The Psychological Impact of Regular Surveillance in Women at Increased Risk for Hereditary Breast Cancer

A clinical empirical exploration

Silvia van Dooren

ISBN: 90-9020121-1

Ontwerp kaft: Annie Schillings, Gulpen

Vormgeving en productie: Mady Reliëf PrePess, Landgraaf

The study described in this thesis was supported by a grant of the Dutch Health Insurance Council (OG-98-03), and was performed at the Department of Medical Psychology and Psychotherapy, Erasmus MC, Rotterdam, in close collaboration with the Departments of Medical and Surgical Oncology of the Daniel den Hoed Cancer Clinic, Erasmus MC, Rotterdam, the Department of Public Health, Erasmus MC, Rotterdam, and the Centre of Human and Clinical Genetics, Leiden University Medical Centre, Leiden.

The Psychological Impact of Regular Surveillance in Women at Increased Risk for Hereditary Breast Cancer
A clinical empirical exploration

De psychologische impact van regelmatige controle bij vrouwen met een verhoogd risico op erfelijke borstkanker
Een klinisch empirische exploratie

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam op gezag van de rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 21 december 2005 om 11.45 uur

door

Silvia van Dooren

geboren te Heerlen

Promotiecommissie

Promotoren

Prof.dr. A. Tibben
Prof.dr. J.G.M. Klijn

Overige leden

Prof.dr. J. Passchier
Prof.dr. M.F. Niermeijer
Prof.dr. C.J. Cornelisse

Copromotor

Dr. C. Seynaeve

Contents

Voor mijn ouders Ine en Marcel
en mijn broer Robert

Chapter 1

Introduction

General introduction

Breast cancer is one of the most common cancer types in the Western world and the leading cause of cancer mortality in women in Europe [1,2]. In the Netherlands, annually about 12.000 new breast cancer cases are diagnosed, mostly above the age of 50 years. Annually, approximately 3500 women die of the disease. As early detection might improve survival, a nationwide population based breast cancer-screening programme for women from the age of 50 onwards was implemented in the Netherlands between 1989 and 1997 [3].

Familial occurrence and young age at onset are well known risk factors. Women having such a family history have an increased risk for the disease, already before the age of 50 years. These women are offered regular surveillance of the breasts and genetic counselling. Repeatedly, it has been reported that women from families with an increased occurrence of breast cancer experience higher levels of psychological distress. Many psychological follow-up studies on the effects of predictive genetic testing for a BRCA1 or BRCA2 mutation have been carried out, as well as studies on the impact of prophylactic surgery in identified mutation carriers. However, studies on the effects of regular breast cancer screening in women at increased risk due to a genetic susceptibility are scarce.

The focus of the current thesis aimed at performing a clinical and empirical exploration of psychological distress in a cohort of women at increased risk of developing hereditary breast cancer adhering to a regular surveillance programme at the Family Cancer Clinic of the Erasmus Medical Centre-Daniel den Hoed Cancer Centre in Rotterdam, the Netherlands.

This introduction provides an overview of the current insights as well as risk assessment methods used in hereditary or familial breast cancer. The major management options for women at increased risk for hereditary breast cancer are briefly described, including the different aspects of breast cancer surveillance. Further, the psychological implications of different aspects of being at risk for hereditary/familial breast cancer are discussed. Finally, the research questions of the current study as addressed in this thesis are described, and an overview of the study procedures is given.

Hereditary breast cancer

Predisposing genes

The earliest known report of hereditary breast cancer originates from 1757 and describes a breast cancer diagnosis in a 19-year old nun with a family history of breast cancer [4,5]. However, it was only until the 20th century that the hereditary nature of the disease became more recognised. At this moment it is assumed that approximately 5-10% of all breast cancer cases can be attributed to an autosomal dominant genetic predisposition [6-8]. A major breakthrough in the field of breast cancer and oncogenetics occurred in 1994 when the BRCA1-gene (BReast CAncer 1) was cloned [9]. A year later a second breast cancer predisposing gene was identified: the BRCA2-gene (BReast CAncer 2) [10]. Since that time it became possible to identify women carrying a mutation in one of these genes through DNA-testing, and to study more specifically the risks associated with, and the outcome of breast (and/or ovarian) cancer due to a BRCA1/2 mutation. For breast cancer it was originally estimated from high-risk families that the cumulative life time risk of developing the disease in mutation carriers was 65-85% by the age of 70 years [11], while in a more recent meta-analysis lower risk percentages of 65% and 45% for BRCA1 and BRCA2, respectively have been described [12]. For ovarian cancer, the initially estimated cumulative life time risk for a female BRCA1 mutation carrier was 63%, and for a BRCA2 mutation carrier 27%. The risk percentages reported in the meta-analysis by Antoniou et al. (2003) were 39% and 11% for BRCA1 and BRCA2 mutation carriers, respectively. By means of current genetic testing, however, a mutation in either BRCA1 or BRCA2 is identified in only 16% of the breast/ovarian cancer cases from families with a suspected genetic predisposition [13,14]. Probably there are other genes involved in breast/ovarian cancer, with different (and probably lower) cumulative lifetime risks. For instance, the recently identified CHEK2*1100delC mutation contributes to an increased breast cancer risk of 1.70 in breast cancer families without an identified BRCA1/2 mutation [14]. Further, mutations in other high-risk cancer susceptibility genes can be associated with breast cancer as well, including PTEN [15] and TP53 [16], but the concrete life time risks of breast cancer in these cases are not exactly known.

Risk assessment

Women from breast cancer families have an indication for genetic counselling and, when they opt for it, genetic testing. Genetic counselling is based upon obtaining a family history including the family size and composition, the occurrence and medical verification of age at onset of breast-, ovarian-, and other cancers, in the family, and the use of genetic epidemiologic tables [17,18]. This way the geneticist is able to estimate the lifetime risk of developing breast cancer for a specific client and to discuss whether or not genetic testing is worthwhile [19].

The size of the breast cancer lifetime risk may depend on the specific risk calculation table that is used. The two risk assessment models frequently used for this purpose are the models developed by Claus et al. (1994) and Gail et al. (1989) [17,18]. Both models take into account the family history of breast cancer, however other known risk factors for developing breast cancer, such as age of menarche or age at first childbirth, are not included in the Claus model. Further, both models have not incorporated the risk associated with bilateral breast cancer, male breast cancer and ovarian cancer. An important further limitation in the use of the Gail model in genetic counselling seems to be the inclusion of only first-degree relatives, since the breast cancer families who present themselves in the family cancer clinic often show a combination of breast cancer in both first- and second degree relatives.

This latter model therefore does not prove to be of good use in the clinical genetic practice [20]. When the probability of detecting a mutation is higher than 10%, DNA testing for a BRCA1/2 mutation is usually offered [21]. Since the DNA test result for breast/ovarian cancer susceptibility may have a far-reaching impact on one's health behaviour, the psychosocial aspects, the family, and the respective plans for the future, the decision to undergo genetic testing involves careful consideration. Reported reasons for women to undergo genetic testing are: obtaining a personal breast cancer risk estimate in order to plan future decisions regarding health behaviour like intensive surveillance or prophylactic surgery, and obtaining certainty about the possibility of having transmitted the gene mutation to children [22,23].

Guidelines

A survey based on experts' opinions on guidelines for surveillance and management of familial breast cancer showed that most of the 16 responding centres from nine European countries used quite similar guidelines [24]. In the Netherlands, women with an increased risk of breast/ovarian cancer due to a genetic susceptibility are offered to attend a Family Cancer Clinic where multidisciplinary care and regular surveillance is provided. The Working group of Clinical Oncogenetics (WKO) and the Dutch working group on hereditary breast cancer (HEBON) have developed guidelines regarding management options. These multidisciplinary working parties provide both 'evidence based' as well as 'expert opinion based' policies.

At the Erasmus MC-Daniel den Hoed Cancer Centre in Rotterdam a multidisciplinary committee on hereditary tumours was founded in 1991 to coordinate both counselling and care issues, as well as research coordination on hereditary breast- and/or ovarian cancer as well as other hereditary cancer syndromes. The members of this working group are represented in the HEBON and the WKO. Further, the Rotterdam working party has developed institutional and regional guidelines concerning referral for breast/ovarian cancer counselling, advises for different risk and age categories in women with or without a history of breast/ovarian cancer. Different options may be discussed with a specific woman, taking into account the particular personal circumstances, consisting of either surveillance or prophylactic surgery, which are further discussed in following paragraphs.

Management options in women at increased risk of breast cancer due to a genetic susceptibility

Regular breast cancer surveillance

In the Netherlands, women with a cumulative lifetime risk of breast cancer of at least 15-20% on the basis of their family history are considered eligible for regular breast cancer surveillance [24]. According to national guidelines, the surveillance for breast cancer consists of biannual clinical breast examination (CBE) and annual mammography, and monthly breast self examination (BSE) is recommended. Screening by means of magnetic resonance imaging (MRI) became optional since 1995 (outside the context of a study, in Rotterdam) [25]. Since November of 1999, MRI as detection method for breast cancer became part of the surveillance programme within the framework of a national, prospective study on the efficacy of breast cancer surveillance in high-risk, genetically predisposed women, the so-called MRISC-study (MRI SCreening) [26].

Monthly breast self examination (BSE) is not proven to be effective in reducing breast cancer mortality [27]. Still, high-risk women are advised to practice it in some countries [24,28]. It is assumed that women who perform BSE on a regular basis become familiar with the structure of their breast tissue (throughout the menstrual cycle), and therefore are more likely to find possible anomalies at an early stage.

The efficacy and/or contribution of clinical breast examination by a physician, to the early detection of breast cancer were not established in randomised trials comparing this screening modality alone versus no screening. In the Dutch MRISC-study, in which women were screened by mammography and MRI next to CBE, the sensitivity of CBE was reported to be only 17.8% [29], while Warner et al. (2004) found a sensitivity of 9.1% [30]. Nonetheless, CBE remains until now an internationally accepted and recommended part of the surveillance programme for high-risk women [31]. An advantage of CBE is said to be the personal contact with the physician/clinical oncologist possibly leading to less reluctance in contacting this physician in case of a suspected anomaly in between scheduled visits [32].

The efficacy of breast cancer screening by mammography is established for women older than 55 years [3], while such data are lacking for younger women. The reasons for this are studies on breast cancer surveillance in high-risk (and therefore young) women were heterogeneous; and, in general, the breast tissue in younger women is denser than in postmenopausal women, making detection of tumours by mammography more difficult [33,34]. Surveillance by mammography of women at increased risk shows a low sensitivity, especially in women with a BRCA1/2 mutation [25]. The sensitivity in these studies varied from 50% to 91% [25,35].

The value in diagnosis and surveillance by MRI has been evaluated in several large prospective studies, after it high sensitivity was established [36-38]. Besides in the Netherlands, MRI surveillance studies are currently ongoing in the United Kingdom [39], Germany [40] and Canada [30]. In the Dutch MRISC-study the sensitivity of the MRI for any breast cancer (DCIS + invasive) was found to be 71% compared to 40% for mammography. In the Canadian study a sensitivity of 77% for MRI compared to 36% for mammography was found. In the British MARIBS study a sensitivity of 77% for MRI compared to 40% for mammography was found. From these studies MRI, as compared to CBE and mammography can be considered more sensitive in detecting breast cancer in high-risk women. Further, breast tumours were found at an earlier stage.

Although the specificity in these studies was found to be lower for MRI than for mammography, in the Netherlands an annual MRI is incorporated as surveillance tool in surveillance schedule for BRCA1/2 mutation carriers opting for surveillance. So far, however, it is unclear whether the incorporation of a MRI scan translates in mortality reduction, while further results of cost-benefit analysis studies are in progress. Therefore, it is warranted that high-risk women are included in surveillance programmes at specialised centres.

Prophylactic mastectomy

Because of the highly increased risk of breast cancer in BRCA1 and BRCA2 mutation carriers, the option of prophylactic bilateral mastectomy (PM), with or without reconstruction, is discussed with female mutation carriers. The procedure implies complete removal of the breast tissue, including the nipple-areolar complex. Retrospective data on 639 high- and moderate risk women showed a reduction of breast cancer of more than 90% after a mean follow-up of 14 years [41]. Seventy-six BRCA1/2 mutation carriers, studied in our Clinic had no case of breast cancer, while in a group of 63 mutation carriers opting for surveillance 8 cases of breast cancer were detected after a mean follow-up of 3 years [42]. An updated analysis after a mean follow-up of 5.2 years in this group of mutation carriers showed no cases of primary breast cancer in the PM group, in comparison with 9 breast cancer cases in the surveillance group. In the PM group one woman had metastatic breast cancer of unknown origin 3.5 years after PM. This is suggestive for an occult invasive breast cancer at the PM procedure [43]. Overall, the risk reduction by PM of 92% remains significant (p=0.02). However, these data also indicate that long-term follow-up of this group of women remains important.

At our institution, approximately 50% of the unaffected mutation carriers opt for PM [44]. Reasons predictive for this choice were: having children and being younger than 55 years. Most women opted for breast reconstruction, which at our institution is done by silicone prosthesis. Nipple reconstruction by tattooing is done later on. Long-term psychological and social functioning after PM was retrospectively examined by Frost et al. (2000) in a cohort of 572 women with a family history of breast cancer who had undergone PM between the years 1960 and 1993. Most women (70%) reported to be satisfied with the choice of PM. Further, it was found that in 74% of the participating women their emotional concern about the development of breast cancer had decreased after PM. These positive findings have to be weighed against the irreversibility of the decision and possible problems associated with a PM procedure [45]. In a 5-year follow-up study from our group investigating the psychological aspects of genetic testing, initiated by Lodder et al., a small subgroup of BRCA1/2 mutation carriers (n=19) had opted for PM after they were identified as a mutation carrier. In this study it was found that 79% of the women felt that surgery was worth any adverse consequences. Furthermore, all women indicated that their fear of developing breast cancer had decreased after PM. Nevertheless, 44% of the mutation carriers indicated that they had been consulting a professional for psychological support [46], the reason for this being related to hereditary cancer in 50% of the mutation carriers.

A retrospective study on long-term satisfaction with prophylactic mastectomy by Bresser et al., conducted at our institution, found that 95% of the 114 participating women indicated they would opt for bilateral prophylactic mastectomy again if they had to decide it once more. However, this apparent satisfaction seemed to be diminished by unanticipated changes in body image and sexual relationship, implying that comprehensive counseling is needed during the decision making process about PM in order to make the patient aware of these possible adverse effects [47].

The psychological and sexual impact of PM is currently more extensively under study in a prospective way by Bresser et al. at the Family Cancer Clinic in Rotterdam.

Psychological implications

Having a family history of breast cancer

Since the hereditary nature of breast cancer became more apparent over time, the psychological impact of a family history of breast cancer in women from these families has been studied. Women from these families experience higher levels of breast cancer specific distress when compared to women without a family history [48-50]. In a group of 217 women form the USA with a family history of breast cancer 27% reported psychological distress at a level indicative for psychological counselling [51]. Breast cancer worries interfering with daily functioning were found in almost one third of a cohort of 140 women, having at least one first-degree relative affected with breast cancer [52]. Studies from more recent date show on average distress scores below clinical level [53], or levels comparable with a group of women without a family history of breast cancer [54]. Elevated levels of breast cancer distress are reportedly caused by: having experienced the process of a breast cancer diagnosis or death in a (close) relative, and the fear of developing breast cancer themselves. It was reported by Zakowski et al. (1997) that in women with a family history of breast cancer, psychological distress was highest in those who had lost a parent due to cancer [50]. However, another study on 60 daughters of breast cancer patients showed only more problems and less satisfaction with sexuality as compared to a control group [55]. Adolescent daughters have more problems than adult daughters with breast cancer related loss of their mother [56]. Hopwood et al. found similar data in comparable groups, although the differences between both groups were non-significant [57]. Giving terminal care to a mother with breast cancer resulted in substantially higher levels of psychological distress [54].

Genetic testing

Since the cloning of the BRCA1 and BRCA2 genes, many studies have reported on the experiences in women who underwent DNA-testing [58-61]. Implications of being a mutation carrier consist of a very high life time risk of developing breast cancer, passing or having passed the mutation on to children, and facing decision making about management options to reduce the breast/ovarian cancer risk. Moreover, family dynamics may play a complex role. Dudok de Wit et al. reported on the first family in the Netherlands, for whom predictive testing for a BRCA1 mutation was performed, and found two important roles becoming apparent within the family. First, the messenger of the news on the hereditary nature of breast cancer within the family has the task of informing the relatives about possibilities to take action in any form. Second, the first utilizer of the predictive DNA-test often becomes an example to the rest of the family [22]. Further, some family members who are proven non-carriers may experience relief on the short term, which on the long term is replaced by feelings of guilt because they escaped the familial risk. This phenomenon has also been found in other studies and is referred to as 'survivor's guilt' [62].

Psychological consequences of carrying a BRCA1 or BRCA2 mutation are far-reaching but rarely induce psychological or psychiatric disturbance necessitating professional intervention [59,63-67]. Data from the Rotterdam Family Cancer Clinic on 5 years follow-up on several psychological distress measures of carriers and non-carriers showed no pathological levels or differences between the two groups [46], although the number of investigated persons was limited.

Adhering to regular surveillance

Adherence of high risk women to breast cancer surveillance guidelines, especially mammography was repeatedly studied [48-51,68]. Before mutation testing for BRCA1/2 became available, Kash et al. (1992) described that 94% of 217 high-risk women adhered to the regularly scheduled mammograms. The women who did not come in for their scheduled mammograms were significantly more anxious. Higher anxiety levels were also observed among women who failed their clinical and breast self examination [51]. Breast cancer worries interfering with daily functioning were frequent in women with poorer adherence to surveillance [52,69]. Other factors are associated with adherence to mammography such as younger age (35-49 yrs), higher educational level, and being employed. Furthermore, women who had a first degree relative with a recent breast cancer diagnosis (i.e. less than one year ago) were less adherent to mammography than women having a first-degree relative diagnosed with breast cancer more than one year ago. In multivariate analyses, however, being highly educated was found to be significantly associated with less breast cancer worries. Lerman et al. suggested that interventions supporting mammography adherence are warranted in worried, lower educated women [52]. A meta-analysis by McCaul et al. (1996) showed that feeling susceptible to the development of breast cancer, having a history of breast complaints and displaying greater worry about breast cancer were all related to an increased degree of adherence to surveillance. Similarly, Diefenbach et al. (1999) found that increased levels of cancer worry significantly predicted for mammography adherence in women with a family history of breast cancer [70]. However, Schwartz et al. (2003) observed that women with a family history of breast cancer having higher levels of cancer worry and/or distress at the baseline measurement were significantly less likely to obtain a mammogram in the next 12 months [53], which is more similar with the negative associations found by Kash and Lerman [51,52,69]. Others found no such association between psychological distress and the uptake rate of mammography [71].

Risk perception

The goal of genetic counselling is to provide women at increased risk for hereditary breast cancer with information on the estimated lifetime risk and the different management options, and to help them make appropriate decisions regarding regular surveillance and/or prophylactic surgery, informing relatives, having children, and other relevant matters. A problem in providing the risk figures is the extent in which these women are able to adequately understand the risks that are presented and integrate them into their decision-making processes. Risk perception is one of the aspects in these processes in women at risk for hereditary breast cancer and studies show a wide variability in accurate risk perceptions concerning the personal risk of breast cancer. Accurate risk recall varied among studies between only 9% and 57% of the women [57,72-77].

Variations in timing of measurement moment, either before, or directly after genetic counselling can partly account for this variability. Since receiving counselling has been proven to improve risk perception this may affect the results in some studies [78], although still, the problem of inaccurate risk perceptions remains [48,65,72,74,76,79,80]. Other explaining factors may be the lack of numerical skills or education, having close personal experiences with affected relatives and showing physical or psychological resemblance with an affected relative may be a (sub)conscious confounder as well. A study by Watson et al. (1998) demonstrated that the recall of risk figures was better when the risks were presented in odds ratios rather than in other formats [74]. Since inaccurate risk perceptions are frequently found to be associated with increased levels of psychological distress in high-risk women, it is important to study this association further [48,57,77]. Of interest is the observation by Hopwood et al. pointing out that not only the objective risk information may be of importance with regard to psychological distress, but also the way this information is processed by the individual [75]. This observation needs further confirmation.

Coping style

Any kind of problem in life may be answered by individually different coping strategies. It is defined as the cognitive and behavioural attempt to master, tolerate or eliminate both internal and external stressors [81-83]. Among women at risk for hereditary breast/ovarian cancer different coping strategies and their association with psychological distress were studied previously. A distinction that is often made is a distinction between a "monitoring" and a "blunting" coping style [84]. "Monitors" confronted with threatening situations seek information and inform themselves about the potential impact of the situation, while "blunters" attempt to distract themselves from the situation by avoiding to think about it. In several studies among women with a family history of breast cancer a monitoring coping style was associated with higher levels of general distress [85] and generalized anxiety [77]. Among women anticipating their BRCA1/2 test result the "monitors" showed higher psychological distress levels as well [86]. A study by Audrain et al. (1997) among women seeking genetic counselling for breast/ovarian risk also demonstrated the association a "monitoring" coping style and general distress, however by including the concept of optimism the association was gone. This implies that the relation between coping and distress may be complex, and other personality aspects than ways of dealing with problems may be important [87].

This thesis

Aims and research questions

In 1999 the national multi-centre, prospective MRISC-study (Magnetic Resonance Imaging Screening) was initiated, aimed at evaluating the efficacy of a breast cancer surveillance programme in women at increased risk of hereditary breast cancer in the Netherlands. These studies provided a unique opportunity to extensively study psychological distress in this cohort of high-risk women adhering to regular breast cancer surveillance programme.

Since this was the first large, prospective study in this group of women (n=357), the main aim of our study was to perform a clinical and empirical exploration of the psychological consequences of being at increased risk for hereditary breast cancer and adhering to a regular surveillance programme.
The research questions explored as part of this thesis were:

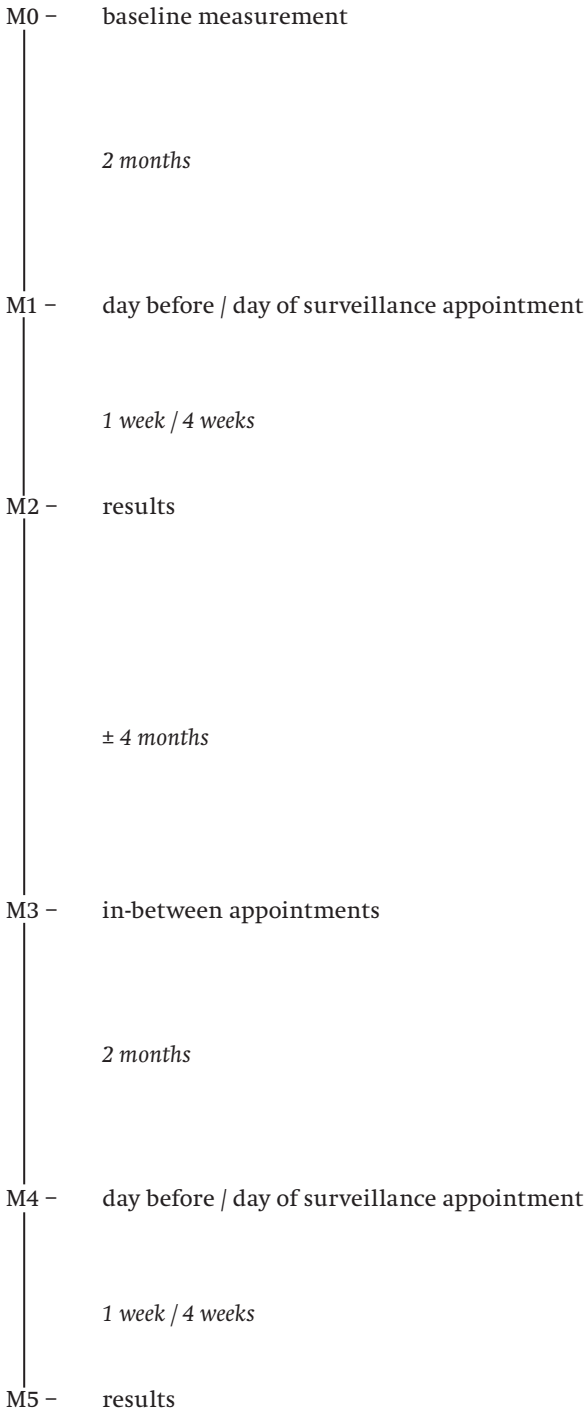
1. What is the impact of breast self-examination frequency on the level of psychological distress? *(Chapter 2)*
2. What is the role of risk perception (cognitive and affective) with respect to the level of psychological distress? *(Chapter 3)*
3. What is the impact of having relatives affected with breast cancer on the level of psychological distress? *(Chapter 4)*
4. What are the experiences of women at risk for hereditary breast cancer with the different screening modalities, particularly Magnetic Resonance Imaging (MRI) of the breasts? *(Chapter 5)*
5. What is the course of psychological distress around two successive bi-annual surveillance appointments at the family cancer clinic? *(Chapter 6)*
6. Are the variables breast self examination frequency, risk perception and having relatives affected with breast cancer, of influence on the course of psychological distress around two successive surveillance appointments in the clinic? *(Chapter 6)*
7. Which of the investigated variables are of significant predictive value for psychological distress, and at which time point during the surveillance programme are they relevant? *(Chapter 7)*
8. What is the impact of coping style on the level and the course of psychological distress? *(Chapter 8)*

Study procedure

Women with an increased risk of hereditary breast cancer participating in the MRISC study (inclusion criteria: a cumulative life time risk of at least 15%, no prior diagnosis of breast cancer) at the Family Cancer Clinic of the Erasmus Medical Centre-Daniel den Hoed Cancer Centre in Rotterdam received a letter on the psychological sub-study along with written patient information, an informed consent form, a form on which they could indicate not to want to participate, and a stamped envelope. Additionally, the physician or oncologist introduced the psychological sub-study and handed out the patient information at the scheduled surveillance appointment. Women who sent back the signed informed consent were enrolled in the psychological follow-up study. The breast cancer surveillance programme within the MRISC study consisted of: annual imaging examination by means of mammography and MRI imaging (within a 6-weeks period), bi-annual physical examination and recommended monthly breast self-examination. A small number (n=29) of the participants in our psychological study were not included in the MRISC study. These latter women though, were screened according to the Dutch national guidelines for women at increased risk for breast cancer, which is rather similar to the study protocol of the MRISC study, except that the annual MRI scan is not included.

Psychological distress was assessed with questionnaires, completed at various moments during the surveillance programme *(see Figure 1)*. The assessments took place around two successive surveillance appointments at the Family Cancer Clinic of the Daniel den Hoed Cancer Centre between January 2001 and May 2003, and were performed on the following time points: two months prior to a surveillance appointment (twice, m0 and m3), on the day of the surveillance appointment (twice, m1 and m4) and one to four weeks after the surveillance appointment (twice, m2 and m5). If the surveillance appointment was physical examination only, the questionnaire was sent one week after this visit; if the surveillance appointment was a combination of physical examination, mammography and MRI, the questionnaire was sent four weeks afterwards.
The main topics addressed in the different questionnaires were demographic variables, the level of psychological distress, coping style (as measured by the Utrechtse Coping Lijst [88]), frequency of breast self examination, breast cancer risk perception, and the (yes/no) presence of relatives affected with breast cancer. Psychological distress was assessed as breast cancer specific distress with the Impact of Event Scale [89] and as general distress with the Hospital Anxiety and Depression Scale [90]. The questionnaire contents are detailed in the following chapters.
In addition, a subgroup of 35 women randomly selected from the study-population was interviewed at three occasions, twice after the regular surveillance appointment at the Family Cancer Clinic, and once at the participant's home, between two surveillance appointments (m3). The structured interviews covered the following areas: experiences with the surveillance procedures, support from partner and children (if present), experience of and need for social support, experience of the increased breast cancer risk, and of breast cancer in the family, and perception of body image. The interview data will be presented elsewhere.

Figure 1. Schematic representation of the different time points at which assessments took place during the surveillance programme



References

1. Jemal A, Thomas A, Murray T, et al: Cancer statistics, 2002. CA Cancer J Clin 52:23-47, 2002
2. Parkin DM, Bray FI, Devesa SS: Cancer burden in the year 2000. The global picture. Eur J Cancer 37 Suppl 8: S4-66, 2001
3. Otto SJ, Fracheboud J, Looman CW, et al: Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 361:1411-7, 2003
4. Eisinger F, Sobol H, Serin D, et al: Hereditary breast cancer, circa 1750. Lancet 351:1366, 1998
5. Le Dran H: Memoire avec un précis de plusieurs observations sur le cancer. Mém Acad R Chir 3:1-54, 1757
6. Whittemore AS, Gong G, Itnyre J: Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. Am J Hum Genet 60:496-504, 1997
7. Ford D, Easton DF, Peto J: Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 57:1457-62, 1995
8. Claus EB, Schildkraut JM, Thompson WD, et al: The genetic attributable risk of breast and ovarian cancer. Cancer 77:2318-24, 1996
9. Miki Y, Swensen J, Shattuck-Eidens D, et al: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66-71., 1994
10. Wooster R, Bignell G, Lancaster J, et al: Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789-92., 1995
11. Ford D, Easton DF, Stratton M, et al: 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., 1998
12. Antoniou A, Pharoah PD, Narod S, et al: Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. Am J Hum Genet 72:1117-30., 2003
13. Peto J, Collins N, Barfoot R, et al: Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 91:943-9, 1999
14. Meijers-Heijboer H, van den Ouweland A, Klijn J, et al: Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet 31:55-9., 2002
15. Liaw D, Marsh DJ, Li J, et al: Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 16:64-7, 1997
16. Malkin D, Li FP, Strong LC, et al: Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250:1233-8, 1990
17. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 73:643-51., 1994
18. Gail MH, Brinton LA, Byar DP, et al: Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 81:1879-86, 1989
19. Verhoog LC, van den Ouweland AM, Berns E, et al: Large regional differences in the frequency of distinct BRCA1/BRCA2 mutations in 517 Dutch breast and/or ovarian cancer families. Eur J Cancer 37:2082-90, 2001
20. van Asperen CJ, Jonker MA, Jacobi CE, et al: Risk estimation for healthy women from breast cancer families: new insights and new strategies. Cancer Epidemiol Biomarkers Prev 13:87-93, 2004
21. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996. J Clin Oncol 14:1730-6; discussion 1737-40, 1996
22. Dudok-de Wit A, Tibben A, Duivenvoorden H, Frets P, Zoeteweij M, Losekoot M, van Haeringen A, Niermeijer M, Passchier J.: Psychological distress in applicants for predictive dna-testing for autosomal, dominant, heritable, late onset disorders. Journal of Medical Genetics 34:382-390, 1997
23. Lerman C, Croyle RT: Emotional and behavioral responses to genetic testing for susceptibility to cancer. Oncology (Huntingt) 10:191-5, 9; discussion 200-2., 1996
24. Vasen HF, Haites NE, Evans DG, et al: Current policies for surveillance and management in women at risk of breast and ovarian cancer: a survey among 16 European family cancer clinics. European Familial Breast Cancer Collaborative Group. Eur J Cancer 34:1922-6., 1998
25. Brekelmans CT, Seynaeve C, Bartels CC, et al: Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol 19:924-30., 2001
26. Kriege M, Brekelmans CT, Boetes C, et al: MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). Fam Cancer 1:163-8, 2001
27. Hackshaw AK, Paul EA: Breast self-examination and death from breast cancer: a meta-analysis. Br J Cancer 88:1047-53, 2003
28. Stefanek M, Hartmann L, Nelson W: Risk-reduction mastectomy: clinical issues and research needs. J Natl Cancer Inst 93:1297-306., 2001
29. Kriege M, Brekelmans CT, Boetes C, et al: Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427-37, 2004
30. Warner E, Plewes DB, Hill KA, et al: Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. Jama 292:1317-25, 2004
31. STOET: Erfelijke tumoren: Richtlijnen voor diagnostiek en preventie, Stichting Opsporing Erfelijke Tumoren en de Vereniging Klinische Genetica Nederland, Werkgroep Klinische Oncogenetica, 2001
32. van Asperen CJ, de Bock GH, van der Horst F, et al: [Screening for breast cancer on basis of individual risk assessment for women ineligible for the national population screening program] Screening op mammacarcinoom buiten het landelijke bevolkingsonderzoek, op grond van individuele risico-inschatting. Ned Tijdschr Geneeskd 145:120-5., 2001

33. Kolb TM, Lichy J, Newhouse JH: Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology 225:165-75, 2002
34. Mandelson MT, Oestreicher N, Porter PL, et al: Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst 92:1081-7, 2000
35. Scheuer L, Kauff N, Robson M, et al: Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol 20:1260-8, 2002
36. Harms SE: Breast magnetic resonance imaging. Semin Ultrasound CT MR 19:104-20, 1998
37. Heywang-Kobrunner SH, Viehweg P, Heinig A, et al: Contrast-enhanced MRI of the breast: accuracy, value, controversies, solutions. Eur J Radiol 24:94-108, 1997
38. Orel SG, Schnall MD: MR imaging of the breast for the detection, diagnosis, and staging of breast cancer. Radiology 220:13-30, 2001
39. Leach MO, Boggis CR, Dixon AK, et al: Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 365:1769-78, 2005
40. Bick U: [An integrated early detection concept in women with a genetic predisposition for breast cancer] Integriertes Fruherkennungskonzept bei Frauen mit genetischer Pradisposition fur Brustkrebs. Radiologe 37:591-6, 1997
41. Hartmann LC, Schaid DJ, Woods JE, et al: Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 340:77-84., 1999
42. Meijers-Heijboer H, van Geel B, van Putten WL, et al: Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 345:159-64., 2001
43. Klijn JGM, Van Geel AN, Meijers-Heijboer H, et al: Long-term follow-up of the Rotterdam study on prophylactic mastectomy versus surveillance in BRCA1/2 mutation carriers. Journal of Clinical Oncology 22:835s-835s, 2004
44. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, et al: Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. Lancet 355:2015-20., 2000
45. Frost MH, Schaid DJ, Sellers TA, et al: Long-term satisfaction and psychological and social function following bilateral prophylactic mastectomy. Jama 284:319-24, 2000
46. van Oostrom I, Meijers-Heijboer H, Lodder LN, et al: Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. J Clin Oncol 21:3867-74, 2003
47. Bresser P, Seynaeve C, Van Gool AR, et al: Satisfaction with Prophylactic Mastectomy and Breast Reconstruction in Genetically Predisposed Women. Plastic and Reconstructive Surgery, in press, 2005
48. Lloyd S, Watson M, Waites B, et al: Familial breast cancer: a controlled study of risk perception, psychological morbidity and health beliefs in women attending for genetic counselling. Br J Cancer 74:482-7., 1996
49. Valdimarsdottir HB BD, Kash K, Holland JC, Osborne MP, Miller GM: Psychological distress in women with a familial risk of breast cancer. Psycho-oncology 4:133-141, 1995
50. Zakowski SG, Valdimarsdottir HB, Bovbjerg DH, et al: Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer. Ann Behav Med 19:362-9., 1997
51. Kash KM, Holland JC, Halper MS, et al: Psychological distress and surveillance behaviors of women with a family history of breast cancer. J Natl Cancer Inst 84:24-30., 1992
52. Lerman C, Daly M, Sands C, et al: Mammography adherence and psychological distress among women at risk for breast cancer. J Natl Cancer Inst 85:1074-80., 1993
53. Schwartz MD, Taylor KL, Willard KS: Prospective association between distress and mammography utilization among women with a family history of breast cancer. J Behav Med 26:105-17, 2003
54. Erblich J, Bovbjerg DH, Valdimarsdottir HB: Looking forward and back: distress among women at familial risk for breast cancer. Ann Behav Med 22:53-9., 2000
55. Wellisch DK, Gritz ER, Schain W, et al: Psychological functioning of daughters of breast cancer patients. Part I: Daughters and comparison subjects. Psychosomatics 32:324-36., 1991
56. Wellisch DK, Gritz ER, Schain W, et al: Psychological functioning of daughters of breast cancer patients. Part II: Characterizing the distressed daughter of the breast cancer patient. Psychosomatics 33:171-9., 1992
57. Hopwood P, Shenton A, Lalloo F, et al: Risk perception and cancer worry: an exploratory study of the impact of genetic risk counselling in women with a family history of breast cancer. J Med Genet 38:139., 2001
58. Meiser B, Gleeson MA, Tucker KM: Psychological impact of genetic testing for adult-onset disorders. An update for clinicians. Med J Aust 172:126-9, 2000
59. Lodder L, Frets PG, Trijsburg RW, et al: Psychological impact of receiving a BRCA1/BRCA2 test result. Am J Med Genet 98:15-24., 2001
60. Claes E, Evers-Kiebooms G, Boogaerts A, et al: Diagnostic genetic testing for hereditary breast and ovarian cancer in cancer patients: women's looking back on the pre-test period and a psychological evaluation. Genet Test 8:13-21, 2004
61. Wood ME, Mullineaux L, Rahm AK, et al: Impact of BRCA1 testing on women with cancer: a pilot study. Genet Test 4:265-72, 2000
62. Tibben A, Vegter-van der Vlis M, Roos RA, et al: [Presymptomatic DNA diagnosis in Huntington's chorea: reactions to the certainty of not being a genetic carrier] Presymptomatische DNA-diagnostiek bij de chorea van Huntington: reacties op de zekerheid niet-gendrager te zijn. Ned Tijdschr Geneeskd 134:701-4., 1990
63. Croyle RT, Smith KR, Botkin JR, et al: Psychological responses to BRCA1 mutation testing: preliminary findings. Health Psychol 16:63-72., 1997
64. Lerman C, Narod S, Schulman K, et al: BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. Jama 275:1885-92., 1996

65. Hopwood P, Keeling F, Long A, et al: Psychological support needs for women at high genetic risk of breast cancer: some preliminary indicators. Psychooncology 7:402-12., 1998
66. Coyne JC, Benazon NR, Gaba CG, et al: Distress and psychiatric morbidity among women from high-risk breast and ovarian cancer families. J Consult Clin Psychol 68:864-74, 2000
67. Lodder LN, Frets PG, Trijsburg RW, et al: 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). Breast Cancer Res Treat 73:97-112., 2002
68. Lerman C, Schwartz M: Adherence and psychological adjustment among women at high risk for breast cancer. Breast Cancer Res Treat 28:145-55., 1993
69. Lerman C, Kash K, Stefanek M: Younger women at increased risk for breast cancer: perceived risk, psychological well-being, and surveillance behavior. J Natl Cancer Inst Monogr 16:171-6, 1994
70. Diefenbach MA, Miller SM, Daly MB: Specific worry about breast cancer predicts mammography use in women at risk for breast and ovarian cancer. Health Psychol 18:532-6, 1999
71. Isaacs C, Peshkin BN, Schwartz M, et al: Breast and ovarian cancer screening practices in healthy women with a strong family history of breast or ovarian cancer. Breast Cancer Res Treat 71:103-12., 2002
72. Evans DG, Blair V, Greenhalgh R, et al: The impact of genetic counselling on risk perception in women with a family history of breast cancer. Br J Cancer 70:934-8., 1994
73. Kash KM, Holland JC, Osborne MP, et al: Psychological counseling strategies for women at risk of breast cancer. J Natl Cancer Inst Monogr 17:73-9, 1995
74. Watson M, Duvivier V, Wade Walsh M, et al: Family history of breast cancer: what do women understand and recall about their genetic risk? J Med Genet 35:731-8., 1998
75. Hopwood P: Genetic risk counselling for breast cancer families. Eur J Cancer 34:1477-9., 1998
76. Watson M, Lloyd S, Davidson J, et al: The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. Br J Cancer 79:868-74., 1999
77. Meiser B, Butow P, Schnieden V, et al: Psychological adjustment of women at increased risk of developing hereditary breast cancer. Psychology, Health and Medicine 5:377-388, 2000
78. Meiser B, Halliday JL: What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. Soc Sci Med 54:1463-70., 2002
79. Cull A, Anderson ED, Campbell S, et al: The impact of genetic counselling about breast cancer risk on women's risk perceptions and levels of distress. Br J Cancer 79:501-8., 1999
80. Burke W, Culver J, Bowen D, et al: Genetic counseling for women with an intermediate family history of breast cancer. American Journal of Medical Genetics 90:361-368, 2000
81. Folkman S, Lazarus RS: An analysis of coping in a middle-aged community sample. J Health Soc Behav 21:219-39, 1980
82. Folkman S, Lazarus RS, Gruen RJ, et al: Appraisal, coping, health status, and psychological symptoms. J Pers Soc Psychol 50:571-9, 1986
83. Folkman S, Lazarus RS, Dunkel-Schetter C, et al: Dynamics of a stressful encounter: cognitive appraisal, coping, and encounter outcomes. J Pers Soc Psychol 50:992-1003, 1986
84. Miller SM: Monitoring and blunting: validation of a questionnaire to assess styles of information seeking under threat. J Pers Soc Psychol 52:345-53, 1987
85. Lerman C, Schwartz MD, Miller SM, et al: A randomized trial of breast cancer risk counseling: interacting effects of counseling, educational level, and coping style. Health Psychol 15:75-83., 1996
86. Tercyak KP, Lerman C, Peshkin BN, et al: Effects of coping style and BRCA1 and BRCA2 test results on anxiety among women participating in genetic counseling and testing for breast and ovarian cancer risk. Health Psychol 20:217-22, 2001
87. Audrain J, Schwartz MD, Lerman C, et al: Psychological distress in women seeking genetic counseling for breast-ovarian cancer risk: the contributions of personality and appraisal. Ann Behav Med 19:370-7, 1997
88. Schreurs PJG, vd Willige G, Brosschot JF: De Utrechtse Coping Lijst:UCL, Herziene handleiding (Utrecht Coping List). Swets & Zeitlinger: Lisse, the Netherlands, 1993
89. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209-18., 1979
90. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70., 1983

Chapter 2

Psychological distress and breast self examination frequency in women at increased risk for hereditary or familial breast cancer

Community Genetics, 2003; 6:235-241

Van Dooren S, Rijnsburger AJ, Seynaeve C, Kriege A, Duivenvoorden HJ, Bartels CCM, Essink-Bot ML, de Koning HJ, Tibben A

Abstract

Background: The Magnetic Resonance Imaging SCreening (MRISC) study evaluates the efficacy and psychological impact of a surveillance programme for women at increased risk for hereditary or familial breast cancer in the Netherlands. Surveillance consists of biannual physical examination, annual mammography, annual MRI and monthly breast self-examination (BSE).

Objective: To examine the association between psychological distress and reported BSE frequency.

Methods: Two months prior to surveillance demographics, BSE frequency, general distress (Hospital Anxiety and Depression Scale and the somatic scale of the SCL-90) and breast cancer specific distress (Impact of Event Scale) were assessed in 316 women (mean age 40.5; range 21 – 63).

Results: The majority (57%) reported performing monthly BSE. Ten percent reported never to perform BSE, 20% less frequent than once a month, and 13% at least once a week. Women below the age of 40, who examine their breasts more frequently than recommended (i.e. at least once a week) were shown to be significantly more distressed than the other women in the sample (p=.03). These women represented 15% of all the women below the age of 40 years in our study sample.

Discussion: Higher breast cancer specific distress scores are observed among younger women who examined their breasts at least once a week. It is important for physicians to be aware of this hypervigilant behaviour, especially since it is correlated with breast cancer specific distress.

Introduction

Breast cancer is one of the most common malignancies in women in Western industrialised countries, where one in every ten women will develop breast cancer during the course of her life. In approximately 5 to 10% of all breast cancer cases, heredity is suspected. In 1994 and 1995 respectively, the BRCA1 and BRCA2 genes were identified [1,2]. Mutations in these genes are inherited in an autosomal dominant way, and mutation carriers have a 60 to 85% lifetime risk of developing breast cancer [3-5]. It is thought that other breast cancer susceptibility genes also play a role, such as CHEK2 [6], but either they are not yet identified or their role is still not clear. High-risk women may opt for intensive surveillance, generally consisting of yearly mammography, 6-monthly clinical breast examination by the physician and monthly breast self examination (BSE) [7]. The efficacy of surveillance in this group of high-risk women is currently unproven [8,9]. Furthermore, the efficacy of BSE as part of the surveillance remains controversial. In a meta-analysis by Hackshaw et al. (2003) it is suggested that regular BSE is not an effective method to reduce breast cancer mortality [10]. However, the studies in this meta-analysis focused mainly on the general population, and did not select samples based on family history or genetic predisposition. Therefore, it is not possible to extrapolate these data on a younger population with an increased risk of developing breast cancer due to a proven or possible genetic predisposition. Indeed, this group of women differs significantly from the general population with respect to breast cancer awareness, because of their experiences with breast (and ovarian) cancer in relatives. As there are no data yet on BSE in this specific group, BSE is still advised as part of the surveillance programme for high risk women in the Netherlands [7].

Several studies have shown that monthly BSE is performed by 15 to 47% of the high risk women [11-15]. Higher levels of breast cancer specific distress have been found to be associated with higher rates of BSE frequency [13-16], while higher general distress has been found to be related with infrequent BSE performance [11,16]. We aimed to obtain more insight into the relationship between psychological distress and BSE-frequency in Dutch women who are at increased risk of developing breast cancer and who adhere to regular surveillance. In November 1999, the MRISC (Magnetic Resonance Imaging SCreening) study started in six family cancer clinics in the Netherlands. The MRISC is an observational study to evaluate the efficacy of MRI as compared to mammography in a surveillance programme for women at increased risk for hereditary or familial breast cancer (MRISC- part A). A longitudinal psychological follow-up study started in September 2000 in the Daniel den Hoed Cancer Centre in Rotterdam, one of the clinics (MRISC- part B). The surveillance programme consisted of an annual MRI-scan in addition to the annual mammography and bi-annual physical examination [9]. Premenopausal women were recommended to perform monthly BSE after menstruation. Postmenopausal women were recommended to pick a fixed day in the month for BSE. Additional to verbal information provided by the physician, women received an information booklet containing written and illustrated BSE-instructions. We hypothesised that a too frequent BSE might be associated with high breast cancer specific distress.

Material and Methods

Participants

At the time of analysis the study included a total of 316 women; 289 women from MRISC-A and an additional 27 women adhering to regular surveillance who were not included in MRISC-A. Hundred and nine women from MRISC-A refrained from participation in the psychological follow-up study. At entry the women did not have a history of breast cancer, and had a cumulative life time risk (CLTR) of developing breast cancer of at least 15% based on the risk tables by Claus et al. [17]. Participants had enough understanding of the Dutch language to fill in the questionnaires and all signed informed consent. Ethical approval was obtained from the Medical Ethical Committee of the Erasmus MC in Rotterdam.

Measures

Demographic variables

Age and duration of adhering to regular surveillance were measured in years. Educational level was divided into three categories, i.e. low, medium and high.

Objective risk status of developing breast cancer

Women were categorised into three risk categories according to their life time risk by means of genetic epidemiological tables [9]. Women in risk category 1 were identified BRCA1 or BRCA2 mutation carriers, with a CLTR of developing breast cancer of approximately 60 to 85%. Women in category 2 had a CLTR between 30 and 50%, and were 1st degree family members of a proven BRCA1/2 mutation carrier, who did not opt for the test themselves, or 1st degree relatives from a breast cancer patient from a non BRCA1/2 mutation family or a family where genetic testing was not performed. Women in category 3 had a CLTR between 15 and 30%. These were women from families with an increased frequency of breast cancer occurrence, or 25% risk carriers in a proven BRCA1/2 family [8,9,18].

Intrusion and Avoidance

Intrusion and avoidance was measured using the Impact of Event Scale (IES). This questionnaire developed by Horowitz et al. (1979) comprises 15 items and can be tailored to a specific event [19], which was 'breast cancer' in this study. The IES measures two common responses to stressful situations: avoidance and intrusion and has four answer categories: not at all (0), seldom (1), sometimes (3) and often (5). The intrusion subscale has a score range between 0 and 35, the avoidance subscale has a score range between 0 and 40. The Dutch version of the IES has been subjected to reliability analysis [20], the avoidance subscale had an internal consistency of 0.66 and the intrusion subscale of 0.72.

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire, 7 items are designed to measure anxiety and 7 to measure depression [21]. Each subscale has a score range between 0 and 21. Scores ranging from 8 to 10 on a subscale identify 'doubtful cases', scores of 11 and more identify 'definite cases'. A Dutch reliability-study revealed an internal consistency of 0.84 for anxiety, 0.86 for depression and 0.90 for the entire scale [22].

Somatic impact

Somatic impact was measured with the somatic subscale derived from the Symptom Checklist-90 (SCL-90). This 12-item list consists of physical symptoms often reported when functional problems occur. Each item can be answered with: not at all (1), a little (2), quite (3), very (4) or extremely (5), providing a score range between 12 and 60 [23]. Internal consistency in the normal population of this subscale is 0.83 [24].

Breast self examination (BSE)
BSE frequency was measured with one question: Do you perform breast self-examination regularly in order to detect possible anomalies? The question had six answer possibilities: no, never; yes, approximately once a year; yes, approximately once every six months; yes, approximately once every three months; yes, approximately once a month; and yes, at least once a week. This variable was recoded into 4 categories: 1. never, 2. once every 3/6/12 months, 3. once a month, and 4. at least once a week.

Design
This study is part of a longitudinal observational study on psychological impact and quality of life within the MRISC part A-study. The analysis in this article was carried out on the first assessment, 2 months prior to the women's appointment in the clinic. The assessments took place between November 2000 and July 2002.

Procedure
Women participating in the MRISC-A study in the Daniel den Hoed Cancer Centre in Rotterdam were sent a letter informing them about the psychological follow-up study along with an information booklet, informed consent form, a refusal form for women who did not want to participate and a prepaid envelope. Additionally, the physicians handed out the information booklets during the women's clinical examination consultation. After returning the informed consent, women were sent their baseline questionnaire to their home (with a prepaid envelope) two months prior to their next surveillance appointment at the family cancer clinic.

Statistical analysis
Participants were compared with the 109 non-participants on age with a t-test for independent samples and on risk category by the method of chi-square (Linear-by-Linear Association). The characteristics of the study sample were tested for differences between the three risk categories by one-way analysis of variance for continuous data and by chi-square test for ordinal data. The empirical structure of the psychological variables was identified by metric principal component analysis. Subsequently, the dimensional structure was established according to the VARIMAX criterion [25]. The fit of the solution was assessed by the sampling adequacy measure (KMO-measure) [26]. Multiple regression analysis was used to determine the relative importance of explanatory variables in estimating psychological distress. The following covariables were entered in the regression analysis: age, number of years of adherence, educational level and risk category. The standardised regression coefficient was used as a measure of the relative importance. The level of significance was set at 0.05 (two-sided). Analysis was carried out using the Statistical Package for Social Sciences (SPSS 11).

Results
Sample characteristics
Sample characteristics are shown in *Table 1*. There was no significant difference in age (p=0.42) and risk status (p=0.25) between women who participated in the follow-up study and the women who did not participate. In this study, the three objective risk categories were not equally represented; 10.4% of women were BRCA1 or BRCA2 mutation carriers (risk category 1), 56.3% were risk category 2 and 33.2% were risk category 3. Mean age was 40.5 years and did not significantly differ between the three risk categories. Mean number of years of adherence to a surveillance programme of the total sample was 5.4 years.

Women in risk category 1 had adhered significantly less long to a surveillance programme than women in the other two categories (3 yrs and approximately 5½ yrs respectively) (p = 0.016). The majority of women had completed a medium level education (55%). There was no significant difference in level of education between the three risk categories. Although the majority (57%) of the study sample reported to follow the recommended guideline for BSE, a considerable proportion did not (43%). Thirteen percent were classed as overperformers, whereas 30% were underperformers, with 20% of women reporting to examine their breasts less often than recommended and 10% reporting to never examine their breasts themselves. Notably, none of the women in category 1 reported to never examine their breasts, and only a minority reported to examine their breasts less often than recommended (6%). Overperformance on the other hand was most striking in category 1 in comparison with the other two risk categories (31% vs. 10% and 12% respectively). The reported frequencies of BSE were significantly different between the three risk categories (p = 0.005). Frequencies of BSE were compared for women above and below the median age (40 yrs). There were no significant differences for the frequency of BSE with respect to age.

Table 1. Characteristics of the study sample [1)]

Variable		Risk category 1 CLTR 60-85% n = 33	Risk category CLTR 30-50% n = 178	Risk category 3 CLTR 15-30% n = 105	Total n = 316
Age mean (sd)		41.5 (10.7)	40.9 (8.7)	5.8 (5.1)	5.4 (4.7)
Number of years adhering mean (sd)*		3.1 (1.7)	5.5 (4.6)	39.5 (8.4)	40.5 (8.9)
Educational level					
Lower level		5 (15%)[2)]	29 (16%)	21 (17%)	55 (17%)
Middle level		18 (55%)	98 (55%)	55 (52%)	171 (54%)
Higher level		10 (30%)	51 (29%)	29 (28%)	90 (29%)
BSE frequency*					
1. Never		-	16 (9%)	15 (14%)	31 (10%)
2. Once every 3/6/12 months		2 (6%)	39 (22%)	20 (19%)	62 (20%)
3. Once a month		20 (63%)	102 (58%)	57 (54%)	179 (57%)
4. ≥ once a week		10 (31%)	18 (10%)	13 (12%)	41 (13%)
BSE frequency †					
1. Never	< 40 yrs ≥ 40 yrs				14 (5%) 17 (5%)
2. Once every 3/6/12 months	< 40 yrs ≥ 40 yrs				34 (11%) 27 (9%)
3. Once a month	< 40 yrs ≥ 40 yrs				81 (26%) 98 (31%
4. ≥once a week	< 40 yrs ≥ 40 yrs				23 (7%) 18 (6%)

[1)] The numbers may vary due to missing values
[2)] Percentages indicate column percentages

* Significantly different for the three risk categories
† BSE frequency by age (split at the median of 40 yrs) for the total group

Structure determination: Metric Principal Component Analysis

Correlations between the psychological variables are shown in *Table 2*. Metric Principal Component Analysis extracted two components, which accounted for 81% of the variance. The solution appeared to be satisfying (KMO = 0.71) [26]. Component I, comprised intrusion and avoidance and therefore was characterised as breast cancer specific distress. Component II comprised anxiety, depression and somatic impact and was characterised as general distress. Rotated component scores are shown in *Table 3*.

Table 2. Correlations between the psychological outcome variables [1)]

	Intrusion	Avoidance	Anxiety	Depression	Somatic scale
Intrusion	1.00	0.001	0.001	0.001	0.001
Avoidance	0.77	1.00	0.001	0.001	0.001
Anxiety	0.48	0.45	1.00	0.001	0.001
Depression	0.26	0.30	0.70	1.00	0.001
Somatic scale	0.29	0.29	0.62	0.59	1.00

[1)] Left lower triangle: Pearson correlation matrix
Right upper triangle: p-values (two-tailed)

Table 3. Rotated component matrix

	General distress	Breast cancer specific distress
Intrusion	0.19	0.92
Avoidance	0.18	0.92
Anxiety	0.82	0.36
Depression	0.88	0.10
Somatic scale	0.84	0.14

Association between Psychological Distress and Breast Self Examination Frequency

At first no significant associations between general and breast cancer specific with BSE frequency were found *(Table 4)*. Subsequently, we considered possible age-related effects in combination with BSE frequency. Therefore, we dichotomised age at the median (40 years) into younger than 40 and 40 years or older *(see Table 1)*. We combined this variable with overperformance of BSE versus the other categories in order to determine whether these women suffered from psychological distress. Again, general distress showed no significant associations *(Table 5)*. However, breast cancer specific distress showed a significant positive association with overperformance in women below the age of 40 ($p = 0.03$).

Table 4. The importance of breast self examination in estimating general distress and breast cancer specific distress (n=276)

	General distress		Breast cancer specific distress	
Variable	β [1)]	p	β [1)]	p
Once every 3; 6 or 12 months	0.1	0.31	-0.08	0.43
Once a month	-0.01	0.95	-0.08	0.44
At least once a week	0.07	0.42	0.05	0.6

[1)] Standardized regression coefficient as a measure of relative importance
Adjusted for age, number of years of adherence, educational level and risk category
The BSE frequency variable was dummy-coded

Table 5. The importance of breast self examination in women younger than 40 years in estimating general distress and breast cancer specific distress (n=276)

	General distress		Breast cancer specific distress	
Variable	β [1)]	p	β [1)]	p
Younger than 40 years performing BSE at least once a week	0.03	0.64	0.13	0.03

[1)] Standardized regression coefficient as a measure of relative importance
Adjusted for age, number of years of adherence, educational level and risk category

Discussion

The majority (i.e. 57%) of women in this Dutch study reported a breast self-examination frequency of once a month, as recommended, which is more than the 15%-47% that has been reported to date [11-15]. Thirteen percent in our study reported a BSE performance of at least once a week, which is similar to the findings by Brain et al. (1999) [14]. Other studies reported percentages between 28% - 33% of overperformance, but these percentages apply to a BSE performance of more often than monthly, and are not further specified [12,15]. A daily BSE performance of 3% and 8% respectively are reported in the studies by Epstein et al. (1997) and Brain et al. (1999) [13,14]. In the study by Epstein, however, all the participants had a first-degree relative diagnosed with breast cancer not more than six months before inclusion in the study. This short time period after diagnosis of breast cancer in a relative may have influenced women to perform excessive BSE [13].

In our study a significant association was found between breast cancer specific distress and BSE overperformance in women below the age of 40. This group of overperformers experiencing breast cancer specific distress amounts to 15% of the women younger than 40 years. Why did particularly the younger overperformers report relatively higher breast cancer specific distress scores? It may be that they are more afraid to develop breast cancer and to be affected in their femininity by the breast cancer therapy. Indeed, breasts can be considered an important factor in determining feminine identity and younger women may rely more on their breasts to feel feminine when compared to older women. Furthermore, younger women are more likely to be either in the phase of finding a partner or in the process of starting a family and having children. In these processes breasts are important with respect to either femininity, self-esteem and sexuality or when breastfeeding becomes an issue.

The causality between younger overperformers and breast cancer specific distress is difficult to determine. As Erblich et al. (2000) stated a vicious cycle may develop whereby BSE performance causes breast cancer specific distress, which in turn results in the need to examine the breasts as often as possible to get momentary reassurance [15]. How can this vicious circle be dealt with? Education about frequency, correctly performing BSE and timing (in premenopausal women) may be needed. Indeed, overperformance has been reported to diminish the accuracy of the examination and can induce unnecessary worries when conducted at the wrong time. Before and during the menstrual period mammary glands can be swollen and some lumps may be mistakenly considered as a tumour, which can (momentarily) result in more distress [13,27]. Moreover, this can lead to unnecessary additional examinations such as ultrasound, puncture and biopsy [28,29,] which in turn induce further distress and overworriness. Some physicians at our institution (the Daniel den Hoed Cancer Centre in Rotterdam) encourage the partner to examine the breasts. This may diminish the psychological distress associated with BSE since he/she may be more able to objectively observe any changes that need professional attention.

Since BSE in the general population has no proven effect on breast cancer mortality [27], some groups argue not to teach high-risk women about BSE at all. As a reflection of this controversy, there are differences in recommending monthly BSE in genetically predisposed women between different countries, partly as a result of differences in cultural norms and values [7,30]. For instance in France, information and training in BSE will be given only on request because of the uncertain effectiveness and the assumption that it may induce anxiety for the women [30]. In contrast with this somewhat paternalistic approach, the Dutch as well as the USA policy still recommend BSE as part of the surveillance programme, thus putting emphasis on the patient's autonomy and control in health-care. Furthermore there are also differences in the uptake of prophylactic mastectomy between cultures and countries. At our institution (the Daniel den Hoed Cancer Centre in Rotterdam), 51% of the unaffected mutation carriers chose prophylactic mastectomy [31], whereas this rate is lower in other cultures and countries[32].

In this respect, we think that the performance and outcome of BSE in genetically predisposed women may be different from the data obtained in women from the general population, since these women have been confronted with breast cancer and the disease process in family members. This may have an impact on the women's awareness of breast cancer and on the way these women deal with this knowledge. An important limitation of this study was that the study sample could neither be considered as representative for the population of high-risk women that adhere to the surveillance programme nor for the high-risk women in general. Although those who did not participate in the psychological follow-up study did not significantly differ from the participants with respect to age and risk status, this does not guarantee an absence of difference on other items such as psychological distress. In view of the abovementioned considerations, further research with respect to the value of BSE in high-risk women is warranted. As long as the Dutch guidelines still recommend BSE as part of the surveillance programme, our findings are of importance for healthcare workers, since they show that there is a subgroup of younger women who perform BSE too often and who are more likely to experience breast cancer specific distress. When recognised, additional counselling and care should be offered and may help to improve the quality of life of the concerned women. Further, our data adds to the knowledge of the impact of breast cancer surveillance programmes in genetically predisposed women, and may be of use for the development and implementation of the guidelines for this group of women in the Netherlands, as well as in other countries.

References

1. Miki Y, Swensen J, Shattuck-Eidens D, et al: A strong candidate for the breast and ova-rian cancer susceptibility gene BRCA1. Science 266:66-71., 1994
2. Wooster R, Bignell G, Lancaster J, et al: Identification of the breast cancer susceptibi-lity gene BRCA2. Nature 378:789-92., 1995
3. Blackwood MA, Weber BL: BRCA1 and BRCA2: from molecular genetics to clinical medicine. J Clin Oncol 16:1969-77., 1998
4. Ford D, Easton DF, Stratton M, et al: 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., 1998
5. Thorlacius S, Struewing JP, Hartge P, et al: Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet 352:1337-9., 1998
6. Meijers-Heijboer H, van den Ouweland A, Klijn J, et al: Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet 31:55-9., 2002
7. Vasen HF, Haites NE, Evans DG, et al: Current policies for surveillance and management in women at risk of breast and ovarian cancer: a survey among 16 European family cancer clinics. European Familial Breast Cancer Collaborative Group. Eur J Cancer 34:1922-6., 1998
8. Brekelmans CT, Seynaeve C, Bartels CC, et al: Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol 19:924-30., 2001
9. Kriege M, Brekelmans CT, Boetes C, et al: MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). Fam Cancer 1:163-8, 2001
10. Hackshaw AK, Paul EA: Breast self-examination and death from breast cancer: a meta-analysis. Br J Cancer 88:1047-53, 2003
11. Kash KM, Holland JC, Halper MS, et al: Psychological distress and surveillance behaviors of women with a family history of breast cancer. J Natl Cancer Inst 84:24-30., 1992
12. Gagnon P, Massie MJ, Kash KM, et al: Perception of breast cancer risk and psychological distress in women attending a surveillance program. Psycho-Oncology 5:259-269, 1996
13. Epstein SA, Lin TH, Audrain J, et al: Excessive breast self-examination among first-degree relatives of newly diagnosed breast cancer patients. High-Risk Breast Cancer Consortium. Psychosomatics 38:253-61., 1997
14. Brain K, Norman P, Gray J, et al: Anxiety and adherence to breast self-examination in women with a family history of breast cancer. Psychosom Med 61:181-7., 1999
15. Erblich J, Bovbjerg DH, Valdimarsdottir HB: Psychological distress, health beliefs, and frequency of breast self- examination. J Behav Med 23:277-92., 2000
16. Lerman C, Kash K, Stefanek M: Younger women at increased risk for breast cancer: perceived risk, psychological well-being, and surveillance behavior. J Natl Cancer Inst Monogr 16:171-6, 1994
17. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 73:643-51., 1994
18. Brekelmans CT, Voogd AC, Botke G, et al: Family history of breast cancer and local recurrence after breast-conserving therapy. The Dutch Study Group on Local Recurrence after Breast Conservation (BORST). Eur J Cancer 35:620-6., 1999
19. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209-18., 1979
20. Brom D, Kleber RJ: De Schokverwerkingslijst. Nederlands Tijdschrift Psychologie 40:164-168, 1985
21. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70., 1983
22. Spinhoven P, Ormel J, Sloekers PP, et al: A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 27:363-70., 1997
23. Derogatis LR, Lipman RS, Covi L: SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull 9:13-28., 1973
24. Arrindell W, Ettema J: Manual SCL-90. Lisse, Swets and Zeitlinger, 1986
25. Kaiser H: The varimax criterion for analytic rotation in factor analysis. Psychometrika 23:187-200, 1958
26. Kaiser H: An index of factorial simplicity. Psychometrika 39:31-36, 1974
27. Epstein SA, Lerman C: Excessive health behaviors in those at risk for physical disorder. J Psychosom Res 43:223-5., 1997
28. Baxter N: Preventive health care, 2001 update: should women be routinely taught breast self-examination to screen for breast cancer? CMAJ 164:1837-46., 2001
29. Thomas DB, Gao DL, Ray RM, et al: Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst 94:1445-57., 2002
30. Eisinger F, Geller G, Burke W, et al: Cultural basis for differences between US and French clinical recommendations for women at increased risk of breast and ovarian cancer. Lancet 353:919-20, 1999
31. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, et al: Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. Lancet 355:2015-20., 2000
32. Eisinger F, Julian-Reynier C, Sobol H, et al: Acceptability of prophylactic mastectomy in cancer-prone women. Jama 283:202-3, 2000

Chapter 3

Psychological distress in women at increased risk for breast cancer: the role of risk perception

European Journal of Cancer, 2004; 40(14), 2056-2063

Van Dooren S, Rijnsburger AJ, Seynaeve C, Duivenvoorden HJ, Essink-Bot ML, Tilanus-Linthorst MMA, de Koning HJ, Tibben A

Abstract

Background: The MRISC-study evaluates a surveillance programme for women at hereditary risk for breast cancer (BC). The psychological burden of surveillance in these women may depend on inaccurate risk perceptions (RP).
Objective: To examine differences in RP between three predefined risk categories and associations with psychological distress.
Methods: Two months before a surveillance-appointment BC-specific distress, general distress, and RP (cognitive and affective) were assessed. Cumulative lifetime risk (CLTR) of developing BC was trichotomised into: 1) CLTR of 60-85% (mutation carriers), 2) CLTR of 30-50%, and 3) CLTR of 15-30%.
Results: On a total of 351 women (mean age 40.5 years) the three risk categories significantly differed in accuracy of cognitive RP. In category 1 60% had an accurate RP, in category 2: 43.7% and in category 3: 33.3%. Overestimators reported significantly more BC-specific distress. After adding affective RP to the model, this effect disappeared. Affective RP showed significant associations with BC specific and general distress.
Discussion: Affective RP is a more important determinant for psychological distress than cognitive RP. This knowledge may be anticipated on during the surveillance appointments, in order to improve and individualise support for these women.

Introduction

One in every ten women in Western industrialised countries will develop breast cancer during the course of her life. In approximately 5 to 10% of all breast cancer cases a genetic predisposition is suspected. In 1994 and 1995 respectively, the BRCA1 and BRCA2 genes were identified [1,2]. Carriers of a mutation in one of these genes have a significantly increased cumulative lifetime risk (CLTR) of developing breast cancer that has been reported to be between 60 and 85% [3-5], while Antoniou and colleagues (2003) recently provided evidence for lower risk percentages in breast cancer patients unselected for family history [6]. Other breast cancer susceptibility genes may also play a role, such as CHEK2 [7], but either their role still has to be elucidated or they are not yet identified. Women from families with a clear family history of breast cancer where a mutation has not (yet) been found are also at increased risk, which mainly has been estimated using risk tables developed by Claus and colleagues [8]. Since the Claus model does not account for bilateral breast cancer, the occurrence of breast cancer in multiple family members as well as the occurrence of ovarian cancer, other models are also being developed, and may eventually provide more accurate risk estimations [9]. One of the management options for women at increased risk is regular surveillance mostly done by means of an annual mammography and biannual clinical breast examination. A monthly breast self examination is recommended.

Perceptions of the risk of developing breast cancer in high-risk women are frequently found to be inaccurate but also show a wide variability. In the literature between 9% and 57% of high-risk women are reported to have accurate risk perceptions [10-16]. This variability can partly be explained by the fact that the risk perception is measured either before or after counselling, with lower percentages obviously representing accurate risk perception before counselling. Meiser and colleagues (2002) conducted a meta-analytic review in order to obtain an effect size of the impact of genetic counselling on the accuracy of risk perception. They found a significant medium effect size ($r=0.56$; $p<0.01$) which demonstrates the efficacy of genetic counselling in improving risk perception [17]. Despite improvements in accurate risk perception after genetic counselling there are still women who continue to overestimate or underestimate their breast cancer risk [10,12,14,18-21]. Several reasons for sustained inaccurate risk perceptions can be given. Lacking sufficient numerical skills or overall education can cause inaccurate risk perceptions [22].

Processing information about heredity can lead to wrong assumptions about one's risk of developing the disease, for instance on the basis of physical or psychological identification with an affected relative [23]. Personal experience with breast cancer in the family may obstruct the adoption of realistic risk perceptions [24]. The format in which the risk information is given may also influence the accuracy of recall of the risk estimation. Watson and colleagues (1998) found that recall of risk is more accurate when risk information is given in odds ratios than in other formats [12].

Women with higher risk perceptions often display more psychological distress, both breast cancer specific and general [11,12,15,16,20,25]. Hopwood and colleagues (2001) found more cancer worries in overestimators than in women who underestimated or who estimated accurately [16]. Meiser and colleagues (2000) found that overestimators had both higher state anxiety as well as breast cancer anxiety [15]. These data result from studies that addressed the level of knowledge of risk, i.e. the cognitive dimension. Women had to indicate how they think about their own risk by ticking a number. Hopwood suggested that not only the objective risk information may be of importance but also the way this information is processed by the individual [13]. This led us to hypothesise that whereas women may give an accurate or inaccurate estimation of their breast cancer risk, the way they feel about this risk may be very much lower or contrastively higher. Further, this felt or affective risk perception may have a more powerful association with psychological distress than cognitive risk perception.

In November 1999 the observational MRISC (Magnetic Resonance Imaging SCreening) study started in the Netherlands evaluating a surveillance programme for women at increased risk of breast cancer due to a genetic or familial predisposition (MRISC- part A). The programme consisted of an annual MRI-scan and mammography, biannual physical examination and monthly breast self-examination. The participants were classified into one of three risk categories, corresponding to a CLTR of either more than 60%, a CLTR of 30-50%, and a CLTR of 15-30% [26]. A psychological follow-up study started in September 2000 (MRISC-part B). Here we describe the association between psychological distress and risk perception in women participating in the MRISC-part B. First we differentiated between a cognitive and an affective component of risk perception in the three different levels of objective risk status. Next we determined the association between general and breast cancer specific distress, and cognitive and affective risk perception. We hypothesised that the women in the different risk categories differed in the perception of their risk; in a way that higher risk perceptions were associated with elevated levels of both types of psychological distress; and that affective risk perception was more prominently associated with psychological distress than cognitive risk perception.

Material and Methods

Participants

In this study a total of 351 women were included; 322 women participated in the MRISC-A study and 29 women adhered to surveillance but were not enrolled in MRISC-A. Hundred and eight women from MRISC-A refrained from participation in the psychological follow-up study. At entry, participants did not have a history of breast cancer, and had a cumulative lifetime risk of developing breast cancer of at least 15% based on risk tables by Claus and colleagues (1994) [8]. For this study, participants were categorized in one of three risk categories by means of a decision tree, which is an adapted form of the tables of Claus that has been developed for this study by a genetic subcommittee [26]. Women in category 1 were identified BRCA1 or BRCA2 mutation carriers with a cumulative lifetime risk (CLTR) of developing breast cancer between 60 and 85%. Women in category 2 had a CLTR between 30 and 50%, and were 1st degree family members of a proven BRCA1/2 mutation carrier, who did not opt for the test themselves, or 1st degree relatives from a breast cancer patient from a non BRCA1/2 mutation family or a family where genetic testing was not performed. Women in category 3 had a CLTR between 15 and 30% and belonged to families with an increased frequency of breast cancer incidence, or were 25% risk carriers from a proven BRCA1/2 mutation family [27,28]. Participants signed informed consent and had adequate understanding of the Dutch language. The Medical Ethical Committee of the Erasmus MC in Rotterdam approved the study.

Measures

Independent variables

Age and the number of years adhering to regular surveillance were measured in years. Educational level was divided into lower, medium and higher level. With lower level meaning primary education or lower vocational education; medium level included lower or higher general secondary education or intermediate vocational education; higher level included pre-university education, higher vocational education or university. Being in a committed relationship and having children were dichotomised into yes and no. The risk category was 1, 2 or 3 *(see participants)* [27,28].

Risk perception was measured by two questions *(see Box 1)*. The first one measured the women's knowledge about her personal risk estimate of developing breast cancer in terms of '1 in x' in combination with percentages (cognitive). The second question assessed risk perception in terms of her feelings about her chance of developing breast cancer with answer-categories in words (affective).

Dependent variables

Intrusion and avoidance were measured using the Impact of Event Scale (IES). This questionnaire developed by Horowitz and colleagues (1979) comprises 15 items and can be tailored to a specific event, namely 'breast cancer' in this study [29]. The IES measures two common responses to stressful situations: avoidance (8 items) and intrusion (7 items) and has four answer categories: not at all (0), seldom (1), sometimes (3) and often (5). Reliability analysis in this study revealed Cronbach Alpha's of 0.84 (avoidance) and 0.86 (intrusion).

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire, measuring anxiety (7 items) and depression (7 items) [30]. Each subscale has a score range between 0 and 21. Reliability analysis in this study revealed Cronbach Alpha's of 0.83 for anxiety and 0.86 for depression.

Somatic impact was measured with the somatic subscale derived from the Symptom Checklist-90 (SCL-90). This 12-item list consists of physical symptoms often reported when functional problems occur. Each item can be answered with: not at all (1), a little (2), quite (3), very (4) or extremely (5), providing a score range between 12 and 60 [31]. Reliability analysis in this study revealed a Cronbach Alpha of 0.81 for this subscale.

Design

The study was part of a longitudinal observational study on psychological impact and quality of life within the MRISC-study. This article concerns the first assessment at 2 months prior to the women's subsequent appointment in the clinic. The assessments took place between November 2000 and April 2003.

Procedure

Women participating in MRISC-A were sent a letter about the study along with written patient information, an informed consent form, a form on which women could indicate that they did not want to participate and a reply-paid envelope. Additionally, for women not having received the mailed information but were adhering to breast surveillance, the physician or oncologist of the family cancer clinic introduced the study and handed out the patient information at the scheduled control visit. After sending back the signed informed consent, women received their baseline questionnaire at home two months prior to their next surveillance appointment at the family cancer clinic, together with a reply-paid envelope. Women who did not return their questionnaire within 4 weeks were sent a reminder.

Genetic counselling

Women from identified BRCA mutation families were eligible for a DNA test and received extensive genetic counselling during the decision process. The identified BRCA1/2 mutation carriers (risk category 1) were again elaborately informed about their risk of developing breast cancer and ovarian cancer at the moment of the test result. Women not choosing to proceed with genetic testing were categorised in risk category 2. All these women received a written summary of the information provided. Risk category 2 furthermore partly consists of women who received inconclusive DNA results after extensive counselling, and a written summary. These women have to face inaccurate risk estimations, although empirical evidence allows improved risk estimation models [9]. The same holds for women belonging to risk category 3. As not all women in this risk category were eligible for a DNA test, a subgroup in this risk category has not received genetic counselling. However, this group of women was extensively informed about their breast cancer risk by the physician or oncologist seeing the women for surveillance at the family cancer clinic of our institution.

Statistical analysis

The characteristics of the study sample were tested for differences between the three risk categories by the method of one-way analysis of variance in case of continuous data and by the method of chi-square (Linear-by-Linear Association) in case of ordinal data. The cognitive risk perception question was trichotomised into underestimation, accurate estimation and overestimation of ones own risk. For risk category 1 the answer: *greater than 1 in 2* was considered as an accurate answer; for risk category 2 the answers: *about 1 in 2* and *about 1 in 3* were both considered as an accurate answer; and for risk category 3 the answers: *about 1 in 4 and about 1 in 7* were both considered as accurate answers. Subsequently this variable was recoded into dummy-variables. The affective risk perception question was considered as a continuous variable.

An ANCOVA (analysis of covariance) was applied to explore how affective risk perception was related to cognitive risk perception for the three risk categories. Covariables were: age, number of years of adherence, educational level, having a relationship and having children. Missing values in the dependent variables were handled as follows: for women who filled in more than 75% of the questions per subscale a total score has been computed, corrected for the total number of questions of the subscale. For women who filled in less than 75% of the questions per subscale no total score was computed. With the dependent variables a two-component structure was determined (details submitted elsewhere).

The first component (Component I) constituted the outcome variables intrusion and avoidance. These are measures of distress as a consequence of intense experience or active avoidance of thoughts and feelings about breast cancer and, therefore, Component I can be characterised as breast cancer specific distress. Component II is characterised by anxiety, depression and the somatic subscale of the SCL-90. Because the questions are to be answered without bearing in mind thoughts and feelings about breast cancer, this component can be considered to be an expression of general distress. Multiple linear regression was used to determine differences between the three risk categories and cognitive and affective risk perception. Multiple linear regression was also used to determine the association between cognitive and affective risk perception and general and breast cancer specific distress.

The meaning of statistical adjustment is that the relationship between the variables of interest (i.e. independent variables) and the dependent variable may be biased, if possible confounding variables are not taken into account. For example, the relationship between risk perception and distress might be biased if age was not taken into account. In this study we considered risk category, age, number of years of adherence, level of education, having a relationship and having children as potential confounder variables that require inclusion as covariates. As a measure of the relative importance the standardised regression coefficient was used. All statistical testing occurred at 0.05 level of significance (two-sided). All analyses were carried out using the Statistical Package for Social Sciences (SPSS 11).

Results

Sample characteristics

The characteristics of 351 participants are shown in *Table 1*. The women who did not want to participate in the psychological follow-up study did not differ significantly from the women who did participate, with respect to age and risk status. The three objective risk categories were not equally represented; 11.4% (n=40) of the sample was BRCA1 or BRCA2 mutation carrier, 56.7% (n=199) of the women belonged to category 2, and 31.9% (n=112) belonged to risk category 3. The mean age of the total group of women was 40.5 years (range 21 – 63 yrs.). Age did not significantly differ between the three risk categories. The mean duration of adherence to a surveillance programme was 5.3 years (range 0 – 30). Women in category 1 were adhering significantly shorter to surveillance than women in the other 2 categories (3 yrs. and around 5.5 yrs. respectively) ($p < 0.004$). Posthoc comparisons of the three categories resulted in a statistical significant difference between the following categories: 1 versus 2 and 1 versus 3 (Bonferroni's correction was applied). The majority of the women completed a middle level education (54%, n= 178). Most of the women (88%, n= 308) had a relationship and 72% (n=251) had one or more children.

Table 1. Demographic characteristics of the study sample [1)]

Variable	Risk category 1 (n = 40)	Risk category 2 (n = 199)	Risk category 3 (n = 112)	Total (n = 351)
Age mean (sd)	40.7 (10.3)	41.0 (8.8)	39.5 (8.3)	40.5 (8.8)
Number of years adhering mean (sd)*	3.0 (12.4)	5.6 (4.4)	5.6 (4.7)	5.3 (4.4)
Educational level				
Lower level	6 (15%)[2)]	34 (17%)	21 (19%)	61 (17%)
Middle level	23 (58%)	106 (53%)	59 (53%)	178 (54%)
Higher level	11 (27%)	59 (30%)	32 (28%)	102 (29%)
Having a partner (yes)	38 (95%)	173 (87%)	97 (87%)	308 (88%)
Having children (yes)	25 (63%)	147 (74%)	79 (71%)	251 (72%)

[1)] The numbers may vary due to missing values
[2)] Percentages indicate column percentages
* Significantly different between the three risk categories

Relationship between risk perception and risk categories

In risk category 1 the majority accurately estimated their own risk of developing breast cancer (60%) *(Table 2)*. Due to the format of the cognitive risk perception question it was impossible for women in category 1 to overestimate their risk. Underestimation in this category occurred therefore in the remaining 40%. In risk category 2, slightly more women underestimated their personal breast cancer risk as compared to accurately estimating it (47.2% and 43.7% respectively). Overestimation occurred in 9.1% of the women in this category. In risk category 3, 33.3% of the women had an accurate estimation of their own risk, against 25% underestimating it and 41.7% overestimating it. For the total sample an accurate risk estimate was given by 42.3% of the women.

Table 2. Accurate risk estimation divided by risk category

Risk category	Underestimation of own risk	Accurate estimate of own risk	Overestimation of own risk
Category 1	40.0%[1)]	60.0%	does not apply
Category 2	47.2%	43.7%	9.1%
Category 3	25.0%	33.3%	41.7%
Total sample	39.4%	42.3%	18.3%

[1)] Percentages indicate row percentages
$p < 0.001$ (Linear-by-Linear Association)

The differences between accurate estimation, over- and underestimation in the three risk categories were significant ($p < 0.001$). Additionally, cognitive risk perception distinguished by risk category was related to affective risk perception. The estimated means, adjusted for the co-variables, are visualised in *Figure 1*. Both risk category and cognitive risk perception were significantly related to affective risk perception ($F = 26.8$, $p < 0.001$ and $F = 86.3$, $p < 0.001$ respectively). When testing for a possible interaction between risk category and cognitive risk perception in relation to affective risk perception, we found a non-significant result ($F = 2.5$, $p < 0.07$).

Psychological distress in relation to cognitive and affective risk perception

The association between cognitive risk perception and general distress was not significant. The association between overestimation and breast cancer specific distress however was significant ($\beta = 0.16$, $p < 0.02$) *(Table 3a)*. Women overestimating their risk reported relatively more breast cancer specific distress. Furthermore, significant positive associations were found for affective risk perception with both breast cancer specific distress ($\beta = 0.16$, $p< 0.02$) and general distress ($\beta = 0.22$, $p < 0.002$) *(Table 3b)*. The association between overestimation and breast cancer specific distress was no longer significant after adding affective risk perception to the regression model ($\beta = 0.10$, $p < 0.13$). This means that, regardless of accurate estimation, overestimation or underestimation, women who had a higher affective risk perception showed higher scores on general distress and breast cancer specific distress.

Table 3a. Association between cognitive risk perception and general and breast cancer specific distress (n = 345)

	General distress		Breast cancer specific distress	
Variable	β [1)]	p-value <	β [1)]	p-value <
Underestimation	0.004	0.95	-0.05	0.39
Overestimation	0.09	0.16	**0.16**	**0.02**

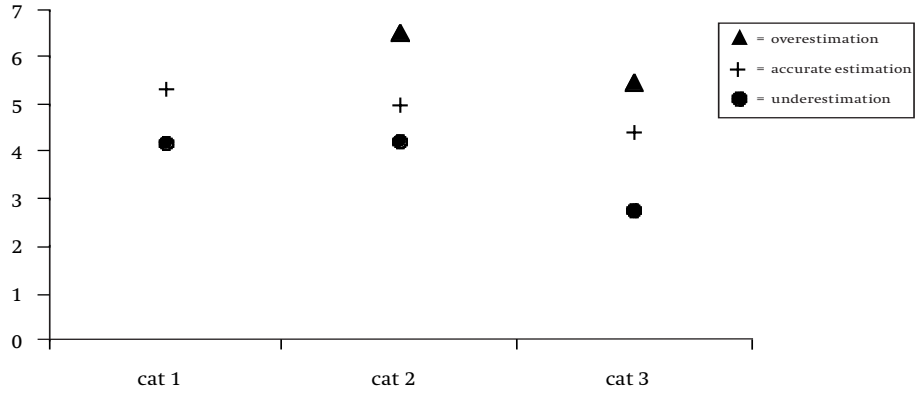
[1)] Standardized regression coefficient as measure of relative importance

Table 3b. Association between affective risk perception and general distress and breast cancer specific distress (n=344)

	General distress		Breast cancer specific distress	
Variable	β [1)]	p-value <	β [1)]	p-value <
Affective risk perception	**0.22**	**0.002**	**0.16**	**0.02**
Underestimation	0.09	0.16	0.007	0.92
Overestimation	0.01	0.95	0.10	0.13

[1)] Standardized regression coefficient as measure of relative importance

Figure 1. Mean scores[1)] on affective risk perception for each risk category distinguished by cognitive risk perception.



[1)] Mean scores were adjusted for the covariables
Numbers on the Y-axis correspond with the answer categories of the affective risk perception question:
1 = very small
2 = small
3 = reasonably small
4 = not small, not high
5 = reasonably high
6 = high
7 = very high

Disussion

Our findings underscore Hopwood's notion that the affective risk perception is important [13] and profoundly associated with psychological distress. Moreover, this association remains irrespective of accuracy of risk perception. Less than half of the women in our sample accurately estimated their personal risk of developing breast cancer. Underestimation of risk was most prominent in risk category 2, whereas overestimation was most prominent in risk category 3. Several factors can explain this observation.

First, this effect may be a consequence of the nature of the genetic counselling. Women in risk category 1 receive extensive counselling, with the inclusion of comprehensive information and a written summary of the consultation. The risk figures provided are rather definite and exact. The majority in this subsample reported an accurate risk perception, which indeed could reflect a good memory and recall of clear data. Information about an elevated risk of developing breast cancer in the categories 2 and 3 is more complex and less concrete, and may therefore not be discussed thoroughly, and/or remembered accurately. Second, women in category 2 who received inconclusive DNA-test results (i.e. a BRCA1/2 mutation could not be identified) may have previously anticipated a higher risk in accordance with a BRCA1/2 mutation. Subsequently, the underestimation of the remaining personal risk may reflect their relief of not being a mutation carrier. Moreover, women not being identified as a mutation carrier were not offered prophylactic surgery as an option, which may have caused additional relief.

The opposite may be true for women in category 3 who may have had no separate genetic counselling and mostly lacked written information. Their knowledge about their elevated risk is not assuaged with a favourable DNA result for BRCA1/2. Further, self-selection may also be determinative in the way that women in category 3 overestimating their risk may be more eager to enrol in a surveillance programme than those who are less worried. Third, the format of the answer categories may have influenced the observed results.

Having a relatively higher risk implies that the chance to estimate it lower is higher. When the objective risk is relatively lower, there is a higher chance to overestimate. Due to the format of the answer categories it is impossible to become an overestimator in risk category 1, because the highest answer category is in fact the accurate answer for women in this category.

Women who reported breast cancer specific distress overestimated their objective risk. However, a higher awareness of (affective) risk was associated with both breast cancer specific and general distress, independent of the adequacy of risk estimation.
Women carrying a BRCA mutation (risk category 1) who underestimated their risk had a relatively lower affective risk perception which was associated with lower distress scores for both general and breast cancer specific distress. This observation may reflect denial or minimisation of their elevated risk, in order to protect themselves against (unnecessary) worries. However these women, in spite of their underestimation and possible denial as a way of self-protection, continue to adhere to the surveillance programme. Indeed, otherwise they would not have been included in this psychological follow-up study. So, in our study sample we did not find indications that the lower distress scores result in a lack of motivation to adhere to recommended guidelines in contrast to what has been suggested by Lerman and colleagues (1993) [32]. In a previous study at our institution we found lower distress scores in mutation carriers opting for surveillance than in mutation carriers opting for bilateral prophylactic mastectomy [33]. Mutation carriers with an accurate risk perception show a mean affective risk perception of 'reasonably high' *(Figure 1)* indicating relatively lower distress, which is consistent with the lower distress scores of mutation carriers opting for surveillance in the study conducted by Lodder and colleagues (2002).

This suggests that the women adhering to the surveillance programme feel comfortable and possibly are confident that an eventual breast tumour will be detected at an early stage. It is interesting to note that 8 mutation carriers with an accurate cognitive risk perception had an affective risk perception of 'very high', indicating higher psychological distress. It is possible that these women are in the middle of a decision making process about an eventual mastectomy. Van Dijk and colleagues (2003) recently reported that higher perceived risk and more breast cancer worry were both significantly associated with the intention to undergo a prophylactic mastectomy [34]. In all three risk categories a considerable number of women had inaccurate risk perceptions, either an underestimation or an overestimation. How much effort should be made to improve the perception of these women? Indeed independently of the level of (in)accuracy all women were adhering to regular surveillance. Inaccurate risk perception therefore did not seem to adversely influence health behaviour.

However, from this study it is not clear how many women do not adhere to screening, or do not even come forward for risk assessment. Our study showed the importance of affective risk perception and the lesser relevance of adequate risk estimation with regard to distress. Counselling should address the way in which women process the information about their given risk estimate (the cognitive dimension). Obviously, more attention is needed for achieving tolerable levels of psychological distress (the affective dimension). The study conducted by Hopwood and colleagues (2001) showed no significant reduction in cancer worries after risk counselling, implying that it is not sufficient to provide only numerical information [16]. On the other hand there are studies demonstrating a decrease in psychological distress after genetic counselling [19,35]. Watson and colleagues (1998) found that 1 year after counselling the level of breast cancer worries remained similar, but this worry was significantly less experienced as a problem by the women [12].

The different outcomes of these studies may be partly explained by the different contents and quality of counselling. We speculate that a significant reduction of distress can be achieved if the counsellor or psychosocial worker comprehensively addresses the emotional issues associated with breast cancer. The psychological approach should be tailored to specific women experiencing high distress, and is dependent on intellectual resources and motivation, introspective capacities and support systems of these women. Specific psychological interventions could include psycho-educational programmes, and interventions from a cognitive-behavioural, psychodynamic, or family-system perspective.
In this way the women can be helped to come to terms with induced problems and find an adequate and creative adjustment. It is important that future studies address the factors that cause a high affective risk perception, which in turn is significantly associated with higher distress. Moreover, both quality of counselling and intervention strategies should be further studied.
In conclusion: physicians and researchers need to be aware of the importance of the affective component of risk perception. It is recommendable that future research should focus on the exact relation between both cognitive and affective risk perception, and psychological distress. Furthermore intervention methods to reduce distress until tolerable levels in women with a high affective risk perception need to be developed and studied.

Acknowledgements

This study is supported by the Dutch Health Insurance Council. We would like to thank all the women who participated in this study.

References

1. Miki Y, Swensen J, Shattuck-Eidens D, et al: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66-71., 1994
2. Wooster R, Bignell G, Lancaster J, et al: Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789-92., 1995
3. Blackwood MA, Weber BL: BRCA1 and BRCA2: from molecular genetics to clinical medicine. J Clin Oncol 16:1969-77., 1998
4. Ford D, Easton DF, Stratton M, et al: 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., 1998
5. Thorlacius S, Struewing JP, Hartge P, et al: Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet 352:1337-9., 1998
6. Antoniou A, Pharoah PD, Narod S, et al: Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. Am J Hum Genet 72:1117-30., 2003
7. Meijers-Heijboer H, van den Ouweland A, Klijn J, et al: Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet 31:55-9., 2002
8. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 73:643-51., 1994
9. van Asperen CJ, Jonker MA, Jacobi CE, et al: Risk estimation for healthy women from breast cancer families: new insights and new strategies. Cancer Epidemiol Biomarkers Prev 13:87-93, 2004
10. Evans DG, Blair V, Greenhalgh R, et al: The impact of genetic counselling on risk perception in women with a family history of breast cancer. Br J Cancer 70:934-8., 1994
11. Kash KM, Holland JC, Osborne MP, et al: Psychological counseling strategies for women at risk of breast cancer. J Natl Cancer Inst Monogr 17:73-9, 1995
12. Watson M, Duvivier V, Wade Walsh M, et al: Family history of breast cancer: what do women understand and recall about their genetic risk? J Med Genet 35:731-8., 1998
13. Hopwood P: Genetic risk counselling for breast cancer families. Eur J Cancer 34:1477-9., 1998
14. Watson M, Lloyd S, Davidson J, et al: The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. Br J Cancer 79:868-74., 1999
15. Meiser B, Butow P.; Schnieden, V.: Psychological adjustment of women at increased risk of developing hereditary breast cancer. Psychology, Health and Medicine 5:377-389, 2000
16. Hopwood P, Shenton A, Lalloo F, et al: Risk perception and cancer worry: an exploratory study of the impact of genetic risk counselling in women with a family history of breast cancer. J Med Genet 38:139., 2001
17. Meiser B, Halliday JL: What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. Soc Sci Med 54:1463-70., 2002
18. Hopwood P, Keeling F, Long A, et al: Psychological support needs for women at high genetic risk of breast cancer: some preliminary indicators. Psychooncology 7:402-12., 1998

19. Cull A, Anderson ED, Campbell S, et al: The impact of genetic counselling about breast cancer risk on women's risk perceptions and levels of distress. Br J Cancer 79:501-8., 1999
20. Lloyd S, Watson M, Waites B, et al: Familial breast cancer: a controlled study of risk perception, psychological morbidity and health beliefs in women attending for genetic counselling. Br J Cancer 74:482-7., 1996
21. Burke W, Culver J, Bowen D, et al: Genetic counseling for women with an intermediate family history of breast cancer. American Journal of Medical Genetics 90:361-368, 2000
22. Woloshin S, Schwartz LM, Black WC, et al: Women's perceptions of breast cancer risk: how you ask matters. Med Decis Making 19:221-9., 1999
23. Rees G, Fry A, Cull A: A family history of breast cancer: women's experiences from a theoretical perspective. Soc Sci Med 52:1433-40., 2001
24. Chalmers K, Thompson K: Coming to terms with the risk of Breast Cancer: Perceptions of women with primary relatives with breast cancer. Qualitative Health Research 6:256-282, 1996
25. Brain K, Norman P, Gray J, et al: Anxiety and adherence to breast self-examination in women with a family history of breast cancer. Psychosom Med 61:181-7., 1999
26. Kriege M, Brekelmans CT, Boetes C, et al: MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). Fam Cancer 1:163-8, 2001
27. Brekelmans CT, Voogd AC, Botke G, et al: Family history of breast cancer and local recurrence after breast-conserving therapy. The Dutch Study Group on Local Recurrence after Breast Conservation (BORST). Eur J Cancer 35:620-6., 1999
28. Brekelmans CT, Seynaeve C, Bartels CC, et al: Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol 19:924-30., 2001
29. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209-18., 1979
30. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70., 1983
31. Derogatis LR, Lipman RS, Covi L: SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull 9:13-28., 1973
32. Lerman C, Schwartz M: Adherence and psychological adjustment among women at high risk for breast cancer. Breast Cancer Res Treat 28:145-55., 1993
33. Lodder LN, Frets PG, Trijsburg RW, et al: 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). Breast Cancer Res Treat 73:97-112., 2002
34. van Dijk S, Otten W, Zoeteweij MW, et al: Genetic counselling and the intention to undergo prophylactic mastectomy: effects of a breast cancer risk assessment. Br J Cancer 88:1675-81., 2003
35. Lerman C, Schwartz MD, Miller SM, et al: A randomized trial of breast cancer risk counseling: interacting effects of counseling, educational level, and coping style. Health Psychol 15:75-83., 1996

Box 1. Questions measuring risk perception

Question 1:
'How do you estimate your chance of developing breast cancer yourself?'
My chance of developing breast cancer is:
❒ very unlikely
❒ about 1 in 20 (i.e. 5%)
❒ about 1 in 10 (i.e. 10%)
❒ about 1 in 7 (i.e. 11 – 19%)
❒ about 1 in 4 (i.e. 20 – 29%)
❒ about 1 in 3 (i.e. 30 – 39%)
❒ about 1 in 2 (i.e. 40 – 50%)
❒ greater than 1 in 2 (i.e. 60 – 80%)

Question 2:
Besides this estimated chance, you possibly have a certain feeling about your chance of developing breast cancer.
'How do you feel your chance of developing breast cancer?'
I feel my chance of developing breast cancer as:
❒ very small
❒ small
❒ reasonably small
❒ not small, not high
❒ reasonably high
❒ high
❒ very high

Chapter 4

The impact of having relatives affected with breast cancer on psychological distress in women at increased risk for breast cancer

Breast Cancer Research and Treatment, 2005; 89, 75-80

Van Dooren S, Seynaeve C, Rijnsburger AJ, Duivenvoorden HJ, Essink-Bot ML, Bartels CCM, Klijn JGM, de Koning HJ, Tibben A

Abstract

Purpose: Being at hereditary risk of breast cancer (BC) may lead to elevated levels of distress because of the impact of the BC-process in relatives.
Objective: Determine the association between psychological distress and BC in relatives. We studied: kind of kinship with the affected relative(s), degree of involvement with the relative's BC, time elapsed since the BC diagnosis of the relative, and loss of a relative as a consequence of BC.
Methods: The study cohort consisted of women at increased risk of developing BC, adhering to regular surveillance and participating in the Dutch MRISC-study. Two months prior to the surveillance appointment, demographics, general and BC specific distress and experience with BC in the family were assessed.
Results: 347 out of 351 participants (mean age 40½) had at least one relative affected with BC. The following variables were significantly, positively related to BC specific distress: having at least one affected sister ($n = 105$; $p < 0.04$); close involvement in a sister's BC process ($n = 94$; $p < 0.03$); and a recent (less than three years ago) BC diagnosis in a sister ($n=30$; $p < 0.03$). General distress did not show any significant associations with the experience of BC in the family.
Conclusion: These findings show the impact of a BC diagnosis in a sister, particularly a recent diagnosis, on psychological distress. Women who have experienced BC in their sister may be in need of additional counselling or of more attention during the surveillance process.

Introduction

Women at increased risk of hereditary or familial breast cancer may have been confronted with breast cancer in a number of relatives, and may have been closely involved in this breast cancer process or not. Several studies have indicated that women from families with an increased occurrence of breast cancer show elevated levels of both breast cancer specific and general distress [1-6]. These studies did not take into account the kind of kinship with the affected relatives. Wellisch et al. (1992) studied psychological distress in daughters whose mothers were affected by breast cancer in relation to the age of the daughter at the time of the mother's breast cancer diagnosis. They found relatively more adjustment problems in adolescent women compared with women who were already in their adulthood at the time of their mother's breast cancer diagnosis [7].

Correspondingly, Hopwood et al. (2001) found that women bereaved of their mothers during adolescence had higher, though non-significant, cancer worries than women who had lost their mothers during adulthood. Daughters who were younger than 10 years of age when their mother died had the lowest cancer worries ($p<0.01$) [8]. Erblich et al. (2000) additionally studied the possible burden of care giving to the affected relative. They found the highest psychological distress scores, both breast cancer specific and general, in women whose mothers had died from breast cancer, and who had taken care of their mother during her illness [9]. With respect to time the impact of experiencing a breast cancer related event in the past year was found to be significantly associated with higher breast cancer anxiety and state anxiety [10].

In November 1999, the MRISC (Magnetic Resonance Imaging SCreening) study started in six family cancer clinics in the Netherlands. The MRISC is an observational study to evaluate the value of MRI as compared to mammography in a surveillance programme for women at increased risk for hereditary or familial breast cancer (MRISC- part A). A longitudinal psychological follow-up study started in September 2000 in the Daniel den Hoed Cancer Centre in Rotterdam, one of the clinics (MRISC- part B). The surveillance programme consisted of an annual MRI-scan in addition to the annual mammography and bi-annual physical examination and recommended monthly breast self examination [11].

The primary objective of the study was to determine the relationship between psychological distress and the kind of kinship with the relative affected by breast cancer. The secondary objective was threefold, to determine the importance of the women's involvement in the breast cancer process of the affected relative, the recency of the breast cancer diagnosis in the relative, and the death of the affected relative as a consequence of breast cancer. Psychological distress was defined in terms of general distress and breast cancer specific distress.

Material and Methods

This psychological study included a total of 351 women; of which 322 women had been included in the MRISC-A study in the Daniel den Hoed Cancer Centre in Rotterdam. These 322 women were screened according the guidelines of the study, meaning that they had an annual mammography, an annual MRI-scan and bi-annual physical examinations. Hundred and nine women from the MRISC-A study refrained from participation in the psychological follow-up study. An additional 29 women who adhered to regular surveillance, but not included in the MRISC-A study also consented to participate in this psychological study. These 29 women were screened by annual mammography and bi-annual physical examinations but did not receive annual MRIscan. At entry the participants did not have a history of breast cancer themselves and had a cumulative life time risk (CLTR) of developing breast cancer of at least 15%, based on risk tables by Claus et al.[12]. Participants needed adequate understanding of the Dutch language to fill in the questionnaires, and they signed an informed consent form. The Medical Ethical Committee of the Erasmus MC in Rotterdam approved the study.

Measures

Independent variables

Age and the duration of adherence to regular surveillance were measured in years. Educational level was divided into three categories, i.e. low, medium and high. Being in a relationship and having children were dichotomised into 'yes' and 'no'. Women were grouped into three risk categories according to their life time risk by means of genetic epidemiological tables [11]. Women in category 1 were identified BRCA1 or BRCA2 mutation carriers with a CLTR of developing breast cancer between 60 and 85%. Women in category 2 had a CLTR between 30 and 50%, and were 1st degree family members of a proven BRCA1/2 mutation carrier, who did not opt for the test themselves, or 1st degree relatives from a breast cancer patient from a non BRCA1/2 mutation family or a family where genetic testing was not performed. Women in category 3 had a CLTR between 15 and 30% and belonged to families with an increased frequency of breast cancer incidence, or were 25% risk carriers from a proven BRCA1/2 mutation family [13,14]. In the questionnaire, we asked participants whether they had any family members affected by breast cancer and what the type of relationship was with this family member. The answering categories were: mother, sister, aunt, grandmother, niece and others (independent of the side of heredity). This last category had to be further specified by the participants. We also asked the number of relatives (except for the mother) who had been diagnosed with breast cancer.

Further, for every relative with breast cancer the participants were asked to indicate how long ago the breast cancer had been diagnosed. Per relative the options were: no longer than 1 year ago; between 1 and 3 years ago, between 3 and 6 years ago and longer than 6 years ago. Also, we asked the participants to indicate to what extent they were personally involved in their relative's disease. The option modalities per relative were completely involved; closely involved; involved at some distance; not at all involved. Lastly, the participants were asked to indicate which of the relatives affected with breast cancer had died as a result of the disease.

Dependent variables
Intrusion and avoidance were measured using the Impact of Event Scale (IES). This questionnaire developed by Horowitz et al. (1979) comprises 15 items and can be tailored to a specific event, namely 'breast cancer' in this study [15]. The IES measures two common responses to stressful situations: avoidance (8 items) and intrusion (7 items) and has four answer categories: not at all (0), seldom (1), sometimes (3) and often (5). Reliability analysis in this study revealed Cronbach Alpha's of 0.84 (avoidance) and 0.86 (intrusion).

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire, measuring anxiety (7 items) and depression (7 items) [16]. Each subscale has a score range between 0 and 21. Reliability analysis in this study revealed Cronbach Alpha's of 0.83 for anxiety and 0.86 for depression.

Somatic impact was measured with the somatic subscale derived from the Symptom Checklist-90 (SCL-90). This 12-item list consists of physical symptoms often reported when functional problems occur. Each item can be answered with: not at all (1), a little (2), quite (3), very (4) or extremely (5), providing a score range between 12 and 60 [17]. Reliability analysis in this study revealed a Cronbach Alpha of 0.81 for this subscale.

Design
The study was part of a longitudinal observational study on psychological impact and quality of life within the MRISC-study. The study procedure is described in detail elsewhere [18]. The analyses in this article concern the first assessment after entry in the study, performed two months prior to the women's next scheduled appointment in the clinic. The assessments took place between November 2000 and April 2003.

Statistical analysis
Differences in distribution of background characteristics between the three risk categories were tested by one-way analysis of variance for continuous data and by chi-square-test for ordinal data (linear-by-linear association). We constructed several new variables out of the variables about breast cancer in the family. First, the 'involvement in the breast cancer process' variables were recoded. For the sake of interpretation and to obtain a substantial number of participants in each group the first two categories and the latter two were combined. Using these combinations the variable 'involved' was computed, with 'yes' meaning complete or close involvement in the disease process of at least one relative regardless of the type of relationship and 'no' meaning remotely or not at all involved in the disease process of a relative with breast cancer. We also computed the number of 'involved'-variables per relative.

Next, the variable 'time' was computed. This variable had four categories and represented the shortest period wherein a relative had been diagnosed with breast cancer. In the case of multiple relatives or a recurrent breast cancer in a relative the shortest period was taken. In concordance with the variable involved we computed a dichotomised variable: shorter than 3 years ago and 3 years ago and longer. We also computed 'time'-variables per relative.

Missing values in the dependent variables were handled as follows: a total score, corrected for the total number of questions of the subscale, was computed for women who filled in more than 75% of the questions per subscale. No total score was computed for women who filled in less than 75% of the questions of a subscale. The five dependent variables (avoidance, intrusion, anxiety, depression and the somatic subscale of the SCL-90) were substantially intercorrelated.

Therefore, we identified the dimensional structure of the five variables. It appeared that these variables could adequately be represented in a two-dimensional solution. The first component (Component I) constituted the outcome variables intrusion and avoidance. These are measures of distress as a consequence of intense experience or active avoidance of thoughts and feelings about breast cancer. Therefore, Component I can be characterized as breast cancer specific distress. Component II comprised anxiety, depression and the somatic subscale of the SCL-90. The questions in these scales refer to symptoms or signs of general discomfort, therefore this component can be considered to express general distress. Details hereof are published elsewhere [18].

Multiple linear regression was used to determine the relative importance of breast cancer in the family in the estimation of psychological distress. Standardised regression coefficients were used as measures of the relative importance. In the analysis, we adjusted for several variables. The meaning of statistical adjustment is that the relationship between the variables of interest (i.e. independent variables) and the dependent variable may be biased, if possible confounding variables are not taken into account. For example, the relationship between involvement in mother's BC process (i.e. mother-involved) and distress might be obscured if age was not taken into account. Therefore, in this study we considered the following factors as potentially confounding: risk category, age, number of years of adherence, level of education, having a relationship and having children. It was important to enter all the involvement variables simultaneously in the regression model to get a valid insight into the impact of the independent variables (e.g. mother-involved). All statistical testing occurred at 0.05 level of significance (two-tailed). Analysis were carried out using the Statistical Package for Social Sciences (SPSS 11).

Results

Sample characteristics

The background characteristics of the 351 participants are shown in *Table 1*. The three objective risk categories were not equally represented; 11.4% of the sample were BRCA1 or BRCA2 mutation carriers, 56.7% of the women belonged to category 2, and 31.9% belonged to risk category 3. The mean age of the total group was 40.5 years (range 21 – 63 yrs). Age did not significantly differ between the three risk categories. The mean number of years adhering to a surveillance programme was 5.3 years (range 0 – 30 yrs). Women in category 1 were adhering significantly shorter to surveillance than women in the other 2 categories (3 yrs. and around 5½ yrs. respectively) ($p < 0.004$). The majority of the women completed a middle level education (54%). Most of the women (88%) were in a relationship and 72% had one or more children.

Table 1. Demographic characteristics of the study sample [1)]

Variable	Risk category 1 (n = 40)	Risk category 2 (n = 199)	Risk category 3 (n = 112)	Total (n = 351)
Age mean (sd)	40.7 (10.3)	41.0 (8.8)	39.5 (8.3)	40.5 (8.8)
Number of years adhering mean (sd)*	3.0 (2.4)	5.6 (4.4)	5.6 (4.7)	5.3 (4.4)
Educational level				
Lower level	6 (15%)[2)]	34 (17%)	21 (19%)	61 (17%)
Middle level	23 (58%)	106 (53%)	59 (53%)	188 (54%)
Higher level	11 (27%)	59 (30%)	32 (28%)	102 (29%)
Having a partner	38 (95%)	173 (87%)	97 (87%)	308 (88%)
Having children	25 (63%)	147 (74%)	79 (71%)	251 (72%)

[1)] The numbers may vary due to missing values
[2)] Percentages indicate column percentages
* Significantly different between the three risk categories (two-tailed)

Breast cancer in the family

Of the 351 women, 4 reported no breast cancer cases in the family, leaving 347 (99%) women with breast cancer affected relatives. *Table 2* shows the number of women reporting a breast cancer diagnosis in at least one of the mentioned relatives, the extent of involvement in the disease process, the recency of the breast cancer diagnosis, and death of a relative due to breast cancer. The majority reported having a mother or an aunt diagnosed with breast cancer. The vast majority of women reporting a mother or sister with breast cancer had been closely involved in the breast cancer process of this relative. One third of the participants had been confronted with breast cancer in a relative less than 3 years ago (33%). Per relative these percentages varied between 1 and 39%. Most participants (75%) had experienced the loss of a relative due to breast cancer.

Table 2. Frequencies of relatives with breast cancer, complete or close involvement in the disease process, and relatives passed away due to breast cancer

Relative	Breast cancer diagnosis		Complete or close involvement in the disease process		Breast cancer diagnosis < 3 years ago		Died of breast cancer	
	n	%	n	%	n	%	n	%
Anyone	347	99	297/347	85	114/343*	33	261/347	75
Mother	248	71	230/248	93	20/247	8	134/248	54
Sister	105	33	94/105	89	30/104	29	44/105	42
Aunt	223	64	59/223	26	40/220	18	121/223	54
Grandmother	108	31	17/108	16	1/103	1	75/108	69
Niece	87	25	14/87	16	33/84	39	32/87	37

* Numbers vary due to missing values

Psychological distress related to breast cancer in the family

First, the association between the kind of kinship with the breast cancer patient and both types of psychological distress were examined, entering all affected relatives simultaneously in the regression model. Results are shown in *Table 3*. There were no significant associations with general distress (data not shown). Having at least one sister affected with breast cancer was significantly and positively associated with breast cancer specific distress ($p< 0.04$). When considering the impact on breast cancer specific distress of having a mother affected with breast cancer exclusively (without entering the other relatives in the regressionmodel), this was not significant ($p< 0.57$).

Table 3. The relative importance of breast cancer in a relative in estimating breast cancer specific distress (n=345) [1)]

	Breast cancer specific distress	
	β	p[2)]
Mother affected	0.08	0.21
Sister affected	**0.14**	**0.04**
Aunt affected	-0.05	0.44
Grandmother affected	-0.02	0.79
Niece affected	0.06	0.30

[1)] The analyses were adjusted for risk category, age, number of years adherence, educational level, having a relationship and having children; all relatives were entered simultaneously in the regressionmodel
[2)] Significance testing was done two-tailed

Secondly, the impact of involvement in the breast cancer process of a relative was examined, entering all relatives simultaneously in the regression model. Again, no significant associations with general distress were found (data not shown). Women who were closely involved in the breast cancer process of their sister showed relatively higher breast cancer specific distress scores ($p < 0.03$) *(Table 4)*. It has to be noted hereby that the majority of the women who had a sister diagnosed with breast cancer felt closely involved in the disease process (89%). When examining the impact of close involvement in the breast cancer process of the mother on breast cancer specific distress exclusively (without entering the other relatives in the regressionmodel), this was not significant ($p < 0.82$).

Table 4. The relative importance of being involved in the breast cancer process of a relative in estimating breast cancer specific distress (n=345) [1)]

	Breast cancer specific distress	
	β	p[2)]
Mother involved	0.02	0.74
Sister involved	**0.14**	**0.03**
Aunt involved	0.04	0.51
Grandmother involved	0.06	0.31
Niece involved	0.09	0.09

[1)] The analyses were adjusted for risk category, age, number of years adherence, educational level, having a relationship and having children; all relatives were entered simultaneously in the regressionmodel
[2)] Significance testing was done two-tailed

Thirdly, we examined the influence of the recency of the breast cancer diagnosis in a family member *(Table 5)*. All relatives were entered in the regression model simultaneously. Once again the association between breast cancer specific distress and having a sister diagnosed with breast cancer less than 3 years ago was significant ($p < 0.03$). Analogously, the impact of a recent breast cancer diagnosis in a mother exclusively on breast cancer specific distress was examined, and again no significant association was found ($p<0.78$).

Table 5. The relative importance of recency of the breast cancer diagnosis in a relative in estimating breast cancer specific distress (n=345) [1)]

	Breast cancer specific distress	
	β	p[2)]
Mother <3 yrs.	0.02	0.77
Sister < 3yrs.	**0.12**	**0.03**
Aunt involved < 3 yrs.	0.05	0.33
Grandmother < 3 yrs.	-0.04	0.46
Niece < 3 yrs.	0.07	0.23

[1)] The analyses were adjusted for risk category, age, number of years adherence, educational level, having a relationship and having children; all relatives were entered simultaneously in the regressionmodel
[2)] Significance testing was done two-tailed

Finally, no significant associations were found between the relatives who died as a consequence of breast cancer and both types of psychological distress (data not shown).

Discussion

The most salient finding in this study is that having a sister with breast cancer and being involved in her disease process was more distressing to women than having experienced breast cancer in the mother. Several studies have shown that having a mother affected with breast cancer contributes significantly to the degree of breast cancer specific distress [6,7,19]. These studies however solely investigated the impact of an affected mother or parent and did not take into account the impact of other affected relatives. Zakowski et al. mentioned that the women in her study had at least one affected 1st degree relative, who could be a mother, sister or daughter, but their focus was on the impact of having parents with cancer. In our study different kind of relatives were entered into the model simultaneously, this way we could demonstrate that breast cancer in a sister has a profound impact, which is understandable since sisters may have close bonds. Awareness of similar genetic risks may even strengthen their relationship and their feelings on this issue. Further, belonging to the same generation, they may more easily identify themselves with each other.

The variable 'time since diagnosis' was dichotomised into less than 3 years ago and 3 years ago and longer. A relatively recent diagnosis in a sister showed significant associations with breast cancer specific distress. Understandably, because a relatively recent diagnosis is an event that needs to be coped with and adapted to. Not only the initial shock of a breast cancer diagnosis, but also the incorporation of the fact that this new breast cancer case may have implications for the woman's own risk of developing breast cancer may cause distress. We asked the women to specify the time of diagnosis in their relatives. In case of multiple sisters or aunts some women specified multiple time points. When the relative was the mother, we concluded that the breast cancer was recurrent (since everybody has one mother), but we were not able to draw this conclusion for other relatives as the women may have had more than one sister or aunt with breast cancer.

Out of the 248 women with a mother with breast cancer, 11 had a mother with recurrent breast cancer. This group, however, was too small to analyse. We exploratively examined the impact of having a mother affected with breast cancer exclusively, thus without taking into account the fact that the women could have also other relatives affected with breast cancer. No significant associations with psychological distress were found.

A possible explanation may be that most mothers of the participating women were diagnosed with breast cancer more than 3 years ago. Furthermore, of the 248 women with a breast cancer affected mother, only 19% also had a sister affected with breast cancer, implying that these groups majorly consisted of different women. The death of a relative due to breast cancer had no significant association with psychological distress implying that being involved in a disease process has more impact than the loss of the relative. When it becomes clear that the relative will succumb to the disease, a process of accepting this upcoming loss may set in and this may make the loss, though emotionally upsetting, more bearable.

When counselling women at risk for breast cancer and discussing predictive testing and the various management options, close attention should be paid to the experience of breast cancer in family members. Other studies from our group have already stressed the importance of key experiences with a hereditary disease, as well as the impact of having a greater number of affected relatives on intrusion and avoidance [20,21]. This study is part of a larger longitudinal study, and therefore the effect of breast cancer in the family will also be examined over time and in relation to surveillance appointments. It is important to conduct further research on the impact of breast cancer in the family on psychological distress in women at increased risk for breast cancer. Each new breast cancer case in a relative can result in increased psychological distress, particularly when breast cancer is diagnosed in a sister and when this diagnosis was less than 3 years ago.

Acknowledgements
We would like to thank all the women who participated in this study.

References

1. Kash KM, Holland JC, Halper MS, et al: Psychological distress and surveillance behaviors of women with a family history of breast cancer. J Natl Cancer Inst 84:24-30., 1992
2. Lerman C, Schwartz M: Adherence and psychological adjustment among women at high risk for breast cancer. Breast Cancer Res Treat 28:145-55., 1993
3. Lerman C, Daly M, Sands C, et al: Mammography adherence and psychological distress among women at risk for breast cancer. J Natl Cancer Inst 85:1074-80., 1993
4. Lerman C, Kash K, Stefanek M: Younger women at increased risk for breast cancer: perceived risk, psychological well-being, and surveillance behavior. J Natl Cancer Inst Monogr 16:171-6, 1994
5. Lloyd S, Watson M, Waites B, et al: Familial breast cancer: a controlled study of risk perception, psychological morbidity and health beliefs in women attending for genetic counselling. Br J Cancer 74:482-7., 1996
6. Zakowski SG, Valdimarsdottir HB, Bovbjerg DH, et al: Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer. Ann Behav Med 19:362-9., 1997
7. Wellisch DK, Gritz ER, Schain W, et al: Psychological functioning of daughters of breast cancer patients. Part II: Characterizing the distressed daughter of the breast cancer patient. Psychosomatics 33:171-9., 1992
8. Hopwood P, Shenton A, Lalloo F, et al: Risk perception and cancer worry: an exploratory study of the impact of genetic risk counselling in women with a family history of breast cancer. J Med Genet 38:139., 2001
9. Erblich J, Bovbjerg DH, Valdimarsdottir HB: Looking forward and back: distress among women at familial risk for breast cancer. Ann Behav Med 22:53-9., 2000
10. Meiser B, Butow P.; Schnieden, V.: Psychological adjustment of women at increased risk of developing hereditary breast cancer. Psychology, Health and Medicine 5:377-389, 2000
11. Kriege M, Brekelmans CT, Boetes C, et al: MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). Fam Cancer 1:163-8, 2001
12. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 73:643-51., 1994
13. Brekelmans CT, Voogd AC, Botke G, et al: Family history of breast cancer and local recurrence after breast-conserving therapy. The Dutch Study Group on Local Recurrence after Breast Conservation (BORST). Eur J Cancer 35:620-6., 1999
14. Brekelmans CT, Seynaeve C, Bartels CC, et al: Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol 19:924-30., 2001
15. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209-18., 1979
16. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70., 1983
17. Derogatis LR, Lipman RS, Covi L: SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull 9:13-28., 1973
18. van Dooren S, Seynaeve C, Rijnsburger AJ, et al: Exploring the course of psychological distress around two successive control visits in women at hereditary risk of breast cancer. Eur J Cancer 41:1416-25, 2005
19. Hopwood P: Breast cancer risk perception: what do we know and understand? Breast Cancer Res 2:387-91, 2000
20. Dudok-de Wit A Tibben A, Duivenvoorden H, Frets P, Zoeteweij M, Losekoot M, van Haeringen A, Niermeijer M, Passchier J.: Psychological distress in applicants for predictive dna-testing for autosomal, dominant, heritable, late onset disorders. Journal of Medical Genetics 34:382-390, 1997
21. Lodder LN, Frets PG, Trijsburg RW, et al: Presymptomatic testing for BRCA1 and BRCA2: how distressing are the pre- test weeks? Rotterdam/Leiden Genetics Working Group. J Med Genet 36:906-13., 1999

Chapter 5

Women's acceptance of MRI in breast cancer surveillance because of a familial or genetic predisposition

Submitted

Essink-Bot ML, Rijnsburger AJ, van Dooren S, de Koning HJ, Seynaeve C

Abstract
Magnetic resonance imaging (MRI) is a promising screening modality for women at increased risk for breast cancer due to a familial or genetic predisposition. We investigated the experience with MRI and preferences for MRI, mammography or clinical breast examination in 178 women adhering to a breast cancer surveillance programme. MRI was reported to cause limited bother and to provide the most reassurance of breast cancer being absent in case of a favourable test result. MRI is acceptable as a screening test for women at increased breast cancer risk and is preferred over mammography.

Introduction
Magnetic Resonance Imaging (MRI) of the breast appears to be more sensitive than mammography in women with a familial or genetic predisposition for breast cancer, resulting in detection of breast tumours at an earlier stage [1,2]. We investigated the experiences with MRI and the preferences for MRI, mammography or clinical breast examination among women adhering to a breast cancer surveillance programme in a period when the performance of MRI as a screening test was yet unknown.

Patients and methods
The MRI screening study (MRISC study) is a prospective cohort study designed to assess the efficacy of mammographic and MRI screening in women at increased risk for breast cancer due to a familial or genetic predisposition. Women with >15% cumulative lifetime risk (CLTR) for breast cancer were screened twice a year, with biannual clinical breast examination (CBE) and annual mammography and MRI. Women with evident symptoms suspicious for breast cancer or a history of breast cancer were excluded. A detailed description of the study, started in 1999, was reported elsewhere1. Within the MRISC study, a study on psychological and health-status effects was performed [3-5]. The burden of MRI was assessed alongside in women undergoing MRI, who completed two additional questionnaires; the first in the morning preceding the MRI scan (t1), the second one week after the first (t2). At the time of completion of the questionnaires, the women knew the results of neither mammography nor MRI.
Variables in the first questionnaire included baseline characteristics [age; CLTR of developing breast cancer (three categories; details, see [1]), previous MRI of the breasts], experienced bother with the timing of MRI (between days 5 and 15 of the menstrual cycle; 2 items with 5 response options, ranging from 'no bother at all' to 'extremely bothersome'); fear to undergo MRI (1 item, 3 response options) and fear for the MRI result (1 item, 3 response options). The second questionnaire included items on the experienced bother of undergoing the MRI scan and of the waiting period for the result (7 items). Finally, women were asked to express their preference for either CBE, mammography or MRI under the assumption that all screening modalities performed equally well; and the level of reassurance they expected to experience from each test, assuming a favourable result (no abnormalities).

Results
Response rate: of the 182 women invited, 178 completed questionnaires at t1, 178 at t2 (176 completed both, 96.7%). Mean age was 42.8 years (standard deviation 8.4, range 25-60). 15.1% (n=27) had a CLTR of developing breast cancer of > 50% because of a proven BRCA1/2 mutation, 53.6 % (n = 96) had a 30-50% CLTR and 31.3% (n=56) had a CLTR of 15-30%. 83.7% had had previous MRI scan(s) for early detection of breast cancer.
The timing of the MRI scan was reported as 'rather', 'very', or 'extremely' bothersome by 11.7% of those women for whom this was applicable (n=120). Preceding the MRI scan, 11.2 % expressed serious worries with respect to undergoing the scan; 5.1 % was seriously worried about the scan result; and 29.8% found the waiting period for the test result 'rather', 'very' or 'extremely' bothersome.

The reported experienced bother on seven aspects of undergoing the MRI scan is shown in *Table 1*. 'Lying in the tunnel' was reported as 'rather' to 'very' bothersome by 21.4%, implying that 78.6% experienced 'some' bother at most. We did not observe significant differences in reported bother between the 3 risk groups (data not shown).
Under the assumption that MRI, CBE and mammography performed equally well, 44.4% expressed a preference for MRI as a screening test, 41.4% for CBE and 14.2% for mammography. 64.4% reported that they would feel completely reassured by a favourable MRI result, whereas this was 40.1% for mammography and 27.8% for CBE, respectively.

Table. Experienced burden of MRI scan of the breasts (percentages; total n=178)

	Insertion of infusion needle	Lying in the tunnel	Lying on one's belly	Not moving	Being alone	Noise of the machine	Duration of time in the tunnel
No bother at all	37.9%	34.8%	50.6%	24.3%	69.5%	40.9%	38.6%
Some bother	52.5%	43.8%	33.1%	58.8%	16.4%	39.8%	45.5%
Rather, very or extremely bothersome	9.6%	21.4%	16.3%	17.0%	14.1%	19.2%	15.9%

Discussion

Women adhering to breast cancer surveillance for breast cancer because of a familial or genetic predisposition reported limited bother from undergoing an MRI scan as a screening test. We conclude that the direct burden of MRI was acceptable to the large majority of women, although these results may be affected by the fact that most women in the present study had had one or more previous MRIs. Women who decided not to have further MRIs after experiencing a first one were thus excluded. In the MRISC study, 4.7% of women under surveillance refused later screening by MRI because of claustrophobia or other reasons [1].

Yet in ignorance of the favourable test characteristics of MRI [1,2]. MRI was preferred as a screening modality over mammography, and MRI was reported to provide the most reassurance of breast cancer being absent in case of a favourable test. We reported in a previous article that women experienced more pain and discomfort during mammography compared to MRI scanning of the breasts, although MRI was associated with more anxiety [in 10.2% (MRI) versus 5.2% (mammography)] [3]. These results are in accordance with the scarce data in the literature [6,7]. Though not directly comparable, the study reported by Liang also suggests that MRI is preferred over routine mammography [8].
We conclude that MRI is acceptable as a screening modality for women at increased breast cancer risk, and preferred by them over mammography.

Acknowledgement

We thank Prof. A. Tibben for his valuable comments on a previous version of the manuscript.

References

1. Kriege M, Brekelmans CT, Boetes C, et al: Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427-37, 2004
2. Warner E, Plewes DB, Hill KA, et al: Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. Jama 292:1317-25, 2004
3. Rijnsburger AJ, Essink-Bot ML, van Dooren S, et al: Impact of screening for breast cancer in high-risk women on health-related quality of life. Br J Cancer 91:69-76, 2004
4. van Dooren S, Rijnsburger AJ, Seynaeve C, et al: Psychological distress in women at increased risk for breast cancer: the role of risk perception. Eur J Cancer 40:2056-63, 2004
5. van Dooren S, Seynaeve C, Rijnsburger AJ, et al: The impact of having relatives affected with breast cancer on psychological distress in women at increased risk for hereditary breast cancer. Breast Cancer Res Treat 89:75-80, 2005
6. Kornguth PJ, Keefe FJ, Conaway MR: Pain during mammography: characteristics and relationship to demographic and medical variables. Pain 66:187-94, 1996
7. Dullum JR, Lewis EC, Mayer JA: Rates and correlates of discomfort associated with mammography. Radiology 214:547-52, 2000
8. Liang W, Lawrence WF, Burnett CB, et al: Acceptability of diagnostic tests for breast cancer. Breast Cancer Res Treat 79:199-206, 2003

Chapter 6

Exploring the course of psychological distress around two successive control visits in women at hereditary risk for breast cancer

European Journal of Cancer, 2005; 41(10), 1416-1425

Van Dooren S, Seynaeve C, Rijnsburger AJ, Duivenvoorden HJ, Essink-Bot ML, Tilanus-Linthorst MMA, Klijn JGM, de Koning HJ, Tibben A

Abstract

In this article we determined the course of psychological distress during a breast cancer surveillance programme in women at increased risk of developing hereditary breast cancer (BC). The sample comprised 357 unaffected women (mean age 40.5 years) adhering to a surveillance programme (MRISC-study). Before and after two successive, biannual surveillance appointments, the Impact of Event Scale (BC-specific distress) and the Hospital Anxiety and Depression Scale (general distress) were administered, totalling four measurement moments. In general, psychological distress remained within normal limits and decreased significantly after a surveillance appointment, except for breast cancer specific distress after the second appointment. Scheduled imaging examinations were not significantly related to distress. The course of BC specific distress differed significantly for risk over-estimators and for young (< 40 years) excessive breast self examiners. The course of general distress differed significantly for women closely involved in a sister's BC-process. These more vulnerable subgroups may be in need of extra counselling and care.

Introduction

Women at increased risk of developing breast cancer due to a genetic or familial predisposition may opt for regular surveillance outside of population screening to aim at early detection of an eventual tumour. Regular surveillance programmes for this group of women mostly consist of recommended monthly breast self examination, biannual clinical breast examination (CBE), and yearly mammography [1].

In the literature evidence can be found indicating increased levels of both general and breast cancer specific distress in high-risk women [2-4], especially on the day of a surveillance appointment [5,6]. Additionally, in earlier studies it has been suggested that there exists a negative linear association between adhering to surveillance and distress, resulting in withdrawal from screening [2,7]. These studies, however, were performed in an era where genetic counselling and testing were not yet available and/or standard provided, and therefore it is important to obtain more data on this topic from nowadays practice. Further, studies that are more recent provided evidence that greater worry is associated with a higher uptake of health care behaviour [8,9]. So far, few data exist on the course of psychological distress after successive surveillance appointments. In this respect, it has been reported that screening appears to be reassuring for women between the age of 50 and 64 with a family history, as compared to women without a family history [10]. In addition, a study on the psychological impact of population based breast cancer screening in the Netherlands (including women aged 50 years and older) provided no evidence for adverse psychological effects after the surveillance appointment [11]. In a group of 52 younger high-risk women, a reduction in breast cancer specific distress was observed 4 months after the women's initial surveillance appointment [12].

Several limitations about these studies can be raised. First, most of these studies have been published before 1998, while the field of hereditary breast cancer has tremendously evolved over the last years. Second, the number of women studied was mostly relatively small, and mainly consisted of women above the age of 50 (except for the study of Gagnon et al.), which is not the group of interest in hereditary breast cancer. Thus, data from younger women adhering to breast cancer surveillance are scarce or lacking. Further, the Magnetic Resonance Imaging (MRI)-scan as an additional screening tool may increase the burden of the surveillance process in this group of women. Preliminary findings from a study about health- related quality of life in women at increased risk for breast cancer showed that 37% experienced some degree of anxiety about undergoing the MRI-scan, versus 27% of women undergoing mammography and 22% undergoing CBE [13].

Our study aimed to examine psychological distress in a large group of genetically predisposed women adhering to a breast cancer screening programme, and participating in the observational MRISC (Magnetic Resonance Imaging SCreening). The MRISC study started in November 1999, and aimed to evaluate the efficacy of a surveillance programme for women at increased risk of breast cancer due to a genetic or familial predisposition (MRISC- part A). The surveillance schedule in the study consisted of recommended monthly breast self-examination, biannual CBE, and annual imaging by means of both a MRI-scan and mammography [14,15]. A psychological follow-up study being part of this study started in September 2000 (MRISC- part B).

In this article, we describe the course of psychological distress, breast cancer specific and general, around two successive surveillance visits for the total group of women. Furthermore, we report on the course of distress in earlier identified subgroups [16-18] revealing significantly more breast cancer specific distress at the baseline measurement moment. These subgroups are: younger (< 40 years), excessive breast self-examiners [16]; breast cancer risk over-estimators [17]; and women closely involved in the breast cancer process of a sister [18]. Additionally, the possible extra burden of scheduled imaging examinations including MRI, was compared to that of physical examination only.

Material and Methods

Participants

In this psychological follow-up study 357 women being at risk for hereditary breast cancer and adhering to regular surveillance were included. At entry, the participants did not have a history of breast cancer, and had a cumulative life time risk (CLTR) of developing breast cancer of at least 15%, based on modified risk tables by Claus et al. [14,19]. Of the 357 women, 328 were included in the MRISC-part A-study. The other 29 women were adhering to regular surveillance as well, but did not have the MRI-scan incorporated in their surveillance programme for different reasons. Thus, screening in this group consisted of recommended monthly BSE, biannual physical examination, and annual mammography, which is in accordance with the national guidelines for this group of women. One hundred and nine women from MRISC-A were not included in the psychological follow-up study.

Measures

Background variables

Age and the number of years adhering to regular surveillance were measured. Educational level was divided into lower, medium, and higher level. Lower level consists of primary or lower vocational education; medium level included lower or higher general secondary education or intermediate vocational education; higher level included higher vocational education or (pre-) university. Having a partner and having children were both dichotomised into yes and no. Women were categorized into three risk categories by the MRISC-study team. Women in risk category 1 were identified BRCA1 or BRCA2 mutation carriers, with a CLTR of developing breast cancer between 60 and 85%. Women in category 2 had a CLTR between 30 and 50%, and were 1st degree family members of a proven BRCA1/2 mutation carrier, who did not opt for the test themselves, or 1st degree relatives from a breast cancer patient from a non BRCA1/2 mutation family or from a family where genetic testing was not performed. Women in category 3 had a CLTR of 15 to 30%. These women belonged to families with an increased frequency of breast cancer, or were 25% risk carriers in a proven BRCA1/2 mutation family [14,15,20].

Breast cancer specific distress
Intrusion and avoidance, two common responses to stressful situations, were assessed at each measurement moment (see Design) using the Impact of Event Scale (IES). This questionnaire developed by Horowitz et al. (1979) comprises 15 items and can be tailored to a specific event, namely 'breast cancer' in this study [21]. Avoidance is measured in 8 items and intrusion in 7 items, and each item has four answer categories: not at all (score 0), seldom (score 1), sometimes (score 3), and often (score 5). The summation score for the total scale ranges between 0 and 75, with a higher score meaning more breast cancer specific distress. Since the Impact of Event Scale has been used in many settings, study samples and cultural contexts cutoff scores are of limited value. However, as an indication for high distress a total score of 26 or more is given [22]. Reliability analysis on the baseline measurement of the current study revealed Cronbach Alpha's of 0.84 for the subscale avoidance, of 0.86 for the subscale intrusion, and of 0.91 for the entire scale.

General distress
The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire, assessed anxiety (7 items) and depression (7 items) at each measurement moment (see Design). Each subscale has a score range between 0 and 21. Cut-off scores per subscale indicative of clinical anxiety and depression are 11 or higher. Obtaining a score of 8 to 10 on each subscale is representative of doubtful cases of anxiety and depression [23]. By combining the scores of the two subscales, a measure for general distress can be obtained. A cut-off score of 18 (on the total HADS) showed the best sensitivity and specificity in a sample of women with advanced breast cancer [24]. Reliability analysis on the baseline measurement of the current study revealed Cronbach Alpha's of 0.83 for anxiety, of 0.86 for depression, and of 0.90 for the entire scale.

Independent variables
From the baseline measurement, performed two months before a surveillance appointment in the clinic (m0, see design), we identified three variables that were found to be associated with elevated levels of psychological distress [16-18]. The first variable addressed the frequency of breast self-examination and was measured with one question: Do you perform breast self-examination regularly in order to detect possible anomalies? The question had six answer possibilities: no, never; yes, approximately once a year; yes, approximately once every six months; yes, approximately once every three months; yes, approximately once a month; and yes, at least once a week. The answers were recoded into excessive self-examination (at least once a week) versus otherwise. This was further combined with the median age resulting in two categories: 1. young (< 40 yrs) excessive breast self examiners and 2. others [16]. This question was asked at the baseline measurement moment (m0).

The second variable concerned risk perception [17], and was measured asking for the women's own risk estimate of developing breast cancer during life in terms of "1 in x" in combination with a percentage. The answer to this question was compared to the objective risk status as assigned by the MRISC study team, and recoded into underestimation, accurate and overestimation. This question was asked twice, namely two months before the first, as well as two months before the second surveillance appointment (m0 and m3, see design). The third variable addressed the degree of involvement in the breast cancer process of a sister [18]. This item was measured by means of a question having four answer-categories: completely involved; closely involved; involved at some distance; not at all involved. Based on the answer to this question the women were divided into two groups: 1. completely or closely involved and 2. involved at some distance, not at all involved or not having a sister diagnosed with breast cancer.

As a fourth factor that could be associated with psychological distress during the surveillance process we considered the type of examination at the surveillance appointment. This appointment either consisted of solely physical examination or of physical examination in combination with scheduled mammography and MRI-scan. For organizational reasons these latter imaging examinations could take place on a separate day.

Design

This study is part of a larger observational study [15] consisting of 6 assessments around two consecutive biannual surveillance appointments in the clinic during a breast cancer screening programme. Data were collected between January 2001 and May 2003. The assessments were performed on the following moments: two months prior to a surveillance visit (twice, m^0 and m^3), the day of the surveillance visit (twice, m1 and m4) and one to four weeks after the surveillance visit (twice, m2 and m5). The assessments m2 and m5 were planned one week after the clinic visit in case of solely physical examination, and four weeks after an appointment consisting of physical examination in combination with imaging examinations (mammography and MRI). For the analysis in this study four assessments were used, the two assessments performed on the day of the surveillance appointment (m1 and m4), and the two assessments administered after communication of the results of the surveillance moment (m2 and m5).

Procedure

The enrolment-procedure of the women in the psychological part of the study has been described elsewhere [16-18]. Before each assessment moment, women received their questionnaire at home together with a reply-paid envelope. Women who did not return their m2 or m5 questionnaire within 4 weeks were sent a reminder. Since the questionnaires on m1 and m4 had to be filled in on the day of the surveillance visit at the outpatient clinic, no reminders were sent when women did not return one of these questionnaires. The Medical Ethical Committee of the Erasmus MC in Rotterdam approved the study.

Statistical analyses

The characteristics of the study sample were tested for differences between the three risk categories by the method of one-way analysis of variance in case of continuous data and by the method of chi-square in case of ordinal data. These analyses were performed using SPPS 11.0. Missing values in the questionnaires Impact of Event Scale and Hospital Anxiety and Depression Scale were handled as follows: for women who filled in more than 75% of the questions per subscale a total score was computed, corrected for the total number of questions of the subscale. For women who filled in less than 75% of the questions per subscale no total score was computed. The total scores on the Impact of Event Scale and on the Hospital Anxiety and Depression Scale were used as a measure of breast cancer specific and general distress, respectively.

Differences between the four assessment moments as well as differences in the course of both types of psychological distress for the distinguished subgroups were tested for significance with the MIXED procedure of SAS 8.2. The significance levels, including the F-ratios were calculated for the different measurement moments, the three distinguished factors (excessive breast self-examination, risk perception, close involvement in the breast cancer process of a sister), and the interactions of the measurement moments and the three above-mentioned factors. The following confounding variables were entered into the analysis: risk category, number of years adhering to surveillance, educational level, having a partner, having children and age. It has to be noted that in the model about the impact of excessive breast self-examination age was not included as a confounding factor, because age was already incorporated into the variable excessive breast self-examination. This vulnerable subgroup namely existed of younger women (below the age of 40) who examined their breasts more frequent than recommended [16].

Table 1. Number of participants per measurement moment

Assessment moment	n (study sample) [1)]	missing	dropout since previous assessment	n (used in analyses)
m1*	357	12	3	342
m2*	354	12	9	333
m4*	329	18	13	298
m5*	295	13	1	281

[1)] Differences in n (study sample) per assessment moment is attributed to the fact that still a number of women has to be assessed; 357-295 = 61 women not yet completely assessed.

* m1 represents the day of the first surveillance appointment during this study; m2 represents 1 to 4 weeks after this first appointment; m4 the day of the second surveillance appointment during this study (6 months after the first); and m5 represents 1 to 4 weeks after this second appointment.

Results

Sample characteristics

The number of participants included in the analysis per measurement moment is shown in *Table 1*. The differences in the number of women participating per measurement moment can be attributed to the fact that inevitably there are missing questionnaires and that in the time that the statistical analyses were done not every woman was completely assessed yet. Characteristics of the participants, distinguished by risk category, are shown in *Table 2*. Most characteristics were not significantly different between the three risk categories, except for the period of adherence, which was lower in the group of mutation carriers. The 29 women who did not undergo a MRI-scan as part of the surveillance programme did not differ significantly from the other participants with respect to the demographic variables as presented in *Table 2*. The women who did not want to participate in the psychological follow-up study did not differ significantly from the women who did, with respect to age and risk status. In *Table 3* the classification of the women into the different subgroups reporting higher psychological distress at baseline is given. Breast cancer risk perception differed significantly between the three risk categories on both the occasions of measurement. In *Table 4* an overview of the type of examination on the two surveillance-moments (m1 and m4) is shown.

Table 2. Patient characteristics distinguished by risk category[1)]

Variable	Risk category 1 CLTR [2)] 60-85% (n = 42)	Risk category 2 CLTR 30-50% (n = 201)	Risk category 3 CLTR 15-30% (n = 114)	Total (n = 357)
Age mean (sd)	40.4 (10.2)	41.1 (8.8)	39.6 (8.3)	40.5 (8.8) range: 21-63 yr
Number of years of adherence mean (sd)*	3.1 (2.4)	5.6 (4.5)	5.6 (4.7)	5.3 (4.4) range: 0-3 yr
Educational level [3)]				
Lower level	7 (17%) [4)]	34 (17%)	21 (19%)	61 (17%)
Middle level	23 (56%)	106 (53%)	59 (53%)	188 (54%)
Higher level	11 (27%)	59 (30%)	32 (28%)	102 (29%)
Having a partner (yes)	38 (95%)	173 (87%)	97 (87%)	308 (88%)
Having children (yes)	26 (63%)	147 (74%)	79 (71%)	252 (72%)

[1)] The numbers may vary due to missing values
[2)] CLTR = cumulative life time risk
[3)] Lower level consists of primary or lower vocational education; medium level included lower or higher general secondary education or intermediate vocational education; higher level included higher vocational education or (pre-)university.
[4)] Percentages indicate column percentages
* Significantly different between the three risk categories (two-tailed)

Table 3. Distribution into the identified subgroups reporting more psychological distress (at baseline)[1)]

Variable	Risk category 1 CLTR [2)] 60-85% (n = 42)	Risk category 2 CLTR 30-50%(n = 201)	Risk category 3 CLTR 15-30% (n = 114)	Total (n = 357)
Young hyper-vigilant breast self examiners	6 (15%) [3)]	10 (5%)	10 (9%)	26 (7%)
Others	35 (85%)	188 (95%)	102 (91%)	325 (93%)
Cognitive risk perception*				
Overestimators C1	--	18 (9%)	45 (42%)	63 (18%)
Accurate estimators C1	24 (58%)	86 (44%)	36 (33%)	146 (42%)
Underestimators C1	17 (42%)	92 (47%)	27 (25%)	136 (40%)
Overestimators C2	--	19 (11%)	42 (42%)	61 (20%)
Accurate estimators C2	18 (50%)	68 (39%)	27 (26%)	113 (36%)
Underestimators C2	18 (50%)	88 (50%)	32 (32%)	138 (44%)
Close involvement in BC process of a sister	11 (27%)	50 (25%)	33 (30%)	94 (27%)
Others	30 (73%)	148 (75%)	79 (70%)	257 (73%)

[1)] The numbers may vary due to missing values
[2)] CLTR = cumulative life time risk
[3)] Percentages indicate column percentages
NB: The number of women belonging to more than one of the abovementioned categories was as follows:
Belong to all three: n = 1
Belong to overestimators and excessive breast self examiners: n = 4
Belong to overestimators and closely involved in BC process of a sister: n = 19
Belong to excessive breast self examiners and closely involved in BC process of a sister: n = 3
* Significantly different between the three risk categories both for C1 (first surveillance appointment) and C2 (second surveillance appointment) (two-tailed)

Table 4. Type of examination on the two surveillance appointments (m1 and m4).

	m1 (n)*	m4 (n)
Physical examination only	196	188
Physical examination in combination with mammography and MRI scan**	160	159

* Due to missing values the numbers do not add up to 357
** For organisational reasons the MRI scan was not always performed on the day of the clinic appointment

Breast cancer specific distress

In *Table 5* the mean scores and standard errors on the Impact of Event Scale as a measure of breast cancer specific distress are displayed, for the total group as well as for the distinguished subgroups. The differences across time and/or several subgroups by means of F-values and p-values are given in *Table 6*.

Table 5. Psychological distress scores per measurement moment distinguished by subgroup

	Breast cancer specific distress mean* (s.e.)				General distress mean* (s.e.)			
	m1	m2	m4	m5	m1	m2	m4	m5
Total sample	9.6 (0.6)	7.3 (0.6)	8.1 (0.7)	7.5 (0.7)	7.9 (0.4)	6.8 (0.4)	7.3 (0.4)	6.6 (0.4)
Young excessive breast self examination								
Yes	12.9 (2.3)	14.3 (2.4)	10.5 (2.5)	10.4 (2.4)	9.2 (1.4)	7.5 (1.4)	8.1 (1.4)	6.3 (1.4)
No	9.3 (0.7)	6.7 (0.7)	7.9 (0.7)	7.3 (0.7)	7.8 (0.4)	6.7 (0.4)	7.2 (0.4)	6.6 (0.4)
Risk perception								
Underestimation	9.6 (0.9)	7.4 (0.9)	6.6 (0.9)	6.8 (0.9)	7.9 (0.5)	7.0 (0.5)	7.0 (0.5)	6.4 (0.5)
Accurate estimation	9.3 (0.8)	6.5 (0.8)	7.6 (0.9)	7.2 (0.9)	7.9 (0.5)	6.3 (0.5)	7.0 (0.5)	6.5 (0.5)
Overestimation	10.2 (1.2)	8.8 (1.2)	12.9 (1.2)	9.9 (1.2)	7.9 (0.6)	7.5 (0.6)	8.7 (0.7)	7.3 (0.7)
Closely involved in sister's BC process								
Yes	10.1 (1.3)	8.4 (1.3)	9.3 (1.3)	8.7 (1.3)	7.9 (0.7)	7.1 (0.7)	6.9 (0.7)	7.1 (0.7)
No	9.4 (0.8)	6.9 (0.8)	7.7 (0.8)	7.1 (0.8)	7.9 (0.4)	6.7 (0.4)	7.5 (0.4)	6.4 (0.4)
Imaging examination on the surveillance visit								
Yes	10.6 (0.8)	8.0 (0.8)	8.9 (0.9)	7.9 (0.9)	8.3 (0.5)	7.1 (0.5)	7.6 (0.5)	6.3 (0.5)
No	8.7 (0.8)	6.6 (0.8)	7.4 (0.8)	7.2 (0.9)	7.6 (0.4)	6.6 (0.4)	7.0 (0.4)	6.8 (0.4)

* Means were adjusted for risk category, number of years adhering to surveillance, educational level, having a partner, having children and age; s.e. = standard error of the mean

Table 6. Differences in course of breast cancer specific and general distress for the total sample and the different subgroups*

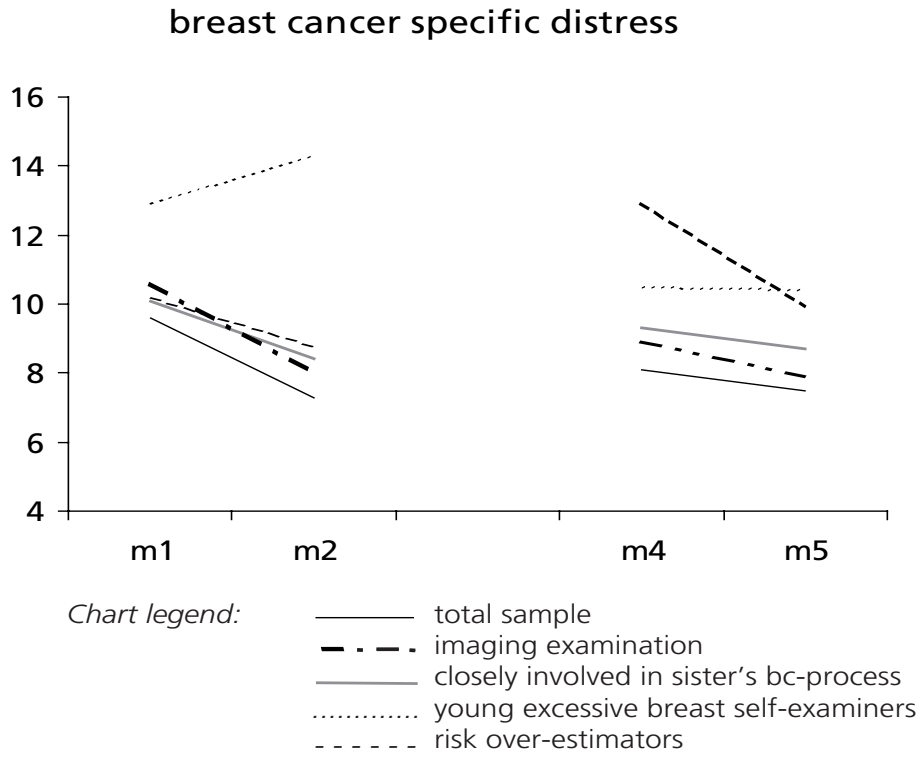
	Breast cancer specific distress		General distress	
	F	p-value <	F	p-value <
Total sample				
m1-m2	20.38	0.00	18.54	0.00
m4-m5	1.28	0.26	6.92	0.01
(m1-m2)-(m4-m5)	5.16	0.02	1.11	0.29
Excessive breast self examiners versus others				
m1-m2	4.12	0.04	0.44	0.51
m4-m5	0.05	0.82	1.24	0.27
(m1-m2)-(m4-m5)	1.45	0.23	0.13	0.72
Accurate- and under-estimators versus over-estimators of breast cancer risk				
m1-m2 (under-. vs over-estimators)	0.35	0.55	0.52	0.47
m1-m2 (accurate-. vs over-estimators)	0.98	0.32	2.58	0.11
m4-m5 (under- vs overestimators)	4.47	0.03	1.13	0.29
m4-m5 (accurate- vs over-estimators)	2.87	0.09	1.13	0.29
(m1-m2)-(m4-m5)(under- vs over-estimators)	3.73	0.05	1.59	0.21
(m1-m2)-(m4-m5)(accurate- vs over-estimators)	3.67	0.06	3.49	0.06
Closely involved in BC process of a sister versus others				
m1-m2	0.55	0.46	0.79	0.38
m4-m5	0.00	0.99	3.88	0.05
(m1-m2)-(m4-m5)	0.27	0.61	0.66	0.42
Mammography/MRI imaging versus physical examination only				
m1-m2	0.23	0.63	0.18	0.67
m4-m5	0.76	0.38	2.96	0.09
(m1-m2)-(m4-m5)	0.09	0.76	0.92	0.34

* Analyses were adjusted for risk category, number of years adhering to surveillance, educational level, having a partner, having children and age

In *Figure 1*, the courses of breast cancer specific distress around both surveillance appointments are shown for the total sample and for each of the examined subgroups. For the total group breast cancer specific distress was higher before the surveillance appointments, and dropped thereafter. The difference in breast cancer specific distress before and after the control visit was statistically significant for the first surveillance appointment only (m1 - m2) ($F = 20.38$, $p < 0.00$). When investigating the course of distress around both surveillance appointments, the slope was significantly different between the first and the second appointment, indicating a higher distress level before the first appointment as compared to the second appointment ($F = 5.16$, $p < 0.02$) (see also *Figure 1)*. Also, excessive breast self examiners showed an increased level of distress as compared to the others, which does not decrease after the surveillance appointment (as compared to the others *(Table 5)*. The course of breast cancer specific distress in younger breast self examiners differed from the other women around the first surveillance appointment. The first group reported significantly higher breast cancer specific distress both before and after the appointment while the others had a lower level of distress before the clinic visit that decreased further after the appointment ($F = 4.12$, $p < 0.04$) *(Table 5/6, Figure 1)*.

The course of breast cancer specific distress around the second surveillance appointment did not differ for the excessive self-examiners versus the others, but the degree of breast cancer distress remained higher in the group over-examiners (ns).

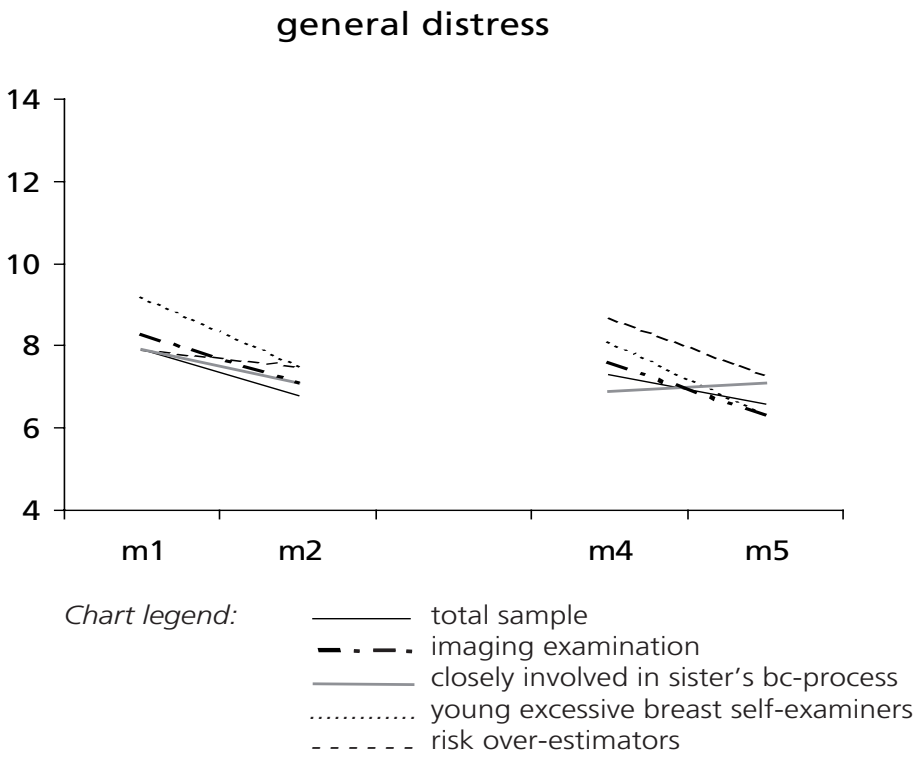
Figure 1. The course of breast cancer specific distress for the total sample and the different subgroups around two successive surveillance appointments



Regarding the relation with breast cancer risk perception, over-estimators have an increased level of distress as compared to the under-estimators at all the assessment moments, but overall the level of distress dropped after the visits. This decrease was not found for under-estimators at the second surveillance visit, but their pre-visit distress level was already low *(Table 5)*. With regard to the course of distress, we found significant differences around the second surveillance appointment between under- and over-estimators ($F = 4.47$, $p < 0.03$) *(Table 6)*. The latter group reported significantly higher breast cancer specific distress, particularly on the day of the second clinic appointment. The course of the distress for both groups also differed significantly from the course around the first appointment in this study ($F = 3.73$, $p < 0.05$). The risk over-estimators showed a fairly steep decrease in distress after the second surveillance appointment, which was a result of the higher distress they displayed on the day of this second surveillance appointment.

Women who have been involved in the breast cancer process of a sister showed higher levels of breast cancer specific distress in comparison with the other women. However, we did not find any significant impact or difference in BC specific distress around the control visits in relation to being involved in the BC process of a sister. Similarly, there were no significant differences between the courses of distress with regard to imaging examinations.

Figure 2. The course of general distress for the total sample and the different subgroups around two successive surveillance appointments



General distress

Data on the intensity and the course of general distress for the total sample, as well as for the different subgroups, are shown in *Tables 5 and 6 and in Figure 2*. For the total group, general distress significantly decreased after both appointments ($F = 18.54$, $P < 0.00$; and $F = 6.92$, $p < 0.01$, respectively) *(Table 5/6)*. Further, the course of general distress around both visits did not significantly differ from each other *(Table 6, Figure 2)*. The only significant difference further observed concerned the women who were closely involved in the breast cancer process of a sister. After the second surveillance appointment, these women reported more general distress than women who were not involved in the breast cancer process of a sister ($F = 3.88$, $p < 0.05$) *(Table 6)*.

Discussion

In general

In this study we investigated the course of psychological distress around two successive, biannual surveillance appointments in a substantial group of women being at increased risk of hereditary breast cancer. The main result of our study was that for the total study sample psychological distress remained within normal ranges during the surveillance programme. Further, both types of distress, breast cancer specific and general, decreased significantly after a surveillance appointment, with the exception for breast cancer specific distress after the second appointment. Remarkably, the fairly steep decrease of breast cancer specific distress after the first measured surveillance appointment appeared to result from the relatively high breast cancer specific distress-score on the day of the clinic appointment (as compared to the lower score on the day of the second assessed visit) *(see Figure 1)*. This observation suggests an effect of administering emotionally upsetting questionnaires on a probably emotionally upsetting moment (i.e. the threat of being diagnosed with an abnormality or breast cancer later that same day). Inspection of the course of general distress indicates that there is a significant decrease in distress after both clinic visits, showing a similar slope for the first and second visit. Thus, it appears that the possible stress inducing effect of administering a questionnaire is limited to questions about breast cancer rather than questions about general well being.

The pre-visit levels of breast cancer specific distress before the second surveillance appointment were considerably lower than before the first surveillance visit, whereas the post-screening levels were similar after both appointments. We hypothesize that the women prepare themselves to face possibly emotionally upsetting questions about breast cancer in combination with an actual confrontation with breast cancer specific cues. According to the courses of both general and breast cancer specific distress as shown in *Figures 1 and 2* there is reason to assume that the regular surveillance appointments reassure the women, since almost every line depicted in these figures is decreasing, though not always significantly. Further, a higher level of distress at the day of the surveillance appointment is in fact understandable. First, the distress may be provoked by the actual threat that an abnormality or breast cancer can be diagnosed. In addition, higher levels of psychological distress may be caused by a lack of control about health when undergoing an examination in the cancer clinic. Moreover, our institute may remind the women of their (close) relatives, who learned their breast cancer diagnosis, were treated, hospitalised, or even died in this clinic. On the other hand elevated distress levels may motivate the women to maintain their need for reassurance and safeguard their participation in a surveillance programme [25].

Vulnerable subgroups

In line with earlier studies [16,17,26,27] we found that with regard to breast cancer specific distress the younger excessive breast self-examiners and the breast cancer risk over-estimators appeared to be more vulnerable than the other participating women. Around the first measured visit in this study, the excessive breast self-examiners reported higher breast cancer specific distress, and around the second appointment the risk over-estimators did (in comparison with women underestimating their breast cancer risk). Moreover, women who were closely involved in the breast cancer process of a sister reported higher general distress after the second appointment (as compared to women not being involved in the BC process of a sister). The observation that excessive breast self-examiners and risk over-estimators reported higher breast cancer specific distress scores during the surveillance process is not entirely surprising as both groups of women were preoccupied by the fear to get breast cancer. With respect to our data, it is noteworthy to realize that 125 women of the total sample belonged to at least one subgroup, which means that at least 35% of the women in our study sample might be considered more vulnerable to psychological distress [16-18].

The observations from our study that young excessive breast self-examiners differed significantly from the remaining women around the first measured surveillance visit and the risk over-estimators did around the second surveillance visit cannot be explained clear-cut. Further studies should focus on the identification more specifically of the determinants for increased distress, i.e. young excessive examiners, over-estimators, and women involved in the breast cancer process of a sister.

In addition, we want to underscore that the women participating in this study not only represent a unique, but also perhaps also a selective group of women. Although in the analyses we adjusted for the period of adherence to regular surveillance, we cannot ignore that these women adhered to breast cancer surveillance for a mean of 5½ years, with a range from first- or second time attendees to adhering for over 10 years. Thus, for a substantial part of these women, the surveillance appointments have become a routine check-up, and we assume that over the years the women probably have found a useful way for themselves of dealing with their high-risk status as well as the regular surveillance appointments at the clinic. Also of importance is the fact that these women participate in a surveillance programme at a Family Cancer Clinic, intending to provide surveillance for all relevant family members. In practice, this means that women may have a feeling of social support from their relatives with the same experiences regarding surveillance. The experience of clinicians and interviews with a random subgroup of study participants led us to conclude that women feel distressed when coming to the clinic appointment. However, the reassurance afterwards is of most importance, after which most women indicate to immediately "go on with their lives" and return to daily activities and hassles. We realize that a longer follow-up of these women is warranted in order to study the course of psychological distress around further surveillance appointments.

Clinical implications

There has been some debate on how extensive and how customary additional psychological support should be offered. Coyne et al. have underlined that the mental health issues may be overemphasized, since in a lot of studies regarding psychological distress in high-risk women the results do not reach clinical significance [28-30]. Esplen et al. (2004) provided data about favourable effects of supportive group therapy for women with BRCA1/2 mutations, although the true effect can only be demonstrated using a randomised controlled study design [31]. In the present study, the mean distress scores were not indicative of persevering psychological distress. This suggests that most women in the surveillance process do not need extensive psychological treatment. Moreover, the elevated distress scores that we observed may very well be analogous to distress levels of women randomly drawn out of a primary care waiting room. However, the observed associations between subgroups that are more vulnerable and distress in this rather large study group should not be discarded. Consequently, some suggestions for providing additional support for these women can be given. We suggest that physicians just directly ask for breast self check more than once a week, risk estimation, and involvement in a sister's cancer process. Another approach would be the use of a one-page questionnaire with regard to the specific issues to be completed by the women. We will develop such a questionnaire as part of a forthcoming intervention study. With regard to the need of specific professional attention for the identified vulnerable subgroups we suggest that the young excessive breast self-examiners might benefit from additional psychological counselling to learn to better cope with their fear. The kind of counselling will be dependent on the dynamics of the fear, the learning capacities of the woman, and her willingness to have professional support. The risk over-estimators may be offered additional genetic counselling to explore why they overestimate their risk. If relevant, additional psychological consultation may be considered.

In view of our earlier results showing that besides the cognitive representation of one's own breast cancer risk an affective component of risk perception also has to be considered as an important indicator of psychological distress, it is of importance to pay attention to this component as well [17]. The women who are closely involved in their sister's cancer process may benefit from general psychological support to learn to adequately manage this type of distress.

Limitations of the study

Because this study was conducted in a clinical practice there was a variation in the intervals between having the examination in the clinic and receiving the results of the examination and thus in the intervals of collecting our data. In case of a physical examination the interval between m1 and m2, or m4 and m5 was one week, and in case of having additional imaging examination this interval was 4 weeks. In the analyses conducted in this study we did not consider these intervals as being different from each other, simply because our point of interest was the level of psychological distress after receiving the results. Another comment concerns the number of statistical analyses. In light of the phenomenon of multiple testing it would have been more appropriate to fix the p-value at 0.01 (two sided). However, we applied a p-value at 0.05 (two sided) because this study was merely an exploration of the course of distress.

In conclusion: we found that breast cancer surveillance in a group of high-risk women does not induce pathological distress over time, and that distress decreases after the control visits. Further, the earlier identified vulnerable subgroups score higher with respect to both breast cancer and general distress during the surveillance programme, and notably risk over-estimators do not show a decrease of distress after the control visit. Our findings implicate that it is worthwhile to discuss extra support with the identified more vulnerable women, focussing on their own distress determinants. It should be further investigated whether this is beneficial on the long run.

Conflict of Interest Statement
None declared

References

1. Vasen HF, Haites NE, Evans DG, et al: Current policies for surveillance and management in women at risk of breast and ovarian cancer: a survey among 16 European family cancer clinics. European Familial Breast Cancer Collaborative Group. Eur J Cancer 34:1922-6., 1998
2. Kash KM, Holland JC, Halper MS, et al: Psychological distress and surveillance behaviors of women with a family history of breast cancer. J Natl Cancer Inst 84:24-30., 1992
3. Lerman C, Schwartz M: Adherence and psychological adjustment among women at high risk for breast cancer. Breast Cancer Res Treat 28:145-55., 1993
4. Lloyd S, Watson M, Waites B, et al: Familial breast cancer: a controlled study of risk perception, psychological morbidity and health beliefs in women attending for genetic counselling. Br J Cancer 74:482-7., 1996
5. Zakowski SG, Valdimarsdottir HB, Bovbjerg DH, et al: Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer. Ann Behav Med 19:362-9., 1997
6. Valdimarsdottir HB, Bovbjerg D, Kash K, Holland JC, Osborne MP, Miller GM: Psychological distress in women with a familial risk of breast cancer. Psycho-oncology 4:133-141, 1995
7. Lerman C, Daly M, Sands C, et al: Mammography adherence and psychological distress among women at risk for breast cancer. J Natl Cancer Inst 85:1074-80., 1993
8. Brain K, Norman P, Gray J, et al: Anxiety and adherence to breast self-examination in women with a family history of breast cancer. Psychosom Med 61:181-7., 1999
9. McCaul KD, Branstetter AD, Schroeder DM, et al: What is the relationship between breast cancer risk and mammography screening? A meta-analytic review. Health Psychol 15:423-9., 1996
10. Gilbert FJ, Cordiner CM, Affleck IR, et al: 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., 1998
11. Scaf-Klomp W, Sanderman R, van de Wiel HB, et al: Distressed or relieved? Psychological side effects of breast cancer screening in The Netherlands. J Epidemiol Community Health 51:705-10, 1997
12. Gagnon P, Massie MJ, Kash KM, et al: Perception of breast cancer risk and psychological distress in women attending a surveillance program. Psycho-Oncology 5:259-269, 1996
13. Rijnsburger AJ, Essink-Bot ML, van Dooren S, et al: Impact of screening for breast cancer in high-risk women on health-related quality of life. Br J Cancer 91:69-76, 2004
14. Kriege M, Brekelmans CT, Boetes C, et al: MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). Fam Cancer 1:163-8, 2001
15. Kriege M, Brekelmans CT, Boetes C, et al: Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427-37, 2004
16. van Dooren S, Rijnsburger A, Seynaeve C, et al: Psychological distress and breast self-examination frequency in women at increased risk for hereditary or familial breast cancer. Community Genetics 6:235-241, 2003
17. Van Dooren S, Rijnsburger AJ, Seynaeve C, et al: Psychological distress in women at increased risk for breast cancer: the role of risk perception. Eur J Cancer 40:2056-63, 2004
18. van Dooren S, Seynaeve C, Rijnsburger AJ, et al: The impact of having relatives affected with breast cancer on psychological distress in women at increased risk for hereditary breast cancer. Breast Cancer Res Treat 89:75-80, 2005
19. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 73:643-51., 1994
20. Brekelmans CT, Seynaeve C, Bartels CC, et al: Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol 19:924-30., 2001
21. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209-18., 1979
22. Neal LA, Busuttil W, Rollins J, et al: Convergent validity of measures of post-traumatic stress disorder in a mixed military and civilian population. J Trauma Stress 7:447-55, 1994
23. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70., 1983
24. Hopwood P, Howell A, Maguire P: Screening for psychiatric morbidity in patients with advanced breast cancer: validation of two self-report questionnaires. Br J Cancer 64:353-6., 1991
25. Lerman C, Trock B, Rimer BK, et al: Psychological and behavioral implications of abnormal mammograms. Ann Intern Med 114:657-61., 1991
26. Hopwood P, Shenton A, Lalloo F, et al: Risk perception and cancer worry: an exploratory study of the impact of genetic risk counselling in women with a family history of breast cancer. J Med Genet 38:139., 2001
27. Meiser B, Butow P.; Schnieden, V.: Psychological adjustment of women at increased risk of developing hereditary breast cancer. Psychology, Health and Medicine 5:377-389, 2000
28. Coyne JC, Benazon NR, Gaba CG, et al: Distress and psychiatric morbidity among women from high-risk breast and ovarian cancer families. J Consult Clin Psychol 68:864-74, 2000
29. Coyne JC, Kruus L, Kagee A, et al: Benign mental health consequences of screening for mutations of BRCA1/BRCA2. Am J Med Genet 107:346-9, 2002
30. Coyne JC, Kruus L, Racioppo M, et al: What do ratings of cancer-specific distress mean among women at high risk of breast and ovarian cancer? Am J Med Genet A 116:222-8, 2003
31. Esplen MJ, Hunter J, Leszcz M, et al: A multicenter study of supportive-expressive group therapy for women with BRCA1/BRCA2 mutations. Cancer 101:2327-40, 2004

Chapter 7

Predicting distress in women at risk of developing hereditary breast cancer

Submitted

Van Dooren S, Duivenvoorden HJ, Seynaeve C, Rijnsburger AJ, Bartels CCM, Klijn JGM, Tibben A

Abstract

In order to tailor psychological support for women at risk for hereditary breast cancer it would be helpful to have a tool to identify psychologically vulnerable women. The objective of this study was to assess the predictive qualities of relevant variables with respect to experiencing psychological distress during a breast cancer surveillance programme in women at increased risk of breast cancer. In 270 high-risk women psychological distress was measured with the Impact of Event Scale, and the Hospital Anxiety and Depression Scale at different moments during the surveillance programme. Predictor variables were: demographics, risk perception, breast self-examination frequency, being closely involved in a sister's breast cancer process and different coping styles as measured by the Utrecht Coping List. In addition, the baseline measurements of the psychological distress variables were used as predictors. The corresponding baseline variable scores best predicted psychological distress variables across time. Furthermore, coping through expressing emotions, seeking social support, and having comforting thoughts were identified as positive coping strategies, as opposed to passive coping and a palliative reaction pattern, which were found to be negative coping strategies. The MR-squared for the four distress variables varied from 0.37 to 0.63. Cross-validation showed the stability of the model performance.

Introduction

Regular surveillance is offered to women at increased risk of developing hereditary breast cancer. This applies for identified BRCA1/2 mutation carriers, 50% risk carriers from BRCA1/2 mutation families (not opting for presymptomatic genetic testing), and women from hereditary breast/ovarian cancer families in which a BRCA1/2 mutation is not identified or genetic testing is not performed. While BRCA1/2 mutation carriers may opt for prophylactic mastectomy as the most effective risk reducing strategy, in general this option is not offered to women from non-BRCA1/2 families (hereditary/familial breast cancer families in which no BRCA1/2 mutation is identified). At this moment, genetic testing allows for the identification of a BRCA1/2 mutation in only approximately one quarter of the assumed genetically susceptible families [1]. Further, not all of the unaffected BRCA1/2 mutation carriers choose for the option of prophylactic mastectomy. At the Rotterdam Family Cancer Clinic in the Netherlands the uptake of prophylactic mastectomy ranges between 35% (affected women) [2] and 51% (unaffected women) [3], which leaves a large group of identified mutation carriers eligible for regular surveillance. However, the majority of high-risk women belong to non-BRCA1/2 families, this implies that the group of women eligible for regular surveillance is a relevantly sized group.

It is known that women at increased risk of developing breast cancer may experience elevated levels of psychological distress [4-8], that in some cases can even be rather severe. Kash et al. (1992) reported that 27% of the studied high-risk women reported psychological distress levels indicating the need for professional counselling in some of these women [9]. However, data on the topic are varied, having been obtained from different study populations and different research questions. From recent reviews of the literature conclusions are that the levels of distress are comparable with distress measures in community samples [10], except for the levels of breast cancer specific worries [11]. Because data on psychological distress in this group of women are varied, and given the rather large group of women who adhere to regular breast cancer surveillance, it is of clinical interest to identify, at an early stage, those women who may experience adjustment problems while adhering to the surveillance programme. Several studies have focussed on the identification of variables that are associated with the uptake of mammography and/or performance of breast self-examination [4,6,7,9,12-16].

A high perception of breast cancer susceptibility and high levels of anxiety have been reported to be associated with the uptake of surveillance, although the reports are inconsistent, some reporting a positive association between distress and mammography utilization [15,16], and others reporting a negative association [6,9,12-14].
So far, predicting psychological distress in women at increased risk of hereditary breast cancer has received rather little attention. Zakowski et al. (1997) examined the impact of the death of a parent due to cancer on psychological distress [8], and showed that women whose parent(s) had died of cancer displayed the highest levels of breast cancer specific distress. However, limitations of this study were the small sample size (n=46), and the fact that only the mentioned one variable was investigated.

As part of the Dutch national MRISC-study (Magnetic Resonance Imaging Screening), which evaluates the efficacy of MRI as compared to mammography in women at increased risk of hereditary breast cancer (i.e. at least 15% lifetime risk) [17,18], the psychological sub-study aims to evaluate the psychological consequences of adherence to breast cancer surveillance. In previous analyses, we identified several subgroups of women who were vulnerable for psychological distress [19-22]. The objective of this study was to investigate which variables were predictors for psychological distress, and at which time points during the surveillance programme were they relevant.

Material and Methods

Participants

The psychological follow-up study enrolled a total of 357 women at increased risk for hereditary breast cancer who adhered to regular breast cancer surveillance. Eligibility criteria were: no history of breast cancer and having a cumulative lifetime risk (CLTR) of developing breast cancer of at least 15%, based on the risk tables by Claus et al. [23]. Due to dropouts and missing values in the questionnaires, the number of women included in the analysis in the current study comprised 270, which is 77% of the total group. The Medical Ethical Committee review board of the Erasmus MC in Rotterdam approved of the study.

Measures

Predictive factors of psychological distress

The following factors were tested for predictive qualities with respect to psychological distress: demographic variables, breast self-examination frequency, breast cancer risk perception (cognitive), being closely involved in the breast cancer process of a sister, and coping style. These variables have been previously described and are therefore only briefly discussed below.

Demographic variables

Age and the duration of adherence to regular surveillance were measured in years. Educational level was divided into lower, middle and higher level. Having a relationship and having children were dichotomised into yes and no. The breast cancer risk category was either 1 (Cumulative Lifetime Risk (CLTR) 60-85%), 2 (CLTR 30-50%), or 3 (CLTR 15-30%), as women were assigned to one of these categories by the MRISC-study team, as has been described earlier [21].

Frequency of breast self-examination (BSE)
BSE frequency was measured with the question: Do you perform breast self-examination regularly in order to detect possible anomalies? The answer possibilities were recoded into four categories: 1. never, 2. once every 3, 6, or 12 months, 3. once a month, and 4. at least once a week.

Breast cancer risk perception
Cognitive risk perception was measured asking for the women's perception of her own risk estimate of getting breast cancer during life in terms of '1 in x' in combination with percentages. The answer to this question was compared to the objective risk status (as assessed by the MRISC study team) and recoded into underestimation, accurate estimation and overestimation.

Involvement in the breast cancer process of a sister
First, the women were asked whether they had a sister diagnosed with breast cancer and, if so, whether they were or had been involved in the breast cancer process of their sister. The answer categories were recoded into: 1. completely or closely involved and 2. involved at some distance, not at all involved or not having a sister diagnosed with breast cancer at all.

Coping style
The Utrecht Coping List (UCL) [24] was administered once at baseline (m0) to determine the coping style of the women. This 47-item questionnaire measures seven different coping styles, with a 4-point scaled response format ranging from 1 (hardly ever or never), 2 (sometimes), 3 (often) to 4 (very often or always). The seven assessed coping styles are: active approach, palliative reaction pattern, avoiding or awaiting the problem, seeking social support, passive coping, coping through emotional expression, and having comforting thoughts.

Outcome variables
The outcome variables were the following psychological distress measures: intrusion, avoidance, anxiety, and depression. Intrusion and avoidance were measured with the Impact of Event Scale [25], anxiety and depression with the Hospital Anxiety and Depression Scale [26]. Both scales have been described in more detail elsewhere [19,21]. We considered the m1-scores of each outcome variable (see Design) as candidate predictive factors for the analyses in this study.

Design and procedure
The psychological observational study consisted of 6 assessments during a breast cancer surveillance programme, and these assessments were scheduled around two successive surveillance appointments between January 2001 and May 2003. The assessment moments took place two months prior to a surveillance appointment (twice), the day of the surveillance appointment (twice) and one to four weeks after the surveillance appointment (twice). In this analysis the outcome variables of four assessment moments were used, namely: the measurements on the day of the surveillance appointment (m1 and m4), and the assessments twice after the appointment (m2 and m5). The data of the measurement moment m1 were used as the baseline assessment for this analysis. This way it is possible to predict psychological distress from the moment the women are at the clinic for their visit. The enrolment procedure of the psychological follow-up study has been described in more detail elsewhere [19-21].

Statistical analysis

As a first step, all selected variables (including the demographic variables) were tested for their predictive quality for each of the four outcome measures (intrusion, avoidance, anxiety, and depression) at each of the different measurement moments (m2, m4, and m5). For each predicted moment the four m1-outcome variables were used as candidate predictive factors as well. This means that for example for predicting intrusion on m2, m4 and m5, not just m1-intrusion but also m1-avoidance, m1-anxiety and m1-depression were included as candidate predictive factors.

The analysis procedure for each separate outcome variable was as follows: every predictive factor being significantly associated with an outcome variable on at least one of the measurement moments was used at every measurement moment. For example, if age was significantly associated with intrusion on m4, though not on m2 and m5, this variable was nevertheless tested for predictive quality on m2 and m5 for the outcome variable intrusion. As an inclusion-criterion the p-value was set at 0.05 (two-tailed) and the exclusion-criterion at 0.10. Both standardized and unstandardized regression coefficients were calculated. In case of a positive t-value, the association was considered to be positive, in case of a negative t-value, the association was considered negative. The following measures were used for checking the model assumptions of multiple regression analysis: inspection of the histogram of the outcome variables, the normal probability plot, the scatterplot of adjusted predicted values against the studentized deleted residuals, and Cook's distance.

As a measure of predictive performance of the model the explained variance (MR^2) for each outcome variable at each measurement moment was used, which therefore resulted in 4 outcome variables multiplied with 3 predicted measurement moments, equaling twelve predictive performance indices. To test the stability of these estimated predictive performances, the results were cross-validated. We conducted a fourfold crossvalidation by splitting the total sample in four subgroups being as much as possible of equal size (i.e. A, B, C, and D, respectively). One of these subgroups functioned as validation-sample while the other three functioned as training sample, resulting in the procedure as described in *Box 1*. For each of these validation samples the MR^2 was established, they were averaged and compared with the MR^2's as found in the total sample. The analyses were carried out using the Statistical Package for the Social Sciences (SPSS 11), and MPlus.

Box 1. Cross-validation procedure

Training sample		Validation sample
A-B-C	→	D
A-B-D	→	C
A-C-D	→	B
B-C-D	→	A

Results

Sample characteristics

The characteristics of the 270 participants included in the analyses of this study are presented in *Table 1*, as well as the characteristics of the 87 participants who were not included because of dropout or missing values on the outcome variables. Possible differences between the 270 participants included in the analyses and the 87 excluded participants were tested for significance, and it appeared that the 87 participants not included in the analyses were significantly younger and significantly less involved in the breast cancer process of their sister. The women included in the analyses had a mean age of 41 years. On average the number of years of adherence to breast cancer surveillance was 5.5 years. The majority of the women (57%) belonged to risk category 2, twelve percent were identified BRCA1/2 mutation carriers and the remaining 83 women (31%) had a CLTR between 15 and 30% (risk category 3). Further, the majority of the sample had a partner, had children and had at least a middle level education. Nineteen percent of the sample overestimated their risk of developing breast cancer, thirty percent was closely involved in the breast cancer process of a sister, and fifteen percent excessively examined their breasts. In *Table 2* an overview is given of the mean scores per psychological distress outcome variable at each measurement moment. On average, according to norm scores, the mean scores remained within normal limits over the study period.

Table 1. General characteristics of the total study population (numbers may vary due to missings)

Demographics	n=270	n=87
Age: mean (sd)	41.2 (8.5)	38.3 (9.5)*
Number of years of adherence: mean (sd)	5.5 (4.5)	4.6 (4.1)
	n (%)	**n (%)**
Risk cat. 1 (CLTR 60-85%)	32 (12)	9 (10)
Risk cat. 2 (CLTR 30-50%)	155 (57)	47 (54)
Risk cat. 3 (CLTR 15-30%)	83 (31)	31 (36)
Having a relationship (yes)	236 (87)	68 (84)
Having children (yes)	198 (73)	53 (66)
Higher level education	78 (29)	22 (27)
Middle level education	142 (53)	49 (61)
Lower level education	50 (18)	10 (12)
Variables associated with distress		
Overestimation	50 (19)	13 (17)
Accurate estimation	108 (40)	38 (49)
Underestimation	109 (41)	27 (34)
Closely involved in BC-process of sister	80 (30)	14 (17)*
Never breast self examination	25 (9)	9 (11)
Once every 3/6/12 months breast self examination	49 (18)	16 (20)
Once a month breast self examination	155 (58)	44 (56)
At least once a week breast self examination	39 (15)	10 (13)
Coping styles	**mean (sd)**	**mean (sd)**
Active coping	18.86 (3.56)	19.06 (3.62)
Palliative reaction pattern	17.74 (3.33)	18.47 (3.37)
Avoiding	15.12 (3.05)	15.29 (3.09)
Seeking social support	14.23 (3.74)	14.29 (3.86)
Expressing emotions	6.08 (1.63)	6.32 (1.63)
Fostering reassuring thoughts	12.67 (2.49)	13.21 (2.64)
Passive coping	11.32 (2.97)	10.85 (2.64)

* significantly different between the two groups ($p<0.05$)

Table 2. Course of psychological variables: mean (sd), n=270

Outcome variable	m1	m2	m4	m5
Intrusion	4.9 (6.3)	4.0 (6.3)	4.4 (6.3)	3.9 (6.0)
Avoidance	4.7 (6.9)	3.3 (5.8)	3.5 (6.4)	3.3 (5.8)
Anxiety	5.4 (3.9)	4.5 (3.9)	4.9 (3.9)	4.2 (3.9)
Depression	2.6 (3.0)	2.5 (3.4)	2.5 (3.3)	2.4 (3.4)

Predictive factors for Intrusion

For each measurement moment, both unstandardized as well as standardized regression coefficients together with their t-values for intrusion were calculated (*see Table 3*). Variables with a significant predictive character for increased levels of intrusion on m2, m4 as well as m5 were: intrusion on the day of the first measured surveillance visit (t-values: 11.87, 10.64, and 10.27, respectively), overestimation of the own lifetime risk of developing breast cancer (t-values: 2.38, 4.74, and 2.42, respectively), and coping through a palliative reaction pattern (t-values: 2.66, 2.08, and 2.98, respectively). Furthermore, an increased level of avoidance on the day of the surveillance visit significantly predicted for more intrusion on the day of the successive surveillance visit (m4) (t-value: 4.10). Coping through expressing emotions significantly predicted for less intrusion on m4 (t-value: −3.05). Furthermore, there was a significant positive association between a passive coping style and intrusion on m4 (t-value: 2.66). Having comforting thoughts predicted for less intrusive feelings on m5 (t-value: −3.29).

Table 3. Predictive factors for Intrusion

Predictive factors	Intrusion m2			Intrusion m4			Intrusion m5		
	B	ß	t-value	B	ß	t-value	B	ß	t-value
Intrusion m1	.59	.61	11.87	0.47	0.47	10.64	0.49	0.52	10.27
Avoidance m1	- .01	-.01	-.16	0.19	0.21	4.10	0.01	0.01	0.18
Age	.02	.03	.95	0.07	0.09	2.93	0.04	0.06	1.58
Relationship	.19	.01	.31	1.04	0.06	1.93	0.44	0.03	0.76
Adherence	-.05	-.04	-.95	-0.03	-0.02	-0.59	-0.06	-0.05	-1.33
Overestimation	1.66	.11	2.38	2.94	0.19	4.74	1.78	0.12	2.42
Almost never BSE	.18	.01	.28	-0.97	-0.06	-1.73	0.42	0.03	0.68
BSE once a month	.04	.00	.06	-0.78	-0.06	-1.52	-0.48	-0.04	-0.82
Palliative reaction	.23	.14	2.66	0.16	0.09	2.08	0.27	0.17	2.98
Passive coping	.19	0.09	1.96	0.23	0.12	2.66	0.17	0.09	1.59
Expressing emotions	-.31	-.09	-1.91	-0.43	-0.12	-3.05	-0.34	-0.09	-1.98
Reassuring thoughts	-.07	-.03	-.59	-0.19	-0.09	-1.96	-0.39	-0.18	-3.29

B = unstandardized regression coefficient
ß = standardized regression coefficient (relative importance)

Predictive factors for Avoidance

Table 4 shows the relevance of the predictive variables for avoidance at the different measurement moments. The only predictive variable, which was consistent through time, was the level of avoidance on the day of the first measured surveillance visit (t-values: 9.81, 14.15, and 9.21, respectively). Avoidance on m2 was significantly predicted by the level of anxiety on m1 (t-value: 2.78). Additionally, avoidance at the second measured visit (m4) was either positively or negatively predicted by: overestimation of the risk of developing breast cancer (t-value: 4.08), seeking social support (t-value: −2.37), and expressing emotions (t-value: −2.63). Coping through a palliative reaction pattern resulted in higher avoidance levels on m5 (t-value: 3.01).

Table 4. Predictive factors for Avoidance

Predictive factors	Avoidance m2			Avoidance m4			Avoidance m5		
	B	ß	t-value	B	ß	t-value	B	ß	t-value
Avoidance T1	0.45	0.52	9.81	0.59	0.63	14.15	0.45	0.53	9.21
Anxiety T1	0.19	0.13	2.78	0.09	0.06	1.45	0.00	0.00	0.04
BSE once a month	-0.39	-0.04	-0.79	-0.34	-0.03	-0.73	-0.49	-0.04	-0.94
Risk overestimation	0.83	0.06	1.23	2.63	0.16	4.08	0.58	0.04	0.81
Palliative reaction	0.14	0.09	1.56	0.11	0.06	1.34	0.28	0.18	3.01
Seeking social support	-0.02	-0.01	-0.32	-0.12	-0.08	-2.37	-0.09	-0.06	-1.54
Passive coping	0.13	0.07	1.30	0.17	0.08	1.82	0.03	0.02	0.29
Expressing emotions	-0.24	-0.07	-1.49	-0.39	-0.10	-2.63	-0.18	-0.05	-1.06
Reassuring thoughts	-0.07	-0.04	-0.65	-0.13	-0.05	-1.20	-0.17	-0.08	-1.49

B = unstandardized regression coefficient
ß = standardized regression coefficient (relative importance)

Predictive factors for Anxiety

In *Table 5* the predictive models for anxiety at the different measurement moments are shown. A high level of anxiety on the day of the first measurement moment (m1) significantly predicted for high anxiety levels on all the subsequent measurement moments (t-values: 9.77, 12.59, and 10.39, respectively). Similarly, displaying a passive coping style significantly predicted for high anxiety levels on the subsequent measurement moments (t-values: 2.74, 3.38, and 2.35, respectively). A high level of depression on m1 was significantly and positively related to anxiety after the first surveillance visit (m2, t-value: 2.94). Finally, it seemed that a longer duration of adherence predicted for decreased levels of anxiety after the second measured appointment (m5, t-value: −2.72).

Predictive factors for Depression

Regarding depression, few predictive factors were identified, as is displayed in *Table 6*. Women reporting feelings of depression on the day of the first measured surveillance visit (m1) were significantly more likely to report feelings of depression on all of the subsequent measurement moments (t-values: 14.53, 10.31, and 11.86, respectively). Furthermore, a high level of anxiety on m1 significantly predicted for depressive feelings around the second control visit, both on m4 and m5 (t-values: 3.35, and 2.88, respectively). Women who reported having a relationship felt significantly less depressed after the first surveillance visit (t-value: −3.13).

Testing the stability of the predictive indices

To establish the robustness of the predictive factors as they were found in the analyses *(Tables 3 through 6)*, the method of cross validation was used as is described in the analysis section. In *Table 7* the explained variances of the predictive models before and after cross validation are shown. The predictive models as presented above showed substantial predictive qualities with MR^2 ranging between 0.37 and 0.63. The corresponding MR^2's after the cross validation did not appear different from the performance of the models before cross validation. This finding justifies the conclusion that there is no real shrinkage in predictive performances. When comparing the predictability of each measurement moment it seemed that on average the m4-moments had the highest MR^2's. When comparing the different outcome measures, anxiety and depression had on average the highest MR^2's.

Table 5. Predictive factors for Anxiety

Predictive factors	Anxiety m2			Anxiety m4			Anxiety m5		
	B	ß	t-value	B	ß	t-value	B	ß	t-value
Anxiety T1	0.19	0.54	9.77	0.63	0.63	12.59	0.56	0.58	10.39
Depression T1	0.52	0.15	2.94	0.08	0.06	1.42	0.11	0.09	1.73
Avoidance T1	0.03	0.05	1.22	0.03	0.06	1.62	0.03	0.06	1.32
Adherence	-0.02	-0.02	-0.64	-0.05	-0.06	-1.95	-0.08	-0.09	-2.72
Risk overestimation	0.58	0.06	1.4	0.68	0.07	1.74	0.39	0.04	0.95
Passive coping	0.14	0.11	2.74	0.16	0.13	3.38	0.13	0.11	2.35
Expressing emotions	-0.06	-0.03	-0.84	-0.12	-0.05	-1.67	0.02	0.00	0.22

B = unstandardized regression coefficient
ß = standardized regression coefficient (relative importance)

Table 6. Predictive factors for Depression

Predictive factors	Depression m2			Depression m4			Depression m5		
	B	ß	t-value	B	ß	t-value	B	ß	t-value
Depression T1	0.81	0.72	14.53	0.62	0.56	10.31	0.70	0.63	11.86
Anxiety T1	0.02	0.02	0.39	0.16	0.18	3.35	0.13	0.15	2.88
Relationship	-0.99	-0.09	-3.13	-0.57	-0.06	-1.67	0.15	0.02	0.42
Risk overestimation	0.60	0.07	1.75	0.37	0.04	0.98	0.33	0.04	0.91

B = unstandardized regression coefficient
ß = standardized regression coefficient (relative importance)

Table 7. Comparison of R-squared of the predictive models with the crossvalidated R-squared per outcome variable per measurement moment

	R-squared of the predictive model	R-squared of the crossvalidations*
Intrusion m2	0.51	0.50
Intrusion m4	0.63	0.57
Intrusion m5	0.44	0.39
Avoidance m2	0.46	0.45
Avoidance m4	0.59	0.61
Avoidance m5	0.37	0.36
Anxiety m2	0.54	0.54
Anxiety m4	0.61	0.63
Anxiety m5	0.54	0.53
Depression m2	0.58	0.58
Depression m4	0.49	0.50
Depression m5	0.54	0.55

* Since there were four crossvalidation samples, the found R-squareds were totaled and divided by four

Discussion

We have developed a predictive index for different psychological distress measures in a unique, large sample of women at increased risk for hereditary breast cancer, compliant with surveillance guidelines, at several moments during a surveillance programme. The identified predictive models proved stable, which justifies the conclusion that, since no real shrinkage of the explained variances occurred, the performances of the predictive models as presented in this article can be considered as substantial.

All psychological outcome measures studied (i.e. intrusion, avoidance, anxiety, and depression) were significantly predicted by their corresponding baseline-score, at the first measured surveillance visit (m1). Thus, it appears that, women reporting high levels of psychological distress on the day of the surveillance visit are significantly more likely to report similar feelings after the surveillance visit and further on during the surveillance programme. This suggests that it is not the surveillance procedure which causes psychological distress in women at increased risk for hereditary breast cancer, but more likely that specific personal features are responsible for increased levels of distress. This phenomenon is in accordance with the results of other predictive analyses. Van Oostrom et al. (2003) described that participants who reported higher levels of breast cancer related distress at baseline (i.e. shortly after blood sampling for genetic testing regarding a BRCA1/2 mutation) experienced higher levels 5 years later as well [27]. In a study conducted by Gritz et al. on the impact of genetic testing for HNPCC a similar effect was found. The baseline distress levels in their study significantly predicted the postdisclosure distress levels, regardless of mutation status [28].

From our data, it further appeared that the predictive qualities of the different analysed variables differed for the various distress measures. Understandably, feelings of anxiety diverge from those of depression. Also the two outcome measures of the Impact of Event Scale (intrusion and avoidance) represent different manifestations of breast cancer specific distress. A finding of importance was that for the outcome variables (except for depression) one or more of the different coping styles significantly predicted the scores.

Passive coping was associated with higher levels of intrusion and anxiety, and therefore seemed a less favourable coping style. This has also been found in another study of our group investigating the effects of prophylactic surgery on psychological distress (Bresser et al., personal communication). Another less favourable coping style that we observed was a palliative reaction pattern (seeking distraction, targeting at not being concerned with the problem), which was found to be associated with higher levels of intrusion and avoidance. At first sight this might seem inconsistent, since being able to distract yourself and not focus at your problems might be expected to have stress-reducing qualities. However, when one consciously has to concentrate on distracting oneself in order not to think about the problem, it probably makes the issue constantly present.

Fortunately, more helpful ways of coping were identified as well. Expression of emotions proved to be helpful in diminishing intrusive thoughts and avoidance behaviour. In addition, reassuring thoughts were helpful to conquer intrusive thoughts and decrease distress. Evidently, the need to avoid stressful disease-related situations was less when women sought social support. We conclude from our data that expression of emotions, having reassuring thoughts, and seeking social support may be strong, positive strategies to deal with the risk- or disease related distress. Pennebaker et al. (1990) found that verbalizing experiences, which occurs in social interactions, is an efficient way to organise events. Furthermore, expression of emotions by writing about deepest thoughts and emotions has been demonstrated to have health benefits as well. This expression of emotions can reflect two processes, the first is that of catharsis, the second view implies the facilitation of insight [29].

The performances of the predictive models were satisfying, though less than perfect. This might be attributed to the usually less than perfect reliabilities obtained by using questionnaires. For example, the reliability of the intrusion subscale at the first and second measurements moments (m1 and m2, respectively) were 0.85 and 0.80. Assuming that the assumptions of the classical test theory are not violated, the relationship between these two variables can reach maximally 0.70 (= 0.85*0.80). In the assumption that the prognostic index score also has a reliability of 0.85, then the correlation of this index and intrusion measured at m2 correspondingly can maximally be 0.70. In this study the performance of the prognostic variables in estimating the intrusion at m2 appeared to be 0.51 (without cross-validation). Hence, the actual performance would be in terms of explained variance (when corrected for the unreliabilities of the prognostic variables and the outcome variable) 0.73 (obtained by 0.51/0.70). However, the performance of the prognostic models when corrected for the unreliabilities of the different measurement instruments can be qualified as satisfactory. Finally, our findings suggest that the prognostic models can be applied for research objectives; while for clinical practice, however, the modelling has to be ameliorated with special attention to enhancement of the precision of the measurement instruments.

Our main conclusion is, that a woman's level of psychological distress at the moment of the biannual surveillance appointment in the clinic is best predictive for her psychological distress levels afterwards. Second, we conclude that someone's particular coping style may have a profound impact on the levels of psychological distress during the breast cancer surveillance programme. A passive way and a palliative way to address problems were associated with higher levels of psychological distress on the different assessment moments, while expressing emotions, seeking social support and being able to think about problems in a reassuring way were associated with decreased levels of psychological distress.
Furthermore, our findings suggest that the screening procedures themselves do not provoke persistent psychological distress, but particular personal features do so.

We think that our data are important for clinical practice because it indicates that an assessment regarding personal and psychological characteristics at the surveillance appointment at a family cancer clinic might provide relevant information concerning the vulnerability of a particular woman. Further elaboration of this type of assessment is warranted in order to identify the vulnerable women who might benefit from additional support.

In the meanwhile it is advised to be aware of the factors which are found in the predictive models, the degree of psychological distress at the surveillance visit, the positive and negative coping styles, overestimation of the personal breast cancer risk, as well as the earlier found factors, excessive breast self examination and being closely involved in the breast cancer process of a sister [19-22], although these last two factors did not emerge in the predictive models. The reason for this is that the combination of the selected variables predicted the outcome variables most optimally. However, this does not imply that these factors are not related to the experience of psychological distress in these women.

References

1. Verhoog LC, van den Ouweland AM, Berns E, et al: Large regional differences in the frequency of distinct BRCA1/BRCA2 mutations in 517 Dutch breast and/or ovarian cancer families. Eur J Cancer 37:2082-90, 2001
2. Meijers-Heijboer H, Brekelmans CT, Menke-Pluymers M, et al: Use of genetic testing and prophylactic mastectomy and oophorectomy in women with breast or ovarian cancer from families with a BRCA1 or BRCA2 mutation. J Clin Oncol 21:1675-81, 2003
3. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, et al: Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. Lancet 355:2015-20., 2000
4. Lerman C, Daly M, Sands C, et al: Mammography adherence and psychological distress among women at risk for breast cancer. J Natl Cancer Inst 85:1074-80., 1993
5. Lerman C, Schwartz M: Adherence and psychological adjustment among women at high risk for breast cancer. Breast Cancer Res Treat 28:145-55., 1993
6. Lerman C, Kash K, Stefanek M: Younger women at increased risk for breast cancer: perceived risk, psychological well-being, and surveillance behavior. J Natl Cancer Inst Monogr 16:171-6, 1994
7. Lloyd S, Watson M, Waites B, et al: Familial breast cancer: a controlled study of risk perception, psychological morbidity and health beliefs in women attending for genetic counselling. Br J Cancer 74:482-7., 1996
8. Zakowski SG, Valdimarsdottir HB, Bovbjerg DH, et al: Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer. Ann Behav Med 19:362-9., 1997
9. Kash KM, Holland JC, Halper MS, et al: Psychological distress and surveillance behaviors of women with a family history of breast cancer. J Natl Cancer Inst 84:24-30., 1992
10. Hay JL, Buckley TR, Ostroff JS: The role of cancer worry in cancer screening: a theoretical and empirical review of the literature. Psychooncology 14:517-34, 2005
11. Hopwood P: Psychosocial aspects of risk communication and mutation testing in familial breast-ovarian cancer. Curr Opin Oncol 17:340-4, 2005
12. Schwartz MD, Taylor KL, Willard KS: Prospective association between distress and mammography utilization among women with a family history of breast cancer. J Behav Med 26:105-17, 2003
13. Lerman C, Rimer B, Trock B, et al: Factors associated with repeat adherence to breast cancer screening. Prev Med 19:279-90., 1990
14. Schwartz M, Taylor K, Willard K, Siegel J, Lamdan R, Moran K.: Distress, personality, and mammography utilization among women with a family history of breast cancer. Health Psychology 18:327-332, 1999
15. McCaul K, Reid P, Martinson B: Does concern about breast cancer inhibit or promote breast cancer screening. Basic and Applied Social Psychology 18:183-194, 1996
16. Diefenbach MA, Miller SM, Daly MB: Specific worry about breast cancer predicts mammography use in women at risk for breast and ovarian cancer. Health Psychol 18:532-6, 1999
17. Kriege M, Brekelmans CT, Boetes C, et al: Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427-37, 2004
18. Kriege M, Brekelmans CT, Boetes C, et al: MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). Fam Cancer 1:163-8, 2001
19. van Dooren S, Rijnsburger A, Seynaeve C, et al: Psychological distress and breast self-examination frequency in women at increased risk for hereditary or familial breast cancer. Community Genetics 6:235-241, 2003
20. van Dooren S, Seynaeve C, Rijnsburger AJ, et al: The impact of having relatives affected with breast cancer on psychological distress in women at increased risk for hereditary breast cancer. Breast Cancer Res Treat 89:75-80, 2005
21. Van Dooren S, Rijnsburger AJ, Seynaeve C, et al: Psychological distress in women at increased risk for breast cancer: the role of risk perception. Eur J Cancer 40:2056-63, 2004
22. Pieterse K, van Dooren S, Seynaeve C, et al: Passive coping and psychological distress in women adhering to regular breast cancer surveillance. submitted

23. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 73:643-51., 1994
24. Schreurs P, van de Willige G, Brosschot JF: De Utrechtse Coping Lijst:UCL, Herziene handleiding (Utrecht Coping List). Swets & Zeitlinger: Lisse, the Netherlands, 1993
25. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209-18., 1979
26. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70., 1983
27. van Oostrom I, Meijers-Heijboer H, Lodder LN, et al: Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. J Clin Oncol 21:3867-74, 2003
28. Gritz ER, Peterson SK, Vernon SW, et al: Psychological impact of genetic testing for hereditary nonpolyposis colorectal cancer. J Clin Oncol 23:1902-10, 2005
29. Pennebaker JW, Colder M, Sharp LK: Accelerating the coping process. J Pers Soc Psychol 58:528-537, 1990

Chapter 8

Passive coping and psychological distress in women adhering to regular breast cancer surveillance

Submitted

Pieterse K, van Dooren S, Seynaeve C, Bartels CCM, Rijnsburger AJ, de Koning HJ, Klijn JGM, van Elderen T, Tibben A, Duivenvoorden HJ

Abstract

Since 2000 the MRISC study evaluates the psychological consequences of regular breast cancer surveillance for women at increased risk for hereditary breast cancer. Coping style may influence these psychological consequences. In a cohort of 357 women at increased risk for hereditary breast cancer, the impact of coping styles on psychological distress was examined, around two consecutive surveillance appointments. With structural equation modelling we found passive coping to be associated with higher levels of both general and breast cancer specific distress. Seeking social support, expression of emotions and thinking comforting thoughts were associated with lower levels of psychological distress. Coping style was not associated with the course of psychological distress around the two surveillance appointments. It is recommendable to take coping styles into account when counselling these high-risk women.

Introduction

Breast cancer is the most common type of cancer in women in the Western World. In 5-10 % of the cases this is due to a genetic susceptibility [1]. By means of genetic testing, a pathogenic mutation in BRCA1 or BRCA2 can be identified as the causal factor at this moment in approximately 16% of the families [2]. When no mutation can be found, women from these families remain at increased risk of breast cancer due to an as yet unidentifiable genetic or familial predisposition. For women with an increased risk for hereditary breast cancer, breast cancer surveillance is one of the management options. In previous studies, it was found that women with an increased risk of breast cancer had more cancer specific distress than women without this risk [3,4]. Several factors have been identified to be associated with increased levels of psychological distress in high-risk women. For example, experiences with cancer-patients in the family are related with higher distress levels, particularly cancer in a parent [5-7]. And more recently it was found that having (had) a sister affected with breast cancer was associated with higher levels of breast cancer specific distress [8]. Heightened risk perceptions have also been found to be associated with heightened distress levels, both general and breast cancer specific distress [4,6,9-11]. Behavioural factors, such as performing excessive breast self-examination were found to be associated with higher levels of distress as well [12-15].

Associations between coping style and psychological distress have been studied also. Coping has been described as the cognitive and behavioural attempts to tolerate or to eliminate both internal and external stressors [16]. Several types of coping styles can be distinguished, each with different associations with psychological distress. Approach coping (trying to do something about the stressor) for instance, was found to be more beneficial than avoidant coping (trying to avoid the stressor). In a cross-sectional study, breast cancer patients who used approach coping had a higher level of psychological well-being [17]. However, in a study on non-participants of the predictive genetic test for melanoma, an active problem-focused coping style was reported to be associated with anxiety [18]. The findings in the literature about the relationship between coping and distress are various, implying that the relation between coping and distress may be more complex, and that other personality aspects should be considered as well.

To our knowledge, no empirical studies have been conducted concerning the association of coping styles and psychological distress in women at increased risk for hereditary breast cancer who adhere to regular surveillance. In 1999 the national observational MRI screening study (MRISC) part A started in the Netherlands evaluating both the effectiveness of regular breast cancer surveillance in women at risk for hereditary breast cancer and the efficacy of MRI as early detection tool for breast cancer [19].

The surveillance programme consisted of yearly imaging of the breast tissue by means of mammography (and eventual magnetic resonance screening (MRI), biannual physical examination by a clinician and instructions for monthly breast self examination. In 2000 the psychological follow-up study (part B) was initiated at the Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Centre in Rotterdam, to evaluate the psychological impact of regular breast surveillance. The objective of the current paper was to determine the impact of coping styles on psychological distress in women at increased risk for hereditary breast cancer, adhering to breast cancer surveillance because of a genetic susceptibility or familial history. The study was conducted around two consecutive biannual breast cancer surveillance appointments, taking place within one year.

Material and methods

Participants

In this study a total of 357 women were included. Hundred and eight women from MRISC-A refrained from participation in the psychological follow-up study. At entry, participants did not have a history of breast cancer, had a cumulative lifetime risk of developing breast cancer of at least 15% and they had signed an informed consent. For this study, participants were categorized in one of three risk categories. Women in category 1 were identified BRCA1 or BRCA2 mutation carriers with a cumulative lifetime risk (CLTR) of developing breast cancer between 60 and 85%. Women in category 2 had a CLTR between 30 and 50%, and were 1st degree family members of a proven BRCA1/2 mutation carrier, who did not opt for the test themselves, or 1st degree relatives from a breast cancer patient from a non BRCA1/2 mutation family or a family where genetic testing was not performed. Women in category 3 had a CLTR between 15 and 30% and belonged to families with an increased frequency of breast cancer incidence, or were 25% risk carriers from a proven BRCA1/2 mutation family [20-22].

Measures

Sociodemographics

Age, educational level, having a partner, having children, and the number of years of adherence to surveillance were measured.

Determinants

The seven different coping styles of the Utrecht Coping List (UCL) were used as determinants of psychological distress [23,24]. The UCL measures coping styles as a disposition and comprises 47 items, with a 4-point Likert-type response format ranging from 1 (hardly ever or never) to 4 (very often or always). The seven coping styles are: 'Active Approach' (taking action to solve the problem, 8 items), 'Palliative Reaction' (seeking distraction, 8 items), 'Avoiding' (9 items), 'Seeking Social Support' (6 items), 'Passive Coping' (not feeling capable of taking action, 7 items), 'Emotional Expression' (showing anger and annoyance, 3 items), and 'Comforting Thoughts´ (3 items) [24]. Previous studies revealed satisfying validity and reliability measures of the UCL [25,26]. The UCL was administered once, at m0 (see Design).

Outcome variables

Psychological distress was measured with the Impact of Event Scale (IES) and the Hospital Anxiety and Depression Scale (HADS). The IES measures 'Intrusion' (7 items) and 'Avoidance' (8 items) [27]. This questionnaire can be tailored to a specific event, which is 'breast cancer' in the current study. The IES has the following response format: 0 (never), 1 (hardly ever), 3 (sometimes), and 5 (often). In this study, the IES was measured repeatedly and the reliabilities (Cronbach's α) of the subscales 'Intrusion' and 'Avoidance' ranged from 0.85 to 0.90 and from 0.85 to 0.88, respectively.

The HADS measures 'Anxiety' and 'Depression' [28]. It is a 14-item questionnaire, with 7 items measuring 'Anxiety' and 7 items measuring 'Depression'. The response format ranges from 0 to 3. In the present study the reliabilities (Cronbach's α) of the HADS range from 0.82 to 0.92 for the subscale 'Anxiety' and from 0.82 to 0.90 for the subscale 'Depression'. The IES and the HADS were administered at all of the measurement moments (see Design).

Design

Women were asked to fill in questionnaires on several time points during the surveillance programme: two months before the surveillance appointment (m0), the morning of the surveillance appointment (m1), 1 to 4 weeks after receiving the results of the visit (m2), four months after the surveillance and two months before the consecutive surveillance appointment (m3), the morning before the consecutive surveillance appointment (m4), and 1 to 4 weeks after receiving the results of the visit (m5). The assessments m2 and m5 were planned one week after the clinic visit in case of physical examination alone, and four weeks after an appointment consisting of physical examination in combination with imaging examinations (mammography and MRI). For reasons of a clear design, scores on measurement moment m0 were not included (except the UCL scores) in the analyses of the current study. The Medical Ethical Committee of the Erasmus MC in Rotterdam approved the study.

Procedures

Women participating in the MRISC-A study in the Daniel den Hoed Cancer Centre in Rotterdam were sent a letter informing them about the psychological follow-up study. Along with this letter came an information booklet, an informed consent form, a refusal form for women who did not want to participate and a stamped envelope. Additionally, the physicians handed out the information booklets during the women's clinical examination consultation. After sending back the informed consent, women were sent their m0-questionnaire to their home. Women who did not return their questionnaire within 4 weeks were sent a reminder. Since the questionnaires on m1 and m4 had to be filled in on the day of the surveillance visit at the outpatient clinic, no reminders were sent when women did not return one of these questionnaires.

Statistical analysis: structural equation modelling

Structural equation modelling (SEM) was applied to explore the level and course of psychological distress, and subsequently to determine the impact of the coping styles on the level and course of the distress. In general, modelling is aimed to identify the most plausible model. The models may differ in the co-variances (or correlations in case of standardized values) to be reproduced from these models. Whereas one model enables a correlation between two constructs, another model requires this correlation to be set at zero (in other words, no correlation is allowed). Whether one or more of these models are plausible, depends on whether they enable to reproduce the observed (co-)variances adequately. Two principles of SEM (i.c. growth analysis) are that individuals are allowed to differ in their level of psychological distress and that they are allowed to differ in their course of psychological distress across time.

It is a scientific principle to build the models as parsimonious as possible, under the condition that the final model is plausible, both theoretically and statistically [29]. Compared to classical MANOVA for repeated measurements, applying SEM to repeated measurements has several advantages: (1) individuals will not have to be measured at exactly the same time point (unequal time intervals are allowed), (2) SEM can handle missing data, (3) the error-variance/covariance matrices across time can be modelled flexibly, (4) SEM enables to introduce time varying covariables, and (5) person specific deviations from the group level are allowed.

The structure of the design of the current study was proper for piece-wise regression modelling, a specific kind of SEM [30,31]. In fact, m4 and m5 are similar to m1 and m2, respectively, whereby both m1 and m4 are surveillance moments, while m2 and m5 are measurement moments after the surveillance appointment in the clinic. M3 is a neutral moment in between. Because of this design, and m3 being the reference moment, the distress scores on m0 were not taken into account in the analyses. Piece-wise regression modelling was performed as follows: the level and the course of breast cancer specific distress was specified in terms of 'Intrusion' and 'Avoidance', and general distress in terms of 'Anxiety' and 'Depression'. This resulted in four different courses to be analysed; each of these four courses was split up into two pieces covering m1 and m2 (first piece) and m4 and m5 (second piece), and m3 was the reference moment. Hereby, the levels and courses of the four outcome variables were compared to the corresponding variable at this reference moment (m3). Centering implies that the time score of the reference moment is set to zero. For each of the four specifications, the level was fixed as follows: [1 1 1 1 1]. To determine the course, the coefficients of the pieces per course were fixed as follows: [-2 -1 0 0 0] for the first piece and [0 0 0 2 1] for the second piece respectively. The number indicates the degree of deviation from m3: i.e. 2 indicates a larger deviation from m3 (value 0) than 1. A negative value indicates an assessment before m3, whereas a positive value indicates an assessment after m3.

To obtain less heterogeneous co-variances, the observed distress scores of all measurement moments were transformed as follows: from the observed score the mean score of m3 was subtracted, and subsequently divided by the standard deviation of m3.
The relationship between breast cancer specific distress and general distress on the one hand and coping on the other hand, was analysed in two phases. The first phase dealt with the piece-wise regression analyses of the four specifications of distress across time (resulting in so-called unconditional models). These analyses uncovered the relationships between and within the different outcome variables. The second phase implied that the impact of coping on the levels and the courses of the four operationalisations of distress were modelled (i.e. conditional models).

In the *first phase*, each of the four outcome variables were reparametrised in terms of level and course. The course was split up in piece 1 (i.e. m1 and m2) and piece 2 (i.e. m4 and m5). After that, it was tested whether: (1) the inter-correlations of the level could be fixed at zero or not; (2) the inter-correlations of the course could be fixed at zero or not: (3) the inter-correlations of the courses within the same outcome variable could be fixed to be equal or not; (4) the auto-correlations of the observed outcome variable (lag 1) could be fixed at zero or not; (5) the cross-correlations of the observed outcome variables within the same measurement moment (lag 0) could be fixed at zero or not.

The *second phase* can be distinguished into five steps: (1) it was explored whether the coping styles were related to the level of the four distress measures, and whether they were related to the first piece and /or to the second piece of the course of distress; (2) it was explored whether the relationship between the coping styles and the two pieces were equal or not. The most plausible model was used in the next step; (3) it was explored whether it was necessary to set the relationship between coping styles and outcome variables to be free; (4) it was explored per outcome variable whether it was allowed to fix one or more relationships between coping styles and courses of distress at zero; (5) it was explored for each coping scale whether it was allowed to fix the levels of the distress specifications at zero.

To test the adequacy of the models, Chi-squared tests were used for determining the model-fit. The value of χ^2, its p-value and the number of degrees of freedom (df) were examined.

A non-significant p-value ($p > .05$) and the ratio $\frac{\chi^2}{df}$<1,5 of would represent a good model-fit.

Four other goodness-of-fit indices were also used: Comparative Fit Index (CFI > 0.95), Tucker-Lewis Index (TLI > 0.95), Root Mean Square Error of Approximation (RMSEA ≈ 0.05) and Standardized Root Mean Square Residual (SRMR < 0.05).

Results

Descriptive statistics

The women who did not want to participate in the psychological follow-up study did not differ significantly from the women who did participate, with respect to age and risk status. The mean age of the participating women was 40.5 years (sd = 8.82; range: 21 to 63). Of the 351 valid responders, 17% reported to have a lower educational level, 54% a medium education level and 28% had a higher educational level. The majority of the women (75%) had a partner and one or more children (70%). The mean duration of adherence to regular surveillance was 5.3 years (sd = 4.42 years; range: 0 to 30). The sample characteristics are presented in *Table 1. Table 2* displays the mean scores and standard deviations of the UCL at assessment moment m0. Furthermore, the mean scores of the UCL have been compared to a Dutch norm group of 63 women. The mean scores on 'Active Approach', 'Palliative Reaction' and 'Seeking Social Support' turned out to be significantly higher compared with the norm group. Conversely, the mean scores on 'Emotional Expression' are significantly lower than those of the norm group.
In *Table 3*, the mean scores and standard deviations of all outcome variables, and a correlation matrix, including the inter- and intra-correlations of the outcome variables at all measurement moments are presented. Both the cross-correlations as well as the autocorrelations were significant at the 0.01 significance level (two-tailed).

Table 1. General characteristics of the total study population (numbers may vary due to missings)

Variable	**mean (sd)**
Age	40.52 (8.82)
Number of years of adherence	5.28 (4.42)
	n (%)
Having a relationship (yes)	263 (75)
Having children (yes)	251 (70)
Higher level education	100 (28)
Middle level education	191 (55)
Lower level education	60 (17)

Table 2. Means and standard deviations of coping styles (UCL) at m0.
The number between brackets displays the score of the normgroup

	m	**sd**
Active Approach	18.91 (17.70)*	3.57 (2.69)
Palliative Reaction	17.91 (16.30)*	3.35 (3.32)
Avoidance	15.15 (14.90)	3.05 (3.01)
Seeking Social Support	14.24 (12.90)*	3.77 (3.57)
Passive Coping	11.21 (11.20)	2.90 (2.58)
Emotional Expression	6.13 (7.07)*	1.63 (1.83)
Comforting Thoughts	12.79 (12.40)	2.53 (2.51)

* = significantly different from norm group at < 0,01 significance level.

Table 3. Intra- and inter-correlations, means and standard deviations of outcome variables across time

		Intrusion					Avoidance					Anxiety					Depression				
	m	m1	m2	m3	m4	m5	m1	m2	m3	m4	m5	m1	m2	m3	m4	m5	m1	m2	m3	m4	m5
Intrusion	m1																				
	m2	**.70**																			
	m3	**.65**	**.68**																		
	m4	**.70**	**.67**	.70																	
	m5	.59	**.62**	**.65**	**.71**																
Avoidance	m1	**.75**	.50	.52	**.65**	.45															
	m2	.58	**.71**	.56	.59	.54	**.66**														
	m3	.49	.49	**.72**	**.65**	.54	**.63**	**.67**													
	m4	.54	.51	.58	**.81**	.53	**.73**	**.63**	.77												
	m5	.44	.43	.50	.59	**.70**	**.60**	**.60**	**.66**	**.71**											
Anxiety	m1	**.63**	.45	.49	.50	.47	.57	.48	.48	.48	.41										
	m2	.48	.53	.45	.45	.46	.46	.53	.40	.41	.38	**.72**									
	m3	.45	.42	.58	.49	.47	.46	.43	.54	.47	.44	**.71**	**.72**								
	m4	.50	.41	.55	**.63**	.47	.52	.44	.59	**.63**	.50	**.77**	**.67**	**.74**							
	m5	.46	.40	.51	.51	**.60**	.44	.45	.52	.48	.54	**.72**	**.72**	**.76**	**.77**						
Depression	m1	.43	.26	.30	.29	.30	.44	.29	.28	.30	.27	**.69**	.56	**.60**	.54	.53					
	m2	.34	.31	.28	.26	.29	.32	.32	.23	.25	.19	.49	**.70**	.56	.45	.49	**.75**				
	m3	.31	.27	.37	.33	.30	.30	.25	.33	.32	.25	.52	.55	**.74**	.56	.57	**.72**	**.75**			
	m4	.37	.33	.44	.46	.35	.38	.32	.43	.48	.35	.56	.53	**.65**	**.74**	**.58**	**.69**	**.65**	**.76**		
	m5	.36	.32	.36	.35	.38	.31	.28	.32	.32	.33	.56	.59	**.67**	**.60**	**.69**	**.73**	**.73**	**.81**	**.79**	
M		5.10	3.98	4.01	4.44	4.11	4.81	3.21	3.13	3.70	3.46	5.38	4.37	4.37	4.86	4.26	2.62	2.35	2.70	2.54	2.40
sd		6.43	6.06	6.42	6.28	6.25	6.98	5.64	5.92	6.75	6.02	3.98	3.70	3.81	4.01	3.88	3.17	3.20	3.61	3.38	3.42

Phase 1: Unconditional models

Based on the five kinds of inter-correlations of the four distress measures in the first phase of regression modelling (see statistical analysis), 32 different possible models were compared on their adequacy ('+' indicates the necessity of a regression, whereas '-' indicates that a regression was not necessary for good model-fit). The Chi square fit-index of the most plausible model was moderate although significant ($\chi^2(86) = 143.46$; $p = 0.00$). The other indices indicated that this model was good (CFI = 0.99; TLI = 0.98; RMSEA = 0.05; SRMR = 0.04). This model implied that the cross-correlations of the observed outcome variables within the same measurement moment (lag 0) could be considered not unequal although they are allowed to deviate from zero.

Phase 2: Conditional models, the impact of coping

In this paragraph phase 2 (the conditional models), in which coping was included as predictor variable, is presented. First, we explored whether the coping styles were related to the level of distress and whether they were related to (the pieces) of the course of distress. Further, it was explored whether the impact of coping was the same for both pieces. These test-options resulted into 9 different models *(see Table 4)*.

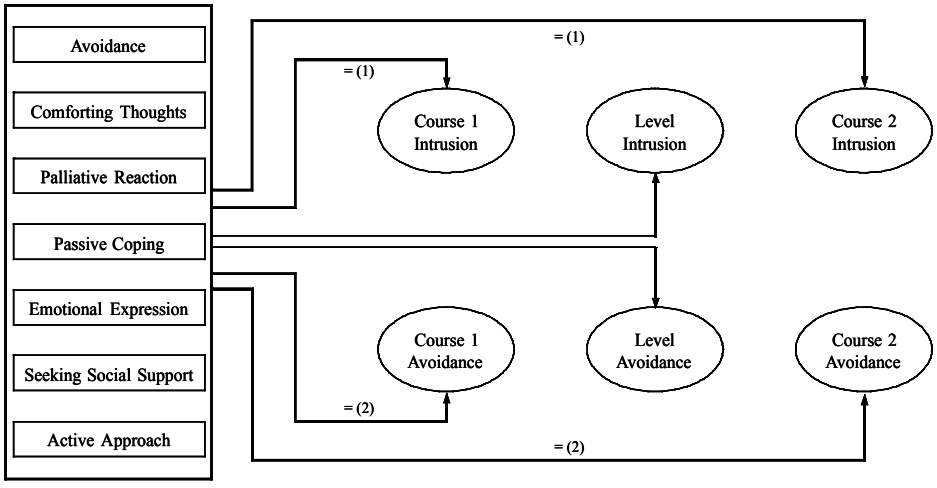
Table 4. Comparison of different models regarding outcome variables and coping style

Model	Level	Course 1	Course 2	Equality of regression weights	χ^2	df	χ^2/df	p value	CFI	TLI	RMSEA	SRMR
1	-	-	+	d.n.a.	290.28	170	1.71	.00	.98	.96	.05	.04
2	-	+	-	d.n.a.	295.43	170	1.74	.00	.98	.96	.05	.04
3	-	+	+	-	289.40	166	1.74	.00	.98	.96	.05	.04
4	-	+	+	+	312.14	194	1.61	.00	.98	.97	.05	.05
5	+	-	-	d.n.a.	289.40	166	1.74	.00	.98	.96	.05	.04
6	+	-	+	d.n.a.	295.43	170	1.74	.00	.98	.96	.05	.04
7	+	+	-	d.n.a.	290.28	170	1.71	.00	.98	.96	.05	.04
8	+	+	+	-	224.12	142	1.58	.00	.99	.97	.05	.04
9	+	+	+	+	245.62	170	1.44	.00	.99	.97	.04	.04

+ = coping was related to level, course 1, and course 2 respectively
- = coping was not related to level, course 1, and course 2 respectively
d.n.a. = does not apply
CFI = Comparative Fit Index
TLI = Tucker-Lewis Index
RMSEA = Root Mean Square Error of Approximation
SRMR = Standardizes Root mean Square residual

The most adequate model was model 9 (χ^2 (170) = 245.62; p = 0.00). In this model, the coping styles were related to the four levels of distress and to the courses of distress as well. Moreover, the regression weights of the coping styles on both pieces of each course of distress were equal. Model 9 is visualized for 'Intrusion' and 'Avoidance' in *Figure 1* (because the figure would be too extensive, general distress operationalisations were left out of it). The equality of the regression weights of the coping styles with the pieces of distress is marked: the regression weights of the variables marked with (1) are equal to each other, and the weights of the variables marked with (2) are equal to each other.

Figure 1. Visualisation of model 9 (Table 5)



The exploration for which coping styles and outcome variables it was required to set the correlations between them to be free (step 3), is shown in part I and II of *Table 5*. In step 4 (part III of *Table 5*), it was explored per outcome variable whether it was allowed to fix one or more relationships between coping styles and courses of distress at zero. The two models used for this exploration are presented in part III of *Table 5*. The relationship between coping styles and the pieces of all courses of distress were constrained to be zero; in other words, coping styles had no significant impact on the course of distress variables (χ^2 (198) = 280.29; p = 0.00).
In step 5, the specific exploration of the impact of coping styles on the level of distress was executed which is demonstrated in part IV of *Table 5*. The impact of avoidance coping and active approach on the levels of psychological distress could be fixed at zero (χ^2 (206) = 287.06; p = 0.00); in other words, these two coping styles had no impact on the level of distress. The other indices for model-fit were also good (CFI = 0.99; TLI = 0.98; RMSEA = 0.04; SRMR = 0.04).

Table 5. Comparison of different models regarding the importance of coping scales on outcome variables

		χ^2	df	χ^2/df	p value	CFI	TLI	RMSEA	SRMR
I.	Relaxing of coping, per coping style								
	Active approach	240.34	166	1.45	.00	.99	.97	.04	.04
	Palliative reaction pattern	243.54	166	1.47	.00	.99	.97	.04	.04
	Avoidance	244.25	166	1.47	.00	.99	.97	.04	.04
	Seeking social support	240.30	166	1.45	.00	.99	.97	.04	.04
	Passive coping	239.90	166	1.45	.00	.99	.97	.04	.04
	Emotional expression	243.68	166	1.47	.00	.99	.97	.04	.04
	Comforting thoughts	243.02	166	1.46	.00	.99	.97	.04	.04
II.	Relaxing of outcome variables separately								
	Intrusion	238.60	163	1.46	.00	.99	.97	.04	.04
	Avoidance	239.96	163	1.47	.00	.99	.97	.04	.04
	Depression	241.43	163	1.48	.00	.99	.97	.04	.04
	Anxiety	239.22	163	1.47	.00	.99	.97	.04	.04
III.	Fixing courses at zero								
	Anxiety and Depression	250.50	170	1.47	.00	.99	.97	.04	.04
	Anxiety, Depression, Intrusion, and Avoidance	280.29	198	1.42	.00	.99	.98	.04	.04
IV.	Fixing courses at zero and the following levels								
	Avoidance and active approach	287.00	206	1.39	.00	.99	.98	.04	.04

CFI = Comparative Fit Index
TLI = Tucker-Lewis Index
RMSEA = Root Mean Square Error of Approximation
SRMR = Standardizes Root mean Square residual

This final model (which is grey shaded) is visualized in *Figure 2.* Non-significant pathways were omitted. The marked pathways represent significant regression weights between the theoretical constructs. The shading of 'Passive Coping' illustrates the impact of this coping style in comparison with the other coping styles. None of the coping styles had an impact on the courses of distress (regression weights were constrained to be zero), therefore no pathways were drawn between these constructs.

Figure 2. Visualisation of final model (Table 6, part IV)

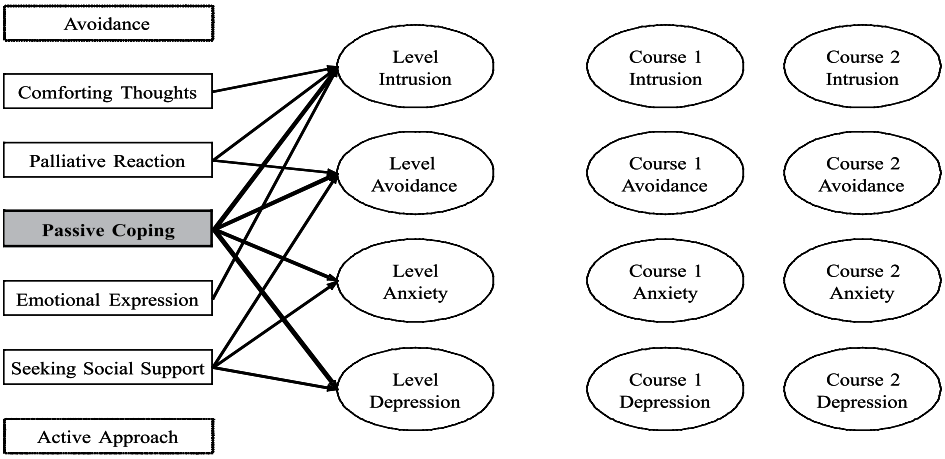


Table 6 presents the standardised regression coefficients of the coping styles on the levels of the outcome variables, which are derived from the final model. 'Passive Coping' had significant positive regression weights for all distress levels (β's between 0.40 and 0.53), meaning that a high score on passive coping was associated with a high level of distress. Also 'Palliative Reaction' had significant positive regression weights, although only for 'Intrusion' (β = 0.18) and 'Avoidance' (β = 0.24). In contrast, 'Seeking Social Support' was significantly associated with lower scores on 'Avoidance', 'Anxiety' and 'Depression' (β's = -0.15, -0.17 and -.017 respectively). 'Emotional Expression' and 'Comforting Thoughts' were associated with lower scores on 'Intrusion' (β's = -.016).

Table 6. Standardized regression weights (ß) of coping scales with distress levels

	Intrusion		Avoidance		Anxiety		Depression	
	ß	t-value	ß	t-value	ß	t-value	ß	t-value
Active approach	.00	0.00	.00	0.00	.00	0.00	.00	0.00
Palliative reaction pattern	**.18**	**2.64**	**.24**	**3.25**	.12	1.85	-.10	-1.65
Avoidance	.00	0.00	.00	0.00	.00	0.00	.00	0.00
Seeking social support	-.01	-0.15	**-.15**	**-2.46**	**-.17**	**-3.23**	**-.17**	**-3.44**
Passive coping	**.49**	**8.56**	**.45**	**7.56**	**.53**	**10.27**	**.40**	**8.15**
Emotional expression	**-.16**	**-2.81**	-.12	-1.99	-.01	-0.23	-.02	-0.46
Comforting thoughts	**-.16**	**-2.39**	-.05	-0.76	-.06	-1.05	.05	0.86

A t-value higher than 2 or lower than –2 is considered to be significant at 0.05 level of significane (two-tailed)

Discussion

Our main finding was the significant impact of passive coping on the levels of all the distress measures as used in this study: intrusion, avoidance, anxiety and depression. Passive coping implies feeling unable to undertake action, isolating oneself from others, escaping into fantasies and/or substance use when feeling tense or nervous. The associations between passive coping and the levels of distress were positive, meaning that women with higher scores on the passive coping style were more anxious and depressed, and had more intrusive thoughts and more tendency to avoid things / ideas that reminded them of breast cancer. Similar results regarding the unfavourable impact of passive coping have also been reported among breast cancer patients [32] and chronic pain patients [33]. The findings of the current study indicate that women at increased risk for hereditary breast cancer who adhere to regular surveillance and who display a passive coping strategy are more vulnerable for psychological distress.

To strengthen the finding that passive coping is of clinical interest, further elaboration of the results of the current study is required. An area that deserves attention concerns the definition of passive coping, what exactly is it and how does it differentiate itself from other adjoining coping behaviours like avoidant coping? Passive coping may not differ at first sight much from avoidant coping. Passive coping implies 'doing nothing' whatever the reasons and motives may be. It is a feeling of being overwhelmed by the problem. In contrast, avoidance coping implies constantly making sure not to be reminded of or confronted with the problem, which has to be considered as an active process. The concept of 'learned helplessness' [34] may correspond more with the concept of passive coping. Learned helplessness implies that when facing an uncontrollable stressor, no other response to the stressor will follow than passive coping. Learned helplessness can be viewed as a phenomenon of nurture principle. Then the question rises whether passive coping can be better understood in terms of this nurture principle or rather in terms of a nature principle. To all probability, the interplay of both nurture and nature principles plays a role in daily functioning.

Although passive coping had no impact on the course of psychological distress during the two consecutive surveillances, it does not imply that passive coping is not of relevance when distress changes across time. To answer this problem, it is necessary to assess passive coping across time as well. In the current study, passive coping was only assessed once, i.e. two months before the first surveillance.

The palliative coping style was associated with increased levels of breast cancer specific distress, namely intrusion and avoidance, and can be regarded as an unbeneficial coping style as well. In contrast, seeking social support was associated with decreased levels of avoidance, anxiety and depression, and could therefore be considered as a beneficial coping style. This finding is congruent with other empirical studies. In the study of Meijer et al. (2002), this coping style was found to be a significant predictor for better psychological adjustment to chronic illness [35]. The results of the current study support the relevance of considering the influence of family dynamics and family communication in future research, since the women have to deal with an increased risk of developing hereditary breast cancer, whereby social support from family members can be beneficial. This is underscored by the observations from a longitudinal study among women carrying a BRCA1/2 gene, reporting a positive association between long-term psychological distress and less open communication about the genetic test result within the family [36]. Other beneficial coping styles in this study were emotional expression and comforting thoughts, both being associated with a decreased level of intrusion.

Another finding was the absence of any impact of active approach coping and avoidance coping behaviours on the level of distress. This is in contrast with the report findings in the literature, in which active ways of coping are frequently found to be beneficial for (mental) health [37] and reducing psychological distress [17]. In the current study, no associations were found between approach coping and the level of psychological distress. The same applies to avoidance coping. To our belief, three explanations are possible. First, an explanation might be found in the stress-coping theory, which states that the way people cope with a certain stressful encounter, depends on the person's appraisals of this situation [38]. Of importance is the controllability of the stressful situation. Women adhering to breast cancer surveillances have little control over their situation, since the surveillance appointments are scheduled for them. Neither more active behaviour nor more avoidant behaviour will result in removal of the stressor. A second explanation might be that the items of the seven UCL subscales are stated in general in stead of breast cancer specific terms. In addition, we doubt whether the validities and reliabilities of the seven subscales of the UCL are satisfying. More elaboration is needed of the theoretical constructs in empirical terms. A third explanation might be the idea that coping styles can be ordered in a hierarchic structure [39]. This hierarchy might contribute to the discrepancy in study results, due to a difference in conceptualisations of the coping styles.

As passive coping turned out to be of interest, it might be that vulnerable women, i.e. scoring high on passive coping, are eligible for psychological intervention. Which treatment is indicated, depends on several factors: the degree of breast cancer specific and general distress (i.e. suffering), the amount and quality of perceived social support (e.g. of the partner), patient's ego strength and patient's motivation for (certain kinds of) psychological intervention.

Limitations of the study

Regarding the final model, it has to be noted that the χ^2-test for model performance was significant, which is not desired in statistical modelling, while the other performance measures suggested that the model-fit was adequate. The most plausible explanation for this discrepancy is that the sample size was rather large. It is well known in statistics that a large sample size induces a higher probability of reaching significancy. Within this framework it is of relevance to mention that the modelling did not take into account that the empirical constructs were inherently fallible. If the modelling was corrected for unreliabilities of the empirical constructs, then the predictive power of the coping subscales would have been higher. This implies that the impact of passive coping on distress would have been more profound. That the modelling was not corrected for these unreliabilities has to be ascribed to the fact that the modelling process would have been highly complicated.
With regard to the UCL, a relevant question is whether applicational factor analysis is a suitable strategy for the determination of the structure of coping behaviour (based on inter-correlations of the items representing the coping behaviour). It might be that a kind of preference scaling is more proper.
A matter that has not been researched for the current paper, but which is of most interest, is the role of other variables with regard to the impact of coping on distress. Further research is indicated on this topic.

Although it might be too early to conclude that improving the coping adequacy of a (vulnerable) subgroup of these women will diminish their level of psychological distress, the findings of the current study are unique and of clinical interest. Nevertheless, further research is needed. The need for modification of unfavourable coping styles may depend on the overall level of distress the women experience during their day to day life.

References

1. Claus EB, Schildkraut JM, Thompson WD, et al: The genetic attributable risk of breast and ovarian cancer. Cancer 77:2318-24, 1996
2. Peto J, Collins N, Barfoot R, et al: Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 91:943-9, 1999
3. Rees G, Fry A, Cull A, et al: Illness perceptions and distress in women at increased risk of breast cancer. Psychology and Health 19:749-765, 2004
4. Lloyd S, Watson M, Waites B, et al: Familial breast cancer: a controlled study of risk perception, psychological morbidity and health beliefs in women attending for genetic counselling. Br J Cancer 74:482-7., 1996
5. Wellisch DK, Gritz ER, Schain W, et al: Psychological functioning of daughters of breast cancer patients. Part II: Characterizing the distressed daughter of the breast cancer patient. Psychosomatics 33:171-9., 1992
6. Hopwood P, Shenton A, Lalloo F, et al: Risk perception and cancer worry: an exploratory study of the impact of genetic risk counselling in women with a family history of breast cancer. J Med Genet 38:139., 2001
7. Erblich J, Bovbjerg DH, Valdimarsdottir HB: Looking forward and back: distress among women at familial risk for breast cancer. Ann Behav Med 22:53-9., 2000
8. van Dooren S, Seynaeve C, Rijnsburger AJ, et al: The impact of having relatives affected with breast cancer on psychological distress in women at increased risk for hereditary breast cancer. Breast Cancer Res Treat 89:75-80, 2005
9. Meiser B, Butow P, Schnieden V, et al: Psychological adjustment of women at increased risk of developing hereditary breast cancer. Psychology, Health and Medicine 5:377-388, 2000
10. Van Dooren S, Rijnsburger AJ, Seynaeve C, et al: Psychological distress in women at increased risk for breast cancer: the role of risk perception. Eur J Cancer 40:2056-63, 2004
11. Watson M, Duvivier V, Wade Walsh M, et al: Family history of breast cancer: what do women understand and recall about their genetic risk? J Med Genet 35:731-8., 1998
12. Brain K, Norman P, Gray J, et al: Anxiety and adherence to breast self-examination in women with a family history of breast cancer. Psychosom Med 61:181-7., 1999
13. Epstein SA, Lin TH, Audrain J, et al: Excessive breast self-examination among first-degree relatives of newly diagnosed breast cancer patients. High-Risk Breast Cancer Consortium. Psychosomatics 38:253-61., 1997
14. Erblich J, Bovbjerg DH, Valdimarsdottir HB: Psychological distress, health beliefs, and frequency of breast self- examination. J Behav Med 23:277-92., 2000
15. van Dooren S, Rijnsburger A, Seynaeve C, et al.: Psychological distress and breast self-examination frequency in women at increased risk for hereditary or familial breast cancer. Community Genetics 6:235-241, 2003
16. Folkman S, Lazarus RS: An analysis of coping in a middle-aged community sample. J Health Soc Behav 21:219-39, 1980
17. Holland KD, Holahan CK: The relation of social support and coping to positive adaptation to breast cancer. Psychology and Health 18:15-29, 2003
18. Riedijk SR, de Snoo FA, van Dijk S, et al: Hereditary melanoma and predictive genetic testing: why not? Psychooncology, 2005
19. Kriege M, Brekelmans CT, Boetes C, et al: Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427-37, 2004
20. Brekelmans CT, Voogd AC, Botke G, et al: Family history of breast cancer and local recurrence after breast-conserving therapy. The Dutch Study Group on Local Recurrence after Breast Conservation (BORST). Eur J Cancer 35:620-6., 1999
21. Brekelmans CT, Seynaeve C, Bartels CC, et al: Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol 19:924-30., 2001
22. Kriege M, Brekelmans CT, Boetes C, et al: MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). Fam Cancer 1:163-8, 2001
23. Schreurs P, Tellegen, B, van de Willige G: Health, stress and coping - The development of the Utrecht Coping Scale. Gedrag - Tijdschrift voor psychologie 12:101-117, 1984
24. Schreurs P, van de Willige G, Tellegen B, Brosschot JF: Utrechtse Coping Lijst: omgaan met problemen (UCL 1988). Lisse, Swets Test Services (STS), 1988
25. Schaufeli W, van Dierendonck D: De betrouwbaarheid en validiteit van de Utrechtse Coping Lijst. Gedrag en Gezondheid 20:38-45, 1992
26. Sanderman R, Ormel J: De Utrechtse Coping Lijst (UCL): validiteit en betrouwbaarheid. Gedrag en Gezondheid 20:32-37, 1992
27. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. Psychosom Med 41:209-18., 1979
28. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70., 1983
29. Jöreskog K: Testing structural equation models, in Bollen KA LJ (ed): Testing structural equation models. Newbury Park, CA, Sage, 1993, pp 294-316
30. Willett JB, Singer JD, Martin NC: The design and analysis of longitudinal studies of development and psychopathology in context: statistical models and methodological recommendations. Dev Psychopathol 10:395-426, 1998
31. Muthen LK, Muthen BO: MPlus User's Guide (ed third). Los Angeles, CA, Muthen & Muthen, 1998-2004
32. Kim Y, Valdimarsdottir HB, Bovbjerg DH: Family histories of breast cancer, coping styles, and psychological adjustment. J Behav Med 26:225-43, 2003
33. Snow-Turek AL, Norris MP, Tan G: Active and passive coping strategies in chronic pain patients. Pain 64:455-62, 1996

34. Seligman ME, Weiss J, Weinraub M, et al: Coping behavior: learned helplessness, physiological change and learned inactivity. Behav Res Ther 18:459-512, 1980
35. Meijer SA, Sinnema G, Bijstra JO, et al: Coping styles and locus of control as predictors for psychological adjustment of adolescents with a chronic illness. Soc Sci Med 54:1453-61, 2002
36. van Oostrom I, Meijers-Heijboer H, Lodder LN, et al: Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. J Clin Oncol 21:3867-74, 2003
37. Bonica C, Daniel JH: Helping adolescents cope with stress during stressful times. Curr Opin Pediatr 15:385-90, 2003
38. Folkman S, Lazarus RS, Dunkel-Schetter C, et al: Dynamics of a stressful encounter: cognitive appraisal, coping, and encounter outcomes. J Pers Soc Psychol 50:992-1003, 1986
39. Chen CC, David A, Thompson K, et al: Coping strategies and psychiatric morbidity in women attending breast assessment clinics. J Psychosom Res 40:265-70, 1996

Chapter 9

Discussion

Discussion

Psychological distress in women at risk for hereditary breast cancer has previously been investigated, however often with varying starting points and study designs. Therefore, the data are not comparable, and sometimes conflicting, as has been reviewed in the introduction. The current study on the psychological impact of regular surveillance in women at risk for hereditary breast cancer is the first prospective study in a well-defined cohort of high-risk women, and provided us with useful information for clinical practice and future research. A particular strength of the study was that the study population consisted of a large, compliant sample of women at increased risk of developing hereditary breast cancer (n=357). Furthermore, because of the prospective design of the study, we were able to explore the levels and the course of psychological distress in a thorough way on multiple measurement moments. Furthermore, the rather large number of women enabled us to identify and explore substantial subgroups that were more vulnerable.

The association between breast self-examination (BSE) and psychological distress has already been studied by Kash and Lerman in the early nineties, an era in which genetic counselling and testing were not yet available [1-3]. In the late nineties, Epstein, Brain, and Erblich reported on this topic as well [4-6]. In these studies overperformance was found to be associated with breast cancer specific distress while Kash found an association between general distress and infrequent BSE.
In our study initially, we did not find any associations at all. However, when adding the concept of age to the performance of BSE, it appeared that especially younger women who performed BSE excessively reported higher levels of breast cancer specific distress. While our findings are mainly in accordance with earlier reported data, it is the first time that this topic has been assessed in a well-defined large group of women at increased risk of breast cancer. Therefore, our results underscore the relevance of overperformance of BSE in combination with age, and reflect a group of women being more vulnerable.

As has been addressed in the introduction, there is an association between the accurateness of the breast cancer risk perception by a particular woman and psychological distress [7-11]. Concerning this issue, Hopwood et al. reported on the importance of affective factors in the concept of risk perception, in contrast with "cognitive" risk perception [12]. In our study, affective risk perception proved to be of more importance than the cognitive component with respect to psychological distress, underscoring the complexity and heterogeneous character of risk perception. Therefore we postulate that genetic counselling should also address the way in which women process the information about their given risk estimate (the cognitive dimension). Obviously, more attention is needed with respect to achieving tolerable levels of psychological distress (the affective dimension) in order to enhance a sound processing of information. Although Hopwood and colleagues (2001) showed no significant reduction in cancer worries after risk counselling, implying that it is not sufficient to provide only numerical information [11], other studies reported a decrease in psychological distress after (extra) genetic counselling [13,14]. By addressing both cognitive and affective aspects of risk perception in more detail in future clients, counselling can be optimised, which hopefully will result in less psychological distress in particular more vulnerable women.

Hereditary breast cancer implies that the disease or its risk may affect every family member on a psychological level [15]. Women from breast cancer families frequently show elevated levels of distress [1-3,10,16,17]. Influences on levels of psychological distress are observed from the nature of kinship [11,18-20], and time elapsed since a relative got breast cancer [9]. However, in all these studies the nature of the kinship that has been investigated concerned the mother-daughter relation.

We specifically differentiated between different kinds of kinship, and we found that particularly having had a sister diagnosed with breast cancer and having been closely involved in the disease process of the sister was associated with increased distress. Further, we demonstrated that the elapsed time since diagnosis is also of importance with respect to the level of psychological distress. Findings by others and ourselves add to the awareness that experiences with the diagnosis, the disease process, and loss due to breast cancer in relatives, are important predictors of psychological distress. Identifying such risk factors for breast cancer specific distress may be enabled by studying the family dynamics in the participating families.

Although the impact of the breast cancer surveillance process on psychological distress has previously been studied as well, most data have been obtained from population-based screening programmes (concerning an older age group, > 50 years, not selected for family history), or originate from the era before that genetic testing/counselling procedures were available [21-23]. Hence, these results cannot easily be extrapolated to our study population, being mainly < 50 years of age, and belonging to families with identified or assumed genetic susceptibility.
In our study, performed in a homogeneous group of women at increased risk for hereditary breast cancer, it was found that the course of distress during the surveillance programme for the total group did not exceed clinically relevant levels of psychological distress. Furthermore, it appeared that the type of examination (i.e. physical examination alone or in combination with mammography and MRI) did not have an effect on the course of psychological distress. So, our data add new information to the already existing literature demonstrating that adhering to breast cancer surveillance does not overly distress the women in general, which is reassuring. However, the courses of psychological distress did significantly differ for some of the identified more vulnerable subgroups (young overperformers of BSE, risk overestimators, and women being closely involved in the breast cancer process of a sister). These observations confirm that the recognised subgroups are indeed more vulnerable.

To our knowledge, our study was the first to address factors predicting psychological distress in high-risk women at different time points during breast cancer surveillance. By investigating different aspects of psychological distress and factors that may be predictive for the level of psychological distress later on in the surveillance programme, physicians are provided with useful information about which women may be more vulnerable for experiencing increased psychological distress, and may need extra attention and support. Furthermore the concept of coping, which is of influence on the level of psychological distress, is relatively new in the field of hereditary breast cancer. Particularly the observation that passive coping has a negative impact on the level of psychological distress, is an important finding. Similar results regarding the unfavourable impact of passive coping have been reported among breast cancer patients [24] and among chronic pain patients [25]. The knowledge of this association in this group of women offers the opportunity to address type of coping in cases where negative coping styles are used, with the hope that particular women may ultimately benefit in terms of levels of psychological distress.

A large group of women consented to participate in this clinical study, which included completing several questionnaires at many moments. Participation in such a study may be experienced as helpful for some women but may also add extra psychological distress when undergoing the screening in others. Therefore, it is of importance to consider some methodological issues that may influence the results of the study. First, because of the large number of questionnaires, which had to be completed at each measurement moment, the reliability of the responses could have been influenced.

Indeed, it is possible that the length of these questionnaires could have caused less motivation to respond seriously, or may have resulted in habituation because of recognition of the questions. Second, in a repeated measures design the women ultimately may develop a resistance to keep filling in the questionnaires, which may cause loss to follow-up. In our psychological study, 49 of the participants (13.7%) were lost to follow-up. The reasons for this in our study were: finding their participation in the study too much of a psychological burden; being preoccupied with a recent breast cancer diagnosis in a relative; having developed breast cancer herself, turning out to be a non-proven BRCA1/2 mutation carrier; or deciding to have a prophylactic mastectomy. Third, it needs to be critically considered which of the questions/questionnaires are really needed to maintain reliable and valid results from this type of studies. Questions providing overlapping information can be tracked by methods of item-response theories (e.g. RASCH-modelling or Structural Equation Modelling).

Clinical implications

The most important and reassuring finding from our study is that the mean distress levels during the surveillance programme do not exceed levels of clinically relevant psychological distress. This means that on average the surveillance programme does not impose a threat to the psychological well being of women at increased risk of hereditary breast cancer, and most women will not be in need of psychological treatment during the surveillance process. On the other hand, we identified subgroups of more vulnerable women, who may benefit form additional support. This knowledge provides extra indications for health care professionals on how to promptly identify those in need of additional psychosocial support or psychological treatment. It is obvious that physicians should be aware that the recognised more vulnerable subgroups of women are at risk for increased psychological distress. So, discussing issues like the frequency of breast self-examination, experiences with cancer in the family, and both components of risk perception, may provide extra information to the physicians with respect to the fears and the degree of psychological distress of the women in question. The different coping mechanisms that were found to be associated with higher or lower levels of distress may provide physicians with important clues about the areas in which problems can occur, or in which (indirectly) positive changes in distress may take place. The negative coping mechanisms were passive coping, and to a lesser extent a palliative reaction pattern. A physician should be especially aware of signals of a passive coping style and a palliative reaction pattern such as isolation from others, depression, or use of tranquillizers. The same holds for women who appear to cogitate about the past, or fantasize a lot.

We suggest considering additional support for the following subgroups.

- Women who excessively examine their own breasts, particularly when they are younger than 40 years of age, may benefit from additional psychological counselling to learn to better cope with their fear.
- For women who overestimate their own risk of developing breast cancer, whereby the affective component is more associated with increased psychological distress than the cognitive component, extra support may initially consist of additional genetic counselling to further explore why a woman overestimates her risk. Depending on the problem, extra information on the accurate risk figures may be offered, and if particularly the affective component is involved referral to a psychologist may be considered to gain insight into the factors that prevent accurate risk perception and to eventually address these factors.
- The women who are closely involved in a sister's cancer process may benefit from general psychological support to learn to adequately manage their distress and concerns about their sister's health and life.

- Women with a negative coping style may also benefit from general psychological support to learn to get insight in their particular way of dealing with problems and to enhance more adequate coping strategies.

Obviously, the kind of help that could be offered to a more vulnerable woman depends on the woman's wishes and motivation to receive additional professional support. The clinician's attention should address the dynamics of the woman's distress, her learning and adjustment capacities and perhaps most importantly her willingness to undergo professional psychological support. Furthermore, recognition of the specific area of her fear can help to offer more specialized help.

Directions for future research

On the basis of the variables identified in this thesis as factors associated with an increased degree of psychological distress it would be useful to develop a user-friendly one-page questionnaire to provide a tool for health care professionals enabling the identification of women who may be more vulnerable for psychological distress. This questionnaire should contain questions about the following topics: the frequency of breast self examination, risk perception (both cognitive as well as affective), the occurrence and time of diagnosis of breast cancer in relatives, the type of relationship with these relatives, the degree of involvement in the disease process of this relative, and the type of coping style. Since the majority of the high-risk women adhering to regular surveillance are not overly distressed, most women will not be in need for psychological counselling. However, for those who are found to be more vulnerable, extra intervention or support may be of benefit and therefore offered, focussing on the particular stressors of a specific woman. It would be of most interest to study the value and impact of such an intervention in a randomised study-design.

Because the last measurement moment analysed in the current psychological study was approximately 9 months after the initial measurement we did not obtain longer follow-up data. Further, since these data are not yet available from the literature, this large and compliant group of high-risk women would be most appropriate to further address the issue of psychological distress after a longer follow-up period. It has been mentioned that being at increased risk for hereditary breast cancer is a family affair for most of the women. Therefore, it would be most useful to more specifically examine the family dynamics in this group of high-risk women, regarding family communication and social support. Finally, we hope that some of the suggested future research questions will be addressed in the near future, resulting in more knowledge about this group of high-risk women and ultimately will lead to a more individualised and appropriate care for a specific woman and family.

References

1. Kash KM, Holland JC, Halper MS, et al: Psychological distress and surveillance behaviors of women with a family history of breast cancer. J Natl Cancer Inst 84:24-30., 1992
2. Lerman C, Kash K, Stefanek M: Younger women at increased risk for breast cancer: perceived risk, psychological well-being, and surveillance behavior. J Natl Cancer Inst Monogr 16:171-6, 1994
3. Lerman C, Daly M, Sands C, et al: Mammography adherence and psychological distress among women at risk for breast cancer. J Natl Cancer Inst 85:1074-80., 1993
4. Epstein SA, Lin TH, Audrain J, et al: Excessive breast self-examination among first-degree relatives of newly diagnosed breast cancer patients. High-Risk Breast Cancer Consortium. Psychosomatics 38:253-61., 1997
5. Brain K, Norman P, Gray J, et al: Anxiety and adherence to breast self-examination in women with a family history of breast cancer. Psychosom Med 61:181-7., 1999
6. Erblich J, Bovbjerg DH, Valdimarsdottir HB: Psychological distress, health beliefs, and frequency of breast self- examination. J Behav Med 23:277-92., 2000
7. Watson M, Lloyd S, Davidson J, et al: The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. Br J Cancer 79:868-74., 1999
8. Kash KM, Holland JC, Osborne MP, et al: Psychological counseling strategies for women at risk of breast cancer. J Natl Cancer Inst Monogr 17:73-9, 1995
9. Meiser B, Butow P, Schnieden, V: Psychological adjustment of women at increased risk of developing hereditary breast cancer. Psychology, Health and Medicine 5:377-389, 2000
10. Lloyd S, Watson M, Waites B, et al: Familial breast cancer: a controlled study of risk perception, psychological morbidity and health beliefs in women attending for genetic counselling. Br J Cancer 74:482-7., 1996
11. Hopwood P, Shenton A, Lalloo F, et al: Risk perception and cancer worry: an exploratory study of the impact of genetic risk counselling in women with a family history of breast cancer. J Med Genet 38:139., 2001
12. Hopwood P: Genetic risk counselling for breast cancer families. Eur J Cancer 34:1477-9., 1998
13. Cull A, Anderson ED, Campbell S, et al: The impact of genetic counselling about breast cancer risk on women's risk perceptions and levels of distress. Br J Cancer 79:501-8., 1999
14. Lerman C, Schwartz MD, Miller SM, et al: A randomized trial of breast cancer risk counseling: interacting effects of counseling, educational level, and coping style. Health Psychol 15:75-83., 1996
15. DudokdeWit AC, Tibben A, Frets PG, et al: BRCA1 in the family: a case description of the psychological implications. Am J Med Genet 71:63-71, 1997
16. Lerman C, Schwartz M: Adherence and psychological adjustment among women at high risk for breast cancer. Breast Cancer Res Treat 28:145-55., 1993
17. Zakowski SG, Valdimarsdottir HB, Bovbjerg DH, et al: Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer. Ann Behav Med 19:362-9., 1997
18. Wellisch DK, Gritz ER, Schain W, et al: Psychological functioning of daughters of breast cancer patients. Part II: Characterizing the distressed daughter of the breast cancer patient. Psychosomatics 33:171-9., 1992
19. Wellisch DK, Gritz ER, Schain W, et al: Psychological functioning of daughters of breast cancer patients. Part I: Daughters and comparison subjects. Psychosomatics 32:324-36., 1991
20. Erblich J, Bovbjerg DH, Valdimarsdottir HB: Looking forward and back: distress among women at familial risk for breast cancer. Ann Behav Med 22:53-9., 2000
21. Gilbert FJ, Cordiner CM, Affleck IR, et al: 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., 1998
22. Scaf-Klomp W, Sanderman R, van de Wiel HB, et al: Distressed or relieved? Psychological side effects of breast cancer screening in The Netherlands. J Epidemiol Community Health 51:705-10, 1997
23. Gagnon P, Massie MJ, Kash KM, et al: Perception of breast cancer risk and psychological distress in women attending a surveillance program. Psycho-Oncology 5:259-269, 1996
24. Kim Y, Valdimarsdottir HB, Bovbjerg DH: Family histories of breast cancer, coping styles, and psychological adjustment. J Behav Med 26:225-43, 2003
25. Snow-Turek AL, Norris MP, Tan G: Active and passive coping strategies in chronic pain patients. Pain 64:455-62, 1996

Summary / Samenvatting

Summary

Although familial/hereditary breast cancer has been recognized for a long time, it is only since the identification of the breast cancer predisposition genes BRCA1 and BRCA2, in 1994 and 1995, respectively that it became possible to specifically further identify and study hereditary breast cancer as a separate entity. First, by means of genetic testing, it became possible to identify women having a mutation in either the BRCA1 or BRCA2-gene, which is known to be associated with a significantly increased cumulative lifetime risk of breast cancer, already starting from a young age on. Further, if a genetic susceptibility for breast cancer in the family is suspected and a mutation is not identified, the cumulative lifetime risk for breast cancer for family members may be estimated by means of risk modelling using genetic-epidemiological tables.

Surveillance programmes were initiated in the Netherlands addressing specifically female relatives before the age of 50, because their risk increase starts well before that age (50 is the age at which population-based screening is started in the Netherlands). In the Netherlands, the MRISC study was initiated in 1999 for women at high risk of hereditary breast cancer, investigating the value of mammography and MRI in the early detection of breast cancer. The studies in this thesis have been performed within the context of this MRISC study focussing on the psychological aspects and quality of life of such a surveillance programme for breast cancer. So far, it is not known what the psychological impact of potential distressing examinations is in this group of women with respect to the extent and course of psychological distress, and the possible factors associated with psychological distress. Therefore, it is important to obtain more data on this issue.

In this thesis we explored several psychological aspects of being at risk for hereditary breast cancer and adhering to regular surveillance. The psychological sub-study, performed within the context of the national MRISC study, was conducted at the Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Clinic in Rotterdam. The participants were 357 women at risk for hereditary breast cancer adhering to a regular breast cancer surveillance programme, and were classified in 3 risk categories by means of cumulative life time risk of developing breast cancer (category 1: identified BRCA1/2 mutation carriers, and categories 2 and 3 with a cumulative life time risk between 30-50% and 15-30%, respectively). They filled in questionnaires on demographic variables, coping and psychological distress (breast cancer specific and general) at different moments during the surveillance programme: two months before an appointment at the family cancer clinic, the day of the surveillance appointment and one to four weeks after the surveillance appointment. These assessment points were repeated around the second scheduled appointment six months later. In the course of the study, 49 patients did not continue to fill in the questionnaires for various reasons.

In *Chapter 1* the literature on different topics closely related to the items addressed in this thesis is reviewed, including the predisposing breast cancer genes, the consequences of genetic testing, as well as the risk assessment procedures. Furthermore the two main management options for women at increased risk of hereditary breast cancer, being either regular surveillance or prophylactic mastectomy, are touched on. The psychological implications of having a family history of breast cancer, of genetic testing and adhering to surveillance are discussed as well. And finally, the aim, research questions and study procedure are described.

In *Chapters 2 - 4*, the results are reported regarding the impact of three factors on the degree of psychological distress, namely the frequency of breast self-examination, the perception of the lifetime breast cancer risk by a respective woman, and the impact of the involvement of having relatives affected with breast cancer.

In *Chapter 2* we found in a sample of 316 women that the majority (57%) performed monthly BSE, 20% did not perform BSE regularly or not at all, and 13% were overperformers doing BSE at least once a week. The group of women performing excessive breast self-examination (BSE) and being younger than 40 years of age experienced significantly more breast cancer specific distress (p=0.03). These women represented 15% of all women below 40 years of age in the study sample. This suggests that education, particularly of younger women, about the frequency, the method and the timing (in premenopausal women) of performing BSE may be worthwhile.

In *Chapter 3*, the impact of breast cancer risk perception on psychological distress is addressed in 351 women with a median age of 40.5 years (range 21-63), whereby distinction was made between cognitive and affective risk perception. We found that the accurateness of cognitive risk perception was significantly different in the three risk categories, being 60%, 43.7%, and 33% in mutation carriers, categories 2 and 3 respectively. While a cognitive risk overestimation was found to be associated with increased psychological distress, the effect of affective risk perception was much stronger. Apart from how high (or low) the women thought their risk of developing breast cancer was (the cognitive perception), we observed that the women who "felt" that their risk of developing breast cancer was high reported significantly more psychological distress. These data are of importance for physicians in order to appropriately assess the specific needs of the women, and to eventually refer them for further counselling and support.

In *Chapter 4*, our results on the association between having relatives affected with breast cancer and psychological distress is described (n=347). Close involvement in a sister's breast cancer resulted in a higher level of breast cancer specific distress (n=94), especially when the breast cancer diagnosis occurred less than three years ago (n=30). We did not find a significant association with (being involved in) the breast cancer process of a mother. Further, general distress was not associated with the experience of breast cancer in the family. These findings underline the need to pay close attention to the experience of breast cancer in family members, when counselling women at risk for hereditary breast cancer, discussing the pros and cons of predictive testing and the various management options. The results presented in *Chapter 2 to 4* underscore that it is important to address these specific issues carefully and systematically in order to appropriately assess psychological distress and to adequately refer vulnerable women for additional support.

In *Chapter 5* the acceptance and burden of Magnetic Resonance Imaging as a surveillance modality, incorporated in the regular breast cancer surveillance programme, was investigated in 178 women. They completed an extra questionnaire on their experiences and their perceptions of the different parts of the surveillance programme. Also their preference for a diagnostic method was addressed assuming equal value. MRI was reported to cause limited discomfort and to provide the most reassurance of breast cancer being absent in case of a favourable surveillance outcome. It has to be noted however, that women who did not want to continue with screening by means of MRI, did not participate in this substudy either (5% in the national MRISC-study).

Subsequent analyses addressed the course of psychological distress around two successive, bi-annual surveillance appointments (n=357) *(Chapter 6)*. In general, psychological distress remained within normal limits during the surveillance programme. Further, we did not observe a difference in the course of psychological distress in women scheduled for either a physical examination alone or in combination with mammography and MRI. Therefore, we concluded that the surveillance procedures itself did not result in excessive psychological distress.

Additionally, we specifically examined the course of distress in the three identified more vulnerable subgroups. Significant differences were found in the courses of breast cancer specific distress in the group of women excessively examining their breasts compared with the other women, and in women overestimating their breast cancer risk compared to under-estimators (cognitive risk perception). The first group reported significantly higher breast cancer specific distress both before and after the appointment while the remaining women had a lower level of distress before the clinic visit that decreased further after the appointment. Around the second surveillance appointment the excessive breast self-examiners did not differ from the remaining women, but the degree of breast cancer distress remained higher in the group over-examiners. The risk overestimators reported significantly higher breast cancer specific distress, particularly on the day of the second clinic appointment, which sharply decreased thereafter.
On the other hand, the course of general distress significantly differed in women who were closely involved in the breast cancer process of a sister. After the second surveillance appointment, these women reported more general distress than the remaining women.

Apparently, general and breast cancer specific distress were associated with different types of variables. Characteristics typically associated with breast cancer, such as excessive breast self examination and breast cancer risk overestimation (cognitive), related to more breast cancer specific distress, while the course of general distress is associated with being involved in the breast cancer process of a sister. The latter variable has obviously to do with breast cancer, but it is also possible that other factors besides breast cancer perhaps were more prominent, such as grief, sadness and worries about the life of ones sister. Since the latter factors were not necessarily focused on breast cancer, they therefore might have become manifest in feelings of general distress.

Because it is useful to identify those women who are at risk of experiencing an increased level of psychological distress, several predictive regression-models were studied and results are presented in *Chapter 7.* General and breast cancer specific distress were subdivided into four different forms of distress, intrusion and avoidance (the components of breast cancer specific distress), and anxiety and depression (the components of general distress). First, we found that the level of distress on the day of the surveillance appointment was most predictive of the levels of distress across time, which suggests that the surveillance procedure itself did not induce the distress. Women with higher levels of distress at baseline remained more vulnerable for distress on the subsequent assessment moments. Furthermore, we found that the women's coping style was particularly relevant in predicting the various forms of psychological distress, and we were able to distinguish between more versus less favourable coping styles. The more favourable coping styles were: expressing emotions, seeking social support and being able to think about problems in a reassuring way. These ways of coping appeared to have positive effects on intrusion and avoidance (breast cancer specific distress) approximately 9 months after the assessment moment of coping style. The level of intrusive thoughts around the second surveillance appointment was positively (i.e. in a favourable way) influenced by being able to have comforting thoughts. Expressing emotions and seeking social support tended to positively influence avoidance around the second surveillance appointment. Less favourable coping styles were: seeking distraction (i.e. palliative reaction pattern) and passive coping. A palliative reaction pattern was found to have a negative impact on intrusion on all assessment moments. Similarly, passive coping was mainly associated with elevated levels of general anxiety on all assessment moments.

Feelings of depression were not associated with any of the coping styles; the best predictor for depressive feelings across time was the depression level at the baseline assessment. The knowledge of these associations may be of help for healthcare workers in the field in order to appropriately identify the necessary counselling and support for high-risk women.

In *Chapter 8* we used the more advanced analysis method of Structural Equation Modelling (SEM) to get a better insight in the exact impact of coping on psychological distress. An important finding was that coping style did not have an impact on the course of distress, while it did on the levels of distress, implying a more trait like function of coping in this study. Favourable coping styles appeared to be seeking social support, expressing emotions and having comforting thoughts. This is in accordance with the findings from the analyses in *Chapter 7*, confirming the association. The SEM-analyses further revealed that showing a palliative reaction pattern had a negative impact on the levels of breast cancer specific distress. The most striking result however, was that passive coping had a profound negative impact on all the distress measures. This suggests that passive coping has to be considered as an unfavourable way of dealing with problems in. Our findings indicate that it is very important to address this issue in high-risk women and to eventually refer these women for eventual additional counselling and support.

In *Chapter 9* we discuss the results of our study in view of results from other studies, as well as clinical implications of our findings, and we provide some directions for future research.

Samenvatting

Hoewel het al langer werd aangenomen dat borstkanker in bepaalde families veroorzaakt werd door een erfelijke aanleg, duurde het tot de ontdekking van de predispositie genen voor borst-/eierstokkanker (BRCA1 en BRCA2), respectievelijk geïdentificeerd in 1994 en 1995, vooraleer het mogelijk werd om dit in bepaalde families verder te onderzoeken en aan te tonen. Door middel van een DNA-test die wordt ingezet op grond van vastgestelde criteria betreffende de familiebelasting, is het mogelijk geworden die vrouwen te identificeren die een mutatie in het BRCA1 of BRCA2 gen hebben. Deze aangetoonde genmutatiedraagsters hebben reeds vanaf jonge leeftijd een significant verhoogd risico op het krijgen van borst-(en/of eierstok-)kanker. Echter, door middel van erfelijkheidsonderzoek wordt in de families waar een erfelijke aanleg wordt vermoed een mutatie in BRCA1/2 slechts aangetoond in ongeveer 20-30% van de gevallen. In de overige families is er waarschijnlijk sprake van een nog onbekende erfelijke factor, die als zodanig ook niet kan worden aangetoond. In dergelijke families wordt het cumulatieve risico op het krijgen van borst- en/of eierstokkanker tijdens het leven voor een specifieke vrouw berekend aan de hand van gevalideerde genetisch epidemiologische tabellen en risicomodellen.

Voor vrouwen met een verhoogd risico op het krijgen van borstkanker op grond van een geïdentificeerde of aangenomen erfelijke aanleg, werd vanaf het begin van de jaren negentig regelmatige controle geadviseerd. Later is dit uitgewerkt in specifieke controleprogramma's, terwijl er vanuit de kliniek ook studies werden geactiveerd om de waarde van borstkankercontrole op deze jonge leeftijd te onderzoeken. In 1999 werd in Nederland de nationale, prospectieve MRISC-studie gestart voor vrouwen met een verhoogd risico op erfelijke borstkanker, waaraan zes academische centra participeerden. In deze studie wordt de bijdrage en de waarde van de mammografie en MRI (Magnetic Resonance Imaging) onderzocht bij de vroegdetectie van erfelijke borstkanker. Omdat het meedoen aan een regelmatig controleprogramma een belangrijke handelingsoptie is voor hoog-risico vrouwen uit belaste families en omdat de onderzoeken die gedaan worden gepaard kunnen gaan met angst en onzekerheid voor een specifieke vrouw, mede in het licht van de ervaringen met kanker bij familieleden die de meeste hebben meegemaakt, werd het van belang geacht ook de psychologische implicaties hiervan in kaart te brengen, temeer daar hierover wereldwijd nog geen prospectieve data beschikbaar waren.

De gegevens waarover in dit proefschrift wordt gerapporteerd werden verkregen van 357 vrouwen uit families met al of niet een aangetoonde erfelijke aanleg, die voor borstkanker worden gecontroleerd op de Polikliniek Erfelijke Tumoren van het Erasmus MC-Daniel den Hoed Oncologisch Centrum in Rotterdam. De meeste vrouwen participeerden in de nationale MRISC studie, waarbij zij op grond van vastgestelde criteria werden ingedeeld in één van de drie risicocategorieën (1: mutatiedraagsters, 2 en 3: risico op borstkanker respectievelijk 30-50% en15-30%). Zij vulden op verschillende momenten gedurende het controleschema vragenlijsten in betreffende demografische gegevens, coping stijl, en psychologische distress (borstkanker-specifiek, en algemeen). Deze vragenlijsten werden ingevuld op de volgende momenten: twee maanden voor de controle in de kliniek, de dag van de controle, en 1 tot 4 weken na de controle. Dit werd verricht rondom 2 halfjaarlijkse controles, waarbij er eenmaal enkel lichamelijk onderzoek werd verricht, en de andere keer ook beeldvormend onderzoek plaatsvond. De onderzoeksgegevens betreffen dus een periode van ongeveer 9 maanden.

In *Hoofdstuk 1* van dit proefschrift wordt een overzicht gegeven van de beschikbare literatuur betreffende verschillende onderwerpen die nauw gerelateerd zijn aan het onderwerp van dit proefschrift. De implicaties van de identificatie van een borstkanker genmutatie worden kort besproken, evenals de procedure van risico-inschatting. Tevens worden de twee belangrijkste handelingsopties die in Nederland besproken worden met vrouwen met een verhoogd risico op erfelijke borstkanker beschreven: regelmatige controles en profylactische mastectomie. Er wordt een overzicht gegeven van de bekende psychologische implicaties van het veelvuldig voorkomen van borstkanker in de familie, van het ondergaan van de DNA-test en van het meedoen aan regelmatige controles. En ten slotte volgt er een overzicht van het doel van deze studie, de onderzoeksvragen, en de manier waarop het onderzoek werd uitgevoerd.

In de *Hoofdstukken 2 - 4* worden de resultaten besproken van de impact van drie verschillende factoren die mogelijk samenhangen met de mate van psychologische distress, namelijk: de frequentie van borstzelfonderzoek, de perceptie van het levenslange borstkanker risico, en de ervaring met familieleden die borstkanker hebben (gehad).
Uit onderzoek bij 316 vrouwen bleek dat borstzelfonderzoek regelmatig wordt gedaan door de meerderheid van de vrouwen (57%), terwijl 20% van de vrouwen geen of nauwelijks zelfonderzoek verrichtten, terwijl 13% dan weer minstens een keer per week zelfonderzoek doet (Hoofdstuk 2). We vonden wel dat vrouwen, jonger dan 40 jaar, die zelf hun borsten overmatig vaak controleren (ten minste 1 keer per week) een verhoogde mate van borstkanker specifieke distress ervaren. Dit betrof 15% van de vrouwen uit deze groep. Onze bevindingen suggereren dat het belangrijk is om het advies voor zelfonderzoek met vrouwen serieus te bespreken, waarbij de voorlichting aan met name jonge vrouwen ten aanzien van de manier van borstzelfonderzoek, de frequentie, en het tijdstip binnen de menstruele cyclus cruciaal is. Voorts is deze bevinding belangrijk omdat het de arts de mogelijkheid biedt hiernaar te informeren en een inschatting te maken van eventuele overbezorgdheid. Indien aan de orde, kan overwogen worden om de vrouw in kwestie verdere ondersteuning aan te bieden, via een mammacare-verpleegkundige, een genetisch consulent of psycholoog.

In *Hoofdstuk 3* wordt de impact van de borstkanker risicoperceptie op het ervaren van psychologische distress beschreven, hetgeen werd onderzocht bij 351 vrouwen. Hierbij werd onderscheid gemaakt tussen de cognitieve perceptie van het risico en de meer gevoelsmatige risicoperceptie. We vonden dat de cognitieve risicoperceptie verschillend was in de 3 verschillende risicogroepen (respectievelijk 60% bij mutatiedraagsters, 43.7% en 33% in categorieën 2 en 3). Hoewel er een samenhang werd gevonden tussen cognitieve overschatting van het eigen borstkankerrisico en het ervaren van meer psychologische distress, was het effect van de gevoelsmatige (affectieve) risicoperceptie op het ervaren van psychologische distress veel sterker. Het bleek dat ongeacht hoe hoog (of hoe laag) de vrouw haar borstkankerrisico cognitief inschatte, die vrouwen die het risico voelden alsof het heel erg hoog was (affectieve perceptie) een significant hogere mate van psychologische distress rapporteerden. Deze gegevens zijn belangrijk voor de kliniek, omdat de betrokken oncologen, genetici, genetic counselors en andere hulpverleners die betrokken zijn bij de zorg voor deze vrouwen hierop kunnen letten en eventueel op kunnen ingaan. Ook voor de psycholoog is deze kennis belangrijk omdat er bij eventuele problemen of verwijzing aandacht aan besteed kan worden.

In *Hoofdstuk 4* worden de resultaten beschreven van de associatie tussen het hebben van familieleden met borstkanker en psychologische distress (n=347). We vonden dat vrouwen die nauw betrokken waren of waren geweest bij het borstkankerproces van een zus een significant hogere mate van borstkanker specifieke distress rapporteerden (n=94). Dit was voornamelijk aan de orde wanneer de borstkankerdiagnose bij de zus minder dan 3 jaar geleden was gesteld (n=30). In onze studie vonden we geen samenhang tussen psychologische distress en het optreden van borstkanker bij de moeder. We vonden ook geen relatie tussen de ervaringen met borstkanker in de familie en distress in het algemeen. Het feit dat vrouwen die borstkanker bij een zus meemaken meer distress rapporteren wijst erop dat het bespreken van ervaringen met borstkanker in de familie belangrijk is bij het counselen van deze vrouwen.

In *Hoofdstuk 5* werd onderzocht wat de vrouwen van de MRI als screenings-instrument vonden, en hoe ze dat beleefden. Hiervoor vulden 178 vrouwen een extra vragenlijst in waarbij gevraagd werd naar het eerder hebben ondergaan en de belevingen bij de verschillende onderdelen van het controleprogramma. Voorts werd aan de vrouwen gevraagd welk onderdeel van het controleprogramma ze verkozen, ervan uitgaand dat ze een zelfde effectiviteit hadden. Uit de gegevens blijkt dat het ondergaan van een MRI van het borstklierweefsel voor weinig ongemakken zorgde en dat een gunstige uitslag van het MRI onderzoek voor de meeste geruststelling zorgde betreffende het niet aanwezig zijn van borstkanker. Hierbij moet wel opgemerkt worden dat vrouwen die om een of andere reden al eerder hadden afgezien van een MRI onderzoek niet in deze analyse werden opgenomen (in de gehele MRISC studie betrof dit ongeveer 5%).

In de analyses beschreven in *Hoofdstuk 6*, werd bekeken hoe het beloop van psychologische distress was rondom twee opeenvolgende halfjaarlijkse controle-afspraken in de kliniek, en voorts werd onderzocht of er een associatie was tussen de aard van de controle (lichamelijk onderzoek alleen, of in combinatie met mammografie en MRI) en de mate van distress. We vonden hierbij dat de psychologische distress in het algemeen binnen normale spreidingswaarden bleef. Verder werden er geen significante verschillen gevonden in het beloop van de distress in relatie tot de aard van de controle. Hieruit blijkt derhalve dat de controle-procedures zelf niet voor een overmatige psychologische distress zorgen. Meer specifiek werd ook het beloop van psychologische distress bestudeerd voor de meer kwetsbare groepen, zoals we die eerder vonden *(zie hoofdstukken 2 tot en met 4)*. Er werden significante verschillen gevonden in het beloop van borstkankerspecifieke distress bij de vrouwen die te vaak hun eigen borsten controleerden in vergelijking met de andere vrouwen, en voor de vrouwen die hun eigen risico op het krijgen van borstkanker overschatten (cognitief) in vergelijking met de vrouwen die hun risico accuraat inschatten of onderschatten. Er werden tevens significante verschillen gevonden in het beloop van algemene distress bij vrouwen die van dichtbij betrokken waren geweest bij het borstkankerproces van hun zus in vergelijking met de overige vrouwen. Het bleek dat borstkankerspecifieke en algemene distress samenhingen met verschillende variabelen. Factoren die typisch met borstkanker te maken hebben, zoals de frequentie van borstzelfcontrole en de inschatting van het eigen borstkankerrisico, waren geassocieerd met borstkankerspecifieke distress, terwijl het beloop van algemene distress geassocieerd is met het nauw betrokken zijn bij het borstanker proces van een zus. Deze laatste variabele heeft uiteraard ook met borstkanker te maken, maar andere factoren dan borstkanker spelen hierbij waarschijnlijk ook een rol, zoals rouw, verdriet en zorgen om het leven van je een zus. Deze factoren zijn niet noodzakelijkerwijs gefocust op borstkanker en uiten zich dan hierbij meer in gevoelens van algemene distress.

De bovengenoemde drie variabelen komen ook bij de bestudering van het beloop van distress weer naar voren als meebepalend voor het ervaren van meer psychologische distress. Het is derhalve belangrijk om deze vrouwen als zodanig te herkennen, waarbij verschillende vormen van ondersteuning nodig kunnen zijn.

Voor artsen en hulpverleners op de polikliniek die te maken krijgen met hoog-risico vrouwen kan het nuttig zijn die vrouwen te herkennen die het qua psychologische distress zwaarder zouden kunnen krijgen in de periode na het polikliniekbezoek om eventueel de zorg aan te passen. Om deze reden werden in *Hoofdstuk 7* meerdere predictieve modellen onderzocht. De algemene en borstkankerspecifieke distress konden worden onderverdeeld in vier vormen van distress-gevoelens: intrusie en vermijding (de componenten van borstkankerspecifieke distress), en angst en depressie (de componenten van algemene distress). Voor deze vier uitkomstvariabelen zijn er modellen gepresenteerd en ontstond er een gedetailleerd overzicht van verschillende factoren die met de verschillende vormen van psychologische distress samenhingen. Allereerst vonden we dat het niveau van distress op de dag van het polikliniekbezoek het meest predictief was voor het niveau van psychologische distress op latere momenten. Dit suggereert dat de controle procedures zelf niet zozeer de distress veroorzaken. Vrouwen die een hogere mate van distress hadden op de dag van het controlebezoek bleven dit ook op latere momenten houden.

Verder vonden we dat de coping stijl (de manieren van omgaan met problemen) voorspellend was voor de mate van de verschillende vormen van psychologische distress. Hierbij werden meer adequate vormen van coping en minder adequate vormen van coping onderscheiden. Meer wenselijk waren het uiten van gevoelens, het opzoeken van sociale steun en het hebben van geruststellende gedachten. Deze manieren van omgaan met problemen hadden een positief effect op intrusie en vermijding (borstkankerspecifieke distress) bij het laatste meetmoment (circa 9 maanden na de beginmeting). Het niveau van intrusie rondom de tweede controle werd op een positieve manier beïnvloed (dit wil zeggen: daalde) door het hebben van geruststellende gedachten. Het uiten van emoties en het opzoeken van sociale steun hadden een positief effect op vermijding rondom het tweede controlebezoek. Minder adequate vormen van coping waren afleiding zoeken op een palliatieve manier, dat wil zeggen afleiding zoeken door bijvoorbeeld veel roken, alcohol drinken of eten, en passieve coping. De palliatieve reacties hadden een negatieve invloed op de mate van intrusie op alle meetmomenten. Een passieve coping stijl had een negatieve impact voornamelijk op angst, maar wel op alle meetmomenten. Gevoelens van depressie werden niet beïnvloed door de manier van coping; de beste voorspeller voor depressie op latere meetmomenten was het niveau van depressieve gevoelens op de dag van de eerste meting tijdens deze studie.

In *Hoofdstuk 8* werd gebruik gemaakt van een meer geavanceerde analyse techniek: Structural Equation Modelling (SEM) om een beter inzicht te kunnen krijgen in de exacte impact die coping heeft op psychologische distress. De meest belangrijke bevinding bij deze analyse was dat coping stijl geen invloed had op het beloop van psychologische distress, maar wel op het niveau van de distress; dit impliceert dat coping stijl hierbij meer beschouwd kan worden als een stabiel persoonlijkheidskenmerk, en dus niet situatie afhankelijk is. Positieve coping stijlen die hierbij naar voren kwamen waren het zoeken van sociale steun, het uiten van emoties en het hebben van geruststellende gedachten. Deze bevindingen komen overeen met de resultaten uit de analyse beschreven in *hoofdstuk 7*, en bevestigen dus deze eerder gevonden associatie.
The SEM-analyses lieten verder zien dat een palliatief reactiepatroon een negatieve impact had op de niveau's van de beide componenten van borstkankerspecifieke distress.

Wat als nieuw gegeven naar voren kwam was de aanzienlijke, negatieve impact van een passieve coping stijl ten aanzien van de vier componenten van psychologische distress. Hieruit kan worden opgemaakt dat een passieve coping stijl beschouwd kan worden als een niet-adequate manier van omgaan met problemen. Deze bevindingen wijzen erop dat het erg belangrijk is om de manier van omgaan met problemen te bespreken met vrouwen die een verhoogd risico op het krijgen van erfelijke borstkanker hebben, en indien relevant de vrouwen met een niet-adequate coping stijl door te verwijzen voor aanvullende counseling en zorg.

In *Hoofdstuk 9* worden de resultaten van de studies in dit proefschrift besproken in het licht van eerdere resultaten uit andere studies, worden er aanbevelingen gedaan voor de hulpverleners die op de polikliniek met deze hoog-risico vrouwen werken, terwijl we ook aanwijzingen geven voor mogelijk toekomstig onderzoek.

Dankwoord

En dan nu het dankwoord. Aan het einde van mijn promotietraject en het einde van mijn proefschrift zou ik graag van deze gelegenheid gebruik willen maken een aantal mensen te bedanken. Mensen die zeer direct betrokken waren bij de totstandkoming van dit proefschrift, maar ook een aantal mensen die op andere wijze bij mij betrokken zijn geweest en die ik hier dus ook zeker wil noemen.

Om te beginnen wil ik graag de ruim 350 vrouwen die mee hebben gedaan aan dit onderzoek bedanken voor jullie bereidheid om de grote hoeveelheid vragenlijsten in te vullen rondom de controles. Dankzij jullie medewerking was ik in staat een goed beeld te krijgen van wat het betekent om een verhoogd risico op borstkanker te hebben.
Ook zou ik graag mijn eerste promotor en dagelijks begeleider Prof. dr. Tibben willen bedanken. Beste Aad, ik vond het erg fijn en leerzaam om door je begeleid te worden. Met name op het gebied van de psychologie achter de vrouwen met een verhoogd risico op borstkanker heb ik veel geleerd, maar ook op andere gebieden die met het doen van onderzoek te maken hebben, zoals het leren opbrengen van geduld en relativeringsvermogen.
Voor mijn tweede promotor Prof. dr. Klijn ook een speciaal woord van dank. Beste Jan, jou zou ik graag willen bedanken voor de betrokkenheid die je toonde bij dit onderzoek en je inbreng van commentaar op artikelen en abstracts.
Mijn co-promotor dr. Seynaeve: beste Caroline, met name je inzet voor en enthousiasme over het onderzoeksproject heb ik enorm gewaardeerd, evenals je zorgvuldige commentaar op mijn artikelen. Doordat je altijd heel erg betrokken bent geweest bij wat ik aan het doen was, bleef ik erg gemotiveerd.

De leden van de kleine commissie: Prof. dr. Passchier, Prof. dr. Niermeijer en Prof. dr. Cornelisse wil ik graag bedanken voor hun inzet bij het beoordelen van het manuscript, en het goedkeuren ervan! Prof. dr. Niermeijer voor de suggesties ter verbetering die hij heeft gedaan en die ik erg op prijs heb gesteld. En Prof. dr. Passchier, beste Jan, niet alleen voor je functie als secretaris van de promotiecommissie wil ik je bedanken, maar zeker ook voor de kansen die je mij gegeven hebt op de afdeling zodat ik me kon ontwikkelen als onderzoekster en als docent. Ook de overige commissieleden wil ik graag bedanken voor hun interesse in dit onderzoek en proefschrift.

En dan mijn gezellige collega's van de afdeling Medische Psychologie en Psychotherapie. Toen ik als pas afgestudeerd 'broekie' vanuit Tilburg naar het verre Rotterdam kwam, vond ik het erg fijn om zo hartelijk ontvangen te worden als nieuwe collega. Gezellig koffie drinken, lunchen, af en toe een vrijdagmiddag borrel!
In de loop der tijd heb ik een kamer gedeeld met verschillende mensen die ik graag zou willen bedanken omdat ik ze allemaal leuke kamergenoten vond: Rianne, Reinier en Antina. En natuurlijk mijn huidige kamergenoot Jolie, ik vind het leuk dat ik het zo goed met je kan vinden, ook buiten werktijd om. Andere collega's die ik specifiek wil noemen zijn Jacqueline, ik vind het erg jammer dat je inmiddels weg bent van de afdeling, maar ben blij dat we nog zoveel contact hebben (zie verderop). Paula, onze congresreizen naar San Antonio en onze uitstapjes naar New Orleans (N'awlins) vond ik heel bijzonder! Veel succes met de afronding van je proefschrift, nog even volhouden! Iris, mijn leuke buurvrouw. Jammer dat je steeds meer op je andere werkplek vertoeft. Saskia, een hele gezellige en ook hele lieve collega: samen vlammen als Bridget en Sonja met de professionaliteitbewaking van docenten! Leonieke, jou moet ik natuurlijk goed in de gaten houden wat betreft de reisjes die je nog gaat ondernemen. Ik wil de wedstrijd wel winnen hoor.

Hoeveel staat het inmiddels? Benno en Adriaan, ik vind het erg leuk om met jullie over onderwijs, zowel inhoudelijk als ook over lastige situaties, te praten. Hugo, niet alleen voor je onmisbare statistische inbreng op al mijn artikelen wil ik je graag ontzettend bedanken, maar ook voor je motiverende peptalks op momenten dat ik door alle spss-variablenames- and –values het bos niet meer zag. Wim, sinds zo'n anderhalf jaar werk ik op verschillende projecten van jou. Dit doe ik met veel plezier en ik hoop dat we deze samenwerking nog een tijd kunnen voortzetten.
Overige (ex-)collega's: Anita, Cecile, Marleen, Chantal, Vivian, Saskia B., Josien, Anne-Sophie, Cora, Michelle, Jan van B., Noortje, Samantha, Jan O., Ruud, Joke, en van het secretariaat Margreet, Ingrid, Loes†, Alice en Ankey wil ik bedanken voor de gezelligheid bij de koffie en de lunch.

Nog drie mensen wil ik graag apart bedanken voor het invoeren van de data, het uittypen van de interviews, het versturen van alle vragenlijsten en andere logistieke zaken: Marja D., Yvonne en met name Marja N. die echt vanaf het begin van het project tot het einde betrokken is geweest. Dank jullie wel!
Dan wil ik hier nog een plaatsje reserveren voor Karlijn, als zeer toegewijde stagiaire heb je een hele mooie bijdrage geleverd aan dit proefschrift (zie hoofdstuk 8). Hartstikke bedankt!

Ook van de mensen werkzaam op de Daniel den Hoed Kliniek wil ik een aantal mensen die mij zeer behulpzaam zijn geweest bij het onderzoek bedanken: Mieke K., bedankt voor het helpen uitzoeken van een heleboel dingen, maar ook voor de vele gezellige etentjes, ik zie je veel meer als vriendin dan als collega! Petra, voor het opzoeken en het doorgeven van gegevens. Cecile, voor het meelezen van artikelen. Karina en Madeleine, voor het meelezen van mijn artikelen en voor het mogen meekijken op jullie poli's. Van het Instituut Maatschappelijke Gezondheidszorg wil ik Harry, Marie-Louise en Rian bedanken voor het meelezen van mijn stukken. De leden van de Werkgroep Familiaire Tumoren van de NVPO wil ik bedanken voor de interessante vergaderingen en leuke contacten.
Annie Schillings wil ik graag bedanken voor het mooie ontwerp dat zij heeft gemaakt voor de kaft van dit proefschrift.

Tot slot nog een aantal personen die buiten mijn proefschrift en mijn werk om, bij mij betrokken zijn. Twee lieve vriendinnen: Nina, onze regelmatige eet- en kletsavondjes vind ik altijd erg gezellig! En Mieke S., jou ken ik al uit Tilburg, ik vind het leuk dat we nog steeds contact hebben, ik vind het altijd erg gezellig om elkaar weer op de hoogte te kletsen van elkaars belevenissen. Dan nog Remy, jou ken ik ook uit Tilburg, we hebben een heleboel leuke dingen gedaan, maar de Winterefteling steekt er nog altijd met kop en schouders boven uit: SUPERpark! En Peter, pasta a la Peter eten en veel vaker gaan quizzen in de Ierse pub!

Mijn twee lieve paranimfen: Jacqueline, ik vind het erg leuk dat je mijn paranimf wilt zijn, je bent een ontzettend lieve meid met wie ik enorm kan lachen en bij wie ik eigenlijk het gevoel heb dat ik altijd terechtkan. En Carin, mijn andere paranimf, deze dingen gelden ook voor jou. Ik kijk altijd erg uit naar onze etentjes of casino-avondjes. Verder behoort ons Noordkaap-avontuur nog altijd tot een van mijn meest bijzondere vakanties, en ik vind het heel fijn dat ik daar met jou ben geweest. En het parachutespringen was natuurlijk ook een onvergetelijke ervaring!

En dan mijn familie: mijn broer Robert en zijn vriendin Maaike, altijd gezellig om elkaar te zien en te kolonisten. En oh ja, de volgende keer terrasje-pakken trakteren wij! En dan mijn lieve ouders, jullie wil ik eigenlijk voornamelijk bedanken dat jullie er gewoon zijn, altijd en onvoorwaardelijk. Hoe ouder (en ook steeds een beetje wijzer, toch?) ik word, hoe meer ik besef wat het belang is van het kunnen terugkijken op een leuke jeugd en het beschikken over een veilige thuishaven!
En dan Ruurd, mijn lieve vriend. Sinds de laatste anderhalf jaar van het promotietraject ben jij in mijn leven en ik kan alleen maar zeggen dat ik daar ontzettend blij mee ben. Al heel snel pikte je het verschil tussen 'nu alleen maar even luisteren' en 'het vinden van een concrete oplossing' op ☺. Maar niet alleen daarvoor wil ik je bedanken, ook voor de fijne tijd die we hebben en voor het feit dat je gewoon een ontzettend leuke vent bent!

Curriculum Vitae

Silvia van Dooren was born on May 2nd, 1976 in Heerlen, the Netherlands. She graduated form high school (gymnasium ß, Bernardinuscollege, Heerlen) in 1994. In 1999 she obtained her MA-degree in developmental and educational psychology at the Katholieke Universiteit Brabant, in Tilburg. Her internship was at Zonhove, where she worked with multiple handicapped children (Dr. M. J.A. Feltzer), and for her Master's thesis she conducted a study at elementary schools in Aruba, where she worked on standardization and norms for MASTER: A computerized screener for learning disabilities (Prof. Dr. H. van der Vlugt & Prof. Dr. F. van de Vijver).

In February 2000 she began her PhD study at the department of Medical Psychology and Psychotherapy of the Erasmus MC in Rotterdam (Prof. Dr. A. Tibben), in collaboration with the departments of Medical and Surgical Oncology of the Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam (Prof. Dr. J.G.M. Klijn). From February 2004 she works as teacher and researcher at the department of Medical Psychology and Psychotherapy of the Erasmus MC, Rotterdam (head: Prof. Dr. J. Passchier). She conducted a systematic review and meta-analysis on the effects of psychotherapeutic and psychopharmacological treatments on personality disorders (Prof. Dr. R.W. Trijsburg).