testing in our collaborative Working Group on Genetic Tumours (with participants from Depts. Surgery, Oncology, Gyneacology, Clinical Genetics, Medical Psychology and Psychotherapy of the Erasmus University Medical Center Rotterdam and the Leyden University, head prof.dr JGM Klijn). Earlier psychological research on genetic testing in the dept. of Clinical Genetics Rotterdam and Leyden (in collaboration with dept. Medical Psychology and Psychotherapy), concerned Huntington Disease (HD) and a comparative study on genetic testing for HD, Hereditary Cerebral Haemorrhage, genetic colon carcinoma, and HBOC. The latter study was developed to investigate differences in distress reactions in the testing period for diseases which are very dissimilar with regard to treatment options (none for HD and Hereditary

Cerebral Haemorrhage) and phenotype (e.g. absence/presence of mental deterioration, gender differences in disease risk). This study indeed found some differences in distress reactions between the groups, among which relatively low distress in subjects tested for HBOC up to 6 months after the result. This might partly be explained by the fact that this small group (n=10) had been extensively informed in a longstanding family study, which might have strengthened their adjustment to the distress of having an increased risk for cancer and by the special attention paid to this first tested group by researchers and (onco)geneticists. This warrants a further investigation of psychological reactions in subjects tested for HBOC.

Most of the psychological data on HBOC were obtained in the United States, also in large, well studied families, with a long time awareness of the genetic nature of cancer. Nowadays, genetic cancer risks also become identified in smaller families without long experience or awareness of the problem in their family. In the present study both groups are represented. Another difference between the Dutch and the American situation is that genetic testing and prophylactic surgery are, unlike in the Netherlands, not financed in the United States.

Findings from such previous studies show that mean distress levels before and after genetic testing for BRCA1/BRCA2 were similar to or lower than those of a normal population, however, there was a high variability in distress levels within the study samples. Distress levels after the result were higher in mutation carriers than in non-mutation carriers, and also positively related to the level of distress prior to disclosure. The latter suggests that high distress may not only be situational, but may also be person related, as also was demonstrated in a study revealing an association between high general distress levels and a less optimistic personality.

Utilisation of prophylactic surgery among BRCA1/BRCA2 mutation carriers considerably varies between countries and centres. In our clinical setting, 51% of the mutation carriers without a history of cancer opted for mastectomy and 68% for oophorectomy. Relevant factors to opt for prophylactic mastectomy were age (≤50), having young children. Other studies demonstrated that women who opted for prophylactic mastectomy had higher levels of distress than women who did not. A decrease in distress was observed after prophylactic mastectomy. The proportion of women reporting dissatisfaction with the cosmetic result and negative effects on the sexual relationship, feelings of femininity and body image was variable in the different studies.

Persons deciding to remain uninformed about their test outcome reported higher levels of depression several weeks later than the group who

obtained the test result (irrespective of the outcome). Moreover, these persons had fewer relatives with breast cancer and less knowledge about HBOC and genetic testing, than those informed about their result. In the few studies addressing psychological consequences for males in families with HBOC, males had lower distress levels than their female counterparts, and they tended to avoid the topic.

Questions of the studies in this thesis concerned: a) the motives of persons at risk to undergo or to refrain from genetic testing for BRCA1/BRCA2, b) psychological consequences of genetic testing for women and men at risk to be a BRCA1/BRCA2 mutation carrier and their partners until one year after disclosure of the result, c) identification of factors predictive for high distress, d) identification of factors related to the choice for prophylactic mastectomy and/or oophorectomy and psychological consequences of the different options for risk management (including distress, body image, the intimate relationship) for women and their partners, and e) attitudes of test applicants towards prenatal testing of a fetus at risk for a BRCA1/BRCA2 mutation. Outcomes may help to improve guidelines for genetic counseling and for psychological support before and after genetic testing.

The procedure of genetic testing for BRCA1/BRCA2 and the psychological study are as follows. After one or more genetic counseling sessions with the clinical geneticist/genetic nurse, a blood sample is obtained in persons deciding to undergo genetic testing for mutation analysis of the family specific mutation. Test-applicants consenting to participate in this psychological study were given questionnaires to complete at home. The interview was usually held in the weeks following blood sampling. Disclosure of the test result took place 6 to 8 weeks later in a face-to-face contact with the clinical geneticist/genetic nurse. Post-test assessments (questionnaires, interviews) took place several weeks after disclosure of the result, and at six and twelve months follow-up.

A group of 85 women at 50% or 25% risk of being a BRCA1/BRCA2 mutation carrier (and 66 partners) completed the pre-test assessment, which was 72% of the total group of women asked to participate. The major reasons for testing were to obtain certainty about 1) having an increased risk for cancer or not (96%), 2) the need for future intensive surveillance and/or prophylactic interventions (86%), and 3) the risk of having transmitted the gene to their offspring (36%). Knowing about risks for future offspring was a reason for 9 of the 31 women considering future offspring **(chapter 2)**. Mean pre-test anxiety and depression levels of test-applicants and partners were similar to those of a

normal Dutch population. The low distress levels may partly be explained by minimizing thinking about a possible unfavourable test-outcome in the period between blood sampling and disclosure of the result.

Elevated to high levels of general and cancer-related distress were seen in about 25% of the women at risk and 10% of the partners, and were associated with a) anticipating an increase of problems after an unfavourable test outcome, b) considering prophylactic mastectomy if found to be mutation carrier, c) having a non-optimistic personality, d) tending to suppress emotions, e) being younger than 40 years and f) being more familiar with serious consequences of HBOC. Recently obtained awareness of the genetic nature of cancer in the family was not predictive for distress.

In **chapter 3** motives for declining genetic testing are described among 13 women at 50% or 25% risk to be a BRCA1/BRCA2 mutation carrier, who participated in a surveillance program for breast/ovarian cancer (the non-tested group). More than half of these women did not completely rule out opting for testing at a later stage. Most of the women seemed to have carefully considered the pros and cons of testing. Motives for declining/postponing testing were: satisfaction with participating in the surveillance program (10/13), not wanting to change risk management (more frequent surveillance/prophylactic surgery) if identified as mutation carrier (4/13), feeling able to cope emotionally with an increased risk for cancer (4/13), and feeling emotionally unprepared to receive an unfavourable test outcome (4/13). Compared with the tested group (n=85), the non-tested group had similar mean distress levels (which were not high), a higher education level, they were more often childless, and were more reluctant towards prophylactic surgery. Furthermore, non-tested women were younger when first confronted with breast/ovarian cancer in a relative, and longer aware of the genetic nature of the disease, which may have made them integrate the risk for cancer in their lives. These results can not be extended to women who neither were tested nor participated in a surveillance program.

Post-test assessments (1 to 3 weeks after disclosure) in 78 female test-applicants (25 mutation carriers, and 53 non-mutation carriers), and 56 partners are described in **chapter 4**.

High post-test anxiety was reported by 20% of the mutation carriers and by 35% of their partners, compared to 11% of the non-mutation carriers and 13% of their partners. Factors significantly related to high post-test anxiety in the tested women were: 1) a high level of pre-test anxiety and 2) being a mutation carrier. Non-mutation carriers with a sister recently identified as a

mutation carrier, had higher post-test levels of depression than the other non-mutation carriers.

Post-test psychological support may be proposed especially to mutation carriers, who already were anxious at pre-test. Most non-mutation carriers may not need psychological follow-up, but those having a sister with a recently diagnosed mutation should be informed about the possibility of depressive feelings and their cause.

In **chapter 5** the course of distress and problems regarding body image and sexuality up to one year after disclosure of the test-outcome are described separately for mutation carriers undergoing mastectomy (n=14), for those opting for surveillance (n=12) and for non-mutation carriers (n=37). Women opting for prophylactic mastectomy had significantly higher distress levels than the other two groups, but their distress levels had considerably decreased 6 to 8 months after surgery. Also, women opting for prophylactic mastectomy were more often in their thirties, more often had young children and had a longer awareness of the genetic nature of cancer in the family than those opting for regular surveillance. Adverse effects of prophylactic mastectomy (mostly with immediate breast reconstruction) concerned the perception of how their breast region looks like and feels, the intimate relationship, physical well-being and self esteem. The decrease in distress in women undergoing prophylactic mastectomy might be a reflection of the decrease in risk for breast cancer and might explain why most were satisfied with this decision, despite these adverse effects. In one woman these effects made her regretting her decision. Oophorectomy, which was followed by hormonal replacement for most premenopausal women, generally gave no emotional or physical problems.
Partners from women who underwent prophylactic mastectomy did not report problems with their wife's appearance, but they had less frequent intimate contact with their spouses 6 to 8 months after surgery.

The psychological impact of genetic testing for HBOC is generally assessed using self-report questionnaires. A shortcoming of such questionnaires is that low distress scores may either indicate normal health, or a state of normality held up due to (un)conscious defense strategies. In **chapter 6,** the relationship is studied between low self-reported distress and the incapability to coherently and truthfully express current experiences and thoughts about one's genetic status (coherence score of an interview transcript). In mutation carriers an incoherent score (7/22) was associated with low distress (six months after disclosure of the result), which may be indicative for defensive denial. In non-mutation carriers (n=35) incoherent scores were associated with *high* anxiety

(several weeks & six months after disclosure of the result), which can not be interpreted as possibly resulting from defensive denial. Instead, one could speculate that in this case, the incoherence resulted from a difficulty to take distance from a threat that is no longer in existence, or from ambivalent feelings due to personal relief from a burdensome perspective, whereas relatives still live under the same threat.

Males from BRCA1/BRCA2 families can opt for genetic testing to know whether or not they may have transmitted the mutation to their children and, if so, to inform them at an appropriate age about the genetic risk and its implications. The psychological consequences of genetic testing for these men have received little attention. In **chapter 7** levels of distress are assessed several weeks before and after disclosure of the test result in 28 men, and their partners. Men were at 50% risk (n=24) or 25% (n=4) of being a mutation carrier, the majority with daughters and half of them with daughters aged over 20 years. Distress levels prior to the result in men and their partners were low. Many men and partners expected the test result to increase their children's problems, but not their own. Men without daughters and those with an optimistic personality especially showed low distress prior to disclosure of the result. Most men reported that they did not actively avoid the issue. High distress after disclosure of the result was reported by one of the four mutation carriers and by 3/17 of the non-mutation carriers. Verbatim transcripts from interviews show that psychological reactions in male mutation carriers (e.g. regarding guilt feelings) largely varied.

Low pre-test distress in males does not seem necessarily to be an indication of avoidance. Future studies may explore psychological reactions in male mutation carriers when the problem becomes more acute, e.g. when a daughter is found to carry the mutation and/or is diagnosed with breast or ovarian cancer.

The possibility of prenatal genetic diagnosis for late onset hereditary disorders, such as HBOC, raises complex ethical questions. Attitudes of mutation carriers (n=26) and non-mutation carriers (n=52) towards the possibility to terminate a pregnancy of a child which is carrier of a BRCA1/BRCA2 mutation are described in **chapter 8**. None of the mutation carriers, and a small minority of the non-mutation carriers considered termination of pregnancy in case of a female or a male mutation carrier fetus to be acceptable for themselves. This indicates that this group generally considered a life worth living, despite burdensome implications of being a BRCA1/BRCA2 mutation carrier. Considering the few actual requests for prenatal diagnosis for BRCA1/BRCA2,

the emotional burden of such a decision and the general reluctance towards terminating a pregnancy of a mutation carrier child (this study), the demand for prenatal diagnosis in HBOC families is expected to remain low. Genetic counseling of couples considering these highly complex and burdensome options should focus on supporting parents in the decision process.

In **chapter 9** the most important results of the studies are summarized and recommendations for clinical practice as well as recommendations for future research are reported.

Non-elevated mean distress levels at pre-test and the unchanged level of distress in mutation carriers from pre- to post-test may be explained by different factors. Firstly, test-applicants seemed to have a strong motivation and a perceived urge to undergo genetic testing: all applied for testing within one year, and the majority within two months after the test became available in their family. Future research may find out whether a group of more ambivalent test-applicants will show stronger distress reactions in the testing period. Secondly, the majority of mutation carriers decided already prior to disclosure of the result which risk management they would opt for if they were found to be mutation carrier. Such 'early anticipation' on the post-test period, may indicate that the work of worrying process, does not only start after disclosure of the result.

Unlike the female mutation carriers, their partners experienced increased distress from pre-test to post-test; one third reported high distress. Partners may have a stronger tendency than the test-applicants themselves to postpone worrying until after the test outcome. This seems to support the rationale of the protocol for genetic testing for HBOC, that partners are included in the pre-test counselling session, in which the choices and consequences after disclosure of the result are discussed.

The lower anxiety levels in male than female test applicants before and after disclosure, did not seem to be explained by an active avoidance of thinking of the disease. The lower distress levels may be explained by 1) the fact that unlike women, men identified as mutation carrier do not face a high cancer risk and difficult choices concerning risk management and 2) the observation that men in general tend to report lower distress levels than women. Future studies are needed to investigate psychological reactions in male mutation carriers when the problem becomes more acute, e.g. when a daughter is found to carry the mutation and/or is diagnosed with the disease.

Higher levels of distress in mutation carriers opting for prophylactic mastectomy than in those opting for frequent surveillance and non-mutation carriers, especially in the weeks prior to and after disclosure, may be explained

by the majority of them being at an especially 'high risk age' (30 to 40 years) and having young children. More research is needed to explore to which extent the prospect of surgery itself may result in a higher state of anxiety. It seems advisable if genetic counselors take notice of women intending to undergo prophylactic mastectomy and to schedule a psychological support session in the weeks following the result for these mutation carriers.

For non-mutation carriers, mutation carriers opting for surveillance and male test-applicants, it might be sufficient to emphasize the possibility of psychological support in the period of genetic testing, and to keep the initiative to request such support by the test-applicant or by the genetic counselor/clinical geneticist. In the disclosure session, non-mutation carriers with a sister who is found to be mutation carrier may be prepared for the possibility of experiencing unpleasant feelings despite their favorable result. Future assessments with distress scales should closely monitor if the proposed support protocol is indeed sufficient.

Informing mutation carriers before and after prophylactic mastectomy about possible adverse effects concerning the perception of the appearance/feeling of the breasts, not feeling sexually attractive, not feeling in the mood for having sex, and having physical complaints, may help to stimulate autonomous decision making and to mentally prepare women for such adverse experiences. Also, the wish to share experiences with other women having undergone prophylactic mastectomy previously, for instance in a patient support group, may be explored.

Distress levels in mutation carriers opting for surveillance were similar to those of non-mutation carriers, which is remarkable. The former women may experience a basic trust by participating in the surveillance program. Interestingly, they became later in their lives familiar with a relative affected with the disease and with the genetic risk than women opting for prophylactic mastectomy and women refraining from testing. A difference between the latter two groups is that women opting for prophylactic mastectomy had known more affected relatives since their first confrontation than non-tested women.

To gain more insight into long-term consequences of having chosen for either prophylactic mastectomy or frequent surveillance (including false positive outcomes followed by biopsies) in mutation carriers, two large prospective projects have been started in our group addressing satisfaction with these decisions and psychological well-being in a larger number of women at a longer follow up. These issues have become especially relevant since the effectiveness of prophylactic mastectomy to prevent cancer in women with the BRCA1/BRCA2 mutation became recently demonstrated.

SAMENVATTING

Kennis over erfelijke risicofactoren voor een aantal later in het leven optredende ernstige erfelijke ziekten, zoals bepaalde vormen van kanker en ziekten van het zenuwstelsel heeft het binnen de betrokken families mogelijk gemaakt om onderscheid te maken tussen hen die wel en niet een risico hebben de ziekte te krijgen. De multidisciplinaire Werkgroep Erfelijke Tumoren van het Academisch Ziekenhuis Rotterdam in samenwerking met het Leids Universitair Medisch Centrum (hoofd werkgroep Prof.dr. J.G.M. Klijn) heeft zich sinds ongeveer 10 jaar toegelegd op de oncologische, chirurgische, gynaecologische, moleculair diagnostische, klinisch genetische en psychologische aspecten van genetische vormen van kanker. Een belangrijke reden om erfelijkheidsonderzoek te willen doen in een familie waarin kanker familiair lijkt bepaald, is dat individuen in zo'n familie op basis van die informatie maatregelen kunnen treffen om het risico op kanker te verkleinen.

Het onderzoek in dit proefschrift is een voortzetting van psychologisch onderzoek binnen een samenwerkingsverband van de afdelingen Medische Psychologie en Psychotherapie (Erasmus Universiteit Rotterdam) en Klinische Genetica (Erasmus Universiteit Rotterdam/Leids Universitair Medisch Centrum) naar genetisch testen voor ziekten in het zenuwstelsel (zoals de ziekte van Huntington en erfelijke hersenbloedingen) en erfelijke vormen van darm en borst/eierstokkanker. Het onderzoek werd gesubsidieerd door de Nederlandse Kankerbestrijding en bestudeert de psychische gevolgen van de mogelijkheid om met behulp van genetisch onderzoek na te gaan of men al dan niet drager is van de genmutatie die samenhangt met erfelijke borst en eierstokkanker.

Van de vrouwen die borstkanker krijgen (in totaal ongeveer 10% van de vrouwen in de westerse wereld, meestal ouder dan 50 jaar), heeft vijf tot acht procent de zogenaamde erfelijke vorm. Deze verschilt van de niet erfelijke vorm, onder andere doordat deze vaak op jongere leeftijd en vaker in beide borsten optreedt. In families waarbij borstkanker erfelijk is, hebben doorgaans meerdere vrouwelijke familieleden deze ziekte en/of eierstokkanker gekregen. In 1994 en 1995 zijn twee genen ontdekt (BRCA1 en BRCA2: 'Breast Cancer 1 en 2') die afwijkingen vertonen in families met erfelijke borst en eierstokkanker (HBOC, hereditary breast and/or ovarian cancer). Met DNA onderzoek kan de afwijking (mutatie) worden opgespoord in BRCA1 en BRCA2 die in de betrokken familie wordt overgeërfd. De overerving is autosomaal dominant: elk kind van een mutatie drager (man of vrouw) heeft

50% kans de mutatie te erven. Vrouwelijke mutatiedragers hebben in hun leven een hoge kans om borstkanker (56-87%) en/of eierstokkanker (10-60%) te krijgen. Zij kunnen vanaf het 25ste levensjaar hun borsten en eierstokken 2 tot 4 keer per jaar laten controleren, hetgeen de kans echter niet uitsluit dat kanker ontdekt wordt als het reeds is uitgezaaid. Om die reden kiest een aantal vrouwen er voor zich preventief te laten opereren door borstweefsel (preventieve mastectomie vanaf 25 jaar) en/of de eierstokken te laten verwijderen (preventieve ovariëctomie, vanaf ongeveer 35 jaar). In het Academisch Ziekenhuis Rotterdam, Daniel den Hoed Kliniek, wordt veelal een directe borstreconstructie toegepast met siliconen-implantaten. Recentelijk is de effectiviteit van deze ingreep door de Rotterdamse groep aangetoond. Mannen die de BRCA1/BRCA2 genmutatie bij zich dragen hebben ook een verhoogd risico op het krijgen van kanker (o.a. prostaat-, borst- en darmkanker), maar dit risico is in vergelijking met dat van vrouwen zeer klein. De genmutatie in BRCA1/BRCA2 kan op veel verschillende plaatsen in de DNA sequentie van het gen voorkomen. Per familie moet dus worden bepaald welke de familiaire mutatie is, en of deze alle gevallen van kanker verklaart. Bij de afdeling Klinische Genetica Rotterdam is de genmutatie gevonden in ongeveer 20-25% van de families waarin borst en/of eierstokkanker familiair bepaald leek, in de overige families is verder onderzoek nodig.

Eerder psychologisch onderzoek naar genetisch testen voor HBOC is vooral gedaan in grote families, voornamelijk in de Verenigde Staten, waarin geteste mensen reeds lang bekend waren met de erfelijke aard van kanker en de mogelijkheid tot onderzoek hiernaar **(hoofdstuk 1)**. Tegenwoordig wordt de genmutatie steeds vaker in kleinere families ontdekt, waarin men nog niet zo lang bekend is met het erfelijkheids probleem. In de studies van dit proefschrift worden individuen uit beide soorten families beschreven. Een ander belangrijk verschil tussen de situatie in Nederland en in de Verenigde Staten is, dat in laatst genoemd land preventieve chirurgie en vaak ook genetisch onderzoek niet vergoed worden door de verzekering.

Resultaten van eerder onderzoek laten zien dat het gemiddelde niveau van psychische stress voor en na genetisch onderzoek voor BRCA1/BRCA2 ongeveer gelijk was aan die van een algemene populatie, maar dat er grote individuele verschillen bestonden. Psychische stress na de testuitslag was hoger bij mensen die de mutatie geërfd hadden dan bij hen die dat niet hadden, en hing ook positief samen met de mate waarin men reeds voorafgaand aan de uitslag psychische klachten had. Dit wijst erop dat een hoge mate van stress niet alleen situatiegebonden, maar voor een deel ook persoonsgebonden is; dit

is nog directer aangetoond in onderzoek waarbij men een positief verband vond tussen veel psychische klachten en een weinig optimistisch karakter.

Het percentage van de vrouwelijke mutatiedragers zonder kanker dat kiest voor preventieve chirurgie verschilt aanzienlijk per land en ook per instituut. In het Academisch Ziekenhuis Rotterdam koos 51% van deze vrouwen voor mastectomie en 68% voor ovariëctomie. Factoren die samenhingen met de keuze voor preventieve mastectomie zijn een jonge leeftijd (<50), en het hebben van jonge kinderen. In andere onderzoeken kwam naar voren dat vrouwen die voor preventieve mastectomie kozen zich meer zorgen maakten over kanker dan vrouwen die daar niet voor kozen. Voorts is een afname van psychische stress na de operatie beschreven. De mate waarin vrouwen aangeven problemen te ervaren met hoe hun borstgebied er na de operatie uitziet, met hun gevoel van vrouwelijkheid en de seksuele relatie, blijkt verschillend per studie.

Mensen die besloten om niet geïnformeerd te worden over hun testuitslag gaven een aantal weken daarna aan dat zij meer depressieve gevoelens hadden, dan degenen die wel geïnformeerd werden (onafhankelijk van de uitslag). Voorts hadden mensen die hun uitslag niet wilden weten minder familieleden met borstkanker en beschikten zij over minder kennis over HBOC en genetisch onderzoek dan zij die daar wel voor kozen. In het kleine aantal psychologische studies dat verricht is naar mannen uit HBOC families komt naar voren dat zij minder psychische stress rapporteerden dan vrouwen, en dat zij ernaar neigden het probleem uit de weg te gaan.

De studies die in dit proefschrift worden beschreven, betreffen attituden en psychisch functioneren van vrouwen (n=85) en mannen (n=28) (en hun partners) die geen kanker hadden (gehad), maar die op grond van hun familiegeschiedenis 50% of 25% kans hadden drager te zijn van een BRCA1/BRCA2 genmutatie en zich daarop lieten testen. Ook zijn in het onderzoek vrouwen opgenomen die besloten deze test niet te ondergaan.

Onderzoeksvragen zijn: a) welke motieven hebben vrouwen en mannen met een risico om drager te zijn van een BRCA1/BRCA2 genmutatie om de genetische test te ondergaan of juist niet te ondergaan? b) wat zijn de psychische gevolgen van genetisch testen voor BRCA1/BRCA2 voor vrouwen en mannen en hun partners tot een jaar na de uitslag van de test? c) welke factoren hangen samen met een hoge psychische stress voor en na de uitslag? d) welke factoren hangen samen met de keuze voor preventieve mastectomie en/of ovariëctomie in mutatiedraagsters en welke psychische gevolgen hebben deze preventieve maatregelen (betreffende psychische stress, lichaamsbeeld en de intieme relatie) voor de vrouwen zelf en hun partners? en e) hoe denken de

onderzochte personen over prenataal onderzoek om na te gaan of het kindje drager is van de mutatie?

De resultaten van dit onderzoek zijn van belang voor het optimaliseren van het erfelijkheidsadvies en psychische begeleiding voor en na genetisch testen voor HBOC.

De procedure van genetisch testen voor BRCA1/BRCA2 en het psychologisch onderzoek verliep als volgt. Na een of meer gesprekken met de klinisch geneticus/genetisch consulent over erfelijkheid en keuzemogelijkheden na een genetische test voor HBOC, werd, indien men besloot zich te laten testen, bloed afgenomen voor DNA-onderzoek. Mensen die besloten zich te laten testen en instemden met deelname aan het psychologisch onderzoek, maakten kennis met de onderzoeker (LNL). Vragenlijsten werden mee gegeven en een afspraak werd gemaakt voor het eerste interview, dat plaatsvond in de periode tussen bloedafname en de testuitslag, 6 tot 8 weken later. De meeste interviews werden thuis afgenomen, soms op de afdeling Klinische Genetica of op een afdeling van een streekziekenhuis. De uitslag van de DNA-test werd gegeven in een gesprek met de klinisch geneticus of de genetisch consulent. Latere afnames van vragenlijsten en interviews vonden plaats enkele weken na de uitslag en zes en twaalf maanden daarna.

Psychische stress in de weken voor de uitslag van de test werd in kaart gebracht voor 85 vrouwen met een kans van 50% of 25% om drager te zijn van de BRCA1/BRCA2 genmutatie (en 66 partners): 72% van de totale geteste groep **(hoofdstuk 2)**. De belangrijkste motieven om de genetische test te doen waren het krijgen van zekerheid over 1) het persoonlijk risico op kanker (96%), 2) het al dan niet nodig zijn van intensieve controles en/of preventieve chirurgie (86%), en 3) het risico om de mutatie doorgegeven te hebben aan het nageslacht (36%). Van de 31 vrouwen die nog een kinderwens hadden wilden 9 graag weten of zij de mutatie door zouden kunnen geven. Het gemiddeld niveau van psychische stress voor de uitslag was vergelijkbaar met dat van een normale Nederlandse vergelijkingsgroep. Dit lage niveau van psychische stress kan mogelijk verklaard worden door een neiging om tussen het moment van bloedafname en de uitslag nog maar niet te veel na te denken over een mogelijk ongunstige uitslag.

Hoge psychische stress en aan borst/eierstokkanker gerelateerde angst werd gevonden bij 25% van de vrouwen en 10% van hun partners. Voor de vrouwen hing dit samen met a) de verwachting dat problemen zouden toenemen na een ongunstige uitslag, b) het plan om preventieve mastectomie te ondergaan als men drager bleek te zijn, c) een niet-optimistisch karakter, d) de

neiging gevoelens niet uit te spreken, e) een leeftijd beneden de 40 jaar en f) meer ervaring met belastende gevolgen van de ziekte bij familieleden. Al dan niet langdurig bekend zijn met erfelijke kanker in de familie had geen invloed op de mate van psychische stress.

Motieven van vrouwen met een 25% of 50% risico om drager te zijn van de BRCA1/BRCA2 die wel voor regelmatige controle, maar niet voor genetisch onderzoek kozen, worden beschreven in **hoofdstuk 3**. De meeste vrouwen hadden goed nagedacht over de voor- en nadelen van testen. Meer dan de helft dacht eventueel aan testen op een later ogenblik. Motieven voor niet-testen waren: tevreden zijn met de regelmatige controle (10/13), geen wens om verdergaande risicobeperking te ondergaan als zij mutatiedrager zouden zijn (zoals intensievere controle/preventieve chirurgie, 4/13), het gevoel goed om te kunnen gaan met het besef van een verhoogd risico op kanker (4/13), en zich mentaal onvoorbereid voelen om te weten dat zij mutatiedrager zouden zijn (4/13). In vergelijking met de geteste vrouwen (n=85), had de niet-geteste groep eenzelfde niveau (vergelijkbaar met dat van een normale vergelijkingsgroep) van psychische stress, een hogere opleiding, minder vaak kinderen, en meer weerstand tegen preventieve chirurgie. Verder waren niet-geteste vrouwen jonger toen ze voor het eerst geconfronteerd werden met borst- of eierstokkanker bij een familielid. Mogelijk hadden zij deze ziekte in de loop van hun leven min of meer geaccepteerd als deel van hun bestaan. De resultaten van dit onderzoek kunnen niet worden gegeneraliseerd naar niet-geteste vrouwen die geen regelmatige controle ondergaan.

Aan de metingen 1 tot 3 weken na de uitslag namen 78 vrouwen en 56 partners deel (**hoofdstuk 4**): 25 van deze vrouwen hadden een genmutatie, 53 hadden deze niet geërfd.

Hoge psychische stress werd aangetoond bij 20% van de mutatiedraagsters en 35% van de partners daarvan, en bij 11% van de niet-mutatiedraagsters en 13% van de partners daarvan. Veelal hing hoge psychische stress samen met hoge stress reeds vóór de uitslag en met het hebben geërfd van het gen. Niet-mutatiedraagsters die een zus hadden die wél mutatiedraagster bleek te zijn, hadden in de weken na de uitslag meer sombere gevoelens dan de andere niet-mutatiedraagsters.

Het lijkt belangrijk extra aandacht te schenken en eventueel psychische begeleiding aan te bieden aan vrouwen die mutatiedrager zijn en die vóór de uitslag al veel psychische stress ervoeren. Voor de meeste niet-mutatiedraagsters lijkt extra begeleiding minder nodig, wel kunnen diegenen die een zus hebben

die wel de mutatie hebben, geïnformeerd worden over gevoelens van somberheid als normale reactie op de voor hen gunstige test-uitslag.

In **hoofdstuk 5** wordt het beloop van psychische stress en problemen met betrekking tot lichaamsbeeld en de intieme relatie beschreven tot een jaar na de uitslag van de test voor mutatie draagsters die voor preventieve mastectomie (n=14) of voor regelmatige controle kozen (n=12) en voor niet-mutatiedraagsters (n=37). Vrouwen die voor preventieve mastectomie kozen hadden duidelijk meer psychische stress gedurende het hele onderzoek dan de twee andere groepen, maar deze stress was wel afgenomen een jaar na de uitslag (6 tot 8 maanden na de operatie). Daarnaast waren vrouwen die voor deze ingreep kozen vaker in de dertig, hadden zij vaker jonge kinderen, en waren zij langer op de hoogte van erfelijke kanker in de familie dan vrouwen die voor regelmatige controle kozen.

Na preventieve mastectomie (meestal toegepast met borstreconstructie) rapporteerde een belangrijk deel van de vrouwen lichamelijke klachten, een verminderd gevoel van zelfvertrouwen, ontevredenheid met hoe hun borstgebied er uit zag en aanvoelde en een verminderde zin om te vrijen. Het feit dat deze vrouwen zich na de operatie minder zorgen hoefden te maken om het krijgen van borstkanker, en dan ook een afname in psychische stress rapporteerden, is wellicht de reden dat de meerderheid tevreden is over hun keuze, ondanks de gerapporteerde negatieve gevolgen. Echter, één vrouw had zoveel last van de gevolgen dat ze spijt kreeg van haar beslissing. Ovariëctomie (bij pre-menopausale vrouwen vaak gevolgd door hormoon substitutie) gaf bij de meeste vrouwen weinig emotionele of lichamelijke problemen. Partners (n=8) van vrouwen die preventieve mastectomie ondergingen, waren even tevreden met het uiterlijk van hun vrouw als de overige partners (n=13), maar gaven zes tot acht maanden na de operatie wel aan minder vaak met hun partner te vrijen.

Psychische consequenties van belastende omstandigheden, zoals het zich genetisch laten testen voor HBOC, worden meestal met behulp van standaard vragenlijsten (over bijv. gevoelens van somberheid of gespannenheid) gemeten. Een beperking van dergelijk onderzoek is dat een lage score op zo'n vragenlijst verschillend verklaard kan worden: ofwel men voelt zich psychisch echt goed, ofwel men geeft aan zich goed te voelen om daarmee (bewust of onbewust) onderliggende nare gevoelens af te weren. In **hoofdstuk 6** wordt nagegaan of er een verband bestaat tussen het in een vragenlijst aangeven dat men zich goed voelt, en het onvermogen om op een samenhangende en invoelbare wijze over ervaringen en gedachten rondom het genetisch onderzoek te vertellen in een interview (coherentiescore van een letterlijk uitgeschreven stuk van het interview). Mutatiedraagsters met een niet-coherente score (7/22)

rapporteerden inderdaad weinig psychische stress zes maanden na de uitslag, hetgeen kan betekenen dat deze vrouwen negatieve gevoelens hebben afgeweerd. Bij niet-mutatiedraagsters (n=35) bleek juist dat incoherente scores samenhingen met veel gevoelens van psychische stress, zowel enkele weken als een half jaar na de uitslag. Voor deze groep betekent incoherentie kennelijk niet dat men negatieve gevoelens heeft afgeweerd. Misschien dat incoherentie bij niet-mutatiedraagsters wijst op het worstelen met het loslaten van een levenslange dreiging van kanker, die er voor naaste familieleden nog wel is.

Mannen uit BRCA1/BRCA2 families kunnen de genetische test ondergaan om na te gaan of zij de mutatie al dan niet aan hun kinderen hebben kunnen overdragen en, als dat zo is, hen hierover in te kunnen lichten wanneer zij daar aan toe zijn. De psychische consequenties voor deze mannen kregen weinig aandacht tot nu toe. In **hoofdstuk 7** wordt de mate van psychische stress voor en na de uitslag van de test beschreven voor 28 mannen, en hun partners. Deze mannen hadden een kans van 50% (n=24) of 25% (n=4) om drager te zijn van de mutatie en de meesten van hen hadden een of meer dochters; de helft van deze mannen had minstens één dochter ouder dan 20 jaar.

In de weken voor de uitslag rapporteerden geteste mannen en hun partners weinig psychische stress. Veel mannen gaven aan dat zij wel een toename van problemen van hun kinderen verwachtten als zij mutatiedrager bleken te zijn, maar niet dat zij hierdoor zelf meer problemen zouden krijgen. Vooral mannen zonder dochter en/of met een optimistisch karakter rapporteerden weinig psychische stress. De meeste mannen gaven aan dat zij het probleem niet actief uit de weg gingen.

Hoge psychische stress na de uitslag van de test werd gevonden bij 1 van de, in totaal (slechts) 4 dragers van de mutatie en bij 3 van de 17 niet-dragers (7 niet-dragers hadden deze vragenlijst niet ingevuld). Uit de interviews bleek dat reacties van de 4 mutatiedragers in de weken na de uitslag (bijvoorbeeld of zij een schuld gevoel naar de kinderen hadden) nogal van elkaar verschilden. Onderzoek naar een grotere groep en over langere tijd moet leren wat de psychische consequenties zijn voor mannelijke mutatiedragers als zij geconfronteerd worden met de gevolgen van het doorgegeven hebben van dit gen, bijvoorbeeld als naar voren komt dat een dochter de mutatie heeft geërfd ofwel borst of eierstokkanker heeft ontwikkeld.

De mogelijkheid om de genetische test te doen bij een ongeboren kind (prenataal onderzoek) om vast te stellen of het kind een mutatie draagt voor een ziekte die later in het leven tot uiting komt, zoals HBOC, werpt een aantal belangrijke morele vraagstukken op. In **hoofdstuk 8** staat beschreven wat

dragers (n=26) en niet-dragers van de mutatie (n=52) vinden van de mogelijkheid een zwangerschap af te breken wanneer de dochter of zoon de mutatie bij zich draagt. Geen van de mutatiedragers, en een kleine minderheid van de niet-mutatiedragers zou dit voor zichzelf acceptabel vinden. Kennelijk is de overgrote meerderheid van mening dat ondanks de belastende gevolgen van het hebben van een BRCA1/BRCA2 mutatie, een leven met deze gevolgen toch de moeite waard is geleefd te worden. De terughoudendheid om zwangerschapsafbreking te overwegen in geval van een kind met de BRCA1/BRCA2 mutatie in ogenschouw nemend, samen met het feit dat in de praktijk slechts zeer sporadisch interesse is getoond voor deze vorm van diagnostiek én de grote emotionele belasting die een dergelijk besluit met zich meebrengt, zou men kunnen verwachten dat de aanvraag voor prenataal onderzoek voor BRCA1/BRCA2 gering zal blijven. Indien deze emotioneel belastende optie toch overwogen wordt door een (echt)paar is het van groot belang om bij de counseling uitgebreid stil te staan bij het zoeken naar een beslissing die voor het paar het meest bevredigend is.

In **hoofdstuk 9** worden de belangrijkste resultaten van de studies in dit proefschrift besproken en komen aanbevelingen voor de klinische praktijk en voor toekomstig onderzoek aan de orde.

Het is enigszins verbazingwekkend dat psychische stress bij geteste vrouwen en mannen vóór de uitslag niet hoger was dan dat van een normale vergelijkingsgroep, en dat vrouwelijke mutatiedragers geen toename van psychische stress vertoonden. Een mogelijke verklaring hiervoor zou kunnen zijn dat deze groep zeer gemotiveerd leek voor de test nadat de mutatie in de familie was gevonden. De meerderheid had dit besluit binnen twee maanden genomen en allen binnen een jaar. Toekomstig onderzoek zal moeten uitwijzen of een groep die wat ambivalenter staat tegenover de test, het wellicht moeilijker krijgt vóór en na de uitslag. Voorts bleek dat de meeste geïdentificeerde mutatiedraagsters reeds vóór de uitslag hadden besloten of zij intensieve controle en/of preventieve mastectomie zouden ondergaan als zij drager zouden zijn. Het feit dat zij kennelijk geanticipeerd hadden op wat na de uitslag op hen afkwam, zou geholpen kunnen hebben bij de aanpassing na de uitslag.

Partners van mutatie draagsters vertoonden wél een toename van psychische stress in de weken na de uitslag, en eenderde van hen rapporteerde zich erg gespannen te voelen. Mogelijk hadden partners meer dan de vrouwen zelf de neiging gehad om het zich zorgen maken over eventueel mutatiedragerschap tot na de uitslag uit te stellen. Het protocol voor genetisch testen voor HBOC benadrukt kennelijk niet ten onrechte dat partners

gestimuleerd worden mee te komen naar de voorbereidende counseling sessies, waarin uitgebreid wordt stil gestaan bij de consequenties en mogelijkheden na een ongunstige testuitslag.

Mannen in dit onderzoek rapporteerden in de periode voor de uitslag minder psychische stress dan vrouwen, maar dit leek niet te berusten op vermijding om bij de situatie stil te staan. Mogelijk wordt dit lage niveau van psychische stress verklaard door het feit dat mannen niet, zoals vrouwen, een hoog risico op kanker hebben als zij drager blijken te zijn en dat zij derhalve ook niet voor moeilijke beslissingen staan omtrent frequente controle of preventieve chirurgie. Daarnaast is het een veel voorkomend resultaat dat mannen geneigd zijn minder psychische stress te rapporteren in een vragenlijst dan vrouwen. Relevant voor toekomstig onderzoek is dat men ervaringen en gevoelens exploreert van mannelijke mutatiedragers die geconfronteerd worden met de gevolgen van het hebben overgebracht van de mutatie, bijvoorbeeld als een dochter preventieve chirurgie ondergaat of als bij haar de ziekte wordt ontdekt.

Dat de mutatiedraagsters die kozen voor preventieve mastectomie duidelijk meer psychische stress rapporteerden dan zij die kozen voor intensieve controle en niet-mutatiedraagsters, voornamelijk in de weken voorafgaand aan en na afloop van de uitslag, zou mogelijk verklaard kunnen worden doordat de meesten van hen een hoog risico op kanker hadden in verband met hun leeftijd (30 tot 40 jaar) en/of jonge kinderen hadden. Er is meer onderzoek nodig om aan te kunnen tonen in hoeverre ook het vooruitzicht van de operatie zelf deze vrouwen meer gespannen heeft gemaakt. Tijdens de genetische counseling zal speciale aandacht voor deze groep mutatiedraagsters nodig zijn en in de weken na de uitslag zou hen standaard psychologische begeleiding aangeboden kunnen worden.

Voor niet-mutatiedraagsters, mutatiedraagsters die voor intensieve controle kiezen en mannen die de test ondergaan, zou het mogelijk voldoende kunnen zijn om hen te wijzen op de mogelijkheid van extra psychologische begeleiding indien zij daar behoefte aan hebben. Een directere benadering zal meer op zijn plaats zijn als de klinisch geneticus of genetisch consulent psychologische begeleiding nodig acht. Het is belangrijk om met behulp van vragenlijsten die psychische stress meten na te gaan of een dergelijke procedure voor psychologische begeleiding afdoende is. Bij het geven van de uitslag aan niet-mutatiedraagsters die een zus hebben die wel mutatiedraagster blijkt te zijn, zou ingegaan moeten worden op de mogelijkheid dat deze vrouwen zich tijdelijk somber kunnen gaan voelen, ondanks hun eigen gunstige uitslag.

Voor en na preventieve mastectomie is goede informatie van groot belang over de eventuele negatieve invloed op hoe het borstgebied na de operatie

aanvoelt en eruit ziet, op de intieme relatie en op lichamelijke ongemakken. Dat kan vrouwen helpen een zelfstandige, weloverwogen beslissing te nemen over deze ingreep en om goed voorbereid te zijn op deze negatieve gevolgen. Eveneens lijkt een belangrijke bron van steun en informatie het bieden van de mogelijkheid om ervaringen uit te wisselen met vrouwen die dezelfde ingreep hebben ondergaan, bijvoorbeeld in de vorm van een lotgenoten groep.

Het is opmerkelijk dat mutatiedraagsters die voor intensieve controle kozen eenzelfde laag niveau van psychische stress rapporteerden tot een jaar na de uitslag, als de niet-mutatiedraagsters. Mogelijk ontleenden zij een gevoel van vertrouwen aan deze controle. Intrigerend is dat deze vrouwen op latere leeftijd geconfronteerd werden met de ziekte bij een familielid en de erfelijkheid daarvan dan de vrouwen die kozen voor preventieve mastectomie en zij die kozen voor niet-testen. Een verschil tussen beide laatstgenoemde groepen is dat vrouwen die kozen voor mastectomie na deze vroege eerste confrontatie gemiddeld vaker meemaakten dat een familielid borst- of eierstokkanker kreeg, dan vrouwen die besloten de test niet te doen.

Hoewel de resultaten van 1 jaar na de uitslag wijzen op een redelijke aanpassing bij de meerderheid van de vrouwen die vroegtijdig wisten dat zij een hoog risico hadden om borst- en/of eierstokkanker te krijgen, is nog weinig bekend over de gevolgen op langere termijn. Om hier meer inzicht in te krijgen zijn twee prospectieve studies gestart naar de psychische gevolgen van langdurige intensieve controle (waarbij dikwijls iets verdachts wordt gevonden wat bij nader onderzoek vaak niet maligne blijkt) en van preventieve mastectomie. Deze onderzoeken zijn met name van belang nu de effectiviteit van preventieve mastectomie om de kans op borstkanker bij mutatiedraagsters sterk te verkleinen recentelijk wetenschappelijk is aangetoond.

'Experiences and expectations beforehand'

In this questionnaire you will find some questions about hereditary breast/ovarian cancer, about the predictive test for this disease and about the influence this test might have on different areas.

1.

I think that if I were found to carry the hereditary factor then I would react as follows		agree	?	don't agree
a.	my quality of life would decrease	1	2	3
b.	my problems would increase	1	2	3
c.	I would be better able to plan future life	1	2	3
d.	I would become depressed	1	2	3
	if you have a partner and/or children:			
e.	the problems of my partner would increase	1	2	3
f.	this will negatively influence my relationship	1	2	3
g.	the problems of my children would increase	1	2	3

2.

I think that if I were found not to carry the hereditary factor then I would react as follows		agree	?	don't agree
a.	my problems would decrease	1	2	3
b.	I would be better able to plan my future	1	2	3
c.	my mood would improve	1	2	3
	if you have children:			
d.	the problems of my children would increase	1	2	3

3.
If the test shows that you are carrying the hereditary factor, do you expect this to be of any influence in obtaining or keeping work in the next 12 months?

[ ] I am certain this will have influence
[ ] I think this may have influence
[ ] I do not know
[ ] I think this may have no influence
[ ] I am certain this will have no influence

4.
Which relatives with breast or ovarian cancer do you know or have you known? (e.g. grandmother, mother, aunt, sister, uncle)

_____ _____ _____

_____ _____ _____

_____ _____ _____

5
The predictive test could be used as a prenatal test (testing of an unborn child during pregnancy). This section will ask you about your attitudes towards prenatal testing. Please answer these questions, even if you do not intend to have any (or any more) children yourself.

5a
Do you want to have any / any more children?

[ ] Yes
[ ] No
[ ] Uncertain

If you answered this question with 'no', or 'uncertain', is this answer related to the possibility of you being a carrier of the hereditary factor?

5b
If you or your partner were pregnant, would you use the predictive test to test the unborn child?

[ ] Yes
[ ] No
[ ] Uncertain

Can you please explain your answer?

5c
Imagine that you or your partner were pregnant:
in which circumstances would you find termination of pregnancy acceptable?

I find termination of pregnancy acceptable for myself if:		**agree**	**?**	**don't agree**
a.	Health of mother is in danger because of pregnancy	1	2	3
b.	Prenatal testing shows a serious disease	1	2	3
c.	Prenatal testing shows Down Syndrome	1	2	3
d.	Prenatal testing shows that the child is female and carrier of the hereditary factor for breast/ovarian cancer	1	2	3
e.	Prenatal testing shows that the child is male and carrier of the hereditary factor for breast/ovarian cancer	1	2	3
f.	I find termination of pregnancy not acceptable at all	1	2	3

'Experiences and attitudes after testing'

It is now six months ago that you received your test-result. Can you please indicate which implications this has had for you?

Since the disclosure of the test result....

... my problems have	[ ] increased
	[ ] decreased
	[ ] remained unchanged
... my quality of life has	[ ] increased
	[ ] decreased
	[ ] remained unchanged
... my relationship has	[ ] changed in a positive way
	[ ] changed in a negative way
	[ ] remained unchanged
... I am	[ ] better able to plan future life
	[ ] not better able to plan future life

Dear Madam,

Some time ago a hereditary factor is found in your family, which is associated with breast and/or ovarian cancer. This enabled to find out whether individuals from your family are carrier of this genetic factor or not (a DNA-test).

Evidence shows that about half the persons for whom this test is available subsequently decide to undergo this test and half decide not to undergo the test. Each person should make such decision for him/herself.

We write you this letter, because we would like to know somewhat more about those persons who have not undergone this test. What motives do they have and how are they doing?
Your ideas and experiences can help us to better adjust our policies to both the persons who apply for genetic testing, and those who do not.

Therefore, we would like to ask you to participate in this study. For this, we would appreciate it if you filled out some questionnaires. This will take you about 20 minutes. Questions concern your reasons for not undergoing the test and topics that are quite personal such as: experiences with cancer in the family, experiences with the genetic studies applied in the family and how you are feeling.

Besides, we would appreciate to hear from your experiences in a personal interview. For this, a colleague from the department Medical Psychology, mrs. L.N. Lodder (MSc), can visit you at home. This interview takes about one hour.

We greatly appreciate your cooperation. It might be that you would like to answer the questionnaires, but not to participate in the interview, or vice versa, which is possible. Participation is completely voluntary. If you would like to have more information about this study, you can contact mrs. Lodder by telephone (tel. 010 408 7988).

Of course this study does not aim to affect your decision. It goes without saying that we fully respect your decision.

Data of this study will be treated confidentially and anonymously and will be used for scientific aims only. The study is carried out in collaboration with the heads of the department of Medical Psychology and Psychotherapy and the department of Clinical

Genetics of the Erasmus University, Rotterdam. The Medical Ethical Board of the University Hospital Dijkzigt also approved the study.

Would you please fill in the attached form and return this to us within 3 weeks by means of the answering envelope? No stamp is required. If you do not respond, we assume that you prefer not to participate.

Thank you very much for your response.

Yours sincerely,

mrs. drs. L.N. Lodder
mw. dr. P.G. Frets
Dept. Clinical Genetics /
Dept. Medical Psychology
and Psychotherapy

Prof.dr. M.F. Niermeijer
Dept. Clinical Genetics

Prof.dr. R.W. Trijsburg
Dept. Medical Psychology
and Psychotherapy

Other members of this projects: Prof.dr. J.G.M. Klijn, dr. C. Seynaeve, drs. M.M.A. Tilanus-Linthorst, drs. C.C.M. Bartels, drs. L. Verhoog (Family Cancer Clinic, Rotterdam Cancer Center (Dr. Daniel den Hoed)/University Hospital, Rotterdam) en drs. E.J. Meijers-Heijboer (Dept. Clinical Genetics)

****

Answering form

Number……..

0 Yes, I agree to participate in the study (interview and questionnaires).
You can call me to schedule the interview or to provide more information about the study.

0 You can send me questionnaires, but I refrain from participation in the interview.

0 You can call me to schedule the interview, but I prefer not to fill out the questionnaires

0 I prefer not to participate in the study.

Any questions/remarks

Dear madam,

In this booklet you will find four questionnaires. It takes about 20 minutes to answer the questions. The first questions concern some data about yourself and about your experiences with the genetic studies applied in the family and experiences with the disease in the family. You are also asked to describe your reasons not to undergo genetic predictive testing.

Questionnaire I: Some questions about yourself and your personal experiences

1. What is your age? ..... years

2. What is your marital status?

   1 married
   2 living together
   3 not married
   4 divorced
   5 widowed

3. Do you have children?

   1 No
   2 Yes: ..... daughter(s), aged .....
   ..... sons(s), aged: .....

4. What do you do in daily life?

   1 I am working for..... hours a week
   2 I am a housekeeper
   3 I am studying
   4 I receive a benefit (AOW, pension, VUT)
   5 Differently: .....

5. For which education did you receive a diploma?

   1 Elementary school
   2 Lower vocational school (e.g. LTS, LEAO)
   3 Secondary school (e.g. (M)ULO, MAVO, MEAO, MTS)
   4 Secondary vocational school (e.g. HAVO/VWO, HBS)
   5 Higher vocational school (e.g. HBO, HEAO)
   6 University
   7 Differently: .....

6. At what age did you first learn about breast or ovarian cancer in your family?

7. At what age did you first become aware of the possibility that breast or ovarian cancer might be hereditary in your family?

8. Which relatives with breast or ovarian cancer do you know or have you known? (e.g. grandmother, mother, aunt, sister, uncle) How did they fare?

Relative:	How did she/he fare?
_____	_____
_____	_____
_____	_____
_____	_____

If you have not known any relative with breast or ovarian cancer, could you then please indicate whether you know other close persons, who have (had) cancer?

Relationship (e.g. *'friend', 'sister in law'*)	How did she/he fare?
_____	_____
_____	_____

9. The next questions concern how you have been informed about the genetic studies to identify the hereditary factor for cancer in your family.

a. Who informed you about the study on hereditary breast/ovarian cancer in your family? (you can give more than one answer, if necessary)

- ☐ A close relative (e.g. sister, father, mother)
- ☐ Another relative (e.g. aunt, cousine)
- ☐ The General Practitioner
- ☐ Another physician
- ☐ Someone else _____

b. How do you feel about being informed by this/these person(s)?

1 I would rather not have been informed
2 I find it good to be informed
3 I am neutral about this

Can you please explain your answer?

c. Have you had any contact with the dept. of Clinical Genetics about the study on hereditary breast/ovarian cancer in your family?

1 Yes 2 No

If you answered this question with 'Yes': How do you feel about this contact?

1 I am satisfied about it
2 I am neutral about it
3 I am not satisfied about it, because:

10. Have the contacts with your relatives changed since you have been informed about the hereditary factor for cancer?

1 Yes 2 Not really 3 No

Can you please explain your answer?

11. You have not undergone the test for hereditary breast/ovarian cancer. Can you describe your reason(s) for this?

12. Some persons who have not undergone the test do consider undergoing this test in the future. What is your idea about this?

13. Could you indicate below which of the following answer describes best how you feel about the hereditary factor? (Please tick that answer)

a. ☐ I have the feeling that I do not carry the hereditary factor.
b. ☐ I have the feeling that I do carry the hereditary factor.
c. ☐ I have the feeling that I might as well carry or not carry the hereditary factor.
d. ☐ I have no particular feeling about whether I do carry the hereditary factor or not.

14. Could you please indicate below with which of the following answering options you do agree?

By undergoing an intensive surveillance program in the hospital, breast cancer can be

a. ☐ seldom detected in time
b. ☐ often detected in time
c. ☐ always detected in time
d. ☐ differently :

Can you please indicate with which of the following statements you agree?

15.

		agree	?	don't agree
a.	I feel safe about participating in the surveillance program	1	2	3
b.	I feel safe about doing breast-self-examination	1	2	3
c.	I consider it as too far-reaching to preventively have my breasts removed	1	2	3
d.	I consider it as too far-reaching to preventively have my ovaries removed	1	2	3

16.

If a woman carries the hereditary factor for breast/ovarian cancer,		agree	?	don't agree
a.	this would not say much about whether she will get cancer or not	1	2	3
b.	she has an increased risk to get cancer	1	2	3
c.	she will certainly get cancer	1	2	3

17.

I think that if I were found <u>to carry</u> the hereditary factor then I would react as follows:		agree	?	don't agree
a.	my problems would increase	1	2	3
b.	I would be better able to plan my future	1	2	3
c.	I would become depressed	1	2	3
d.	I would obtain more certainty	1	2	3
	if you have children:			
e.	the problems of my children would increase	1	2	3

18.

I think that if I were found <u>not to carry</u> the hereditary factor then I would react as follows		agree	?	don't agree
a.	my problems would decrease	1	2	3
b.	I would be better able to plan my future	1	2	3
c.	my mood would improve	1	2	3
	if you have children:			
d.	the problems of my children would decrease	1	2	3

Experiences of women who applied for genetic testing for hereditary breast and ovarian cancer concerning *body image* and *sexuality*

Your answers in this questionnaire are anonimously analysed

Could you please indicate to which extent you agree with the statements on the following pages.

EXAMPLE

'I am doing fine at the moment'

If you **'definitely disagree'** with this statement, then put a cross at the left:

I am doing fine Definitely X Definitely
disagree |-------|-------|-------|-------|-------| agree

If you **'disagree to a certain extent'** with this statement, then put the cross as follows:

I am doing fine Definitely X Definitely
disagree |-------|-------|-------|-------|-------| agree

If you **'agree to a certain extent'** with this statement, then put the cross as follows:

I am doing fine Definitely X Definitely
disagree |-------|-------|-------|-------|-------| agree

If you **' definitely agree'** with this statement, then put a cross at the right:

I am doing fine Definitely X Definitely
disagree |-------|-------|-------|-------|-------| agree

If you **'neither agree or disagree'** with this statement, then put the cross in the middle.

1. I find it important to look good	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
2. I pay much attention to my appearance	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree

The following questions concern the past three months.

In the past three months.....

3. I was satisfied with my appearance when dressed	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
4. I felt quite feminine	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
5. I felt very conscious about my appearance	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
6. I was satisfied with my appearance when undressed	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
7. I had difficulty watching my body when undressed	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
8. I had difficulty touching my breasts	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
9. I was satisfied with the appearance of my breasts	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
10. My breasts felt pleasant	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
11. I felt sexually attractive	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree

Can you please indicate to which extent you agree with the following statements?

12. I find cuddling or kissing very important	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree

13. I find sexual contact (intercourse or other ways of sexual contact) very important	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree

In the past three months:

14. I found it pleasant to cuddle or kiss my partner	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
15. I had the feeling that my partner found it difficult to touch me	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
16. I cuddled or kissed my partner less often than usually	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
17. I had the feeling that my partner found it difficult to make love to me	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
18. I had the feeling that my partner was not in the mood for having sex	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
19. I had sex with my partner less often than usually	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
20. I was not in the mood for having sex	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
21. having sexual contact frightened me	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
22. I had difficulty getting excited	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
23. I was afraid that having sex would cause pain or would be physically unpleasant	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree

Did you have sex with your partner in the past three months?
If you did not, you can skip the next two questions and continue to answer question 28. If you did, you can continue by answering the next question.

In the past three months

24. I found it pleasant to have sex with my partner	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
25. I could communicate well with my partner about what I find pleasant when we make love	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
26. pain in my breasts restrained me from having sex with my partner	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
27. I had the feeling that my partner found me sexually attractive	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree
28. I was ashamed of my body when undressed	Definitely disagree	|-------|-------|-------|-------|-------|	Definitely agree

The following question is an open-ended question

29. Has something changed in your sexual relationship in the past three months? If so, what has changed?

30. Did you find the questions in this list..... ?

- O burdensome
- O too personal
- O making sense

If you like to ad any comment, please do so below.

Questions about consequences of surgery of the breasts

1. To which extent do you suffer from physical complaints (such as pain, a stiff feeling in the skin, little strength in the arms)?

0	1	2	3	4	5	6	7	8
Not at all								Very much

2a. How are your feelings of self-confidence at the moment?

0	1	2	3	4	5	6	7	8
I feel very confident about myself								I feel not at all confident about myself

2b. Does the fact that you do not have your own breasts anymore affect your sense of self-confidence?

0	1	2	3	4	5	6	7	8
My self-confidence has definitely increased ever since								My self confidence has definitely decreased ever since

3. How does your breast region feel when sitting or walking?

0	1	2	3	4	5	6	7	8
It feels not strange at all								It feels very strange

4. Imagine that you did not have a breast reconstruction. How would you feel about that?

0	1	2	3	4	5	6	7	8
That would have been fine with me								I would find that very difficult

Questions about consequences of surgery of the breasts and the ovaries

5. To which extent do you suffer from physical complaints resulting from the surgical removal of your ovaries?

0	1	2	3	4	5	6	7	8
Not at all								Very much

6. How do you feel about the fact that your ovaries have been surgically removed?

0	1	2	3	4	5	6	7	8
I have no difficulty with it								I have much difficulty with it

Questions about consequences of surgery of the breasts and/or the ovaries

7. What is your perception, after all, of the surgery you underwent?

0	1	2	3	4	5	6	7	8
I have much less difficulty with it than expected								I have far more difficulty with it than expected

8. Do you ever think: 'I had better not undergone this surgery'?

0	1	2	3	4	5	6	7	8
I am never thinking that way								I am thinking that way all the time

Dankwoord

Als eerste wil ik alle mensen in dit onderzoek bedanken voor hun bereidheid om in een zeer belastende periode in hun leven hun ervaringen met mij te delen en deze tevens keer op keer weer in een lange vragenlijst weer te geven. Als ik hen niet zo uitgebreid persoonlijk had gevolgd, had ik nooit feeling kunnen krijgen met de mens die schuilgaat achter een getal of een lijn in een grafiek.

Petra Frets, beste Petra, mijn directe begeleider en co-promotor, jou wil ik van harte bedanken voor alle energie die jij van het begin tot het eind in de voortgang van het project hebt gestoken, zelfs wanneer jij zelf veel energie moest ontberen door medische, maar ook werk gerelateerde vervelendheden. Ik vond het bijzonder prettig met jou samen te werken. Ten eerste had ik het gevoel vaak met jou op één lijn te zitten wat betreft ideeën over het onderzoek en de onderzochten (al nam het op een lijn zitten een wat bizarre vorm aan, toen wij ons op een ochtend op congres bezoek in Rome in exact dezelfde kledij gestoken zagen). Ten tweede liet jij mij op een voor mij zeer goed voelende wijze zelfstandig mijn werk doen zonder mij te laten zwemmen. En tot slot heb ik het erg fijn gevonden bij jou zo nu en dan mijn hart te kunnen luchten bij tegenslagen op het werk en privé, ofwel ergens hartelijk om te lachen.

Wim Trijsburg, mijn eerste promotor, beste Wim, jou wil ik bedanken voor de vaak zo heldere kijk op de kern van wat ik duidelijk wilde maken in de hoofdstukken van dit proefschrift. Terecht floot jij me soms terug als ik interpretaties verwarde met empirische gegevens. Op persoonlijk vlak heb ik ook veel van je geleerd, ons contact verliep niet altijd even makkelijk, maar heeft mij wel beter naar mijzelf doen kijken (overigens niet zonder de hulp van de externe supervisie die jij voor mij regelde, waar ik je in retrospect ook dankbaar voor ben).

Professor Niermeijer, mijn tweede promotor, beste Professor Niermeijer, u ben ik dankbaar voor het mij treffender op papier hebben leren verwoorden. Uw geest moet letterlijk scherp zijn om uit drie zinnen één passende volzin te kunnen snijden. Al stemde het mij niet altijd gunstig op de momenten dat ik een stuk vol doorgekraste zinnen terug kreeg... Daarnaast bewonder ik uw inzet en betrokkenheid bij het tot stand komen van het proefschrift tot het laatste moment (met als toppunt dat u mij recentelijk vanuit het ziekenhuis, hooguit een dag na een operatie, telefonisch trachtte te bereiken). Dit alles heeft mij zeker gesteund en geïnspireerd, vooral in de laatste fase waarin ik dat extra nodig had.

Beste en lieve collega's van de MPP, al ben ik al bijna twee jaar weg van de afdeling, ik koester zeer goede herinneringen aan de contacten met jullie. Een aanloop had ik echter wel nodig, ik kwam op een afdeling vol AIO's die al in de eindfase zaten en voelde mij een beetje, zoals Adriaan ooit terloops juist inschatte (nog maar koud gestart met analytische psychotherapie) als een nakomer in een gezin. Zoals het oudere broers en zussen betaamt zijn jullie eerdere AIO's, Alec, Karina, Christine, Annelien, en Adriaan (gefeliciteerd, je hebt de door anderen in het leven geroepen weddenschap gewonnen!) reeds gepromoveerd. Irma, jouw tijd komt nu gelukkig ook weer gauw! Gelukkig voor het nakomer gevoel kwamen zich zeer kort op elkaar allemaal nieuwe enthousiastelingen op de afdeling nestelen, bij name wil ik noemen Chantal, Marleen, Cecile, Anita, Vivian, Peter en later ook Paula. Weldra vormden wij een gezellige hechte groep die veel lief, maar misschien nog meer leed (de ene life event volgde de andere in schokkend tempo op) met elkaar deelde. Ik verwacht niet dat ik ooit nog in zo'n fijne collega groep zal verkeren als met jullie. Bedankt voor jullie zeer positieve invloed op mijn welbevinden op het werk en voor het mij op de hoogte brengen elke keer als er weer iets gezelligs ging gebeuren. Opdat we dat nog maar lang levend houden!

Rianne, jij was mij kamergenoot. Wat een fanatiekelingen waren wij. De enigen zowat die met de deur dicht werkten. Toch ontdekten wij steeds meer dat dit ook de mogelijkheid bood gesprekken met elkaar te voeren die niet voor een ieders oor bestemd waren, bijv. naar aanleiding van op ons gemoed inwerkende mails. Ik vind het jammer dat ons contact, vooral door mijn toedoen, zo minimaal werd sinds ik weg ben, maar het etentje houden we nog tegoed! Oja, en nogmaals sorry voor de bende die ik er soms van kon maken. Als ik nu naar beneden kijk besef ik dat jij mij helaas niet afdoende hebt kunnen afleren de grond als tafel te gebruiken.

Hugo Duivenvoorden, psycho-methodoloog en statisticus, jou wil ik bedanken voor je enthousiasme en toewijding wat betreft de wetenschappelijke en methodologische kant van mijn onderzoek. Hoewel er een moment was dat wij elkaar daarin wat kwijt raakten (jouw ideeën van een doorgewinterde wetenschapper rijmden niet altijd met die van een beginnend, eigenwijs onderzoeker), had ik het gevoel dat wij het toch wel met elkaar konden vinden. Overigens van jouw gestructureerde wijze van klussen afhandelen (ik had mijn briefje nog niet geschreven of er lag al een antwoord in mijn postvak) kan ik als 'niet bepaald psychasteen' persoon nog wel wat leren.

Hoewel iedereen een steen heeft bijgedragen aan dat ik een goede tijd heb gehad op de afdeling, wil ik nog bij name noemen: Saskia, bijzonder hoe jij een persoonlijke sfeer kan creëren doordat je altijd zo jezelf bent. Josien, ik vond het leuk dat jij zo trouw was wat betreft het komen lunchen en koffie drinken, temeer omdat je een gezellig mens bent, en ik vind het dan ook jammer dat ik jou amper heb gezien sinds ik weg ben. Aad, het zo nu en dan mogen

aanschouwen hoe jij 'glashelder' inter en intra psychische dynamiek kon vatten heeft mijn wens mij te bekwamen in het therapie vak vergroot. Benno, jouw enthousiasme voor het psychologie onderwijs voor studenten geneeskunde heeft zeker een rol gespeeld bij mijn ontdeking dat onderwijs geven erg leuk is. Opvallend was niet alleen je persoonlijke betrokkenheid bij de studenten, maar ook bij collega's. Ik heb mij dan ook op bepaalde momenten zeer gesteund gevoeld door jou.

Dan wil ik de mensen danken die mij niet alleen door hun aanwezigheid, maar ook op een wat directere manier geholpen hebben bij het kunnen volbrengen van dit onderzoek. Corrie, jij was de secretaresse die de langste adem had bij de vaak zeer saaie klussen die het onderzoek met zich mee bracht. Helaas liep jouw contract af, op een moment dat die adem nog niet op was. Behalve dat jij je zeer werklustig en consciëntieus toonde, kon ik het ook goed met je vinden. Dat ik de afgelopen 2 jaar nauwelijks contact met je heb gehad, wil niet zeggen dat jij ook bovenaan mijn prioriteiten lijst van telefoontjes staat. Alike en Ankey, jullie ook zeer veel dank voor jullie bijdrage aan het project.

En dan is er het zeer trouwe, goed functionerende algemene secretariaat dat ik wil bedanken, een drie-vrouwschap die het hart van de afdeling vormt en die ook mij, vooral in het afgelopen jaar fantastisch heeft geholpen. Het is niet voor te stellen en zeer verdrietig, dat een van hen, Loes, in augustus j.l., slechts een paar maanden na het vernemen dat zij ernstig ziek was, is overleden. Juist omdat ik het niet van dichtbij heb meegemaakt, voelt dit zeer onwezenlijk. Loes was de persoon tot wie ik mij altijd richtte met financiële vragen en juist in deze tijd is op die manier haar gemis voelbaar. Margreet en Ingrid, maar ook de andere secretaresses van de afdeling, voor jullie is het gemis heel tastbaar en ik wens jullie veel sterkte met het verwerken van dat jullie samenwerking zo plotseling beëindigd is.

Jan Passchier, hoofd van de MPP, beste Jan, jou wil ik bedanken voor het mijn baas zijn geweest, wat zich vooral uitte in de jaarlijkse functioneringsgesprekken, die ik altijd als zeer prettig heb ervaren. Overigens wil ik je ook zeggen dat ik, nu ik op een niet-wetenschappelijk afdeling werk, wel eens met weemoed terug denk aan het wekelijks een uur bij elkaar komen om te praten over 'research', 'journals' of 'refeer'.

Dan zijn er de secretaresses en ander personeel op de afdeling Klinische Genetica die ik hartelijk wil danken voor hun bijdrage aan het project. Bij name wil ik drie mensen noemen. Hanne, Anja en Conny, aan jullie heb ik te danken dat veel mensen in mijn onderzoek konden instromen en dat relatief weinig mensen van deelname afzagen. Extra dankbaar ben ik omdat het niet altijd makkelijk geweest moet zijn om mensen die net zeer belastende informatie hebben ontvangen te vragen mee te doen aan het onderzoek Bijzonder leerzaam was het ook om soms de counseling sessies bij te wonen. Jullie

bereidheid mij te vertellen over de medische en genetische kant van de test was onontbeerlijk. Hanne, jij ook bedankt voor alle ritjes naar de Daniel den Hoed, en incidenteel naar Goes of Vlissingen.

Ook zonder de bijdragen van de medewerkers van de Daniel den Hoed had mijn proefschrift niet kunnen worden wat het is. Vooral Jan, Carolien, Leon, Carina, Madeleine en Bert wil ik hier hartelijk voor danken.

Dan waren er nog twee leuke en bekwame redders in nood, die ik zeer dankbaar ben voor het doen van een aantal interviews overal in het land, met vrouwen die het gen niet hadden geërfd, toen mijn inspiratie en tijd daarvoor niet meer toereikend was. Ellen, de reden dat jij moest stoppen trof mij zeer. Ik ga je voor de promotie nog eens bellen. Conny, door de drukte ben ik niet meer in gegaan op jouw gezellige aanbod een duik te nemen in het door bomen omringde zwembad. Het lijkt me in ieder geval heel leuk als je bij de promotie en/of het feest aanwezig kan zijn.

De portiers van Hoboken wil ik hartelijk danken voor al die avonden dat zij vlak voor de 'night shift', voor mij een extra ronde moesten maken om de zijvleugel van de MPP af te sluiten.

Doordat het voor mij onmogelijk werd naast de taken die het proefschrift, mijn werk en de opleiding met zich meebrachten ook nog tegemoet te komen aan de taken waar mijn huis steeds zichtbaarder om vroegen, was jij Greetje hierbij onmisbaar voor mij. Nogmaals, veel dank hiervoor.

Dan zijn er natuurlijk mijn vriendinnen, die een belangrijke rol hadden in het besef dat het leven niet alleen zwaar, maar ook gezellig en verkwikkend kan zijn. Christina, het is ongelooflijk hoe ik elke donderdagavond opnieuw blij en tevreden naar huis fiets na onze intieme post-sport dineetjes. Wie had ooit gedacht toen wij vroeger onze hut bouwden en altijd te laat naar school renden en later fietsten, dat jij nu mijn paranimf zou zijn. Als een paranimf ben jij nu, maar een vriendin zul je altijd blijven. Myrte, jij bent wel de meest ingewijde in het wel en wee rond mijn AIO-schap en proefschrift tijd. Bedankt voor het luisteren naar mijn verhalen o.a. tijdens het joggen of struinend door de straten van Parijs, en voor dat jij mijn paranimf wil zijn.

Wilma, leuk hoe jouw combinatie van intellectueel en trendy zijn recentelijk op mijn antwoordapparaat samen kwam toen jij aangaf wat jij zoal in Roma Aeterna was tegen gekomen, en vervolgens meldde dat je een leuke DJ voor het feest had opgesnord. Koosje, bedankt voor onder andere Garamond! Femke, jou ken ik relatief kort, maar jij hebt de afgelopen twee jaar een belangrijke rol in mijn leven gehad. Dat jij mij voorspiegelde dat ik bijna het onmogelijke van mezelf vroeg door werk, opleiding met proefschrift te willen combineren heeft mij geholpen mij minder schuldig te voelen op de momenten

dat ik wat langer uitsliep of tijd nam voor bezinning op mijn persoonlijk leven. Katelijne, jou ben ik zeer dankbaar voor de prachtige omslag. Grappig dat het zien van schoonheid een 'love at first sight' gevoel kan geven…

Veel vriendinnen, familie en kennissen heb ik in de afgelopen jaar veel minder gezien dan mij lief was, hetgeen ik oprecht betreur. Ik heb kunnen ervaren wat ik zou missen als deze contacten echt zouden verwateren en hoop daarom in de periode die komt weer een en ander goed te kunnen maken. Heleen, jij staat hierbij wel erg hoog op mijn prioriteiten lijst. Zullen we maar 2 avonden achter elkaar in Spanjer afspreken?

Lieve Jeroen, jij was deelgenoot van de enige dag in de week dat ik niet werkte. En wat voor een dag was dat. Ik kan mij niet voorstellen op een meer relaxte en fijne manier deze bijtank dagen te hebben kunnen doorbrengen. Bedankt daarvoor en voor het geduld dat je moest opbrengen daar de drukte steeds weer langer duurde dan verwacht. Temeer daar geduld, zoals je zei, niet je sterkste kant is….

En dan nog mijn naaste familie. Van mijn broer en zus heb ik net als met tal van andere levenszaken, ook nu de kunst weer wat kunnen afkijken. Het niet de eerste hoeven zijn die een spannende ontwikkeling doormaakt en het bij tijd en wijle tips en ondersteuning krijgen voelt wel veilig en vertrouwd. Ik dank jullie daarvoor, en Arno, jou in het bijzonder voor het mij geholpen hebben bij de lastige klus van het invoegen van de grafieken. Pappa en mamma, mijn dank aan jullie zit hem niet in de eerste plaats in al die concrete dingen waar ik jullie voor zou kunnen danken, maar in datgene wat er gewoon is. Zoals dat jullie zonder woorden accepteerden dat de frequentie van mijn langskomen wel erg drastisch afnam in de afgelopen twee jaar. Maar nog meer in het gevoel dat jullie er onvoorwaardelijk voor mij zijn. Dat is bijzonder waardevol.

Tot slot voel ik de behoefte mijn dank te richten naar een hogere entiteit, die mij de kracht, doorzettingsvermogen en de hersenen heeft gegeven om deze klus te kunnen klaren.

Curriculum Vitae

Litanja Lodder was born in Amstelveen on January 7th, 1970. She graduated from high school (gymnasium β, Herman Wesselink College Amstelveen) in 1988. Subsequently, she lived in Paris for one year, where she studied the French language and worked as an au pair. In 1989 she returned to Amsterdam to start a degree in French language and literature (first year degree *-propaedeuse-* in 1990) at the University of Amsterdam, after which she took up a degree in Psychology. In 1991 she obtained her first year degree *-propaedeuse-* in psychology. In the years that followed she specialised in clinical psychology and studied French translating. For her graduation, she carried out a research project at the department 'Psychosocial research and Epidemiology' at the Antoni van Leeuwenhoek cancer hospital and did a clinical stage for ambulant patients at 'the RIAGG Zaanstreek/Waterland'. In September 1995 she graduated cum laude in clinical psychology.

In November 1995 she started her PhD study at the departments of Medical Psychology and Psychotherapy and of Clinical Genetics, Erasmus University Rotterdam (in collaboration with the Daniel den Hoed Cancer Clinic).

In January 2000 she has taken up a clinical role within a department for ambulant patients with emotional problems as well as a part-time unit specialized in treatments for mood disorders, at Parnassia, the Hague. This work is part of a post-graduation education program for starting psychologists working in a mental health setting (Opleiding tot Gezondheidszorg Psycholoog, centrale RINO groep) which ends December 2001.