Psychological impact of genetic testing for Lynch syndrome in new patients with colorectal cancer and educational-support groups for female BRCA-mutation carriers

Karin Landsbergen
Psychological impact of genetic testing for Lynch syndrome in new patients with colorectal cancer and educational-support groups for female BRCA-mutation carriers

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Karin Maria Landsbergen
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Promotores
  Prof. dr. N. Hoogerbrugge
  Prof. dr. J.B. Prins

Manuscriptcommissie
  Prof. dr. J.W.H. Leer
  Prof. dr. J.H.W. de Wilt
  Mw. dr. E. Bleiker

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The end of all our exploring will be to arrive where we started and know the place for the first time.

- T.S. Eliot, *Four Quartets* -
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CHAPTER 1

General introduction
General introduction

Until recently it was customary for genetic testing to be done many years after cancer diagnosis and the main reason for genetic testing was a cancer related family history. In the near future, a change in timing of genetic counselling and testing from patients given time after cancer diagnosis towards recently diagnosed patients is to be expected. Physicians will offer these patients referral for genetic counselling and testing at a point in time when patients are still adjusting to the diagnosis of cancer and therefore emotionally vulnerable. There is a gap in knowledge on the psychological impact of a confrontation with a high genetic risk of Lynch syndrome shortly after a personal colorectal cancer diagnosis.

Clinical aspects Lynch syndrome

Colorectal cancer is one of the most frequent malignant tumours in industrialised countries. Worldwide more than one million patients will be diagnosed with CRC in 2010 \(^1\). In the Netherlands, more than 11,500 people are diagnosed with colorectal cancer each year \(^2\). This means that around 1 in 20 Dutch people will develop colorectal cancer during his or her life. The majority of colorectal cancer patients have sporadic disease and only a minority of colorectal cancers have a genetic cause. One well-described colorectal cancer genetic syndrome is Lynch syndrome (formerly known as HNPCC) which probably accounts for 3-5% of all colorectal cancers \(^3^\text{-}^8\). Lynch syndrome is an autosomal dominant inherited disorder characterized by an increased risk to develop colorectal cancer (60-90% lifetime risk) and an increased risk of extra-colonic tumours, especially endometrial cancer (25-70% lifetime risk); the mean age to develop colorectal cancer is 41-54 years, to develop endometrial cancer 45-50 years \(^9^\text{-}^16\). Lynch syndrome is caused by heterozygous germ line mutations in mismatch repair (MMR) genes such as \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2} \(^7^\text{-}^17\) or by \textit{EPCAM} deletions \(^18^\text{-}^19\). Due to failure of the MMR mechanism errors in microsatellite repeat sequences are not corrected causing microsatellite instability (MSI) \(^20^\text{-}^21\). MSI is easily detectable in tumour-DNA, providing a useful pre-screening tool for Lynch syndrome \(^22\).
**Relevance of Lynch syndrome detection**

Colorectal cancer has a premalignant stage of adenomas (polyps). The main aim of the colonoscopies is to prevent the development of cancer by means of detecting and removing polyps. Lynch syndrome mutation carriers are advised to have regular colorectal screening. In the Netherlands, colorectal cancer screening recommendation includes colonoscopies, usually starting at the age of 25, with a maximum interval of 24 months between each examination. It has been proven that intensive surveillance of colorectal cancer in Lynch syndrome families is very effective with a fast reduction of mortality and morbidity 23-25. For female Lynch syndrome mutation carriers surveillance also includes annual gynaecologic examination, starting between 30-35 years 26-29. Endometrial cancer surveillance in female Lynch mutation carriers seems more effective with endometrial biopsies than with transvaginal ultrasound alone 28. Surveillance for other types of Lynch associated cancers is only indicated in case of familial occurrence of these cancers (e.g. bladder or stomach carcinoma). Another major advantage of the detection of Lynch syndrome, is the resulting possibility of genetic testing of relatives. This so
called presymptomatic genetic testing can detect with certainty who and who is not a carrier of the Lynch syndrome predisposing mutation in the family. Genetic testing of healthy family members allows those who do not carry the mutated gene to avoid costly and burdensome surveillance. Such family members can experience reduced anxiety to develop cancer because they are not at increased risk. In summary, Lynch syndrome detection leads to more effective surveillance and subsequently prevents premature death from colorectal cancer.

The traditional Lynch syndrome detection procedure

Clinical aspects
When a patient is diagnosed with colorectal cancer and other established criteria are fulfilled, the general practitioner or treating physician can discuss referral for genetic testing. In the Netherlands, genetic counselling and testing is provided at hereditary cancer clinics. There, a family pedigree will be drawn which is used to establish fulfilment of the Amsterdam criteria and Bethesda guidelines. The clinical (Amsterdam) criteria can be used to recognize families and patients at high risk for Lynch syndrome; the Bethesda guidelines describe patients who merit MSI testing.

The Revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:
1) Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2) Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors*, regardless of age.
3) Colorectal cancer with the MSI-H # histology Ø diagnosed in a patient who is less than 60 years of age Ж.
4) Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5) Colorectal cancer diagnosed in two or more first- or second degree relatives with HNPCC-related tumors, regardless of age.
Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome and carcinoma of the small bowel.

MSI-H= microsatellite instability-high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.

Presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

There was no consensus among the workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.

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AMSTERDAM CRITERIA II

There should be at least three relatives with colorectal cancer (CRC) or with a Lynch syndrome-associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis.

- One relative should be a first-degree relative of the other two,
- At least two successive generations should be affected,
- At least one tumor should be diagnosed before the age of 50 years,
- FAP should be excluded in the CRC case if any,
- Tumors should be verified by histopathological examination.

Testing the patient’s tumour for the presence of MSI is the first technical step towards detection of Lynch syndrome. Only after the patient has been enabled to make a well-informed decision regarding genetic risk assessment and after informed consent, the genetic counsellor will initiate the genetic testing procedure. In case of a MSI-positive test result, the patient will be considered to be at high risk for Lynch syndrome. In order to pinpoint the deficient MMR-gene and to establish the exact cause of the microsatellite instability immunohistochemistry analysis (IHC) and DNA germ line mutation analysis are subsequent steps. After detection of a pathogenic germ line mutation, genetic testing becomes available for relatives at risk. In summary, the current model for detection of Lynch syndrome starts with a physician who signals a patient with a family history indicating a hereditary form of colorectal cancer. MSI testing of tumour tissue will then be initiated by the genetic counsellor, but only after extensive genetic counselling and informed consent.
The genetic counselling procedure

Because of specific characteristics of hereditary diseases and genetic tests, extensive genetic counselling as an integrated part of the genetic testing procedure is widely recommended. The genetic counsellor has to ensure that individuals have all relevant information to enable them to make their own decisions. This includes knowledge of the genetic risks, as well as a clear appreciation of the short-term as well as the long-term consequences, that may result from a particular course of action. Issues that are explored in the context of genetic testing for hereditary cancer include strategies for coping with an abnormal result and likely support from family and friends, family and reproductive issues including the genetic implications for relatives and implications for future employment and insurance. Moreover, the counsellor helps the patient to gain insight into his personal motives, perceptions and capability of coping with the result. The information provided can have great impact on the psychosocial well-being of the counselled individual and their family members. Time taken in genetic counselling is an important factor and additional professional psychosocial support may be needed as part of the genetic counselling process.

Psychological impact of genetic testing under the traditional method

Predictive testing for Lynch syndrome is welcomed by a majority of individuals at risk and does not induce major psychological problems. Some patients as well as healthy relatives may experience increased distress immediately after disclosure of genetic test result, especially patients with higher pre-test levels of distress, lower quality of life, lower social support and those with many colorectal cancer deaths in the family. A patient’s former experience of cancer may play an important role in genetic testing responses. Studies, which address the psychological impact of genetic counselling and testing for hereditary colorectal cancer in healthy individuals or given time after cancer diagnosis generally indicate that genetic information does not result in adverse psychological outcomes in the long term.

Family communication in the context of genetic testing for cancer

Effectiveness of genetic testing strongly depends on family communication. The index patient, i.e. the first person in a family in whom a genetic condition is established, is often one who has been diagnosed with cancer. Communication by this index patient allows other family members to have access to information,
to adequate surveillance programs and if possible to DNA-testing. The women in the family often take responsibility for informing other family members. Generally, families prefer the information to be provided by relatives rather than by clinicians. The family context and history is relevant to participation in genetic testing and screening and it may help to address communication strategies and disclosure of information about risk. Next to the influence of family communication on genetic testing uptake, family support was found to be associated with perceptions of the benefits of and barriers to colonoscopy. The ways in which families communicate with each other may have a major impact on uptake of genetic testing and attendance at screening. The quality of communication with the family regarding hereditary cancer is important as those individuals who hesitate discussing such issues report more psychological distress in the first 6 months after genetic test disclosure. A review shows that directive counseling to encourage disclosure to relatives is usually well-supported. Knowledge of patients' medical and psychosocial barriers to inform relatives is a prerequisite to improve effectiveness of genetic testing for Lynch syndrome. Family communication may be inhibited by a desire not to cause worry, by estranged relationships, infrequent contact and concerns about the impact on insurance and employment. Motives for avoiding family communication might lie in expected psychological distress, questions about death or protective buffering, i.e. the desire for mutual protection. In studies on the impact of genetic testing only a minority report changes on family relationships and those are mainly positive. Family relationships are perceived more frequently as positive than negative and individuals report feeling closer to family members as a result of genetic testing. Adverse effects mainly comprise the relationship with siblings and parents. Similarly, parental guilt, the creation of a conspiracy of silence about hereditary cancer and more emotional distance are reported occasionally. When long-term distress occurred it was associated with less open communication about the test result with the family and changes in relationships with relatives. The ability of relatives to provide social support is of importance for the relationship since relatives are perceived as key social support providers to facilitate adjustment to genetic testing. Support of the family is an important buffer against hereditary cancer distress.
The additional Lynch syndrome detection procedure: MIPA

Clinical aspects
The detection of patients at risk for Lynch syndrome based on signaling familial occurrence of colorectal cancer appeared is not optimal. To improve the recognition of patients at risk for Lynch syndrome additional methods were developed. Because almost all tumours of patients with Lynch syndrome have a deficient mismatch repair system, these additional methods are based on tumour testing. Microsatellite instability (MSI)-testing of the tumour can be used as an efficient pre-screening tool for Lynch syndrome. In the so-called MIPA-method, the pathologist starts recognition of patients at risk for Lynch syndrome by selecting a tumour for MSI-testing and after that sending the MSI-test result to the clinician. MIPA-testing is performed in a selection of patients who are recently diagnosed with colorectal cancer and who fulfil one of the individual Bethesda criteria. The next step of the MIPA-method is discussion of the MSI-test result and of referral to genetic counselling with a patient with an MSI-positive tumour (high risk Lynch Syndrome) by the clinician. When a tumour is MSI-positive, a visit to a hereditary cancer clinic is scheduled for both medical, technical and psychosocial reasons. Model-based analysis has shown that by the MIPA-method, 2.2 more Lynch syndrome mutation carriers can be identified compared to the traditional method alone. The MIPA-method is incorporated in the most recent Dutch Guideline Hereditary Colorectal Cancer.

MIPA CRITERIA

1) Colorectal cancer < 50 years.
2) Second colorectal cancer < 70 years (synchrone or metachrone).
3) Colorectal cancer and a cancer associated with Lynch syndrome < 70 years.
4) Colorectal adenoma with high grade dysplasia < 40 years.

In 2007, more than 11,500 of new cases of colorectal cancer were registered in the Netherlands. On average 1 in 8 of all patients with colorectal cancer will fulfil the selection criteria for MIPA. This amounts to 1440 patients per year in the
Netherlands. Of this population approximately 20% will be MSI positive and thus offered genetic testing. Most of these patients will have at least 10 relatives (children, sibs, uncles and aunts) who might be at risk for Lynch syndrome also. Hence, each year approximately 3000 individuals need to be informed of their risk for Lynch syndrome related cancers by patients shortly after their own colorectal cancer diagnosis in the Netherlands.

**Psychological impact of MIPA on the patient: MIPAPS**

![Diagram](image.png)

**Figure 2** Detection of high risk for Lynch Syndrome by MIPA-testing.

MIPA-testing is performed at the initiative of a pathologist, either because the CRC is diagnosed below 50 years or because it is the second CRC below 70 years. An MSI-positive tumour means the patient is at high risk for Lynch syndrome. In the MIPAPS-study psychological assessment took place immediately after MSI-test disclosure and 6 months later.

The most striking psychological difference between MIPA and the traditional method is the timing of the message of a potential risk for hereditary colorectal cancer. A positive MSI test is discussed with the patient very shortly after the colorectal cancer diagnosis. Therefore, patients are confronted with three major
tasks in quick succession: 1) to cope with their diagnosis of colorectal cancer, 2) to cope with a possibly hereditary predisposition for colorectal cancer and 3) to discuss this hereditary predisposition for colorectal cancer with children and relatives. A positive MSI test does not prove that a predisposition for Lynch syndrome is present. Nonetheless, the MIPA-strategy involves an unexpected message of being at high risk for hereditary cancer. For decades, ethical issues in genetic counselling and testing have emphasized an individual’s right to chose not to know their genetic status or even that they have an increased risk for carrying a mutation. Informed consent procedures were put in place to protect the individual’s right to self determination: more specifically, their right to make autonomous decisions about their health care. Moreover, the MIPA-strategy involves an offer of referral for genetic counselling and genetic testing shortly after surgery and probably even during adjuvant treatment for colorectal cancer. At that moment a patient might be expected to be especially emotionally vulnerable. One could hypothesize that individuals who visit a hereditary cancer clinic after careful reflection and on their own initiative may be better prepared for a negative test result than patients who are referred at the time of treatment. Although genetic testing for Lynch syndrome does not lead to clinically relevant levels of distress in general, little is known about the impact of genetic testing shortly after a colorectal cancer diagnosis. Further, little is known whether specific subgroups are more vulnerable for genetic testing related distress shortly after a colorectal cancer diagnosis.

A number of models coming from health psychology can be used to gain insight in psychological aspects regarding genetic testing for hereditary cancer. Gooding et al demonstrated that theories like the Common Sense Model of Self-regulation and the Transactional Model of Stress and Coping of which the Stress and Coping Model of Baum is an elaboration, provide a solid framework for studying genetic testing related issues. According to Baum et al, the extent to which genetic testing for disease causes significant distress varies as a function of the test result, characteristics of the disease, uncertainty remaining after testing, the degree of uncertainty reduction, the availability of active coping options and personal factors such as social support, perceived risk, beliefs about disease and social skills. Stressors have the capacity to threaten or harm. The extent to which an individual appraises events as dangerous or harmful depends on mediating situational or exposure variables. If the result is experienced as threat or as an excessive demand, stress and associated physiological, behavioural and cognitive changes will occur.
The selection of patient related determinants in the MIPAPS study (chapter 5) is based on the Stress and Coping Model from Baum et al. In the MIPAPS study psychological distress in patients is defined by general psychological distress, measured by the Symptom-Checklist-90 (SCL-90) and cancer specific distress measured by the Impact of Event Scale (IES-CRC). Our hypothesis is that MSI-testing in recently diagnosed patients with CRC (MIPA-testing) is followed by high psychological distress. Social support and cancer risk perception are studied as possible predictors of patients’ distress.

**Preceding research on genetic testing following cancer diagnosis**

A majority of newly diagnosed colorectal cancer patients find an offer of genetic testing for hereditary colorectal cancer to be highly acceptable. Other studies addressed the impact of genetic counselling and testing among women with a recent diagnosis of breast cancer. Despite emotional vulnerability due to recent breast cancer diagnosis and treatment, recently diagnosed patients seem as interested in genetic testing as patients diagnosed longer ago. The main reason for women affected with breast cancer to have a genetic test is to make relatives more alert to their own risk even though informing family members is perceived as a difficult task. Patients with breast cancer who were approached at the time of adjuvant radiotherapy and who immediate decline from genetic risk assessment tend not to consider genetic testing as relevant for them. Early decliners are found to be more hesitant and anxious about the influence of the test result on their future, and often opt to postpone further testing. Late-decliners are themselves afraid of the test result or withdraw after a relative’s objection. Breast cancer patients who are approached for genetic counselling during adjuvant radiotherapy do not report additional psychological distress either in the short term or the long term and neither do their partners. Patients who are young, single with little social support, less optimistic, those who use an avoiding coping style, experience a lower quality of life or who are previously depressed need extra attention. Highly distressed patients with highly distressed partners are most likely to experience high distress in the long term. While there is comprehensive knowledge on cancer susceptibility testing itself, less is known about the psychological impact of genetic testing shortly after cancer diagnosis and even less on the impact of genetic testing among newly diagnosed patients with colorectal cancer. Above mentioned studies indicate that psychological consequences of genetic
risk assessment shortly after cancer diagnosis can be expected to be mild. Nevertheless, genetic counselling and testing of patients who are diagnosed with cancer may cause prolonged uncertainty in a minority of patients. Awareness of the increased risk of second cancer and of the genetic contribution to an increased risk of cancer for their children may lead to an increased level of cancer specific distress. The message of being at high genetic risk for cancer may reactivate distress related to cancer diagnosis and treatment. Therefore, psychological consequences of these two potentially distressing events in tandem need to be examined and vulnerable patients need to be identified.

Summary
Signalling and detecting Lynch syndrome families is important to prevent premature death of patients and relatives. Unfortunately, the traditional detection method of hereditary colorectal cancer appears inefficient. A new strategy for the identification of hereditary colorectal cancer was developed, which should improve the recognition of Lynch syndrome from 25 to 75%. In this strategy tumours of newly diagnosed colorectal cancer patients are selected by the pathologist within a few days after cancer operation for a pre-screening test of hereditary cancer, known as the micro satellite instability (MSI)-test. Patients are selected if they are diagnosed with colorectal cancer before age 50 or if they have multiple Lynch syndrome associated cancers before age 70. Patients with a positive MSI-test result are at considerable risk for Lynch Syndrome. There is not much known about the psychological impact of a confrontation with a genetic cancer risk shortly after a personal colorectal cancer diagnosis.

Hereditary Breast Cancer with or without Ovarian cancer

Clinical aspects
Hereditary Breast and Ovarian Cancer caused by a germline mutation in BRCA1 or BRCA2 is a common hereditary cancer syndrome. The BRCA1 and BRCA2 genes were identified in 1994 and 1995 respectively. Germline mutations in BRCA1 and BRCA2 account for approximately 3-5% of all breast and ovarian cancers. Women with a BRCA1/2 mutation have a cumulative lifetime risk (up to the age of 70 years) of breast cancer of 39-85% and of ovarian cancer of 11-63%. After a history of breast cancer, the life-time risk of cancer in the contralateral breast ranges from 35 to 64%.
CRITERIA FOR REFERRAL FOR HB(O)C

**Breast cancer**
- Breast cancer before age 35 years.
- Bilateral breast cancer with primary tumor before age 50 years.
- Breast cancer before age 50 and ovarian cancer in the same branch of the family.
- Man with breast cancer and woman with breast cancer in same branch of the family.
- Two or more first degree relatives with breast cancer, of which at least one tumor before age 50 years.
- Multiple first and second degree relatives with breast cancer.

**Ovarian cancer**
- Ovarian cancer before age 50 years.
- Ovarian cancer and breast cancer in same branch of the family or in one patient.

**Relevance of BRCA detection**

Genetic testing for BRCA1/2 mutations offers the opportunity to choose cancer risk reduction strategies. Current surveillance protocols entail clinical breast examination, annual mammography and annual contrast-enhanced breast magnetic imaging (MRI) starting from the age of 25 years. Regular breast cancer surveillance aims at early detection of breast cancer, but does not guarantee the detection of a tumour before metastasis has occurred. Ablation of the breasts is effective with respect to cancer risk reduction. It was shown that the remaining risk of developing a primary breast cancer after prophylactic bilateral mastectomy (PBM) is very low. Regular surveillance of the ovaries starts at 35 years of age and includes annual gynecological examination, transvaginal ultrasound examination and serum CA-125 assay. Screening by means of the current modalities fails to detect ovarian cancer at an early stage and provokes a high number of false positive findings and so the option of prophylactic bilateral salpingo-oophorectomy (PBSO) may be discussed with BRCA1/2 mutation carriers from age 40 years. After PBSO a small residual risk of developing extra ovarian, peritoneal cancer remains. It is estimated that removing the ovaries and fallopian tubes reduces the risk of developing breast cancer by 50%.
Psychological impact of genetic testing for HBOC

Many studies are available on the psychological impact of the process of genetic testing for a BRCA1/2 mutation. Meta-analysis has shown that BRCA-mutation testing generally does not lead to a decline in patient well-being. Individuals who seek referral for genetic testing may be less distressed compared to those who refrain from genetic testing. Of all individuals undergoing BRCA testing, 10-27% is clinically distressed. Predictors for long-term hereditary cancer distress are the level of hereditary cancer distress shortly after blood sampling for genetic testing, the experience with affected relatives, having young children, perception of high cancer risk and hesitation to discuss the test result with family members. In general, distress levels are not higher than those in the general population or in a primary care population, but some women at high risk for BRCA-related distress need more attentive care. Passive coping and an emotionally oriented illness representation are significant and consistent predictors of hereditary cancer distress and cancer worry. Predictive factors for hereditary cancer distress 6 months after genetic testing are pre-test levels of distress, complicated grief, number of affected first-degree relatives, strong emotionally oriented illness representation, illness coherence, passive coping, distraction seeking, young age (<13 years) at the time a parent was affected by cancer and problematic family communication. Identifying unhelpful illness representations, cognitive restructuring and stimulating active coping styles may be appropriate interventions to help distressed individuals undergoing genetic testing.

Psychological impact of BRCA-related cancer risk management

Expressed motivations for obtaining prophylactic surgery are a fear of developing breast and ovarian cancer, risk reduction, obligation felt by women towards family members, physician’s advice, worries about effectiveness of regular surveillance and genetic testing. Higher age is found to be related with PBSO. Most women can undergo PBM and/or PBSO without developing major emotional distress and the vast majority of women do not regret prophylactic mastectomy and breast reconstruction. After PBM, anxiety and cancer-related distress are significantly reduced. Compared to female BRCA1/2 mutation carriers who favour surveillance, women opting for PBM report higher distress and cancer worry and distress levels significantly decrease after surgery. Predictors of distress at 6 months after PBM are a high level of cancer-related distress one week before surgery and being a mutation-carrier. In contrast, having comforting
thoughts is negatively associated with cancer-related distress. Cancer-related distress before PBM was predictive of cancer-related distress one year after surgery.

It is shown that only 60% of the women are satisfied with the results of breast reconstruction. Nearly half of all women experienced adverse affects regarding their sexual relationship and this was unrelated to satisfaction with the procedure. A decline in sexual functioning was related to perceived lack of information, expectations that were not met, ongoing physical complaints and limitations in daily life, altered feelings of femininity and body image and perception of the partner’s negative view of the sexual attractiveness of his wife. Thus, the impact of prophylactic surgery on body image and sexuality should not be underestimated.

**Psychosocial care for female BRCA-mutation carriers**

Few supportive services exist for women who test positive for BRCA1 and BRCA2 mutations, even though they face a complex choice between intensive surveillance and prophylactic surgery. A challenging issue for many health care professionals is how to optimally guide and support these women in making the psychologically most appropriate choice as both intensive breast cancer surveillance and prophylactic mastectomy are medically possible in most developed countries. The decision regarding breast cancer risk management involves the processing of complex and evolving information and choices. Generally, the decision is not a medically urgent one and women can take time to process all the information and to talk about it with others. All family cancer clinics in the Netherlands offer individual professional support for women from HBOC and HBC families. A supportive-expressive group intervention appeared to be relevant for and highly acceptable to women who carry mutations in BRCA1/BRCA2 and appeared to be an optimal forum for exploring key-issues such as the notification of test results to family, guilt regarding transmission of a mutation and decision-making regarding risk-reducing options. For more than ten years social workers of the family cancer clinic of the Radboud University Nijmegen Medical Centre in the Netherlands have organized educational-support groups for recently proven female BRCA-mutation carriers. The main goal of an educational-support group is assisting women in making an informed choice regarding cancer risk management, while respecting and taking into account their private lives and circumstances. Evaluation of patient care in clinical practice is necessary to be able to monitor and if necessary improve psychosocial interventions. For these
reasons, the second part of this thesis addresses breast cancer risk management behaviour, emotional distress and family communication in the context of educational-support groups for recently proven female BRCA-mutation carriers.

Aims and outline of the thesis

Referral for genetic testing shortly after the diagnosis of cancer is becoming more common. This implies a shift in timing regarding a patient’s confrontation with genetic risk assessment. The psychosocial impact of genetic testing on patients with a recent diagnosis of colorectal cancer is not yet known.

The first part of this thesis addresses the psychological impact of offering genetic testing to patients with colorectal cancer. First, a literature review was conducted to determine the psychological impact of colorectal cancer during the first year after diagnosis and the impact of genetic testing for Lynch syndrome in patients affected with colorectal cancer (chapter 2). Next, the psychological impact of MSI testing under the traditional Lynch detection method was examined and described. The study focus was the relation of time between CRC diagnosis and MSI-analysis with colorectal cancer specific distress (chapter 3). In the MIPAPS-pilot study, the reactions of patients to an offer of genetic testing directly after the diagnosis of colorectal cancer (MIPA-method) were explored (chapter 4). In the MIPAPS study psychological distress of patients with colorectal cancer and of caregiver distress of their partners were determined immediately after MIPA-testing and 6 months later (chapter 5).

The second part of this thesis addresses the evaluation of educational-support groups for recently proven female BRCA-mutation carriers. Breast cancer risk management preferences of women with a recent diagnosis of a BRCA1/2 mutation were assessed. Their mastectomy status after two years and following participating in an educational-support group were explored (chapter 6). In chapter 7, overall BRCA-related issues following participating in an educational-support group for women with a recently detected mutation were addressed.

A general discussion is provided in chapter 8. Implications for clinical practice are discussed and suggestions for further research are made.
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Chapter 1  General introduction
1 Psychological impact of genetic testing for Lynch syndrome in new patients with colorectal cancer
Karin Landsbergen
Judith Prins
Han Brunner
Floris Kraaimaat
Nicolene Hoogerbrugge

Genetic testing for Lynch syndrome in the first year of colorectal cancer: a review of the psychological impact
Abstract

Introduction  An increasing number of patients with colorectal cancer (CRC) receive genetic counselling within 1 year after diagnosis. Little is known whether specific subgroups are more vulnerable to genetic testing related distress.

Material and methods  A literature review was conducted to identify the psychological impact of CRC in the first year, and the additional impact of genetic testing. The electronic databases of PubMed, PsychInfo, Embase and the Cochrane Library were searched to identify all reports published between January 1997 and October 2007 on the psychological impact of (1) CRC-diagnosis up to 1 year after treatment and of (2) genetic testing for Lynch syndrome in patients with CRC.

Results  Studies on the psychological impact of genetic testing in newly diagnosed patient with CRC were not available. Either CRC patients diagnosed several years ago were studied and the focus was also often on the psychological impact of genetic testing prior to DNA-test disclosure. They show that limitations in emotional and social functioning can persist up to 1 year after CRC treatment, especially in those with a stoma or diagnosed before age 60. Female patients and male patients diagnosed before age 50 appear to be more vulnerable to genetic test-related distress.

Conclusion  It is well known that being treated for CRC has great impact on psychological functioning. Little is known about the psychological impact during the first year after diagnosis and very little is known about the additional psychological effect of genetic testing for hereditary cancer in this period. We found presumptive evidence that specific subgroups of patients with CRC are more vulnerable to genetic-testing-related distress.
Introduction

Up to 5% of patients with colorectal cancer have Lynch syndrome (hereditary non-polyposis colorectal cancer (HNPCC)) [1-3]. Unfortunately, only a small proportion of the expected number of patients undergo genetic testing. Identification of a hereditary predisposition can be life-saving. When more patients are traced with hereditary colorectal cancer, an increasing number of relatives can receive appropriate surveillance, which will prevent premature death from colorectal cancer [4]. To enhance the detection of Lynch syndrome, a special strategy has been developed for risk patients who cannot be recognized by family history. This new strategy called MIPA involves MSI-testing by pathologist in new patients with CRC below the age of 50 [5]. It is being introduced at an increasing number of hospitals. In this strategy, the pathologists select patients and tumour specimens for microsatellite instability (MSI) testing. In case of a positive MSI test, the patient is at risk for Lynch syndrome and thus referred for genetic counseling to a clinical genetic center.

For the patients, the difference between the new strategy and the existing procedure is that genetic counselling and testing is discussed very shortly after the diagnosis of colorectal cancer, instead of a long period after diagnosis and treatment. In this early stage after diagnosis, patients with colorectal cancer may be more emotionally vulnerable. Concurrently, these patients are confronted with three major tasks: (1) to cope with their cancer, (2) to cope with the consequences of a possible genetic risk and (3) to consider informing and discussing genetic counseling and DNA-testing with their blood relatives. Extended work already has been accomplished on familial cancer in general, including colorectal patients tested for Lynch syndrome. In a number of reviews on familial cancer, colorectal cancer was included as one of the familial cancers [6, 7]. Many studies describe the psychological impact of pre-symptomatic testing for Lynch syndrome [8-22]. From these studies it can be concluded that in general genetic counselling and pre-symptomatic testing for Lynch syndrome can lead to increased distress immediately after DNA-test disclosure but does not lead to long-term adverse effects. Other related studies assessed experiences of patients and family members with genetic counselling for hereditary cancer and [23], the impact of attendance of a familial colorectal clinic on cancer-related concerns [24], subjective perception regarding colorectal cancer [25, 26], compliance with screening after testing [25]], genetic testing for Lynch syndrome in colorectal cancer survivors who were more than 1 year after diagnosis [27] and quality of life after various surgical procedures [28].
Obviously, this new Lynch detection strategy gave rise to systematically survey relevant data related to the issue of the impact of symptomatic genetic testing in patients with colorectal cancer in their first year after colorectal cancer diagnosis. A literature review was conducted to identify the psychological impact of colorectal cancer, focusing on the impact of the malignancy during the first year after primary treatment and of the additional impact of genetic testing for Lynch syndrome in affected patients.

**Material and methods**

The electronic databases PubMed and PsychInfo were searched to identify all the reports published between January 1997 and October 2007 on the psychological impact of colorectal cancer and genetic testing for hereditary colorectal cancer (Lynch syndrome) in patients during their first year of colorectal cancer. Two searches were performed in each database. Search 1 retrieved literature on the psychological impact of the diagnosis and treatment of colorectal cancer. A sensitive search strategy was adopted using the following keywords: colorectal cancer, colorectal tumour(s), colorectal carcinoma, colorectal neoplasms, psychological distress, psychological adaptation, coping, emotional adjustment, anxiety, depression and quality of life. Using these keywords, 470 abstracts were retrieved: 415 from PubMed and 55 from PsychInfo. After removing doubles, one of the reviewers (KL) checked all the titles and abstracts. Full text copies were obtained when the studies had possible relevance. Inclusion criteria were (1) studies on patients in their first year with colorectal cancer (2) psychological outcome measurements, (3) peer-reviewed articles in English, French or Dutch. From studies with a prospective design with long-term follow-up, only the results up to 1 year were retrieved. Exclusion criteria were (1) Patients with colorectal cancer aged >70 years. These patients are not generally referred for genetic testing due to their advanced age. (2) Colorectal cancer disease management studies and subjective experiences. (3) Qualitative design. (4) Research into non-standard medical treatment. (5) Publications of which no relevant data (mean scores) could be retrieved. Based on these criteria, 17 studies remained (see Fig.1).

Search 2 retrieved literature on the psychological impact of genetic testing in patients with colorectal cancer. The keywords in search 1 were used in combination
with the terms genetic testing, genetic predisposition to disease, genetic screening, genetic counseling and genetics. Using these keywords, 101 abstracts were retrieved. After removing doubles, one of the reviewers (KL) checked all the titles and abstracts. Full text copies were obtained of all the possibly relevant studies. Inclusion criteria were (1) patients diagnosed with colorectal cancer (2) psychological outcome measurement, (3) peer-reviewed articles in English, French or Dutch. Exclusion criteria were (1) Pre-symptomatic/predictive testing, because our focus was on the impact of genetic testing in patients diagnosed with colorectal cancer. (2) Qualitative design. (3) Genetic testing for Familial Adenomatous Polyposis (FAP). (4) Publications of which no relevant data (mean scores) could be retrieved. Based on these criteria, ten studies remained (see Fig.1).
Additional free text searches were performed in PubMed, Psychlnfo as well as in the Cochrane Library database and in Embase using all the above-mentioned keywords to select reviews on the psychological impact of colorectal cancer and genetic testing for hereditary colorectal cancer. However, none of these searches led to any relevant publications.

Methodological quality
The studies were assessed according to the guidelines for levels of evidence and grades of recommendation, supplied by the Oxford-Centre for Evidence-based Medicine. A level of evidence LE1 refers to RCT studies, LE2 to cohort studies, LE3 to case-control studies, LE4 to case-series and LE5 to expert opinions (http://www.cebm.net/levels_of_evidence.asp).

Results

I Psychological impact of colorectal cancer

Table 1 gives a summary of each of the 17 papers [29-45] included in our review. The vast majority of the patients with colorectal cancer were older than 50 years. As a result of the heterogeneity of psychological variables and used measurement instruments of the retrieved studies, a limit was set in describing those studies that used the European Organization for Research and Treatment in Cancer (EORTC) QLQ-C30 scale. In ten out of the 17 studies, the European Organization for Research and Treatment in Cancer (EORTC) QLQ-C30 scale had been used to measure the quality of life of the patients [29-32, 35, 41, 43-46]. This scale has frequently been used to assess health-related quality of life in various groups of cancer patients [47].

The mean scores on functional status were retrieved from the studies, because an important aim of this review was to evaluate functioning after treatment for colorectal cancer. The scores are presented in Table 2. Our comparison may not do justice to the special qualities of each individual study, as their designs were intended to provide answers to specific research questions, not to facilitate comparability. Nevertheless the comparison adds new dimensions to our knowledge in this area. To evaluate the significance of these function scores, they were compared to reference data from a random sample (n = 2081) of the general
According to the MIPA (MSI test by pathologist) procedure, MSI-positive patients are usually informed about the results and offered genetic testing within 3 months after surgery. Therefore, clear distinction is made between psychological functioning in the first 3 months after treatment and in the subsequent period up to 1 year after treatment. In the publications of Schmidt [42] and Tsunoda [44] the EORTC-QLQ-C30 data were presented in graph and mean data could not be obtained and used reliably. The study of Wilson et al. [45], only presented mean data on EORTC-QLQ-C30 Global Health Status. Therefore, these three studies are not reflected in Table 2.

Regarding the psychosocial impact of CRC with other instruments than the EORTC-QLQ-C30, it appeared that often different questionnaires were used, concerning patients at different ages, with different types of colorectal cancer and often with different times of data collection. Still, an overall impression was obtained that demands of illness, especially psychosocial and existential concerns, were greater among the youngest age group below 45 years. Moreover, patients with a stoma showed higher levels of depression and poorer social function than non-stoma patients. Especially men with a stoma reported sexual problems as did patients after treatment for rectal cancer.

**Impact of colorectal cancer on functional status**

**Up to 3 months after treatment**

Table 2 shows that compared to the reference data, colorectal cancer led to reduced social functioning (especially in the patients with a stoma) as well as to decreased role and physical functioning [29-32, 37, 41, 43]. Patients of younger than 65 years and those with a stoma reported reduced health-related quality of life 6 weeks after surgery [45]. In the group with rectal cancer the men suffered from more problems with their sexual functioning after abdominoperineal resection than the women [43]. It can be concluded that immediately after treatment for colorectal cancer, physical, social and role functioning were diminished especially in patients with a stoma, compared to levels of physical, social and role functioning of a selected sample of adults [47] and of patients with lung cancer (another common malignancy worldwide) [49, 50].
<table>
<thead>
<tr>
<th>Author</th>
<th>LE</th>
<th>N</th>
<th>Mean age at inclusion years (SD) [range]</th>
<th>Time of data collection</th>
<th>Study method/questionnaires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kopp et al. [37]</td>
<td>1</td>
<td>79</td>
<td>72.4 [53–90]</td>
<td>At discharge and 6 months after treatment</td>
<td>EORTC QLQ-C30/CR38</td>
</tr>
<tr>
<td>Marijnen et al. [38]</td>
<td>1</td>
<td>990</td>
<td>64 [NP]</td>
<td>Pre-treatment, 3, 6, 12, 18 and 24 months after treatment</td>
<td>RSCL; VAS</td>
</tr>
<tr>
<td>Allai et al. [29]</td>
<td>2</td>
<td>53</td>
<td>58 (11)</td>
<td>Pre- and 12–16 months post</td>
<td>EORTC QLQ-C30/CR38</td>
</tr>
<tr>
<td>Arndt et al. [30]</td>
<td>2</td>
<td>309</td>
<td>65.1 (9.4)</td>
<td>1 year after diagnosis</td>
<td>EORTC QLQ-C30</td>
</tr>
<tr>
<td>Engel et al. [32]</td>
<td>2</td>
<td>299</td>
<td>&lt;70 n = 212; &gt;70 n = 87</td>
<td>At treatment and annually to 4 years follow-up</td>
<td>EORTC QLQ-C30/CR38</td>
</tr>
<tr>
<td>Fatma et al. [31]</td>
<td>2</td>
<td>160</td>
<td>50 [18–83]</td>
<td>During visit first line MD</td>
<td>FACT-C; Spitzer QoL</td>
</tr>
<tr>
<td>Fernsler et al. [33]</td>
<td>2</td>
<td>121</td>
<td>51.9 [26–82]</td>
<td>Through computer networks</td>
<td>DOII; SWBS</td>
</tr>
<tr>
<td>Gall et al. [34]</td>
<td>2</td>
<td>338</td>
<td>&lt;60 n = 43; 60–69 n = 77; &gt;70 n = 218</td>
<td>6 weeks, 6 months after treatment until 2 years follow-up</td>
<td>HADS; SF12; PSVQ</td>
</tr>
<tr>
<td>Guren et al. [35]</td>
<td>2</td>
<td>42</td>
<td>67 [38–78]</td>
<td>Start and end treatment and 4–6 weeks follow-up</td>
<td>EORTC QLQ-C30/CR38</td>
</tr>
<tr>
<td>Klemm et al. [36]</td>
<td>2</td>
<td>21</td>
<td>51.9 (NP)</td>
<td>Via online CRC support group</td>
<td>DOII</td>
</tr>
<tr>
<td>Nordin and Glimelius [39]</td>
<td>2</td>
<td>139</td>
<td>67 (NP)</td>
<td>&lt;12 weeks after diagnosis</td>
<td>RDCQ; IES; MAC; HADS</td>
</tr>
<tr>
<td>Norum [40]</td>
<td>2</td>
<td>94</td>
<td>62 [40–76]</td>
<td>16 months after treatment</td>
<td>IES</td>
</tr>
<tr>
<td>Ross et al. [41]</td>
<td>2</td>
<td>249</td>
<td>64.5 (NP)</td>
<td>3, 6, 12 and 24 months after initial treatment</td>
<td>EORTC QLQ-C30/CR38</td>
</tr>
<tr>
<td>Main outcome measures</td>
<td>Main psychological findings</td>
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<td>-----------------------</td>
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</tr>
<tr>
<td>Quality of life</td>
<td>Six months after surgery, global quality of life approximated normal values but deficits remained in role, physical and social functioning</td>
<td></td>
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</tr>
<tr>
<td>Health-related quality of life and overall perceived health</td>
<td>Few QoL differences between PRT+ and PRT− group. PRT negative effect on sexual functioning, deteriorating over time</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Quality of life</td>
<td>Compared to pre-RT scores, at 1 year, improvement in emotional state, perspective of the future, global QoL. Sexual dysfunction increased, particularly in men</td>
<td></td>
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<tr>
<td>Quality of life</td>
<td>Severe limitations in emotional and social functioning predominantly in patients younger than 60 years</td>
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<tr>
<td>Quality of life</td>
<td>Compared to a general population sample, patients had the largest differences with regard to role and social functioning</td>
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</tr>
<tr>
<td>Quality of life</td>
<td>&gt;40% of the patients reported signs of psychological distress, 35% expressed fear of dying</td>
<td></td>
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<tr>
<td>Demands of illness; spiritual well-being</td>
<td>DOI greater among men, the youngest subjects (26–45 years), who received treatment in the previous 2 months. Women reported greater spiritual well-being than men</td>
<td></td>
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</tr>
<tr>
<td>Anxiety, depression, health-related quality of life</td>
<td>At baseline, mental HRQoL scores consistent with average values in the population. Levels of anxiety and depression consistent with or lower than population norms</td>
<td></td>
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</tr>
<tr>
<td>Quality of life</td>
<td>At the end of RT, physical and social functioning and global quality of life poorer than population norms. HR QoL scores returned to pre-treatment levels 4–6 weeks after RT</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Demands of illness</td>
<td>The 10 most intense demands predominantly psychosocial and existential concerns. Respondents in the youngest age group (&lt;45 years) greater demands</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diagnosis reactions; impact of event; adjustment to cancer, anxiety; depression</td>
<td>Patients with CRC more confrontational attitude than those with gastric cancer; avoidance in men lower than in women, mental adjustment better in women</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Impact of event</td>
<td>Less than one-third of the patients reported a moderate to high level of psychological distress</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Quality of life</td>
<td>Patients with stoma higher levels of depression and poorer social functioning than non-stoma patients. Male patients with stoma more sexual problems than males without</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
**Table 1** Continued

<table>
<thead>
<tr>
<th>Author</th>
<th>LE</th>
<th>N</th>
<th>Mean age at inclusion years (SD) [range]</th>
<th>Time of data collection</th>
<th>Study method/questionnaires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmidt et al. [42]</td>
<td>2</td>
<td>253</td>
<td>$&lt;70 \ n = 168; &gt;70 \ n = 85$</td>
<td>Pre-surgery, 3, 6, 12 and 24 months after treatment</td>
<td>EORTC QLQ-C30/CR38</td>
</tr>
<tr>
<td>Schmidt et al. [43]</td>
<td>2</td>
<td>368</td>
<td>64.9 (11.1)</td>
<td>Pre-surgery, at discharge, 3, 6, 12 and 24 months after treatment</td>
<td>EORTC QLQ-C30/CR 38</td>
</tr>
<tr>
<td>Tsunoda et al. [44]</td>
<td>2</td>
<td>100</td>
<td>64 [33–83]</td>
<td>Pre-treatment and monthly follow up to 1 year</td>
<td>EORTC QLQ-C30</td>
</tr>
<tr>
<td>Wilson et al. [45]</td>
<td>2</td>
<td>201</td>
<td>68.2 [36–91]</td>
<td>6 weeks after treatment</td>
<td>EORTC QLQ-C30; FACT-C; SF12; EQ-5D</td>
</tr>
</tbody>
</table>

Questionnaires: EORTC QOL-C30/CR38, DOII, SWBS, FACT-C, Spitzer QoL, SF12, PV5Q, RSCL, VAS, IES, EQ-5D, RDCQ, MAC

NP: not present; MD: medical doctor; RT: radiotherapy; PRT: pre-operative radiotherapy; (HR)QoL: (health-related) quality of life; LE: level of evidence

**Table 2** EORTC QLQ-C30 functioning scores concerning the psychological impact of colorectal cancer (scores from 0 to 100, higher score means better functioning)

<table>
<thead>
<tr>
<th>Time of data collection</th>
<th>Physical</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Refdata Servaes* et al. [48]</td>
<td>6–70 months after breast cancer treatment</td>
<td>72.6 (18.8)</td>
</tr>
<tr>
<td>Schwarz and Hinz† [47]</td>
<td>A-selected non-cancer population</td>
<td>92.0 (15.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88.7 (17.5)</td>
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</tbody>
</table>
### Main outcome measures

<table>
<thead>
<tr>
<th>Main psychological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality of life</strong></td>
</tr>
<tr>
<td>Role functioning better in patients &lt;70 years. Younger patients more sexual problems</td>
</tr>
<tr>
<td>QoL below baseline early postoperative period, after 3 months, global health, emotional and physical functioning improved. Men high levels of strain related to sexual problems</td>
</tr>
<tr>
<td>Physical and role functioning below preoperative values 1 month after surgery, returned to preoperative values &lt;3 months. Global health, emotional and social functioning improved within 3 months</td>
</tr>
<tr>
<td>Physical and mental health-related quality of life</td>
</tr>
<tr>
<td>Patients &lt;65 years and those with a stoma poor health-related quality of life</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Role</th>
<th>Emotional</th>
<th>Cognitive</th>
<th>Social</th>
<th>Global health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>71.4 (22.7)</td>
<td>71.2 (21.8)</td>
<td>73.7 (24.0)</td>
<td>82.5 (22.8)</td>
</tr>
<tr>
<td>Female</td>
<td>89.8 (21.7)</td>
<td>86.6 (23.7)</td>
<td>81.8 (18.8)</td>
<td>92.7 (15.0)</td>
</tr>
<tr>
<td>Study</td>
<td>Time of data collection</td>
<td>Physical</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt et al. [43]</td>
<td>Before surgery</td>
<td>86.1 (20.4) 78.5 (22.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>At discharge</td>
<td>64.4 (27.1) 50.6 (25.7)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>3 months after surgery</td>
<td>74.5 (22.8) 60.4 (24.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 months after surgery</td>
<td>76.8 (20.9) 66.4 (23.5)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>12 months after surgery</td>
<td>78.1 (21.8) 68.3 (25.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kopp et al. [37]</td>
<td>At discharge</td>
<td>54.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 months after surgery</td>
<td>69.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arndt et al. [30]</td>
<td>1 year after diagnosis</td>
<td>79.5 (24.0)</td>
<td></td>
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</tr>
<tr>
<td>Engel et al. [32]</td>
<td>1 year after surgery</td>
<td>81.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross et al. [41]</td>
<td>Follow-up after surgery</td>
<td>No stoma 75.2 (1.8)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>FU stoma 67.3 (4.3)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Initial stoma 82.2 (4.4)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Initial stoma and FU stoma 78.5 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guren et al. [35]</td>
<td>Before radiotherapy</td>
<td>78 (25.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alla et al. [29]</td>
<td>Before radiotherapy</td>
<td>No stoma 88</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Stoma 77</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12–16 months after radiotherapy</td>
<td>No stoma 90</td>
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<tr>
<td></td>
<td></td>
<td>Stoma 80</td>
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</tr>
</tbody>
</table>

ND, no mean data available

*EORTC QLQ-C30 reference data, mean and standard deviation (brackets) from severely fatigued disease-free breast cancer patients (n = 57)
*EORTC QLQ-C30 reference data, mean and standard deviation (brackets) from an a-selected general non-cancer adult population (n = 2028)
*Data from the RCT group, standard deviation scores range between 22.8 and 32.4 score points at discharge and between 16.1 and 29.5 score point 6 months after surgery
*If n > 100 SD is 9.0-37.0 (SD scores derived from original SEM scores)
*FU stoma, stoma at follow-up, SD scores derived from original mean data and CI scores
*SD scores derived from original SEM scores
*No SD scores could be obtained
<table>
<thead>
<tr>
<th>Role</th>
<th>Emotional</th>
<th>Cognitive</th>
<th>Social</th>
<th>Global health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>82.7 (30.5)</td>
<td>66.5 (23.8)</td>
<td>58.5 (26.0)</td>
<td>85.1 (19.6)</td>
<td>74.8 (26.1)</td>
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<tr>
<td>41.3 (39.5)</td>
<td>63.4 (23.5)</td>
<td>52.6 (25.4)</td>
<td>75.5 (26.1)</td>
<td>72.8 (26.5)</td>
</tr>
<tr>
<td>66.0 (32.2)</td>
<td>70.8 (25.0)</td>
<td>66.0 (25.4)</td>
<td>80.4 (25.4)</td>
<td>78.0 (24.4)</td>
</tr>
<tr>
<td>68.6 (32.3)</td>
<td>71.4 (23.6)</td>
<td>66.9 (23.8)</td>
<td>81.6 (23.2)</td>
<td>80.8 (23.5)</td>
</tr>
<tr>
<td>72.0 (31.4)</td>
<td>71.3 (23.6)</td>
<td>68.2 (24.3)</td>
<td>81.8 (22.7)</td>
<td>82.2 (23.7)</td>
</tr>
<tr>
<td>46.5</td>
<td>66.3</td>
<td>70.9</td>
<td>72.1</td>
<td>52.6</td>
</tr>
<tr>
<td>61.6</td>
<td>73.3</td>
<td>73.7</td>
<td>74.9</td>
<td>63.6</td>
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<td>82.6</td>
<td>73.7</td>
<td>65.3</td>
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<td>79.3 (1.9)</td>
<td>83.9 (1.5)</td>
<td>84.7 (1.5)</td>
<td>93.8 (1.3)</td>
<td>72.9 (1.5)</td>
</tr>
<tr>
<td>68.2 (6.0)</td>
<td>80.1 (4.1)</td>
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<td>84.1 (3.7)</td>
<td>65.1 (4.3)</td>
</tr>
<tr>
<td>84.4 (5.9)</td>
<td>86.7 (4.1)</td>
<td>88.8 (4.1)</td>
<td>92.3 (3.6)</td>
<td>73.5 (4.4)</td>
</tr>
<tr>
<td>78.4 (2.9)</td>
<td>82.7 (2.3)</td>
<td>86.9 (2.2)</td>
<td>89.4 (1.9)</td>
<td>72.9 (2.3)</td>
</tr>
<tr>
<td>87 (16.2)</td>
<td>84 (15.6)</td>
<td>ND</td>
<td>72 (29.8)</td>
<td>72 (24.6)</td>
</tr>
<tr>
<td>86</td>
<td>74</td>
<td>88</td>
<td>92</td>
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<td>81</td>
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<td>89</td>
<td>90</td>
<td>94</td>
<td>91</td>
<td>7</td>
</tr>
</tbody>
</table>
Between 3 and 12 months after treatment

Reduced role, emotional and social functioning continued up to 1 year after treatment. The women reported poor physical functioning [43] compared to the reference data [47] and the scores from a severely fatigued breast cancer group [48]. Global health status scores of the patients with colorectal cancer were also poorer than the reference data [47]. Severe limitations were found in emotional and social functioning up to 1 year after treatment. These problems were especially likely to affect patients of younger than 60 years [30]. In the men, strain due to sexual impairment appeared to persist [29, 43, 46]; the men with a stoma had more sexual problems than those without [41]. Rectal cancer patients reported poor role and social functioning compared to the reference data [47] up to 1 year after treatment [32]. In the patients who had pre-operative radiotherapy, emotional functioning was impaired compared to the norm data [47]. At 12–16 months after radiotherapy, these scores had returned to normal levels [29]. Thus, severe problems with emotional and social functioning persisted up to 1 year after treatment, especially in the patients of younger than 60 years and in those with a stoma.

Impact of colorectal cancer on demands of illness and spiritual well-being

In two studies, patients younger than 45 years reported greater demands of illness (hardships or stressors that require coping or adjustment to illness) than the older patients [33, 36]. Fernsler et al. [33] also showed that such demands of illness were greater in men and in men and women who had received treatment in the previous 2 months; in contrast, the women reported significantly higher spiritual well-being than the men. This leads to the conclusion that colorectal cancer caused more hardships and stressors in men and in patients diagnosed before the age of 45 years.

II Psychological impact of genetic testing for Lynch syndrome

Summaries of the ten relevant studies are shown in Table 3. Nearly all the studies had gathered data on the patients before disclosure of the genetic test result. Two studies had made assessments pre-test and post-test [18, 33, 51], whereas one study had only made assessments post-test [52]. Very few studies gave specific details about the time interval since the diagnosis of colorectal cancer and
inclusion in the study [53, 54]. Table 3 also shows the diversity in outcome measures and (self-administered) questionnaires to gather data [18, 51, 55-58]. The aim of this review was to determine how patients with colorectal cancer reacted to (the offer of) genetic testing. Therefore, the psychological reactions were documented according to stage of genetic testing the patients had reached at the time of the studies. The process of genetic counselling was divided into three distinct stages: (1) Period of genetic counselling and if desired, having a blood sample taken. (2) Period of waiting for the result of the DNA analysis. (3) Period after disclosure of the genetic test result.

**Psychological reactions before genetic counseling**

The three relevant studies showed that patients with colorectal cancer tended to have positive attitude towards genetic testing [56, 57, 59]. Their most common motivation to undergo genetic testing was concern about the risk of colorectal cancer in close relatives. Motivation was the highest in the younger patients, in those with early stage disease and in those who had more frequent thoughts about hereditary colorectal cancer [57]. In a group of patients with colorectal cancer who attended an information session about Lynch syndrome, 28% developed a clinically significant level of cancer-worry-related distress [56]. In conclusion, motivation to undergo genetic testing was primarily the need to know if close relatives were at increased risk for colorectal cancer and was strongly present in younger patients.

**Psychological reactions before and after genetic counseling**

Other studies obtained data on the patients after patients had consented to have a blood sample taken for DNA analysis. Keller [55] and Murakami [51] found clinically relevant depression scores before and after genetic counseling in 19 and 5% of the patients, respectively. Another study reported clinically relevant anxiety levels in 32% of the patients before genetic counseling, whereas the scores dropped to 16% after genetic counseling [55]. In a group of patients who had given a blood sample for genetic testing, the prevalence of depressive symptoms was 24%, although all the scores remained within the clinically normal range [54]. Patients in the age group of younger than 50 years had higher levels of anxiety and depression but the scores were within the normal range; their data also showed significant associations between pre-test distress, a history of familial mortality from colorectal cancer and anticipation of becoming depressed post-test [53]. Characteristics associated with depression were female sex, less formal
Table 3: Characteristics of studies on the psychological impact of diagnostic genetic testing for Lynch syndrome on patients with colorectal cancer (n = 10)

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Inclusion age mean (SD)/median [range]</th>
<th>Time of data collection</th>
<th>Study method/questionnaires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Espen et al. [53]</td>
<td>220</td>
<td>63 (9.6)</td>
<td>At pre-test</td>
<td>IES, STAI, CES-D</td>
</tr>
<tr>
<td>Gritz et al. [16]</td>
<td>155</td>
<td>&gt;50 n = 56; &lt;50 n = 99</td>
<td>At pre-test, 2 weeks, 6 and 12 months after result disclosure</td>
<td>CES-D, STAI, RIES, QLI and Saq</td>
</tr>
<tr>
<td>Ho et al. [59]</td>
<td>62</td>
<td>42 (9.9)</td>
<td>Pre and post result disclosure</td>
<td>DBS, C-HADS, C-MBSS, LOT</td>
</tr>
<tr>
<td>Keller et al. [55]</td>
<td>65</td>
<td>Patients 50.3 (12.2); at risk persons 37.0 (9.1)</td>
<td>Pre and 4–6 weeks after genetic counselling</td>
<td>MOS-SF12, GBB, HADS, IES and Saq</td>
</tr>
<tr>
<td>Keller et al. [56]</td>
<td>73</td>
<td>49 (17)</td>
<td>After information session on HNPCC</td>
<td>Saq</td>
</tr>
<tr>
<td>Kinney et al. [57]</td>
<td>98</td>
<td>64 (13)</td>
<td>Before genetic counselling or testing</td>
<td>Saq</td>
</tr>
<tr>
<td>Loader et al. [52]</td>
<td>36</td>
<td>59.9 (6.7)</td>
<td>3 and 12 months after result disclosure</td>
<td>SF36, IES, SSSQ, BSS</td>
</tr>
<tr>
<td>Murakami et al. [51]</td>
<td>42</td>
<td>50 [21–69]</td>
<td>After first genetic counselling session for HNPCC and 1 month after result disclosure</td>
<td>SCID ASD/PTSD/PTSS and Saq</td>
</tr>
<tr>
<td>Main outcome measures</td>
<td>Main psychological findings</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Impact of event, state and trait anxiety and depression</td>
<td>Women higher levels of intrusion and avoidance compared to males. Patients diagnosed before 50 years significantly higher levels of anxiety and depression than those diagnosed after 50 years. Diagnosed within one year significantly lower levels of intrusion and avoidance, than those over 2 years after diagnosis. Significant associations between pre-test distress, family history of CRC and mortality related to CRC and anticipation of becoming depressed at post-test</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Depression, state and trait anxiety, impact of event test result, quality of life, cancer worries and perceived cancer risk</td>
<td>Mean scores of all outcome measures within normal limits for cancer-affected participants. Affected and unaffected carriers higher mean test-specific distress scores at 2 weeks post result disclosure compared to non-carriers; scores decreased in affected carriers and all unaffected participants from 2 weeks to 12 months post result disclosure. Unaffected mutation carriers may experience increased distress during the immediate post result disclosure period.</td>
<td></td>
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</tr>
<tr>
<td>Decisional consideration, attitude genetic testing, anxiety, depression, coping style</td>
<td>Participants even more concerned about well-being and reactions of their significant others than their own well-being in their decisional consideration process. Those with higher depression levels tended to emphasise more on the negative consequences of learning test results</td>
<td></td>
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<tr>
<td>Health state and complaints, anxiety, depression, impact of event, evaluation of counselling</td>
<td>Distress and HNPCC related worries declined after counselling. Distress decrease partly attributable to increase in personal self-confidence. One-third reported enhanced family communication specific to hereditary cancer. Twenty-five per cent reported cancer-related worries before testing. This dropped to 13% post-genetic counselling.</td>
<td></td>
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</tr>
<tr>
<td>Cancer worry, attitude genetic testing, family communication</td>
<td>Distress clinically significant in 28% of participants. Restricted family communication was reported frequently. Positive attitude towards obtaining a gene test result predominated</td>
<td></td>
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</tr>
<tr>
<td>Knowledge and risk perception CRC genetics, health behaviour, knowledge/interest genetic test</td>
<td>61% worries about relative’s CRC risk, 64% concerned about being a carrier. 81% had never heard of genetic test for hereditary CRC. 72% stated they would take the test. Predictors to take the test: younger age, less advanced stage of disease and more frequent thoughts about CRC being hereditary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health state, impact of event, social support, preventive behaviour</td>
<td>At 12 months post result disclosure more knowledge in carriers, younger when DNA tested or younger at CRC diagnosis. All but one told relatives about their gene mutation. Self-assessed mental health better in married patients</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acute stress disorder, post-traumatic stress disorder or symptoms and feelings of guilt</td>
<td>None of the participants met the criteria for major depression, ASD or PTSD 1 month after result disclosure. 7% met the criteria for minor depression and 5% had PTSS. The only predictor of psychological distress was the presence of a history of major or minor depression. 12% had feelings of guilt</td>
<td></td>
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</tr>
<tr>
<td>Author</td>
<td>N</td>
<td>Inclusion age mean (SD)/median [range]</td>
<td>Time of data collection</td>
<td>Study method/questionnaires</td>
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<tr>
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<td>-----------------------------</td>
</tr>
<tr>
<td>Vernon et al. [54]</td>
<td>200</td>
<td>ORPS</td>
<td>After provision of blood sample for DNA analysis</td>
<td>CES-D, STAI, SSSQ, MBSS</td>
</tr>
<tr>
<td>Vernon et al. [58]</td>
<td>269</td>
<td>&lt;50 n = 105; &gt;50 n = 164</td>
<td>After provision of blood sample for DNA analysis</td>
<td>CES-D, STAI, MBSS, SSSQ, QLI and Saq</td>
</tr>
</tbody>
</table>

Questionnaires (R)IES, CES-D, STAI, (C)HADS, SF12, (C)MBSS, Sarason SSS, QLI, DBS, LOT, SCID
Saq, self-administered questionnaires; ORS, only presented in relation to psychological scores; CRC, colorectal cancer; HNPCC, hereditary non-polyposis colorectal cancer (Lynch syndrome)

education, fewer sources of social contact; associations with anxiety were younger age, less formal education, Non-Caucasian race, more severe disease and fewer sources of social contact [54]. Intrusion scores reached clinically relevant levels in 14% of the patients [55]. Higher intrusion and avoidance scores were found in women and in the patients who had been diagnosed with colorectal cancer less than 1 year previously, although all the scores remained within the normal clinical range [53]. Clinically relevant cancer-worry-related distress was detected in 25% of the patients before genetic counseling, but after genetic counseling, this dropped to 13% [55]. In conclusion, most psychological distress scores remained within the normal range before the result of the genetic test was disclosed, although a minority of the patients developed clinically relevant anxiety and depression levels. Vulnerable subgroups were female patients and male patients diagnosed before the age of 50 years.

**Psychological reactions after disclosure of the genetic test result**
Disclosure of the genetic test result led to significant depression scores in 7% of the patients and post-traumatic stress symptoms in 5% [51]. Lynch syndrome mutation carriers showed higher test-specific distress than non-carriers but these
Main outcome measures | Main psychological findings
--- | ---
Depression, state and trait anxiety, social support, quality of life and coping style | Prevalence of depression symptoms was 24%. Female sex, less formal education, fewer sources of social contacts and less satisfaction with them were associated with high scores on the CES-D scale. Characteristics associated with high anxiety were younger age, less formal education, non-White race, advanced local-regional disease, fewer social contacts and less satisfaction with them.

Depression, anxiety, coping style, social support, quality of life and intention genetic testing | 90% intended to learn genetic test results. Intention positively associated with income, quality of life, a belief that being tested will help family members prevent cancer, being worried about carrying an altered gene and belief that one has ability to cope with test results. Negative association with belief that genetic counselling is too much trouble relative to benefits.

scores returned to baseline between 2 and 12 weeks after receiving the test result [18]. The only predictor of psychological distress after disclosure of the test result was a history of depression [51]. It can be concluded that disclosure of the genetic test result did not lead to any relevant levels of psychological distress in most patients. Vulnerable subgroups seemed to be patients with pre-test distress, high familial mortality from colorectal cancer and a history of depression. Therefore, a subgroup of vulnerable patients whose genetic test discloses Lynch syndrome mutation carrier ship may benefit from extra psychological counselling.

**Discussion**

This literature review shows that little is known about the additional psychological impact of obtaining a genetic test disclosure in newly diagnosed patients with colorectal cancer. Only ten studies were identified on diagnostic genetic testing in colorectal patients. Most of these studies measured distress prior to genetic test disclosure, but did not obtain data after disclosure of the test result. Prior to disclosure of the genetic test result, female patients and men who were diagnosed...
with colorectal cancer before the age of 50 years appeared to be more vulnerable to genetic-test-related distress. A history of depression and high levels of pre-test distress were strongly associated with genetic-test-related distress and cancer related worries. It is generally known that a young age at diagnosis and multiple family members with cancer are hallmarks of heredity. Therefore, significant levels of anticipated psychological distress prior to disclosure of the genetic test result in patients with a history of familial mortality from cancer [53] can also be regarded as relevant to patients with colorectal cancer who are suspected of Lynch syndrome carriership.

The few studies available on distress after disclosure of the genetic test result revealed ambiguous results. For patients with different types of cancer, the impact of genetic testing many years after the initial cancer diagnosis and treatment was strongly influenced by their former experience of cancer [7]. Dorval hypothesized that after disclosure of the genetic test result, cancer patients may be more aware of their own risk developing a second primary tumour and be more conscious of the contribution of genetics to an increased risk of cancer in their offspring [60]. When genetic testing was offered to recently diagnosed colorectal cancer patients, the majority did not object to an active approach [61]. Individuals at high-risk for Lynch syndrome proved to know very little about microsatellite instability (MSI) testing, a hallmark for patients at risk for Lynch syndrome, but held positive attitudes towards MSI test utility [62].

This literature review also shows that most patients with colorectal cancer experience diminished physical, social and role functioning during the first 3 months after primary treatment. Decreased emotional and social functioning could persist for up to 1 year after treatment, especially in patients of younger than 60 years and in those with a stoma. Specific subgroups of patients with colorectal cancer appeared to be more vulnerable to genetic-testing-related distress, but their actual levels of distress did not generally reach clinical significance. Reduced emotional and social functioning may be related to the many taboos that still surround bowel dysfunction [63]. Especially the younger patients reported severe distress due to maladjustment to their colorectal cancer. Having a stoma can lead to feelings of stigmatization and lead to withdrawal from social activities [64, 65]. Recurring themes in patients with colorectal cancer are loneliness and isolation [63]. It might be expected that disabilities after colorectal cancer treatment prevent the younger patients from going to work and contribute
to their impaired social and role functioning, but it was found that most patients with colorectal cancer returned to work after treatment [64, 66]. An additional source of distress especially in younger male patients was the possible impact on sexual functioning [64, 67]. Studies have shown that after treatment for rectal cancer, sexual problems were common, inadequately discussed and/or treated by physicians [67]. Furthermore, the potential for impotence due to treatment for colorectal cancer was a serious concern especially in patients of younger than 60 years [64].

**Conclusion**

This review identifies the psychological impact of colorectal cancer during the first year after treatment and indicates specific subgroups of patients with colorectal cancer who could be vulnerable to genetic-testing-related distress. Most of the retrieved studies on diagnostic genetic testing for Lynch syndrome exclusively measured distress prior to genetic test disclosure and focused on patients who were diagnosed with colorectal cancer several years ago. Therefore, we are still unable to identify the psychological impact of genetic testing for Lynch syndrome in recently diagnosed patients with colorectal cancer.

**Acknowledgements**

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References

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66. Sanchez NM, Richardson JL, Mason HR (2004) The return to work experiences of colorectal cancer survivors. AAOHN J 52:500-10
A review on the psychological impact of CRC and of genetic testing for Lynch syndrome
Karin Landsbergen
Judith Prins
Han Brunner
Nicoline Hoogerbrugge

Shortened time interval between colorectal cancer diagnosis and risk testing for hereditary colorectal cancer is not related to higher psychological distress.
Abstract

Introduction Current diagnostic practices have shortened the interval between colorectal cancer (CRC) diagnosis and genetic analysis for Lynch syndrome by MSI-testing. We studied the relation of time between MSI-testing since CRC diagnosis (MSI-CRC interval) and psychological distress.

Material and methods We performed a cross-sectional study in 89 patients who had previously been treated for CRC. Data were collected during MSI-testing after genetic counseling. Psychological distress was measured with the IES, the SCL-90 and the POMS; social issues with the ISS, ISB and the ODHCF.

Results The median time of MSI-CRC interval was 24 months (range 0-332), with 23% of the patients diagnosed less than 12 months and 42% more than 36 months prior to MSI-testing. In 34% of the patients cancer specific distress was high (IES scores > 26). Mean psychopathology (SCL-90) scores were low, mean mood states (POMS) scores were moderate. Interval MSI-CRC was not related to psychological distress. High cancer specific distress was reported by 24% of patients diagnosed with CRC less than 12 months ago versus 39% and 35% by those diagnosed between 12-36 months and more than 36 months ago respectively. Distress was positively related to female gender ($p=0.04$), religiousness ($p=0.01$), low social support ($p=0.02$) and difficulties with family communication ($p<0.001$).

Conclusion Shortened time interval between CRC diagnosis and MSI-testing is not associated with higher psychological distress. Females, religious persons, those having low social support and those reporting difficulties communicating hereditary colorectal cancer with relatives are at higher risk for psychological distress.
Introduction

In the Netherlands more than 11,000 people are diagnosed with colorectal cancer each year [1]. This means that around 1 in 20 Dutch people will develop colorectal cancer in their lifetime. The majority of colorectal cancer patients have sporadic disease and only a minority of colorectal cancers has a genetic cause. One well-described colorectal cancer genetic syndrome is Lynch syndrome which is estimated to account for 3-5% of all colorectal cancer [2, 3]. Lynch syndrome is an autosomal dominant inherited disorder characterized by an increased risk to develop colorectal cancer (60-90% lifetime risk) and an increased risk of extra-colonic tumors, especially endometrial cancer (25-70% lifetime risk); the age at diagnosis for colorectal cancer is most often between 41-54 years, for endometrial cancer between 45-50 years [2, 3]. Lynch syndrome mutation carriers are advised to have regular colorectal screening, starting at the age of 25, with a maximum interval of 24 months between each examination [4]. Regular surveillance reduces morbidity and mortality by 65% over 15 years in previously unaffected relatives and also reduces the risk of a second colorectal cancer in patients [5]. Lynch syndrome is caused by mutations in one of the mismatch repair (MMR) genes and is characterized by tumors that show microsatellite instability (MSI), which is found in more than 90 percent of tumors from patients with Lynch syndrome [2]. In current practice, MSI analysis is used as a pre screening tool selecting families for further analysis of MMR gene defects [6].

Undoubtedly cancer diagnosis is a traumatic life event [7]. Genetic counseling and testing for hereditary cancer can also be a strong stressor [8]. It may cause uncertainty about future cancer which may lead to an increased level of cancer specific distress, activating intrusion or avoidance or both [9]. After genetic counseling, greater awareness of the increased risk of second cancer and of the genetic contribution to an increased risk of cancer for their children may lead to an increased level of cancer specific distress [8]. Additionally a positive genetic test result may reactivate or aggravate distress related to cancer diagnosis and treatment [10].

Studies, which address the psychological impact of genetic counseling and testing for hereditary colorectal cancer in healthy individuals or given time after cancer diagnosis, generally indicate that genetic information does not result in adverse psychological outcomes in the long term [11-14]. However, due to a change in various protocols, the time between colorectal cancer diagnosis and genetic counseling and testing for Lynch syndrome is decreasing. This is partly due to MSI
testing by pathologists, for instance in tissue of patients diagnosed before age 50 or from patients with a second CRC before age 70 [15]. A striking psychological difference with former practice is that these patients are confronted with a possibly hereditary predisposition for Lynch syndrome coincident with treatment for CRC. Little is known about the psychosocial impact of genetic testing in patients with a recent diagnosis of colorectal cancer.

The aim of the current study is to investigate whether high levels of overall psychological distress are present during MSI-testing and whether these levels are correlated with time since colorectal cancer diagnosis. For that purpose we use both the Impact of Event Scale (IES), the Symptom Checklist-90 and the Profile Of Mood States (POMS); the IES because more recently diagnosed patients might be more vulnerable to reactivation or aggravation of cancer specific distress and the SCL-90 and the POMS to measure general psychological distress during the past week. Concerns of heredity mediated distress and cancer specific distress may affect both the overall level of distress. However, this cannot be distinguished in our sample.

Material and methods

Study design and procedure
A cross-sectional study was performed to determine psychological distress in patients previously treated for colorectal cancer just after initiation of MSI testing. All patients visited the Department of Clinical Genetics of the Radboud University Medical Centre Nijmegen in the Netherlands. Before MSI-testing was started, comprehensive genetic counseling took place to ensure that the patient understands the implications of the MSI-test. MSI-testing was performed after informed consent of the patient. Inclusion criteria of the study were 1) patients with colorectal cancer 2) fulfilling one of the Bethesda criteria for MSI-testing [4] and 3) having a CRC to be tested for MSI. Patients were excluded in case of 1) previous MSI-testing or 2) current treatment for psychiatric disorders. In every patient medical history for psychiatric disorders and former and current psychiatric treatment is taken. From Augustus 2007 to September 2009, 191 eligible patients were approached by their genetic counselor (n=14) to participate the study. Of these potential eligible patients16 patients considered participating too stressful, three patients were in a terminal phase and two patients had already received the
MSI-test result. Four patients were in current psychiatric treatment and therefore excluded from study participation. Of 77 from the remaining 81 patients personal reasons for non-participation were retrieved being "not interested" (64%), "too busy" (25%) and "just forgotten" (11%). Finally, written informed consent was obtained from 89 participants in accordance to the rules of the Committee on Research Involving Human Subjects, Region Arnhem-Nijmegen in the Netherlands. Psychological and social data were collected by validated questionnaires immediately after initiation of MSI-testing, still before MSI-test disclosure. Information regarding family cancer history was retrieved from medical records.

**Measures**

**Demographic and colorectal cancer information**
Data were obtained on age, gender, marital and parental status, education, religion, cancer status and on having a first degree relative with cancer.

**Psychological distress**

* Cancer specific distress*
The Impact of Event Scale (IES) [16, 17] was geared towards colorectal cancer as distressing event (scoring 0,1,3,5). A total score of 9-25 reflects moderate adaptation difficulties, a score above 26 indicates serious adaptation difficulties [18]. The IES is widely used as a measure of cancer specific distress within the context of genetic counselling and testing for hereditary cancer [19, 20].

*Psychopathology*
The Symptom Checklist-90 (SCL-90) is a 90-item indicator for psychopathology. A SCL-90 score above 160 is indicative for serious psychological complaints, a score above 200 is indicative for a psychiatric disorder [21].

*Mood states*
The Profile of Mood States-Brief (POMS-SF) [22] measures depression (range 0-32), anger (range 0-28), fatigue (range 0-24), tension (range 0-24) and vigour (range 0-20).

**Social support**
The Inventory for Social Support (ISS) [23] comprises 3 scales: potential emotional trust (range 5-20), actual trust (range 3-12) and visits (range 2-8).
Family communication

Family communication was assessed with an adaptation of the Openness to Discuss Hereditary Cancer in the Family Scale (ODHCF) [24, 25]. Openness was assessed with the item “I discuss hereditary colorectal cancer with my partner, children, parents, brothers, sisters, uncles and aunts, nephews and nieces, respectively, i.e. never (1), rarely (2), sometimes (3) and often (4). Family communication difficulties and in need of help were assessed similarly (range 7-24).

Statistical analysis

The SPSS 16.0 statistical package was used to analyze the data. Correlations between cancer specific distress (IES), psychopathology (SCL-90) and mood states (POMS) were assessed by the Spearman Rank Correlation. Time between colorectal cancer (CRC) diagnosis and the initiation of MSI-testing was defined as “Interval MSI-CRC” and measured in months. Interval MSI-CRC was divided in 3 categories: shortly after CRC diagnosis (< 12 months after diagnosis), recuperating from cancer treatment (12-36 months after diagnosis) and diagnosed with cancer longer ago (> 36 months after diagnosis). Interrelations between the interval CRC-MSI, various other personal variables (i.e. gender, marital and parental status, religion, cancer and cancer treatment related, having a first degree relative with cancer, social support, family communication) and cancer specific distress were analyzed. The IES was dichotomized, where 26 was used as cut-off value for clinically high levels of psychological distress [16]. Multivariate logistic regression analysis was performed for all variables that were analyzed in univariate analysis and were statistically significant correlated with the IES > 26, with stepwise removal of non-significant variables. Odds ratios (OR's) were calculated to describe associations between personal characteristics and the IES > 26 and presented with their 95% confidence intervals (95% CI). P-values < 0.05 were considered statistically significant (two-tailed).

Results

From Augustus 2007 till September 2009, 193 patients with a history of colorectal cancer were approached by their genetic counselor after genetic counseling and initiation of MSI analysis. Eighty-nine patients were included (response rate 46%). No significant differences were found regarding sociodemographic and colorectal cancer related characteristics between participants and non-participants.
Sociodemographic and colorectal cancer related characteristics
Most participants were female (64%), married or cohabiting (83%), had children (88%) and considered themselves religious (72%). The median age at CRC diagnosis was 49 years with the youngest patient diagnosed at age 24 years. The median age at initiating MSI-testing was 55 years (range 32-85 years). The median time of the CRC-MSI interval was 24 months (range 0-332 months). So the range in time since cancer diagnosis was large, with 23% of the patients diagnosed less than 12 months and 42% of the patients diagnosed with cancer more than 36 months ago. Colorectal cancer related characteristics of the study sample are provided in Table 1.

Table 1 Colorectal cancer (CRC) related characteristics of the study sample

<table>
<thead>
<tr>
<th>Patients with a history of CRC (n=89)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lynch syndrome alert</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRC &lt; 50 years</td>
<td>52</td>
<td>58</td>
</tr>
<tr>
<td>2x Lynch syndrome related tumor* &lt; 70 years</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>First degree relative with cancer</td>
<td>65</td>
<td>73</td>
</tr>
<tr>
<td><strong>Cancer treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery without adjuvant therapy</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Surgery with chemotherapy (CT)</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td>Surgery with radiotherapy (RT)</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Surgery with both CT and RT</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td><strong>Time between CRC and MSI-analysis</strong></td>
<td></td>
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</tr>
<tr>
<td>&lt; 12 months</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>12-36 months</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>&gt; 36 months</td>
<td>37</td>
<td>42</td>
</tr>
</tbody>
</table>

*, endometrial cancer and carcinomas of stomach, small bowl, biliary tract, brains, sebaceous gland, upper urinary tract and ovaries.
Social characteristics

Social support and family communication characteristics are provided in Table 2. Mean social support scores were comparable to those of a norm group in the Dutch population [23]. The mean family communication openness score was moderate; mean family communication difficulties and in need of help scores were low. Of the males, 22% reported difficulties regarding family communication about hereditary colorectal cancer versus 55% of the females. Regarding the item “in need of help”, 25% of the males versus 46% of the females felt the need for help in discussing hereditary cancer with the family.

Levels of psychological distress

The mean level of psychological distress (IES) was 16.90 (SD 21.7). More than one third of the study sample reported clinically elevated levels of distress (IES > 26), of whom 39% females and 25% males. Significantly more patients who considered themselves religious reported an IES level above 26 compared to non-religious patients (41% versus 16%, \( P=0.04 \)). Patients who reported difficulties regarding family communication were more likely to report an IES level above 26 (47%) than patients with good family communication (24%) \( (P=0.02) \). Of the patients diagnosed with colorectal cancer less than 12 months ago fewer reported high psychological distress (24%), than patients diagnosed between 12-36 months ago (39%) and those diagnosed more than 3 years ago (35%).

Relations with the total level of psychological distress (IES-total)

In table 3 Spearman rank correlations between patient’s personal sociodemographic / psychosocial characteristics and the total level of psychological distress are shown. The total level of psychological distress was significantly correlated with gender \( (P=0.04) \), being religious \( (P=0.01) \), social support visits \( (P=0.02) \), family communication difficulties \( (P< 0.001) \) and family communication in need of help \( (P=0.009) \). No relation was found of time between CRC diagnosis and MSI-testing with levels of psychological distress.

Relations with high levels of psychological distress (IES >26)

Being religious and family communication difficulties were significantly correlated with high levels of psychological distress, OR 0.28 (95% CI 0.09-0.91;\( P=0.03 \)) and OR 0.34 (95% CI 0.14-0.85; \( P=0.02 \)), respectively. Multivariate logistic regression analysis showed that the presence of high psychological distress was independently related to family communication difficulties, OR 0.37 (95% CI 0.14-0.95;\( P=0.04 \)).
Psychopathology and mood states

Psychopathology and mood states scores of the study sample are shown in Table 2. The mean psychopathology scores of our participants were low [21], while three patients reported high levels of psychopathology (mean 229, range 209-255). Mean POMS subscales scores were higher compared to patients with gynaecological cancer of whom the majority experienced stage I disease [26] but lower than patients with cancer awaiting bone marrow transplantation [27]. No statistically significant correlations were found between “Interval MSI-CRC” and the SCL-90 or between “Interval MSI-CRC” and the POMS subscales. The SCL-90 and the POMS correlated significantly with the IES and to avoid duplication of results we decided not to report all retrieved data.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Psychological and social characteristics of the study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a history of CRC (n=89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Mood states a</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>2.6</td>
</tr>
<tr>
<td>Anger</td>
<td>2.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.4</td>
</tr>
<tr>
<td>Tension</td>
<td>3.2</td>
</tr>
<tr>
<td>Vigor</td>
<td>10.7</td>
</tr>
<tr>
<td>Psychopathology b</td>
<td>122.8</td>
</tr>
<tr>
<td>Social support c</td>
<td></td>
</tr>
<tr>
<td>Potential trust</td>
<td>17.1</td>
</tr>
<tr>
<td>Actual trust</td>
<td>7.2</td>
</tr>
<tr>
<td>Visits</td>
<td>6.2</td>
</tr>
<tr>
<td>Family communication d</td>
<td></td>
</tr>
<tr>
<td>Openness</td>
<td>14.4</td>
</tr>
<tr>
<td>Difficulties</td>
<td>8.3</td>
</tr>
<tr>
<td>In need of help</td>
<td>7.0</td>
</tr>
</tbody>
</table>

a, POMS Brief; b, SCL-90; c, ISS; d, ODHCF.
### Table 3  Correlations with the level of colorectal cancer specific distress (IES-total)

<table>
<thead>
<tr>
<th>Patient’s characteristics</th>
<th>Colorectal cancer distress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.218*</td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>- 0.029</td>
</tr>
<tr>
<td>Having children</td>
<td>0.014</td>
</tr>
<tr>
<td>Being religious</td>
<td>0.272**</td>
</tr>
<tr>
<td><strong>Colorectal cancer related</strong></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>- 0.081</td>
</tr>
<tr>
<td>Cancer treatment</td>
<td>- 0.007</td>
</tr>
<tr>
<td>First degree relative with cancer</td>
<td>- 0.110</td>
</tr>
<tr>
<td><strong>Genetic risk assessment</strong></td>
<td></td>
</tr>
<tr>
<td>Months between CRC and MSI</td>
<td>- 0.005</td>
</tr>
<tr>
<td>Interval CRC-MSI in 3 time categories $^b$</td>
<td>- 0.029</td>
</tr>
<tr>
<td><strong>Psychological characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.447**</td>
</tr>
<tr>
<td>Anger</td>
<td>0.348**</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.287**</td>
</tr>
<tr>
<td>Tension</td>
<td>0.462**</td>
</tr>
<tr>
<td>Vigor</td>
<td>- 0.279**</td>
</tr>
<tr>
<td>Psychopathology</td>
<td>0.532**</td>
</tr>
<tr>
<td><strong>Social Support</strong></td>
<td></td>
</tr>
<tr>
<td>Potential trust</td>
<td>- 0.178</td>
</tr>
<tr>
<td>Actual trust</td>
<td>0.119</td>
</tr>
<tr>
<td>Visits</td>
<td>- 0.243$^*$</td>
</tr>
<tr>
<td><strong>Family Communication</strong></td>
<td></td>
</tr>
<tr>
<td>Openness</td>
<td>- 0.081</td>
</tr>
<tr>
<td>Difficulties</td>
<td>0.397**</td>
</tr>
<tr>
<td>In need of help</td>
<td>0.275**</td>
</tr>
</tbody>
</table>

$^a$, Rs, Spearman Rank correlation; $^*$, $P < 0.05$; $^{**}$, $P < 0.01$;

$^b$, $< 12$ months, 12-36 months and >36 months since CRC diagnosis.
Discussion

The findings suggest that the level of psychological distress is not related to time between colorectal cancer diagnosis and MSI testing. In fact, patients diagnosed with colorectal cancer less than 1 year ago reported less psychological distress than patients diagnosed with cancer longer ago. Contemplation and consideration of the cancer is more likely to occur once active treatment for cancer in the hospital is over. Experiencing intrusive thoughts may be a signal that people are working through the implications of the cancer [28]. In line with this, a previous study showed that 15% of patients with breast cancer became distressed not until after end of treatment, in the reentry phase [29].

Our study results indicate that in general genetic testing during the treatment phase of CRC may not be harmful for patients with CRC. However, approximately one third of the patients reported clinically high levels of psychological distress. The prevalence rate of high cancer distress is higher than the 3-24% reported in the literature [8, 13, 19, 30-32]. This might be explained by selection bias whereby individuals who chose to participate in the study were more distressed compared to those who did not.

We analysed which patients were at highest risk for distress and found three risk factors: gender, religion and reduced social support including impaired family communication. In our study female patients reported higher levels of psychological distress than male patients. This fits with many other studies in which gender is found to be related to psychological distress upon genetic testing [33] and with a review which demonstrated that female patients with colorectal cancer are most vulnerable for hereditary cancer genetic testing related distress [34]. Unexpectedly, religious patients were found to report the highest levels of psychological distress. Previous studies showed that patients use spiritual and religious resources to understand and cope with morbidity and mortality [35] and that this helps people cope with genetic uncertainty [36]. We note that there are positive and negative patterns of religious coping [35] and in this study we did not measure distinct religious coping patterns. It might be that in our study sample negative religious coping patterns dominated. In a study with participants tested for BRCA1 mutations no significant associations between religiosity and psychological distress were observed [37]. We conclude to this point that religious coping in the context of genetic testing is an area in which more studies are needed. Finally, low social support and difficulties with family communication were related to higher levels of psychological distress. This is consistent with a
study among colorectal cancer survivors undergoing genetic testing for Lynch syndrome in which higher levels of cancer related distress was related to less social support [38]. Genetic testing and hereditary cancer are family matters. Family system characteristics may influence the way the individual and the family as a whole copes with hereditary cancer [39]. Our data showed that difficulties and being in need of help regarding family communication about hereditary cancer were related to psychological distress. Participants more frequently reported cancer related distress when they perceived family communication about hereditary cancer as inhibited [40]. The quality of communication is of paramount importance where open family communication may be an important buffer against hereditary cancer distress [40]. Patients who report difficulties regarding communicating hereditary cancer with the family seems vulnerable to high levels of psychological distress. Questioning family communication can identify these patients. Former experiences with cancer may also play an role in genetic testing responses [41]. Experiences with cancer in the family may result in an increased psychological vulnerability during genetic testing for hereditary cancer [25]. However, we found no relation between either cancer treatment or having a first degree relative with cancer and the level of psychological distress. The latter finding is in contrast with a study which showed that having a first degree relative with colorectal disease predicted a higher level of distress about colorectal cancer [42]. Previous studies found being unmarried [43] and having children [33] as predictors of psychological distress related to genetic testing for hereditary cancer. In our study sample however, no correlations were found between marital or parental status and the level of psychological distress.

To our knowledge, this is the first study that measures psychological distress in relation to time between colorectal cancer diagnosis and genetic testing for hereditary cancer. Moreover, this is the first study measuring psychological distress at the time of testing for being at high risk for Lynch syndrome by MSI-analysis. A point of attention is that response rate was low and our study sample may reflect selection-bias. Although demographic and cancer related characteristics of the participants and the non-participants did not differ significantly, psychological characteristics of the non-responders were not obtained. Other limitations of the study is the relatively small sample size and the cross-sectional design. To determine the causal effect of MSI-testing on levels of psychological distress a prospective randomized study design is preferred.

Our results suggest that high levels of psychological distress are not related to the duration of the time period between MSI-testing since CRC diagnosis. We carefully
conclude that patients who are either female, religious, having low social support or those reporting difficulties in communicating hereditary colorectal cancer with relatives are at higher risk for psychological distress.

Acknowledgements

We are very grateful to the participants for their valuable contribution to the study, to Riki Willems for identification of potential participants and to the genetic counselors for their collaboration. The study was supported by a grant of the Netherlands Digestive Diseases Foundation (SWO 05-07).
15. The Dutch Association of Comprehensive Cancer Centres Dutch Guideline Hereditary Colorectal Cancer http://www.oncoline.nl. 9-1-2008

Chapter 3
Psychological distress in patients with CRC following MSI-testing after genetic counseling
Karin Landsbergen
Judith Prins
Han Brunner
Nicoline Hoogerbrugge

Genetic testing offered directly after the diagnosis of colorectal cancer: a pilot study on the reactions of patients
Abstract

Introduction When colorectal cancer is diagnosed before the age of 50 years, then consideration should be given to a hereditary cause. Indications of heredity can be found in tumour tissue with the aid of microsatellite instability (MSI) testing. A positive MSI test means an increased risk of hereditary colorectal cancer, the so-called Lynch syndrome. Until recently, the usual approach was to postpone genetic testing for colorectal cancer until the family history had been studied extensively and information had been made available by a clinical geneticist about the possible consequences. However, it is now possible for MSI testing to be performed on the initiative of the pathologist when the newly diagnosed patient with colorectal cancer is younger than 50 years. This speeds up the procedure considerably. The psychological effects of discussing genetic testing and referring patients during treatment for colorectal cancer are currently unknown. This paper describes an exploratory study on the experience of eight colorectal cancer patients with the new Lynch syndrome detection strategy.

Material and Methods The patients were interviewed at home using a semi-structured questionnaire based on the multicausal model of problem analysis and adapted with items for colorectal cancer and genetic testing.

Results Three coordinating themes were found: (1) ‘a changed life after the diagnosis of colorectal cancer’, (2) ‘warning for the future’ and (3) ‘communication with family’. It was a considerable challenge for these patients to cope with the physical and psychosocial consequences of colorectal cancer. The majority regarded possible carriership of a hereditary disposition for the Lynch syndrome as useful medico-preventive knowledge for their children. The timing of the confrontation with genetic testing was considered to save time in receiving follow-up advice for their children. However, these patients were apprehensive about having to discuss a hereditary disposition for cancer with their family.

Conclusion In this early phase, coping with the diagnosis of colorectal cancer and the consequences of treatment mainly determined the reactions of these patients and their physical well-being. This small group of patients were of the opinion that the advantages of genetic testing will weigh-up against the disadvantages.
Introduction

It is important to distinguish sporadic colorectal cancer from hereditary forms of colorectal cancer. In the case of a proven hereditary disposition for colorectal cancer, it is possible to perform tailored medico-preventive and genetic testing of family members [1]. Until recently, the usual approach was to postpone genetic testing for colorectal cancer until the family history had been studied extensively and information about possible consequences of certain findings had been made available by a clinical geneticist. At the beginning of 2008, a new national guideline was published in the Netherlands on hereditary colorectal cancer [2]. An important new element is that in all new patients of younger than 50 years who are diagnosed with colorectal cancer, the pathologist searches for evidence of a hereditary cause. This takes place on the basis of molecular characteristics of the tumour, so-called micro-satellite instability (MSI) testing. With the additional of the Lynch detection-MIPA strategy (MIPA = MSI testing on the indication of a pathologist), patients with an indication for genetic testing can be detected more efficiently [3]. This MSI testing cannot diagnose heredity in patients who have recently undergone surgery for colorectal cancer, but it can detect an increased risk of the Lynch syndrome, the most common hereditary cause of colorectal cancer. If the MSI test is positive, the treating physician can decide to refer the patient to a clinical geneticist for genetic counselling. This might be followed by DNA analysis to detect or exclude the presence of the Lynch syndrome. Genetic testing will show that 1 out of 10 of the colorectal cancer patients selected using the MIPA strategy has an actual hereditary cause [4]. The changes in the guideline do not apply to patients who have been treated for colorectal cancer in the past. They will be referred for genetic testing on the basis of any findings suspicious of colorectal cancer and/or uterine cancer in the family anamnesis [5-8]. Therefore, referral for DNA analysis is occurring more and more frequently directly after the diagnosis of colorectal cancer. Thus, these new patients are being confronted in quick succession with: 1) the diagnosis of colorectal cancer, 2) a possible hereditary disposition for colorectal cancer and 3) the obligation to discuss a possible hereditary disposition for colorectal cancer with their children and family. Within this population, about 20% will have an MSI-positive tumour. According to the new guideline, about 220 patients per year in the Netherlands will be offered genetic testing in the period directly after surgical removal of the tumour. This pilot study explored the reactions of the patients to this procedure.
Material and methods

In a group of 55 patients who took part in a cost-effectiveness study on the MIPA strategy [3], nine had an MSI-positive tumour. All nine patients were approached. After giving informed consent, eight of the participants were interviewed at home (interview duration 1-1.5 hours). For this purpose, we designed a semi-structured questionnaire based on the multicausal model of problem analysis and adapted it for colorectal cancer and heredity [9]. The first questions the patients answered addressed cognition, emotions and behaviour in relation to their colorectal cancer and its treatment. Subsequently, the same questions were asked in relation to an increased risk of having a hereditary disposition for the Lynch syndrome and the offer of referral for genetic testing directly after receiving the diagnosis of colorectal cancer. The interviews were typed out and evaluated using systematic thematic analysis [10]. Medical and demographic data were retrieved from the medical files.

Table 1  Cancer-related characteristics of the 8 interviewees

<table>
<thead>
<tr>
<th>Patient (No.)</th>
<th>Cancer localisation</th>
<th>Age at diagnosis (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jejunum</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Endometrium</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>Coecum</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>Duodenum</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>Ascending colon</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>Ileum</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Descending colon</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>Bladder</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Ascending colon</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>Sigmoid</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Endometrium</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Renal pyelum</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>Transverse colon</td>
<td>44</td>
</tr>
</tbody>
</table>
The study was approved by the Committee for Human Research Arnhem-Nijmegen, the Netherlands.

Table 1 shows the cancer-related characteristics of these patients. Mean age at the diagnosis of colorectal cancer was 45 years (range 36-58 years). Mean age at the diagnosis of a Lynch-associated tumour was 51 years (range 42-60 years). Three out of the eight patients had a stoma.

Results

Impact of colorectal cancer
Table 2 shows all the themes identified in relation to colorectal cancer. The patients remarked that since the start of their symptoms, it had sometimes taken a whole year to make the diagnosis of colorectal cancer. Chronic fatigue was having a heavy impact. In addition, changes in defecation patterns and the presence of a stoma were also affecting daily functioning. “Whenever I go anywhere, the first thing I do is to make sure I know where the toilet is and sometimes my stoma makes such disgusting noises that I wish the floor would open up and swallow me”. The patients said that because of these problems, they had to be careful not to become socially isolated. Deep thoughts about what had happened to them physically and anxiety about lymph node metastases were taking up a large part of their day: “They told me that I have been lucky, but why am I still so scared?” Confrontation with the finiteness of life was not only causing deep anxiety, but had also meant that these patients were living their lives with more attention and consciousness. As a result of the changes in their attitudes towards life, there had also been changes in the relationships within the family, the broader family circle and with friends; contact had intensified or broken down: “Many people often talk a great deal, but they don’t really say anything. It was only then that I realised people don’t listen and they just want to talk about themselves”. Three patients were receiving professional psychosocial help to cope with the diagnosis of cancer. The diagnosis of colorectal cancer had also had considerable impact on the patients’ work situation and consequently, on their financial position.
### Table 2 Themes identified in relation to colorectal cancer

<table>
<thead>
<tr>
<th>Themes</th>
<th>No. of times mentioned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Healthier diet</td>
<td>5</td>
</tr>
<tr>
<td>Doctor-patient communication</td>
<td>4</td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>4</td>
</tr>
<tr>
<td>Problems with defaecation or stoma</td>
<td>3</td>
</tr>
<tr>
<td>Psychosocial Worried about lymph node metastases</td>
<td>6</td>
</tr>
<tr>
<td>Changed attitude towards life</td>
<td>6</td>
</tr>
<tr>
<td>Loss of job/finances</td>
<td>3</td>
</tr>
<tr>
<td>Professional psychosocial help</td>
<td>3</td>
</tr>
<tr>
<td>More enjoyment of partner and children</td>
<td>2</td>
</tr>
<tr>
<td>Changes in social contacts</td>
<td>2</td>
</tr>
<tr>
<td>Impact of simultaneous life-events</td>
<td>1</td>
</tr>
</tbody>
</table>

### Impact of genetic testing for the Lynch syndrome

Table 3 shows all the themes identified in relation to the Lynch syndrome. Two patients stated that even before their own diagnosis, they had often thought that it could not be a coincidence that there were so many people with cancer in the family. Thus, the message about the possible existence of heredity did not come as a surprise to them. In half of the patients, genetic testing had extra cognitive and emotional meaning, because it provided an explanation of why they had developed cancer at such a young age. Persistent guilt issues about what they had done wrong (e.g. unhealthy diet) could be exchanged for a “guilt-free” hereditary disposition of their colorectal cancer. The early offer of genetic testing was received positively. A characteristic citation from the whole patient group was: “I think that it would have been more difficult emotionally if I had not been confronted with genetic testing until a couple of years after my diagnosis. Then that would be another new kick in the face and I would probably have to start coping with the cancer all over again. Now we can have everything sorted out in one go and if it’s true, then it is better that we know”. There were positive thoughts about genetic testing regarding the medico-preventive value for the children. In this respect, the patients mentioned that early discussions about genetic testing meant that important time was being saved. The possible hereditary nature of the colorectal cancer served as a warning for the patient, the children and the rest of the family: “If it really is the case, then it would be best for them to go for
check-ups”. Looking at the future, the hope predominated that genetic testing would mean that the same thing would not happen to the children. The part that the patients dreaded most was to have to talk to the rest of the family if DNA analysis showed that their cancer was definitely hereditary. “Obviously, it is not a nice subject, but health comes first, so I really am going to tell them!”. Some of the patients said that they would find it extremely useful if the Clinical Genetics Centre would organise family-information meetings for this inwardly complex and concurrently often emotionally-loaded material.

<table>
<thead>
<tr>
<th>Themes</th>
<th>No. of times mentioned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td></td>
</tr>
<tr>
<td>Medico-preventive value for the children / family</td>
<td>6</td>
</tr>
<tr>
<td>Time-saving / warning</td>
<td>5</td>
</tr>
<tr>
<td>Own risk of 2nd primary tumour</td>
<td>3</td>
</tr>
<tr>
<td>Hereditary component expected</td>
<td>2</td>
</tr>
<tr>
<td>“If only they had found out sooner”</td>
<td>1</td>
</tr>
<tr>
<td>Psychosocial</td>
<td></td>
</tr>
<tr>
<td>Hope for the future</td>
<td>5</td>
</tr>
<tr>
<td>Explanation for the cancer (in the family)</td>
<td>4</td>
</tr>
<tr>
<td>Dreading communication with the family</td>
<td>4</td>
</tr>
<tr>
<td>Need for organised information meeting for the family</td>
<td>1</td>
</tr>
</tbody>
</table>

**Discussion**

The patients indicated that the emotional burden was considerable and that this was mainly due to the diagnosis of cancer and the consequences of the treatment. They described the chronic fatigue, the loss of their working environment and the lack of control over defecation. These three items, covered by the theme “changed life after the diagnosis of colorectal cancer” were restricting their social lives. This confirms previous research into patients with colorectal cancer, particularly those with a stoma, whose role and physical functioning deteriorated in the first three months after surgery [11-16]. Poorer role, emotional and social functioning often
persist in the first year after surgery, especially in patients diagnosed with colorectal cancer before the age of 60 years [12].

In relation to the reactions to the MSI-positive nature of the tumour, the two coordinating themes were “warning for the future” and “communication with family”. In this small group of patients, the offer of genetic testing for the Lynch syndrome was seen as a hopeful source of preventive information for their children, but they were dreading having to talk to their family about it. The majority of patients said that they considered early confrontation with a possible hereditary disposition for colorectal cancer to be an important time saving in the acquisition of follow-up advice for their children. This predominantly positive reaction from patients to the offer of genetic testing directly after the diagnosis of colorectal cancer confirms an earlier report on a Scottish study on 111 patients of younger than 55 years who had recently been diagnosed with colorectal cancer [17]. An important difference from the MIPA study was that the Scottish patients had received a basic form of genetic counselling before undergoing genetic testing. In addition, after giving informed consent, blood samples had been taken for germ line DNA analysis. In the MIPA study, the patients had received the MSI test result from their surgeon and it was decided afterwards whether or not there would be referral to a clinical geneticist. The patients in our study stated that it would have been more difficult if there had been an interval of several years between the diagnosis of cancer and confrontation with genetic testing. Other studies also reported that a positive genetic test result can lead to reactivation of stress related to cancer diagnosed in the past [18]. In the period directly following the diagnosis of colorectal cancer, it is unlikely that the patients will be able to estimate the long-term psychosocial burden of genetic testing. Patients with cancer sometimes underestimate their reaction to genetic testing, because they are convinced that the worst, having cancer, has already happened to them [18].

In view of the fact that these patients had been suffering from complaints for many months or even years before they were diagnosed with colorectal cancer, it is understandable that they hope that genetic testing will spare their children from the same fate. These patients expect that as a result of genetic testing, their children will undergo regular abdominal examinations and that if they have any complaints between check-ups, they will quickly be referred to a medical specialist.

Many patients were dreading having to discuss the possible hereditary disposition for the Lynch syndrome with their family, despite the preventive value of the information. The literature on family communication in relation to genetic testing
showed that information about a hereditary disorder with good preventive opportunities, such as a hereditary disposition for intestinal polyps and colorectal cancer, does not always reach all the family members concerned [19, 20]. This means that lives can be saved by carefully supporting patients and supervising them in spreading the message within their family [21-23]. To supervise patients in the choice and consequences of genetic testing for the Lynch syndrome, specialised psychosocial care is available at every Clinical Genetics Centre in the Netherlands [24, 25].

Need for further research

Our study was limited to a very small number of patients, so it is too early to draw conclusions about the psychological impact of conducting MSI testing on tumours from recently diagnosed patients with colorectal cancer. Nevertheless it was striking to observe that the patients' reactions to the offer of genetic testing directly after surgery were largely positive. To draw firm conclusions about the psychosocial burden of confrontation with genetic testing directly after the diagnosis of colorectal cancer, it is necessary to perform prospective research into a larger group of patients. Such research has been started, subsidised by the Netherlands Digestive Diseases Foundation (Grant SW05-07).
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4. de Bruin JH, Kievit W, Lijtenberg MJ et al (2005) [More hereditary intestinal cancer can be detected if patients with colorectal carcinoma that are selected by the pathologist are examined for microsatellite instability]. Ned Tijdschr Geneeskd 149:1792-8

Karin Landsbergen
Judith Prins
Han Brunner
Peter van Duijvendijk
Fokko Nagengast
Han van Krieken
Marjolijn Ligtenberg
Nicoline Hoogerbrugge

Submitted
Psychological distress following microsatellite instability testing for Lynch syndrome by pathologists in new colorectal cancer patients
Abstract

Introduction According to the Dutch Guideline Hereditary Colorectal Cancer 2008, pathologists test for high risk of Lynch syndrome by MSI-testing immediately after tumour resection in patients recently diagnosed with colorectal cancer (CRC) below 50 years or with a second CRC below 70 years (MIPA). The aim of the present MIPAPS-study is to investigate general distress and cancer specific distress during six months following MSI-testing.

Material and methods From March 2007 until September 2009, 400 newly diagnosed patients with CRC from 30 Dutch hospitals whose CRC had been tested for MSI were approached by surgeons to participate in the study. Levels of general distress (SCL-90) and cancer specific distress (IES) were assessed immediately after MSI-test disclosure (T1) and 6 months later (T2).

Results Response of MSI-positive and MSI-negative patients was 23/77 (30%) and 58/323 (18%), respectively. Levels of general distress and cancer specific distress were moderate. In the MSI-positive group, percentages of patients with high general distress decreased after 6 months from 27% to 18%, while they remained stable in the MIPA-negative group, from 14% to 18%. High cancer specific distress decreased in the MSI-positive group and remained stable in the MSI-negative group, from 39% to 27% and from 38% to 36%, respectively. Women were more prone to high levels of distress, as were patients who had low social support or a high perceived cancer risk.

Conclusion For the majority of CRC patients, MSI-testing shortly after CRC diagnosis is followed by levels of psychological distress that are similar to other CRC patients.
Introduction

Each year, more than one million patients are diagnosed with colorectal cancer (CRC) worldwide and Lynch syndrome accounts for approximately 3% of this incidence [1]. Identifying Lynch syndrome is highly relevant because surveillance reduces morbidity and mortality in family members carrying a mutation in one of the mismatch repair genes [2]. Patients at risk for Lynch syndrome can effectively be detected with a microsatellite instability (MSI) test, a molecular genetic test on tumour DNA of a CRC [3-6]. In Lynch syndrome almost all CRCs show high MSI. Conversely, in patients diagnosed with CRC at relatively young age finding high MSI is strongly associated with genetic susceptibility [7] and can therefore be used as an indicator for Lynch syndrome. Traditionally, patients have an MSI-test after referral to a clinical genetic department because of multiple CRCs in the family. However by family history, only a minority of the patients with Lynch syndrome is identified [8-11]. A new cost-effective and efficient guideline was shown to enhance the recognition of patients at risk for Lynch syndrome [5, 12, 13]. With this MSI-testing-indicated-by-a-Pathologist (MIPA)-test [5, 12, 13], pathologists initiate MSI testing in a selection of recently diagnosed patients with one of the following criteria, called MIPA-criteria: 1) CRC diagnosed before age 50; 2) second CRC before age 70 [5, 14, 15]. Pathologists report the MSI-test result to the surgeon. When the MSI-test is positive, the surgeon is advised to consider referral of the patient for genetic counselling and eventually germline DNA-analysis. One year before the introduction of the MIPA-procedure only 30% of the patients at risk for Lynch syndrome was recognized as such by the traditional procedure based on family history [16]. This is in line with other studies showing that family history is insufficient for recognizing patients at risk for Lynch syndrome [8-11]. After introduction of the MIPA-procedure in teams including surgeons and pathologists the recognition of patients at risk for Lynch syndrome increased substantially [13].

The MIPA-procedure implies that CRC patients are simultaneously confronted with 1) a diagnosis of and treatment for cancer; 2) a possibly hereditary predisposition for Lynch syndrome and 3) the need to inform children and relatives about their possible cancer risks. CRC itself is already responsible for considerable physical and psychosocial morbidity [17]. We asked to what extent MSI-testing will add to this distress. Newly diagnosed CRC patients who were offered genetic testing for hereditary CRC considered such testing at that point in time highly
acceptable [18]. However, the actual psychosocial consequences of discussing a high genetic risk for Lynch syndrome on CRC patients during their treatment phase are scarcely known. The aim of the present study is to investigate distress and cancer specific distress of the patients. Also social support and cancer risk perception were studied as possible predictors of patients’ distress [19-22]. Furthermore caregiver experiences of the partners were investigated during six months following MSI-testing in relatively young and recently diagnosed patients with CRC.

Material and methods

Patients and design
A prospective multi-centre study was performed in recently diagnosed patients with CRC to assess psychological and cancer specific distress and experiences of the partners following MSI-testing [5]. Inclusion criteria were 1) a diagnosis of CRC below age 50 years, or 2) a second CRC below age 70 years. Psychological assessment by questionnaires took place immediately after the MSI-test disclosure (T1) and 6 months later (T2). Patients who were diagnosed with cancer more than 6 months ago were excluded. We used a follow-up of 6 months because for patients whose diagnosis warrants adjuvant therapy the treatment trajectory can be up to 12 months or more [23]. Since adjuvant therapy might also affect levels of psychological distress this variable was included in our analyses.

Procedure
From September 2006 until March 2007, 30 Dutch hospitals were invited to participate in the MIPAPS (= Psychosocial impact MIPA strategy) study. The hospital selection was based on those hospitals which had previously participated in the MIPA implementation study [13] and was supplemented with hospitals in neighbouring regions. From March 2007 until September 2009, 400 newly diagnosed patients with CRC who had an MSI-test were identified and eligible for this study. The patient’s surgeon was requested to invite the MIPA patient and his or her partner to participate in the MIPAPS study. Time limit for inclusion by the treating physician was set on 6 months after CRC diagnosis. As soon as written informed consent was received questionnaires were sent to both patients and their partners. The study was approved by the local Ethical Committee (CMO nr. 2006/042).
Assessments

Distress
The Symptom Check List-90 (SCL-90) is a 90-item questionnaire for psychopathology with a 5-point Likert scale (scoring 1-5). A total SCL-90 score above 160 is indicative for high psychological distress, a score above 200 is indicative for a psychiatric disorder [24, 25]. The Profile of Mood States-Short Form [26] was used to assess affective states. Items are rated on a 5-point scale (0-4), resulting in scores for depression 0-32, anger 0-28, fatigue 0-24, tension 0-24 and vigour 0-20. This questionnaire was previously validated for cancer patients [27].

Cancer specific distress
The Impact of Event Scale (IES) [28, 29] was used to assess CRC specific distress. All 15 items were rated on a 4-point Likert scale (scoring 0,1,3,5) with total IES scores ranging from 0 to 75. A total IES score of 9-25 is indicative of moderate adaptation difficulties and a score ≥ 26 is considered indicative of clinical adaptation difficulties and reflects a need for psychological or psychiatric support [30].

Colorectal cancer risk perception
Lifetime risk of CRC was measured with the Cancer Risk Perception List [20-22], measured with a single question “My chance of getting colorectal cancer again is...” where patients marked their risk perception on a Visual Analogue Scale (VAS 0-100%). Absolute risk ranges were classified as follows: 0-20 (low); 20-40 (moderate); 40-60 (fairly high); 60-80 (high); 80-100 (very high).

Social support
Social support was assessed on a 4-point Likert Scale with the Dutch self-report questionnaire Inventory for Social Support (ISS). The inventory comprises 3 scales: 1) Potential emotional trust: range 5-20, moderate 13-15; 2) Actual emotional trust: range 3-12, moderate 5-7 and 3) Visits: range 2-8, moderate 5-6 [31], with a higher score indicating higher social support.

Caregiver experiences of the partner
The partner of the patient filled in two questionnaires. Caregiver reaction was measured by the CRA-D, using the 7-item subscale self-esteem. The perceived impact is rated on a 5-point Likert scale, a higher score representing lower
self-esteem [32, 33]. Perceived distress caused by informal care was measured using the validated 9-item Dutch self-report questionnaire EDIZ [34]. Total scores may be interpreted in three categories 9 to 20 (low load), 21 to 32 (overload) and 33 to 45 (serious overload) [35].

**Statistical analysis**

Demographic and clinical characteristics of the MSI-positive and the MSI-negative group were analysed using the independent T-test for continuous and the Pearson’s exact \( \chi^2 \) test and McNemar test for categorical variables. General linear models for repeated measurements were used to test for differences in psychological distress and caregiver experiences over time. Correlations between distress and demographical variables, social support and cancer risk perception were assessed by the Spearman’ Rank Correlation, represented by Spearman rho (\( p \)). The SPSS 16.0 statistical package was used to analyze the data and the probability level for statistical significance testing was set at 0.05 (two-tailed).

**Results**

**Patient characteristics**

Response rates of the patients with an MSI-high CRC (MSI-positive) and a microsatellite stable-CRC or MSI-low CRC (MSI-negative) were 23/77 (30%) and 58/323 (18%), respectively. No significant differences between participants and non-responders were found considering age at diagnosis or gender. The participating CRC patients (n=81) were aged 48 ± 10 years. Baseline data were received 5 ± 3 months after CRC diagnosis and 50% of the participants were male. Baseline characteristics (T1) of the two groups are provided in table 1. Both groups had similar demographic characteristics. Tumour characteristics were significantly different. As expected in the MSI-positive group more patients were found with a right-sided tumour and a low TNM tumour stage. Moreover, these MSI-positive patients received less often adjuvant therapy. Of the MSI-positive and MSI-negative patients, 13 (56%) and 37 (63%) partners participated respectively (28 female, 22 male).

**Distress**

At baseline no significant differences in psychological distress (SCL-90) between the MSI-positive and the MSI-negative group were found. Mean scores of
Table 1 Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>MSI-positive group^[a]</th>
<th>MSI-negative group</th>
<th>p</th>
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<tbody>
<tr>
<td>Age at cancer diagnosis</td>
<td>48 ± 10</td>
<td>48 ± 12</td>
<td>ns*</td>
</tr>
<tr>
<td>Male</td>
<td>12 (52%)</td>
<td>29 (50%)</td>
<td>nsb</td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>23 (100%)</td>
<td>50 (86%)</td>
<td>nsb</td>
</tr>
<tr>
<td>Having Children</td>
<td>21 (91%)</td>
<td>49 (89%)</td>
<td>nsb</td>
</tr>
<tr>
<td>Educational level &gt; high school</td>
<td>14 (61%)</td>
<td>30 (52%)</td>
<td>nsb</td>
</tr>
<tr>
<td>Religious</td>
<td>17 (74%)</td>
<td>34 (59%)</td>
<td>nsb</td>
</tr>
<tr>
<td>CRC diagnosed below 50 year</td>
<td>15 (65%)</td>
<td>38 (66%)</td>
<td>nsb</td>
</tr>
<tr>
<td>Second CRC diagnosed below 70 year</td>
<td>7 (32%)</td>
<td>20 (35%)</td>
<td>nsb</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
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</thead>
<tbody>
<tr>
<td>Right sided tumour location</td>
<td>11 (50%)</td>
<td>15 (26%)</td>
<td>0.06b#</td>
</tr>
<tr>
<td>TNM stage I or II</td>
<td>16 (73%)</td>
<td>26 (45%)</td>
<td>0.04b*</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>12 (55%)</td>
<td>40 (78%)</td>
<td>0.04b*</td>
</tr>
</tbody>
</table>

\^[a] MSI-positive means that the MSI-test in the tumour is positive and is performed at the initiative of a pathologist, either because the CRC was diagnosed below 50 years or because it was the second CRC below 70 years; *, Independent Samples T-test; b, Pearson Chi-Square test; *, p <0.1; *, p <0.05; ns, not statistically significant.

Psychological distress of the study sample were moderate at both T1 (131 ± 38) and T2 (131 ± 46), as compared to patients with for example breast cancer (151 ± 45) or haematological cancer (145 ±33), and similar to patients with a variety of other solid tumours (130 ± 25) [36]. In the course of the study differences in psychological distress between the two groups were found (figure 1A). Concerning the level of psychological distress a significant interaction effect between MSI-test result and time of assessment was observed, indicating a decrease of psychological distress in the MSI-positive group and an increase in the MSI-negative patient group between T1 and T2 (p=0.03). Although statistically significant, the observed change in psychological distress may be not clinically relevant because mean distress levels did not reach the cut-off score of 160 (indicative for high distress). At T1, almost double the amount of high psychological distress was reported in the MSI-positive group (27%) compared to the MSI-negative group (14%), but this...
Figure 1  **A** Course of mean levels of psychological distress in 22 MSI-positive\(^\wedge\) and 51 MSI-negative patients with CRC. **B** Course of mean levels of caregiver experiences in 13 partners of MSI-positive\(^\wedge\) patients and 37 partners of MSI-negative patients with CRC, a lower CRA-D score indicates higher caregiver’s esteem, a higher EDIZ score indicates higher perceived distress by informal care.

\(^\wedge\) MSI-positive means that the MSI-test in the tumour is positive and is performed at the initiative of a pathologist, either because the CRC was diagnosed below 50 years or because it was the second CRC below 70 years.
difference was not statistically significant. In the MSI-positive group, percentages of patients with high distress decreased after 6 months from 27% (T1) to 18% at T2 ($p=0.5$), while remaining stable in the MSI-negative group, from 14% (T1) to 18% (T2) ($p=0.6$). So, at T2 high psychological distress was reported by 18% of both the MSI-positive and the MSI-negative group still. In figure 2, it is shown that per patient in general psychological distress remained stable over time, both in the MSI-positive and MSI-negative group. Psychological distress was significantly correlated with female gender ($p=0.269$, $p=0.02$), low social support (potential trust $p=-0.298$, $p=0.01$, visits $p=-0.263$, $p=0.03$) and high CRC lifetime risk perception ($p=0.318$, $p=0.006$). No significant relation was found between levels of distress with TNM stage or adjuvant therapy.

Figure 2 Psychological distress per MIPAPS patient at T1 and T2. A score above the cut off of 160 (dotted line) indicates high psychological distress.
In table 2 mean levels of mood states (POMS) of both the MSI-positive and the MSI-negative group at T1 and T2 are provided. All mean affective states were within the same range of other patients diagnosed with cancer [27]. No significant differences were found between the MSI-positive and the MSI-negative group.

**Cancer specific distress**
At baseline, cancer specific distress levels were within the same range in the MSI-positive and the MSI-negative group. Mean scores of cancer specific distress in the study sample were moderate at both T1 (21 ± 15) and T2 (21 ± 17). Over time no significant differences of cancer specific distress levels were found in both groups. At T1, 38% of the total group reported high cancer specific distress (IES≥26), 39% and 38% in the MSI-positive and the MSI-negative group, respectively. At T2, cancer specific distress was slightly decreased in the MSI-positive group and had remained stable in the MSI-negative group, from 39% to 27% (p=0.3) and from 38% to 36% (p=1.0) respectively. Cancer specific distress scores were significantly correlated with female gender (p=0.328, p=0.005). No significant relation was found between these levels and TNM stage or adjuvant therapy.

**Social support and cancer risk perception**
Mean social support levels were moderate compared to a norm group of healthy adults in both the MSI-positive and the MSI-negative group at T1 and T2 [31]. Additionally, no significant differences in social support levels between groups were found (table 2). In table 2 is shown that at T1 patients of both groups reported a fairly high-risk perception for being diagnosed with CRC in the near future. Risk perception at T2 significantly increased from 43% to 50% (p=0.03) in the total group; in the MSI-negative group from 43% to 48% (p=0.2), in the MIPA-positive group from 44% to 53% (p=0.07).

**Partners experiences**
There were significant time effects on both CRA-D and EDIZ levels (p=0.01 and p=0.04, respectively) indicating that the negative impact of care giving decreased in both groups (figure 1B). In the group of partners, caregivers self esteem (CRA-D) was within the same range of partners of patients with other types of cancer [37] (table 2). Caregivers distress by informal care (EDIZ) was reported by 49% and 38% of all partners at T1 and T2, respectively. No significant differences in self esteem and distress were found between the MSI-positive and the MSI-negative group. No significant correlation was found between partner’s gender and caregiver experiences.
Table 2 Psychosocial outcomes of MSI-positive (n=22*) and MSI-negative (n=51*) patients and their partners (n=13 and n=37 respectively), immediately after MSI-test disclosure (T1) and 6 months later (T2)

<table>
<thead>
<tr>
<th></th>
<th>MSI-positive patients</th>
<th>MSI-negative patients</th>
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<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td></td>
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<tr>
<td><strong>CRC patients</strong></td>
<td></td>
<td></td>
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<tr>
<td>Psychological distress</td>
<td>137 ± 45</td>
<td>127 ± 51</td>
<td>-10 ± 27</td>
</tr>
<tr>
<td>Cancer specific distress</td>
<td>22 ± 22</td>
<td>18 ± 17</td>
<td>-4 ± 14</td>
</tr>
<tr>
<td>Depression</td>
<td>4 ± 6</td>
<td>3 ± 5</td>
<td>-1 ± 4</td>
</tr>
<tr>
<td>Anger</td>
<td>5 ± 6</td>
<td>5 ± 6</td>
<td>0 ± 4</td>
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<tr>
<td>Fatigue</td>
<td>8 ± 6</td>
<td>5 ± 6</td>
<td>-3 ± 5</td>
</tr>
<tr>
<td>Tension</td>
<td>5 ± 5</td>
<td>4 ± 5</td>
<td>-1 ± 3</td>
</tr>
<tr>
<td>Vigor</td>
<td>9 ± 4</td>
<td>11 ± 5</td>
<td>2 ± 5</td>
</tr>
<tr>
<td>Cancer risk perception</td>
<td>44 ± 23</td>
<td>53 ± 23</td>
<td>10 ± 23</td>
</tr>
<tr>
<td><strong>Social support</strong></td>
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<tr>
<td>Potential emotional trust</td>
<td>16 ± 4</td>
<td>16 ± 4</td>
<td>0 ± 4</td>
</tr>
<tr>
<td>Actual emotional trust</td>
<td>7 ± 2</td>
<td>7 ± 2</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>Visits</td>
<td>6 ± 1</td>
<td>6 ± 2</td>
<td>0 ± 1</td>
</tr>
<tr>
<td><strong>Partners of CRC patients</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Caregiver’s esteem</td>
<td>29 ± 4</td>
<td>27 ± 5</td>
<td>-3 ± 5</td>
</tr>
<tr>
<td>Perceived stress by care</td>
<td>21 ± 4</td>
<td>18 ± 5</td>
<td>-2 ± 5</td>
</tr>
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</table>

* MSI-positive means that the MSI-test in the tumor is positive and is performed at the initiative of a pathologist, either because the CRC was diagnosed below 50 years of age. **Delta** means the difference scores (T2-T1), based on the original scores before rounding. 1; SCL-90; 2; IES-CRC; 3; POMS; 4; Life Time Risk to get CRC again. 5; ISS; 6; CRAD; 7; EDIZ; 8; patients who filled in both questionnaires (T1 and T2).
Discussion

To our knowledge this is the first multicentre study concerning psychological distress, following genetic pre-screening for Lynch syndrome by MSI-testing in recently diagnosed patients with CRC. Our data suggest that disclosure of the MSI-test result does not result in high levels of distress, for the majority of these patients. Distress and cancer specific distress levels were moderate in both the MSI-positive and the MSI-negative group. It is important to note that a minority of our patients with CRC did report high levels of psychological distress and cancer specific distress after MSI-testing. These levels decreased over time in the MSI-positive group and remained stable in the MSI-negative group. Six months after MSI-test disclosure, almost a year after CRC diagnosis, about 20% of all CRC-patients was still highly distressed and about 40% still experienced high cancer specific distress. These levels of psychological distress were independent of MSI-test result, but related to patient’s characteristics such as female gender, social support and cancer risk perception. In our study the overall prevalence of high psychological distress was lower than in a previous study in which 32% of newly diagnosed patients reported high distress [25]. From literature it is known that two-thirds of patients with cancer will adapt to their diagnosis without any psychological intervention [25]. This initial psychological adaptation to a cancer diagnosis is highly influenced by pre-existing psychosocial factors [38]. These results highlight the necessity for identifying those patients with high levels of distress.

The results of our study in recently diagnosed young CRC patients are in line with studies among patients recently diagnosed with breast cancer who were actively approached for genetic counselling and testing. In this group of patients, overall no short-term or long term additional psychological distress was found [39, 40]. One of the previously given explanations is that the possibly hereditary nature of cancer is not nearly as distressing as the diagnosis of cancer itself [41]. A genetic diagnosis may lead to understanding the origin of CRC and reduce feelings of guilt and psychological distress. Another explanation might be that in general the MSI-positive CRC patients have a good overall prognoses and such patients were less often treated with adjuvant therapy in our study. Therefore, the potentially negative effect of being at high risk of Lynch syndrome may have been psychologically compensated. Worse prognosis and more often treatment with adjuvant therapy might also explain why levels of distress and cancer specific distress of the MIPA-negative CRC patients remained stable over time. However, we could not detect any effect of adjuvant therapy on psychological distress.
The partners of both groups of CRC patients showed moderate to high levels of caregiver esteem. These levels are comparable to those described in literature of partners of patients with CRC [33] or with other types of cancers [37]. The partners of both groups perceived decreasing levels of distress over time. This is in concordance with previous literature describing that the treatment phase is experienced as the most stressful phase in which emotional and informational support is needed most [42].

The MIPA-procedure greatly enhances the efficiency of genetic counselling because patients with an MSI-high CRC are at high risk for being a mismatch repair (MMR) gene mutation carrier. Ten out of the 22 MSI-high CRC patients (45%) were subsequently found to be carrier of a mutation in one of the MMR genes (n=6 MLH1, n=2 MSH6 and n=2 PMS2). In 6 of these patients (27%) MSI was explained by non-hereditary hypermethylation of the MLH1 promoter. The DNA-test result at T2 was not significantly correlated with psychological distress or cancer specific distress.

One limitation of our study is the low response rate for inclusion. This may have biased our results especially if selection by the surgeon has occurred in such a way that patients with a bad prognosis or with emotional problems were less likely to be recruited into the study. This would have resulted in an underestimation of psychological distress. At present we cannot assess whether such a bias is present in our study cohort. However, we note that levels of psychological distress in our sample were lower than those previously described in the literature. Another reason for low response rate may be the complex logistic inclusion procedure of the present study [13], which could result in communication of the test result to the patient after the inclusion period of 6 months. After surgery it could take several months before a written MSI-test report was sent to the surgeon and another couple of weeks before communication with the patient. Many patients did not fulfill the time period inclusion criteria.

We conclude that despite some methodological concerns, our study data indicate that MSI-testing does not increase psychological distress in the majority of patients with CRC.

Acknowledgments
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References


Psychological distress in recently diagnosed patients with CRC following MIPA-testing
PART 2

Educational-support groups for female
BRCA-mutation carriers
Karin Landsbergen
Judith Prins
Yvonne Kamm
Han Brunner
Nicoline Hoogerbrugge

Female BRCA-mutation carriers with a preference for prophylactic mastectomy are more likely to participate in an educational-support group and to proceed with the preferred intervention within two years.
Abstract

Introduction Women with a BRCA-mutation face a complex choice between breast cancer surveillance and prophylactic mastectomy. We determined risk management preferences shortly after genetic test disclosure and mastectomy status after a median observation period of 2 years. The effect of an educational-support group on the realization of risk management preference was explored.

Material and Methods We included 163 newly disclosed BRCA-mutation carriers with no history of cancer, whose breast cancer risk management preferences were recorded. All carriers were offered the opportunity to participate an educational-support group. Mastectomy status was checked after a median observation period of 2 years.

Results Of the total sample 27% had an initial preference for mastectomy and 48% attended an educational-support group. After a median observation period of 2 years, 30% of the total sample had undergone prophylactic mastectomy. Of the women with a preference for surveillance 90% of educational-support group attendees and 88% of the other mutation carriers were still under surveillance. The number of women with a preference for mastectomy who actually had a mastectomy performed, was significantly higher in the group that attended an educational-support group as compared to those who did not, 89% and 63% respectively (OR 4.8, \( P = 0.04 \)). Strong predictors for prophylactic mastectomy within 2 years were younger age and prior preference for mastectomy (\( R^2 = 0.57 \)).

Conclusion Nearly all BRCA-mutation carriers proceed with their initial choice for surveillance or prophylactic mastectomy. The study provides presumptive evidence that educational-support group participants decide to undergo prophylactic mastectomy earlier than non-attendees.
Introduction

Germline mutations in BRCA1 and BRCA2 confer high risks of breast and ovarian cancer [1-6]. A meta-analysis of ten studies estimated the lifetime risk of breast cancer in BRCA1 mutation-carriers to be 47–66% and 40–57% in BRCA2 mutation carriers. The ovarian cancer risk was estimated at 35–46% in BRCA1 mutation carriers and 13–23% in BRCA2 mutation carriers [7]. Women with mutations in either of these genes are thus at great increased risk of breast cancer and are usually offered breast cancer surveillance which includes at least annual clinical breast examination, annual mammography and annual contrast-enhanced breast magnetic resonance imaging (MRI) [8-10]. These women may also opt for prophylactic bilateral mastectomy, with or without breast reconstruction [11-13]. There is large international variation in rates of uptake of prophylactic bilateral mastectomy in BRCA-mutation carriers, ranging from 3 to 51% [14-19].

A challenging issue for many health care professionals is how to optimally guide and support these women in making the psychologically most suited choice as both intensive breast cancer surveillance and prophylactic mastectomy are medically possible in most Western countries. All nine Family Cancer Clinics in The Netherlands offer individual psychosocial support for women from hereditary breast-ovarian cancer families [20]. For more than 10 years psychosocial workers of the Radboud University Medical Centre Nijmegen have additionally organized educational-support groups for proven female BRCA-mutation carriers. The decision regarding breast cancer risk management involves the processing of complex and evolving information and choices [21]. Generally, the decision is not a medically urgent one and women can take time to process all the information and to talk about it with others [22]. Therefore, the goal of such an educational-support group is assisting women in making an informed choice respecting and taking into account their private lives and circumstances. For clarity, the starting point is that one preference is not better or worse than the other.

Many factors influence women’s breast cancer risk reducing management preference over the course of time, including age and levels of breast cancer anxiety [21, 23-26]. Overall, younger age and higher levels of breast cancer anxiety are strong predictors of prophylactic mastectomy. Little is known about the effect of an educational-support group on breast cancer risk management decisions. In the whole process of women’s decision making, an educational-support group for women with an BRCA1 or BRCA2 mutation is one of many events which might influence a woman’s decision. After having organized these groups for a few
years, the clinical impression emerged that after participation an educational-support group many women opted for prophylactic mastectomy. Women may evolve in their choice due to new or complementary information. However, the question arose whether an educational-support group for female BRCA-mutation carriers might have an undesirable side-effect, that is unintended persuasion towards prophylactic mastectomy. This meant that we wanted to investigate this specific psychosocial intervention for female BRCA-mutation carriers. The clinical relevance is that this adds to our knowledge on how to guide and support these women in daily clinical practice and to be able to ameliorate specific and pointed psychosocial care for the still increasing group.

Therefore, the aims of this study were to determine to what extent the initial preference for breast cancer surveillance or prophylactic mastectomy was proceeded at a median of 2 years after first breast cancer surveillance visit and to explore the effect of an educational-support group on the realization of risk management preference.

Patients

The study sample consisted of 163 women without a personal history of breast or ovarian cancer, with a deleterious BRCA-mutation. These women were seen at the Human Genetics Department of the Radboud University Medical Centre Nijmegen from September 1999 to September 2005. According to the genetic counseling protocol, all women were contacted by a psychosocial worker within 2 weeks after genetic test disclosure with the offer of individual psychosocial support. All healthy carriers were also offered the opportunity to participate in an educational-support group.

Participants of an educational-support group

Eligible participants were women with a newly disclosed BRCA-mutation without a personal history of breast cancer and without a current psychiatric disorder. Women participating in the group were expected to attend at least 6 of the 8 sessions. The medical information sessions were accessible to the women, their spouses, family members and close friends. Sessions on psychosocial issues were accessible to women only.
Structure of an educational-support group
The complete programme included 8 sessions of two and a half hour each, with an interval time of 4–6 weeks. The sessions had alternately a psychosocial (5 sessions) and a medical information (3 sessions) focus. A group was organized and guided non-directively by two psychosocial workers, specialized in hereditary cancer. It had a closed character for the purpose of optimal group binding. This meant that no newly informed BRCA-mutation carrier could join the group after the first session. To create optimal interaction effects the number of participants was between 8 and 12.

Contents of an educational-support group
Psychosocial themes
The first psychosocial session was always focused on making acquaintance, sharing family stories related to being a BRCA carrier, personal beliefs and experiences concerning cancer. The second session centered on coping with anxiety and tension due to cancer risk and on past and anticipated grief. Themes in the third session were family communication, reproductive decisions and issues related to work and insurance. The last two sessions concentrated on making breast cancer risk management choices. One session aimed to outline the physical and psychosocial consequences of each possible choice. Four women with a BRCA-mutation who had received their genetic test result several years ago were invited as “experts by experience”. To give a complete picture, two women who had chosen surveillance and two who had opted for prophylactic mastectomy were invited. Women shared their narratives regarding the impact of intensive breast cancer surveillance or about their process towards, during and after prophylactic mastectomy. Positive as well as negative experiences were discussed openly. In this session body image and sexuality were also intensively discussed. In all sessions participants were invited to put forward and discuss psychosocial topics.

Medical themes
Three sessions were coordinated by medical specialists involved in the Family Cancer Clinic of the Radboud University Nijmegen Medical Centre in the Netherlands. In the first medical session an internist provided information on breast cancer risk factors and imaging of breast cancer. In the second session a gynecologist explained both the advantages and disadvantages of ovarian screening, prophylactic salpingo-oophorectomy and attendant menopause. A
videotape of a laparoscopic preventive risk reducing salpingo-oophorectomy was shown. In the last medical session both a surgeon and a plastic surgeon presented a complete picture on prophylactic mastectomy and various breast reconstruction procedures. Care was taken to allow enough room for questions and interaction with the medical specialists.

Methods

We prospectively assessed breast cancer risk management preferences of 163 female BRCA-mutation carriers at first breast cancer surveillance visit. This first surveillance visit was planned shortly, usually between 1 and 2 months after BRCA genetic test disclosure and always took place before first attendance of an educational-support group. The standard question at first surveillance visit was whether the women had a preference for either intensive breast cancer surveillance or prophylactic mastectomy. When a woman did not have a preference for preventive surgery or were indecisive, the procedure of intensive breast cancer surveillance was followed and recorded as such. So it was either prophylactic mastectomy or not (yet). All newly disclosed mutation carriers were offered the possibility of group participation and each group started in the first year after genetic test disclosure latest. As soon as more than 10 female mutation carriers had indicated wanting to participate, a group was organized. In practice the next group started between 2 and 8 months after DNA-test disclosure, so usually less than 6 months after first breast cancer risk preference assessment.

Breast cancer risk management status was assessed by checking medical files after a median observation period of 2 years. Over 90% of the women went in surgical follow-up in the Radboud University Nijmegen Medical Centre. In the Radboud University Nijmegen Medical Centre, most women opt for prophylactic mastectomy followed by breast reconstruction by means of tissue expanders. The average waiting list for a preventive mastectomy including breast reconstruction with tissue expanders is 1–2 months. Only in case of preventive breast surgery followed by DIEP flap reconstruction the waiting list could be 1 year.

We asked for breast cancer risk management preference which we note is a thought and thus a cognitive expression. After 2 years we checked mastectomy status which in contrast is a behavioral expression. Women’s choice regarding reducing their cancer risk mainly concerns their breasts, according to current protocols proven BRCA-mutation carriers are advised to have their ovaries
removed from age 38–40 years onward. Patients with breast cancer detected during surveillance were excluded from final analysis, since this would substantially impact on their previous decision. Sociodemographic, medical, family cancer and genetic test related characteristics were retrieved from medical records.

Data analysis
The SPSS 16.0 statistical package was used to analyze the data. Frequencies were used to describe the study sample. Group comparisons were tested for statistical significance. Spearman rank correlations were calculated for continuous variables and Pearson’s χ² analyses for categorical variables. Age was divided into four categories based on quartiles. A Pearson’s χ² test was adopted to examine the association between educational-support group attendance, breast cancer risk management preference at first surveillance visit, and breast cancer risk management status after a median observation period of 2 years. Odds ratios (OR) were calculated to describe associations between the determinants and actual breast cancer risk management status at a median of 2 years after genetic test disclosure and presented with their 95% confidence intervals (95% CI). P-values <0.05 were considered statistically significant. A multivariate logistic regression analysis using Backward Wald was applied with prophylactic mastectomy as independent, dichotomized variable (0 = still under surveillance and 1 = obtained surgery). Odds ratios (OR) were calculated to describe associations between the determinants and the rate of patients who underwent prophylactic mastectomy and presented with their 95% confidence intervals (95% CI). The percentage of variation that the independent variable could explain was calculated using Nagelkerke $R^2$.

Ethics
The study was performed according to the rules of the Committee on Research Involving Human Subjects, Region Arnhem-Nijmegen in the Netherlands.

Results
From September 1999 to September 2005 six educational-support groups were organized. A group started within 1 year after women’s genetic test disclosure. The team of psychosocial workers and the medical specialists running the groups remained the same over the study period. All participants were present at least at
6 out of 8 sessions. Of all 163 female BRCA-mutation carriers, 79 (48%) women participated in an educational-support group and 84 (52%) did not. Of all proven female BRCA-mutation carriers we excluded 30 women with a history of breast cancer and 5 women with a history of ovarian cancer during the study period. Breast cancer was detected in 12 patients during breast cancer surveillance. Of these 12 patients 7 women did participate a BRCA group and 5 women did not. These women were excluded from analysis, so for final analysis, 151 female BRCA-mutation carriers remained.

**BRCA group participants versus non-participants**

No significant differences between group participants and non-participants were found regarding demographic (age, children), medical (postmenopausal), family cancer history (mother and/or sister with breast cancer), BRCA genetic test related (BRCA1 or BRCA2, maternal or paternal inheritance) variables or having received individual psychosocial support. Psychosocial support records were retrievable from 2003 onward. From both the 79 group participants and from the 84 non-group participants 31 records were available. From the group participants 19 women and from the non-group participants 18 women received individual support, i.e. 61 and 58% respectively. In both groups individual psychosocial support mainly focused on the emotional preparation of upcoming preventive operations and on the provision of emotional care after preventive surgery. Only breast cancer risk reducing management preference at first surveillance visit was significantly different. Educational-support group participators were less likely to opt for breast cancer surveillance being 52/79 (66%) versus 67/84 (80%) for non-participators. Consequently, more participants preferred mastectomy 27/79 (34%) than did non-participants 16/84 (19%; \( P = 0.05 \)).

**Breast cancer risk management preference at first visit**

The data in Table 1 show breast cancer risk reducing management preference of 163 female BRCA-mutation carriers at first breast cancer surveillance visit. Of these BRCA-mutation carriers, 119 (73%) women had a preference for intensive breast cancer surveillance and 44 (27%) for prophylactic mastectomy. Mother’s age at breast cancer was significantly lower for women with a preference for prophylactic mastectomy compared to women with a prior preference for surveillance being 41 years (range 28–67), versus 50 years (range 27–71), respectively (\( P = 0.03 \)). More women with an expressed intention to undergo a prophylactic mastectomy in the future participated in an educational-support group, compared to women
with an intention to undergo surveillance, that is 61% versus 44% respectively ($P = 0.05$).

Table 1 Breast cancer risk reducing management preference of 163 female BRCA1/2 mutation carriers as expressed during first breast cancer surveillance visit shortly after genetic test disclosure

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer surveillance</th>
<th>Prophylactic mastectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N$</td>
<td>% or [range]</td>
</tr>
<tr>
<td>$N = 163$</td>
<td>119</td>
<td>73%</td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>27</td>
<td>23%</td>
</tr>
<tr>
<td>30–40</td>
<td>34</td>
<td>29%</td>
</tr>
<tr>
<td>40–50</td>
<td>35</td>
<td>29%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>23</td>
<td>19%</td>
</tr>
<tr>
<td>Daughters</td>
<td>59</td>
<td>50%</td>
</tr>
<tr>
<td>Sons</td>
<td>49</td>
<td>41%</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>21</td>
<td>18%</td>
</tr>
<tr>
<td>Mother with BC</td>
<td>39</td>
<td>33%</td>
</tr>
<tr>
<td>Mother’s age at BC in years (median)</td>
<td>50</td>
<td>[27–71]</td>
</tr>
<tr>
<td>Sister with BC</td>
<td>28</td>
<td>24%</td>
</tr>
<tr>
<td>Youngest sister’s age at BC in years (median)</td>
<td>39</td>
<td>[26–61]</td>
</tr>
<tr>
<td>Youngest relative’s age at BC in years (median)</td>
<td>39</td>
<td>[18–80]</td>
</tr>
<tr>
<td>BRCA1</td>
<td>77</td>
<td>65%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>42</td>
<td>35%</td>
</tr>
</tbody>
</table>

| Inheritance                    |     |             |     |             |          |
| Maternal                       | 79  | 71%         | 31  | 78%         | 0.4$^b$  |
| Paternal                       | 33  | 29%         | 9   | 22%         |          |
| Educational-support group attendance | 52  | 44%         | 27  | 61%         | 0.05$^b$ |

BC Breast cancer

$^*$Because of missing values % do not always add up to 100%

$^b$Pearson chi-square test

$^c$Spearman’s rank correlation

* considered statistically significant
Breast cancer risk management status 2 years after first breast cancer surveillance visit

The data in Table 2 show the actual breast cancer risk reducing management decisions of 151 BRCA-mutation carriers after a median of 2 years after first breast cancer surveillance visit. From these 151 mutation carriers, 70% were still under surveillance and 30% underwent prophylactic mastectomy. Age was significantly different in the group of women who were still under surveillance and in those who underwent prophylactic mastectomy. Women aged between 30 and 50 more often underwent prophylactic mastectomy than did those younger than 30, or older than 50 (P = 0.02). Mother’s age at breast cancer was significantly lower for women who underwent prophylactic mastectomy than for women who were still under breast cancer surveillance (P = 0.03). Also educational-support group attendance was significantly related to obtaining prophylactic mastectomy within 2 years after first breast cancer surveillance visit (P = 0.05).

Multivariate logistic regression analysis showed that age between 30 and 50 and prior preference for mastectomy were two strong predictors for actually performing mastectomy (OR respectively 9.6, P = 0.03 and OR 42.3, P < 0.001. The estimate of explained variance of the multivariate model was 57% (Nagelkerke $R^2 = 0.568$).

Influence of a BRCA psycho-education group on breast cancer risk management decisions

In Table 3 a comparison is given concerning actual breast cancer management decisions 2 years after the initial breast cancer surveillance to breast cancer risk management preference as expressed at the initial breast cancer surveillance visit, separately for women who had attended an educational-support group and those who had not.

Prior preference surveillance

The data indicate that attending an educational-support group does not change prior preference of breast cancer surveillance or prophylactic mastectomy. Of the 48 women with a preference for surveillance, 90% were still under surveillance after a median observation period of 2 years. Similarly, of the 60 women with a preference for surveillance who did not attend an educational-support group, 88% were still under surveillance.
Table 2 Breast cancer risk reducing management performance of 151 female BRCA1/2 mutation carriers after a median observation period of 2 years after first breast cancer surveillance visit after genetic test disclosure

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer surveillance</th>
<th>Prophylactic mastectomy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N$</td>
<td>% or [range]</td>
<td>$N$</td>
</tr>
<tr>
<td>$N = 151$</td>
<td>105</td>
<td>70%</td>
<td>46</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>30</td>
<td>29%</td>
<td>5</td>
</tr>
<tr>
<td>30–40</td>
<td>26</td>
<td>25%</td>
<td>18</td>
</tr>
<tr>
<td>40–50</td>
<td>28</td>
<td>26%</td>
<td>18</td>
</tr>
<tr>
<td>&gt;50</td>
<td>21</td>
<td>20%</td>
<td>5</td>
</tr>
<tr>
<td>Daughters</td>
<td>52</td>
<td>50%</td>
<td>21</td>
</tr>
<tr>
<td>Sons</td>
<td>41</td>
<td>39%</td>
<td>18</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>19</td>
<td>18%</td>
<td>8</td>
</tr>
<tr>
<td>Mother with BC</td>
<td>35</td>
<td>34%</td>
<td>17</td>
</tr>
<tr>
<td>Mother’s age at BC in years (median)</td>
<td>47</td>
<td>[27–71]</td>
<td>41</td>
</tr>
<tr>
<td>Sister with BC</td>
<td>23</td>
<td>24%</td>
<td>11</td>
</tr>
<tr>
<td>Youngest sister’s age at BC in years (median)</td>
<td>39</td>
<td>[26–61]</td>
<td>37</td>
</tr>
<tr>
<td>Youngest relative’s age at BC in years (median)</td>
<td>39</td>
<td>[18–80]</td>
<td>35</td>
</tr>
<tr>
<td>BRCA1</td>
<td>66</td>
<td>63%</td>
<td>30</td>
</tr>
<tr>
<td>BRCA2</td>
<td>36</td>
<td>34%</td>
<td>13</td>
</tr>
<tr>
<td>Inheritance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>68</td>
<td>65%</td>
<td>33</td>
</tr>
<tr>
<td>Paternal</td>
<td>29</td>
<td>20%</td>
<td>10</td>
</tr>
<tr>
<td>Educational-support group attendance</td>
<td>46</td>
<td>44%</td>
<td>29</td>
</tr>
</tbody>
</table>

For this analysis, all 12 women detected with breast cancer were excluded.

$BC$ Breast cancer

*Because of missing values % do not always add up to 100%

$^{b}$Pearson chi-square test

$^{*}$Spearman’s rank correlation

$^{*}$ considered statistically significant
### Table 3  Influence of a educational-support group on breast cancer risk management stability

<table>
<thead>
<tr>
<th>Intention at first visit: breast surveillance</th>
<th>Actual status</th>
<th>Actual status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prophylactic mastectomy</td>
<td>Surveillance</td>
</tr>
<tr>
<td>Group yes</td>
<td>5 (10%)</td>
<td>43 (90%)</td>
</tr>
<tr>
<td>Group no</td>
<td>7 (12%)</td>
<td>53 (88%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intention at first visit: prophylactic mastectomy</th>
<th>Actual status</th>
<th>Actual status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prophylactic mastectomy</td>
<td>Surveillance</td>
</tr>
<tr>
<td>Group yes</td>
<td>24 (89%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Group no</td>
<td>10 (63%)</td>
<td>6 (38%)</td>
</tr>
</tbody>
</table>

* considered statistically significant

### Prior preference mastectomy
Of the 27 women with an intention to undergo prophylactic mastectomy and participating in an educational-support group, 89% actually had undergone a prophylactic mastectomy 2 years after first breast cancer surveillance visit after genetic test disclosure. These women were significantly more inclined to have a prophylactic mastectomy performed than women with the same preference who did not attend an educational-support group (89% vs. 63%, OR 4.8, $P = 0.04$). Of 16 women with a prior preference for prophylactic mastectomy, who did not join an educational-support group 38% were still under breast cancer surveillance 2 years after first surveillance visit.

### Discussion
Nearly all BRCA-mutation carriers follow their first preference for breast cancer surveillance or prophylactic mastectomy. This is in line with a study which indicates that most women have already formed stable risk-management preferences.
before DNA test disclosure [26]. Educational-support group participants seem to
decide to undergo prophylactic mastectomy shorter after making preference
decision then non-participants. A recent study showed that women who choose
prophylactic mastectomy often do so within months of receiving BRCA positive
results [27]. An explanation for the advanced decision to undergo prophylactic
mastectomy by group attendees compared to non-attendees might be that the
occurrence of group members getting cancer during surveillance had effect on
the other educational-support group members. This could have triggered feelings
of anticipated regret, i.e. the amount of regret women think they would have if
they were diagnosed with breast cancer after rejecting the option of prophylactic
mastectomy [26]. In contrast, aberrant findings on imaging with mammography
or MRI during breast cancer surveillance do not induce a preference for mastectomy
[28]. In the group of women with an initial preference for mastectomy, who did
not attend an educational-support group, 38% was still under surveillance. These
women had no other notable features compared to the women with a prior
preference for mastectomy who did join a group, except that none of these
women had a sister with a history of breast cancer. We initially asked for women’s
preference about breast cancer risk management but finally determined breast
cancer risk behaviour by checking medical files. Thus although data suggest that
not-attending a group changes preference from prophylactic mastectomy in
breast cancer surveillance, we cannot say with certainty that women’s preferences
have changed.

We realize that an important limitation of this study is the selection and allocation
bias since women with different baseline attitudes towards breast cancer risk
management self-selected themselves to attend (or not) the educational-support
group. This is a difficulty when trying to draw conclusions regarding exclusive effects
of the group. Whether the intent to attend a group and the intent to prefer mastectomy
are associated with for example the same (active) coping style, might be an interesting
topic for further research. There might also be an effect of individual psychosocial
support on cancer risk management decisions. However, received individual support
was comparable for group participants and non-group participants, plausibly
resulting in a comparable effect on cancer risk management decisions.

Considering this it can be concluded that most female BRCA-mutation carriers
are steadfast in their breast cancer risk management preference, as expressed
during first breast cancer surveillance visit shortly after genetic test disclosure.
Our data also provides presumptive evidence that an educational-support group
strengthens the initial expressed intention to undergo prophylactic mastectomy.
**Implications for daily care**

It is commonly recommended that women with a *BRCA*-mutation have access to support groups throughout the decision process [22]. We emphasize that a well-structured educational-support group may provide support without intentionally inducing any specific breast cancer risk management strategy. The current body of knowledge does still not answer the question whether by participating an educational-support group women are better able to cope with their *BRCA* carrier ship in daily life and if these women are satisfied by this additionally offered care. Therefore we have recently started a prospective study to investigate the effects of these educational-support groups on psychosocial well-being and family communication.
References


Karin Landsbergen
Han Brunner
Peggy Manders
Nicoline Hoogerbrugge
Judith Prins

Educational-support groups for BRCA-mutation carriers satisfy need for information but do not affect emotional distress
Abstract

Introduction Due to high cancer risks, women carrying a BRCA1/2 mutation face a complex choice between breast and ovarian cancer surveillance and prophylactic surgery. The aim of this study is to evaluate educational-support groups, which are offered to facilitate mutual support between BRCA-mutation carriers and to provide adequate information.

Material and methods Female BRCA-mutation carriers were approached by a social worker after genetic test disclosure and offered participation in educational-support groups. Data regarding emotional well-being, breast cancer risk knowledge and perception, cancer risk management behaviour and family communication were collected both before (T1) and after group participation (T2).

Results Of the 34 participants mean levels of negative mood states at T1 were significantly higher compared to those of a norm group (depression \( p<0.001 \), anger \( p<0.001 \), fatigue \( p=0.04 \), tension \( p=0.03 \)) and remained high at T2. Self-perceived breast cancer risk and frequency of cancer thoughts were high both at T1 and T2. Breast cancer risk knowledge was accurate both at T1 and T2; women either followed current surveillance advices or obtained prophylactic surgery. Communication with the family of origin was significantly reduced at T2 compared to T1 \( (p=0.02) \). At T2 all women indicated that group participation highly met their needs of BRCA-related information to support their decision-making processes regarding cancer surveillance or prophylactic surgery.

Conclusion After following an educational support group female BRCA-mutation carriers were able to make cancer risk management decisions but still reported high levels of emotional distress while family communication appeared diminished.
Introduction

Women carrying a BRCA1/2 mutation face considerable health risks with a cumulative lifetime risk for breast cancer of 39-85% and for ovarian cancer of 11-63% at age 70 years [1, 2]. From the age of 25 years these women are usually advised intensive breast cancer surveillance which entail annual mammography and annual contrast-enhanced breast magnetic resonance imaging (MRI) and monthly self-breast examination (SBE) [3, 4]. Regular breast cancer surveillance aims at early detection of breast cancer but does not guarantee the detection of a tumor before metastasis has occurred. Those women may also opt for prophylactic bilateral mastectomy (PBM) [5-7] which is highly effective with respect to cancer risk reduction [8-11]. From the age of 35 years, BRCA-mutation carriers are also offered regular ovarian cancer surveillance [4]. Screening by means of the current modalities fails to detect ovarian cancer at an early stage and provokes a high number of false positive findings [12]. Because prophylactic bilateral salpingo-oophorectomy (PBSO) from age 35-40 years is the most effective risk reducing strategy PBSO should be the cornerstone in the discussion with BRCA1/2 mutation carriers regarding risk management [13]. PBSO significantly reduces ovarian cancer risk [8, 9] while a small residual risk of developing extra ovarian, peritoneal cancer remains [14]. Moreover, it is estimated that removing the ovaries and fallopian tubes halves the risk of developing breast cancer [15, 16].

After genetic test disclosure BRCA-mutation carriers face the processing of complex and evolving information and choices between cancer surveillance and PBM with or without breast reconstruction [17-20]. Additional stressors include communication of the dissemination of the genetic risk to relatives together with fears and worry concerning the health of offspring. Also concerns regarding insurance issues, potential confusion or misinterpretation concerning the complex genetic knowledge and ongoing fears of one’s own risk for cancer may play an important role after genetic test disclosure [21-23]. A challenging issue for professionals is how to guide and support these women in making the psychologically most suited choice regarding cancer risk management. Few services exist for women carrying a BRCA-mutation [24]. Supportive expressive groups have been found very helpful in cancer populations for facilitating psychological adjustment to a life threatening illness [25, 26]. Features of such groups are the facilitation of mutual support, the creation of a sense of normalization through shared experience, the encouragement of emotional
expressiveness, the promotion of family and social support, the enhancement of an expanded coping repertoire, vicarious learning through others and acceptance of being at high cancer risk [27, 28]. Women carrying a BRCA-mutation appear interested in psychosocial group support [29]. A previous study showed that a supportive-expressive group intervention was highly acceptable to female BRCA-mutation carriers. It appeared to be a good forum for them to explore key-issues such as the notification of test results to family, guilt regarding transmission of a mutation and decision-making regarding risk-reducing options [30]. It was also demonstrated that speaking to a peer was a highly valued intervention for women considering PBM because this dialogue enabled them to answer questions of which they felt professionals could not know first-hand [31].

Since 1997, social workers of the hereditary cancer clinic of the Radboud University Nijmegen Medical Centre in the Netherlands have been organizing educational-support groups for recently proven female BRCA-mutation carriers. Main goals of these educational-support groups are providing professional BRCA-related information and facilitating mutual support. Next to information sessions provided by medical specialists and supportive sessions guided by medical social workers, the educational-support group programme includes a session with women carrying a BRCA-mutation who are ‘experts by experience’. The aim of the present study is to evaluate educational support groups for female BRCA-mutation carriers in clinical practice. This study addresses questions concerning informational needs and effects of the groups on emotional well-being, breast cancer risk perception, cancer risk management behaviour and family communication.

Material and methods

Study design
The educational-support groups were offered to patients in clinical practice and evaluated in an uncontrolled study.

Study sample and procedure
The study cohort consisted of women who had previously undergone genetic counselling and mutation testing at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre in the Netherlands. Between March 2005 and September 2008, women carrying a BRCA-mutation were contacted
within 2 weeks after genetic test disclosure and offered the opportunity to participate an educational-support group. Individuals were excluded from group participation if they met the following criteria: 1) a personal history of breast- or ovarian cancer, 2) a history of a major psychiatric disorder (e.g. psychosis), as classified in the Diagnostic and Statistical Manual of Mental Disorders, the DSM-IV-TR [32] and 3) unwillingness to attend at least 6 of the 8 group sessions. Each new educational-support group started when 12 women were on the waiting list. In practice a new group started within a year after BRCA genetic test disclosure. In order to enable women with a day-job to participate, the meetings were held in the evening.

**Structure of an educational-support group**
The programme included eight sessions of two and a half hour, every 4-6 weeks. The focus of the sessions alternated between psychosocial support (5 sessions) and medical information (3 sessions). Sessions on psychosocial issues were only accessible to female BRCA-mutation carriers. The medical information sessions were also accessible to their spouses, family members and close friends. A group was guided non-directively by two medical social workers specialized in hereditary cancer. It had a closed character for the purpose of optimal group bonding. To create optimal interaction effects the maximal number of participants was 12.

**Contents of an educational-support group**
**Psychosocial issues**
The first psychosocial session was focused on sharing medical and/or family histories related to being a BRCA carrier, personal beliefs and experiences concerning cancer. The second session focussed on coping with anxiety and tension due to cancer risk and on past and anticipated grief. Themes in the third session were family communication, reproductive decisions and issues related to work and insurance. The last two sessions focussed on making breast cancer risk management choices. One session aimed to outline the physical and psychosocial consequences of each possible choice. Four women with a BRCA-mutation who had received their genetic test result several years ago were invited as “experts by experience”; two women who had chosen surveillance and two who had opted for prophylactic mastectomy were invited. Women shared their narratives regarding the process and impact of intensive breast cancer surveillance or prophylactic mastectomy. In this session body image and sexuality were also intensively discussed. In the last meeting women shared their personal choices
regarding breast cancer risk management with each other and the support group was evaluated orally. Questions and interaction between group members were encouraged.

**Medical information**
Three sessions were coordinated by medical specialists involved in hereditary cancer. In the first medical session an internist provided information on breast cancer risk factors and imaging of breast cancer. In the second session, a gynaecologist explained both the advantages and disadvantages of ovarian screening, PBSO and attendant menopause. A videotape of a laparoscopic preventive risk reducing BSO was shown. In the last medical session both a surgeon and a plastic surgeon presented a complete picture on BPM and various breast reconstruction procedures. Questions and interaction with the medical specialists were encouraged.

**Measures**
Baseline data were collected one week before the start of the educational-support groups (T1). Follow-up data were completed within two weeks after the last group meeting (T2). Measurements contained both data from medical records and self-report questionnaires.

**Emotional well-being**
Emotional well-being was operationalized in terms of mood, social anxiety, self-confidence and body confidence. Mood was measured with the Profile of Mood States (POMS) Brief [33]. It consists of an inventory for measuring five types of moods: depression, anger, fatigue, vigour and tension. The POMS is a reliable and valid questionnaire for measuring emotional well-being. The subscales have been previously assessed for reliability and validity, demonstrating Cronbach’s alphas ranging from 0.66-0.95 with a mean of 0.80 [34]. Impact of BRCA carriage on self-confidence was assessed with a single item ‘Can you indicate how BRCA carriage influences your self-confidence ?, i.e. ‘positive’ or negative’. Impact on body confidence was assessed with a similar question.

**Breast cancer risk knowledge and perception**
Breast cancer risk knowledge was defined in terms of knowledge of absolute lifetime breast cancer risk and knowledge of relative lifetime breast cancer risk. Knowledge of absolute lifetime breast cancer risk was measured as follows: “My
risk of developing breast cancer is...". Patients marked their lifetime risk perception on a Visual Analogue Scale (VAS 0-100%). Knowledge of relative lifetime breast cancer risk was measured on a 7-point Likert scale as follows: "Compared to the average Dutch woman, my risk of getting breast cancer is ‘very much lower’ (1) through ‘equal to’ (4), to ‘very much higher’ (7)".

Breast cancer risk perception was assessed by the items self-perceived breast cancer risk and frequency of cancer thoughts. Perceived (subjective) breast cancer risk was assessed on a 7-point Likert scale using the item “Independent of my actual risk, I feel my risk of developing breast cancer is ‘not likely’ (1) to ‘very likely’ (7)”. These three items regarding breast cancer risk knowledge and perception were used in similar studies on the impact of genetic testing for hereditary cancer with an adequate reliability, i.e. Cronbach’s alpha of 0.73 (post-genetic counselling) [35-38]. Frequency of cancer thoughts was measured as follows: “How often do you think about your chances of getting cancer?”, i.e. ‘daily’, ‘weekly’, ‘monthly’, ‘few times a year’, ‘never’. At both T1 and T2, an open-ended question addressed the impact of BRCA carriership on daily life: “The most important consequence my BRCA carriership has on daily life is...”.

Cancer risk management behaviour
Cancer risk management behaviour was defined in terms of breast cancer surveillance, ovarian cancer surveillance, PBM, PBSO and BSE. Intention towards breast cancer risk management was measured as follows: “What is your current intention to preventive measures regarding your breasts?”, i.e. intensive breast cancer surveillance or prophylactic surgery. Intention regarding ovarian cancer risk management was assessed by a similar question. BSE was measured with the item “How often do you check your breasts for cancer?”, i.e. ‘daily’, ‘weekly’, ‘monthly’, ‘few times a year’, ‘never’.

Family and other BRCA-related communication
Familial communication concerning hereditary cancer was assessed by the Openness to Discuss Hereditary Cancer in the Family Scale, which is based on the Openness to Discuss Cancer in the Family Scale [39] and adapted and used in other studies on the impact of genetic testing for hereditary cancer [37,40]. To gain more insight in the aspect of women’s BRCA-related family communication, a self-developed questionnaire addressed additional BRCA communication related issues. BRCA-related communication in general was measured with the item: “How
often do you discuss BRCA carriership?", i.e. ‘daily’, ‘weekly’, ‘monthly’, ‘few times a year’, ‘never’. Communication with the General Practitioner was assessed by a similar question. The need to discuss BRCA carriership was assessed with two items: “Would you like to discuss BRCA more often than is sometimes possible?”, i.e. ‘yes’ or ‘no’ and “Would you like to discuss BRCA less often than is sometimes necessary?”, i.e. ‘yes’ or ‘no’.

**Patient evaluation of educational-support groups**

Whether the medical information regarding BRCA was perceived as sufficient was assessed with the item “Do you consider the BRCA-related medical information which you received sufficient?, i.e. ‘yes’ or ‘no’. An open-ended question addressed the source of BRCA-related information: “Who or what provides you with BRCA-related information?” An additional open-ended question addressed the matters on which the participant had wanted more information. At T2, two open-ended questions regarding the consequences of having participated in an educational-support group were inserted.

**Data analysis**

Frequencies were used to describe the study sample. Correlations between variables were assessed by the Spearman' Rank Correlation for continuous variables and for the ordinal variables which were obtained on a 5 or 7-Point Likert scale. The Point Biserial Correlation was used to assess correlations for dichotomous variables. To analyze changes in the self-report measures between T1 and T2, the Paired Samples T-test was used for continuous variables. The McNemar test was used for categorical variables which were all dichotomized before analysis. To determine if there were major differences between the four groups regarding depression scores at T1, the Kruskal-Wallis test was applied. To compare our POMS and ODHCF data with data from literature, the Welch's two sample t-test was used. This test is intended for use with two samples having possibly unequal variances. Levels of POMS negative mood states were considered high when mean levels were statistically significant higher than POMS levels of a sample from the female Dutch general population [33]. Breast cancer risk was considered accurate when it was between the genetic counselled risk of 60-80% Life Time Risk (LFT). Relative breast cancer risk was considered accurate when stated as ‘very high’. Self-perceived breast cancer risk was considered high when stated as “my risk of developing breast cancer is ‘very likely’. Frequency of cancer thoughts was considered high when stated as ‘daily’ or ‘weekly’. BSE frequency was considered
accurate when stated as ‘monthly’, i.e. accurate according to the Dutch guideline on hereditary breast and ovarian cancer [41]. Participants’ answers to the open questions regarding the reported benefits of the educational-support group were categorized in themes conducting deductive qualitative content analysis [42]. The probability level for statistical significance testing was set at 0.05 (two-tailed). The SPSS 16.0 statistical package was used to analyze the data.

**Ethics**
Written informed consent was obtained from all participants in accordance to the rules of the Committee on Research Involving Human Subjects, Region Arnhem-Nijmegen in the Netherlands.

**Results**

**Study sample**
Between March 2005 and September 2008, a pathogenic \( BRCA \)-mutation was detected in 194 women not previously affected with cancer. Those women were approached by a medical social worker to participate in an educational-support group. Fifty-three women did not return phone-calls inviting them to participate. Of the 141 women with whom contact was obtained, 98 women (70%) declined from group participation to avoid \( BRCA \)-related issues or due to practical reasons (exact percentages not available). Of the remaining 43 potential group participants, two women (1%) were excluded due to a current psychiatric disorder. Over a period of four years a total of 41 female \( BRCA \)-mutation carriers, i.e. 29% of all contacted women, participated in one of the four groups, of whom 34 women (83%) participated in the current study. Waiting list time for the next group ranged from 1-12 months, the median waiting time was 4 months. The four groups, of which the first started September 2005 and the last in September 2008, consisted of ten, ten, twelve and nine female \( BRCA \)-mutation carriers of whom respectively seven, nine, ten and eight participated in the study. At T2, 27 women (79%) had completed both the first and the last questionnaire. Demographic and \( BRCA \)-related characteristics of the study sample are provided in Table 1.
Table 1 Baseline demographic and BRCA-related characteristics of female BRCA-mutation carriers (N=34)

<table>
<thead>
<tr>
<th></th>
<th>Before participation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Married</td>
<td>97</td>
</tr>
<tr>
<td>With children</td>
<td>79</td>
</tr>
<tr>
<td>Daughters N</td>
<td>21</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>13.6 (11.1)</td>
</tr>
<tr>
<td>Sons N</td>
<td>22</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>12.6 (11.7)</td>
</tr>
<tr>
<td>Educational level &gt; high school</td>
<td>41</td>
</tr>
<tr>
<td>Employed</td>
<td>88</td>
</tr>
<tr>
<td>Dutch native</td>
<td>100</td>
</tr>
<tr>
<td>BRCA1</td>
<td>68</td>
</tr>
<tr>
<td>Age BRCA detection in family</td>
<td>38.5 (10.5)</td>
</tr>
<tr>
<td>Age BRCA detection participant</td>
<td>39.6 (10.0)</td>
</tr>
</tbody>
</table>

Correlations between breast cancer perception, emotional status, cancer risk management behavior and family communication
Self-perceived breast cancer risk and absolute breast cancer risk appeared highly correlated. All negative emotions (depression, anger, fatigue, tension, low self-confidence) appeared highly correlated and had no correlation with vigor or with influence of BRCA on body confidence. Risk management of the breast was significantly correlated with SBE and risk management of the ovaries, while no correlation was found between risk management of the ovaries and SBE. Negative emotions were significantly correlated with perceived risk perception and risk management of the breasts. Absolute breast cancer risk was significantly correlated with communication in the nuclear family. Relative breast cancer risk was negatively correlated with vigor, but not correlated with negative emotions. Cancer thoughts were negatively correlated with lower self-confidence and positively correlated with discussing BRCA in general.

Emotional well-being
POMS negative emotions were high at T1 compared to those of a group of females in the Dutch general population [33] and remained high at T2. The mean score for
depression appeared 2.4 times higher ($p<0.001$), for anger 1.9 times higher ($p<0.001$), for fatigue 1.5 times higher ($p=0.04$) and for tension 1.4 times higher ($p=0.03$) than the corresponding general population scores [33]. The POMS positive vigour score was similar to the vigour score of the norm group [33]. Higher levels of POMS negative emotions compared to a norm group of healthy adults were 63% for depression, 70% for anger, 67% for fatigue and 59% for tension. It should be noted that of all these women, 41% had high scores on all subscales at T1. A positive influence of BRCA on self-confidence was reported by 72% of the women at T1; this percentage falls to 50% at T2 ($p=0.2$). A negative influence of BRCA on body confidence was reported by 86% and by 82% of the women at T1 and T2, respectively (Table 2).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>BRCA-related emotional well-being of 27 female BRCA-mutation carriers before and after participating an educational support group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>POMS $^a$</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Depression</td>
<td>6.9 (6.7)</td>
</tr>
<tr>
<td>Anger</td>
<td>6.0 (5.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.6 (6.3)</td>
</tr>
<tr>
<td>Vigor</td>
<td>10.7 (4.9)</td>
</tr>
<tr>
<td>Tension</td>
<td>7.4 (5.6)</td>
</tr>
<tr>
<td>Self-perceived breast cancer risk high</td>
<td>60</td>
</tr>
<tr>
<td>BRCA influence on self-confidence</td>
<td>72</td>
</tr>
<tr>
<td>BRCA influence on body-confidence</td>
<td>14</td>
</tr>
</tbody>
</table>

$^a$, Profile of Mood States; $^b$, Paired-samples T-test; $^c$, McNemar test; $P<0.05$ is considered statistically significant.

Breast cancer risk knowledge and perception
Participants report an accurate absolute breast cancer risk, i.e. 77% Life Time Risk (LFT) at T1 and 72% LFT at T2 ($p=0.3$). Both at T1 and at T2, 93% of the women report an accurate relative breast cancer risk, very high compared to ‘the average Dutch woman’. Self-perceived breast cancer risk is high in, respectively 60% and
63% of the participants at T1 and T2. Frequency of cancer thoughts is very high (i.e. daily/weekly) in 81% of the women at T1 and in 93% at T2 (p=0.4). Regarding the open-ended questions at T2, two frequently reported influences of BRCA on daily life were “cancer risk thoughts” and “future worries”.

Cancer risk management behaviour
The intention towards PBM was present in 37% of the women at T1, in 44% of the women at T2 (p=0.7). An intention towards undergoing PBSO was present in respectively 71% and 81% of the women at T1 and T2. (p=0.6), including women who were not 35 years yet, but stated they would certainly have preventive surgery of their ovaries in the future. Accurate monthly breast self-examination was performed by respectively 67% and 78% of the women at T1 and T2 (p=0.4).

Family and other BRCA-related communication
Following an educational-support group communicating with the nuclear family did not change (p=0.4), while BRCA carriership was significantly less often discussed with parents and sibs (p=0.02). Family communication openness scores for both nuclear family and family of origin of study participants were significantly lower (p=0.006 and p=0.02 respectively), than those of a group of women (n=175) from proven BRCA1/2 families during genetic counselling [37]. Both at T1 and T2, 85% of the women discuss BRCA carriership daily or weekly with relevant others and almost half of the women discuss BRCA carriership with the General Practitioner. At T1, 30% wants to discuss BRCA more often and 15% less often than is sometimes possible. At T2, these percentages have reversed with an overall tendency towards less need to discuss BRCA carriership in general at T2 (Table 3).

Reported benefits of participating an educational-support group
At T1, 85% of the women and at T2 all women report to have received sufficient BRCA-related medical information to make well-informed decisions regarding cancer risk management. At T1, 81% and at T2 up to 100% (p=0.06) of this information is provided by genetic counsellors, medical social workers, medical specialists and by peer-information received at the educational-support group. At T1, 21% of the women (n=7) had wanted more medical information regarding PBM, at T2 this percentage have fallen down to zero. With open questions, the most reported effects of group participation were information and mutual support (Table 4).
Table 3  Family and other BRCA-related communication status of 27 female BRCA-mutation carriers before and after participating an educational-support group

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family communication a</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Nuclear family</td>
<td>24.1 (5.2)</td>
<td>22.4 (6.2)</td>
<td>0.2b</td>
</tr>
<tr>
<td>Family of origin</td>
<td>25.8 (7.4)</td>
<td>22.2 (7.3)</td>
<td>0.02b*</td>
</tr>
<tr>
<td>With others regularly c</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>With general practitioner regularly d</td>
<td>85</td>
<td>85</td>
<td>1.0d</td>
</tr>
<tr>
<td>Wants to discuss BRCA more often</td>
<td>30</td>
<td>19</td>
<td>0.5d</td>
</tr>
<tr>
<td>Wants to discuss BRCA less often</td>
<td>15</td>
<td>33</td>
<td>0.2d</td>
</tr>
</tbody>
</table>

*a, Measured with the Openness to Discuss Hereditary Cancer in the Family Scale; b, Paired samples T-test; c, regularly: daily/weekly; d, McNemar test; P <0.05 is considered statistically significant.

Table 4  Reported benefits of participating an educational support group (N=27 female BRCA1/2 mutation carriers)

<table>
<thead>
<tr>
<th><strong>BRCA-related information</strong></th>
<th>Before %</th>
<th>After %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>85</td>
<td>100</td>
<td>0.1a</td>
</tr>
<tr>
<td>From genetic counselor (before) supplemented by group (after)</td>
<td>81</td>
<td>100</td>
<td>0.06a</td>
</tr>
<tr>
<td>Most important effect BRCA on daily life: cancer risk worries</td>
<td>56</td>
<td>52</td>
<td>1.0a</td>
</tr>
<tr>
<td>Most important effect BRCA group: support /information</td>
<td>-</td>
<td>56 / 44</td>
<td></td>
</tr>
</tbody>
</table>

*a, McNemar test, P <0.05 is considered statistically significant.
Discussion

Women carrying a BRCA-mutation who attended an educational-support reported less family communication after the group meetings, while high emotional distress, and adequate breast cancer risk knowledge, perception and management behaviour were unchanged. Following an educational-support group, women discussed BRCA significantly less often with their parents and sibs. Women may experience a lack of support when communication on this subject is limited [37]. However, diminished family communication with parents and sibs is not necessarily problematic because there is no explicit clinical need to discuss BRCA carriership with these relatives repeatedly. We observed that discussions on BRCA with sisters who were proven non-carriers or with brothers decreased over time. Women reported an attenuated need to discuss BRCA-related issues in general. These women require tailored information regarding BRCA carriership and the option to discuss management strategies in detail with relevant others such as professionals from the hereditary cancer clinic and experienced experts. Women indicated that participating in the educational-support group met their needs for information and support and enabled them to make more well-informed decisions regarding their "BRCA-future". These findings suggest that the group was very helpful to women's decision-making regarding risk-reducing options and are in line with a previously reported study [30]. Female BRCA-mutation carriers in our study reported high levels of negative emotions both before and following an educational-support group.

It is not possible to generalize this findings to the large population of female BRCA-mutation carriers, since of all contacted female BRCA-mutation carriers, only 29% accepted the offer to participate in the educational-support groups, so selection bias may have occurred. These women may have decided to participate in the educational-support groups, because they experienced high levels of distress. These female participants may for instance had a monitoring coping style, i.e. are more inclined to seek information and support, react with greater psychological distress both before and after genetic counselling and are less satisfied with the information received during genetic counselling [43]. This is supported by clinical experience by which participating women can roughly be divided in two groups: 1) those who openly expressed their cancer distress and were actively looking for ways to deal with BRCA-related cancer risks and 2) those who considered PBM and were especially looking for information regarding preventive breast surgery and breast reconstruction. Next, it is also possible that
the group in some way catalysed the expression of emotions by having the women reflect on personal BRCA-related issues [30]. As time between BRCA genetic test disclosure and start of the group ranged considerably, psychosocial variables may have been influenced by many events during this waiting period. Support needed just after disclosure will be different from support needed many months after disclosure. However, in this small study sample it is impossible to take this waiting time interval into account in the analyses. Overall, the results of this study should be considered carefully, since further research on this topic is needed with a larger study sample and using a randomised controlled study design.

From these data we cautiously conclude that in this cohort risk knowledge is accurate after BRCA genetic counselling, while self-perceived breast cancer risk and negative mood states levels are high. Following an educational-support group women were able to make cancer risk management decisions, high levels of negative moods remained and communication on BRCA-related issues with the family of origin was diminished.

We cautiously conclude that BRCA-related information may well be offered in an educational-support group setting as still 19% of BRCA-related information could be added. However, because high emotional distress did not improve and family communication diminished after participating in a group we consider separating the offer of BRCA-related information from a full program of emotional support. As an alternative to these group sessions we believe that a more effective strategy may be to offer individual psychosocial support to those with high levels of emotional distress. Individual psychosocial support will then focus on BRCA-related negative moods and family communication.

Acknowledgments
We are very grateful to all women carrying a BRCA-mutation who participated in the groups and in the study. We also thank Ria ter Winkel for her help in data collection and Dr. Rogier Donders for his valuable contribution to statistical analysis.
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CHAPTER 8 General discussion
General discussion

The aim of the first part of this thesis was to address psychological distress after pre-screening for Lynch syndrome by MSI-testing during active treatment for CRC. Until recently, the usual approach was to postpone MSI-testing for Lynch syndrome until the family history had been studied extensively and information about all possible consequences had been made available by a clinical geneticist during genetic counseling. According to the Dutch Guideline Hereditary Colorectal Cancer [1] pathologists instead of clinical geneticists initiate MSI-testing in newly diagnosed patients who fulfill one of the following criteria, called MIPA-criteria: 1) CRC diagnosed before age 50 or 2) second CRC before age 70. MSI-testing which is indicated by a pathologist is called MIPA-testing and generally takes place immediately after tumour resection. The pathologists reports the MIPA-test result to the surgeon who can discuss referral to a clinical geneticist with his or her patient. A striking psychological difference between traditionally cancer genetics practice and MIPA-testing is that MIPA-patients are confronted with a possibly hereditary predisposition for Lynch syndrome shortly after their cancer diagnosis and often during active treatment for CRC. At that time these patients may be extra emotionally vulnerable to genetic testing related distress. Although the potential medical preventive benefit of MIPA-testing has been proven [2] minimizing potential psychological harm is of utmost importance.

The aim of the second part of this thesis was to evaluate educational-support groups for female BRCA-mutation carriers. The challenge for these women is to make well-informed decisions about available cancer risk reduction strategies while processing uncertain outcomes [3]. In addition to facing difficult medical management decisions these women are confronted with complex psychosocial issues [4]. Requests by applicants for predictive genetic testing to get in contact with others facing a similar situation resulted in setting up support-groups for female BRCA-mutation carriers. Working with educational-support groups is a methodical way of giving care to people who are at risk for a certain disease before their problems escalate. In the Radboud University Nijmegen Medical Centre in the Netherlands, social workers have been organizing educational-support groups for female BRCA-mutation carriers from 1997 onwards. Female mutation carriers regularly indicated, both in surveys and orally, to be strengthened in making BRCA-related choices through group participation. This clinical observation is important, but needs more evidence. Based on all findings implications for clinical practice will be discussed and directions for future research will be reflected on.
Part i  Summary of the main findings

The key findings of the studies described in the first part of this thesis are:

1) Most patients with CRC experience diminished physical, social and role functioning during the first 3 months after primary treatment. Reduced emotional and social functioning continues up to 1 year after treatment for CRC, especially in patients diagnosed before age 60 or with a stoma. In male patients strain due to sexual impairment is found; female patients report higher spiritual well-being than men. After genetic counseling and testing for Lynch syndrome a minority of patients with CRC reports clinically relevant anxiety and depression levels. Most vulnerable to genetic testing related distress are female patients and male patients diagnosed with CRC before age 50 (literature review, chapter 2).

2) Shortened time interval between CRC diagnosis and MSI-testing is not associated with higher levels of psychological distress. Prone to high distress are women and patients who are religious, with low social support or those reporting difficulties in communicating hereditary colorectal cancer with relatives (traditionally MSI-testing study, chapter 3).

3) Newly diagnosed patients with CRC whose tumours are tested for the presence of MSI consider timely medico-preventive knowledge for their children as most valuable but are apprehensive about having to discuss hereditary CRC with relatives. Physical and psychological well-being are particularly impacted by the diagnosis and treatment for CRC (MIPAPS-pilot study, chapter 4).

4) MIPA-testing is not followed by high levels of psychological distress in general. High general distress is reported by 18% and high cancer specific distress by 40% of the total MIPA-group. No significant distress differences are found between the MIPA-positive (high risk Lynch syndrome) and the MIPA-negative group (low risk Lynch syndrome). Six months after MIPA-test disclosure, both distress and cancer specific distress decrease in the MIPA-positive group while remaining stable in the MIPA-negative group. Perceived distress by care giving is reported by half of all partners but is also independent of MIPA-test result (MIPAPS study, chapter 5).

In this chapter the above key messages and their implications will be discussed. First, psychological distress following MIPA-testing will be addressed. Next, the psychological impact of CRC will be discussed. Finally, vulnerability to high psychological distress will be reflected on.
Psychological distress following MIPA-testing

In the introduction of this thesis it was hypothesized that MSI-testing in recently diagnosed patients with CRC (MIPA-testing) was followed by high psychological distress. The extent of psychological distress after MIPA-testing was defined by the extent of general distress as measured by the Symptom-Checklist-90 (SCL-90) and the extent of CRC specific distress measured by the Impact of Event Scale (IES-CRC). Mean distress levels were comparable to those reported in other studies on testing for hereditary cancer [5-7]. In both the MIPA-positive and the MIPA-negative group high levels of general distress and cancer specific distress were reported, but these levels were not significantly different between the groups. Perceived distress by the partners of these patients were not different between the MIPA-positive and the MIPA-negative group either. In our study on traditionally MSI-testing we found that shortened time interval between CRC diagnosis and MSI-testing was not associated with higher levels of psychological distress (chapter 3). Moreover, all patients in our MIPAPS pilot study (chapter 4) indicated that the CRC diagnosis and its subsequent treatment dominated their feelings of distress, not the knowledge of being at increased risk for Lynch syndrome. All our findings point in the same direction, namely that in general MSI-testing in recently diagnosed patients with CRC is not followed by clinically elevated levels of psychological distress.

An explanation for not finding high levels of psychological distress following MIPA-testing is given by the patients of our MIPAPS-pilot study (chapter 4). In this sample all patients considered MIPA-testing as highly valuable just because of this early timing. First, because of the thus obtained timely medical-preventive value for their children. As has been previously reported, ‘obtaining certainty’ about their own risk as well as that of their children, is an important motive for and psychological benefit of undergoing genetic testing [8-10]. Second, because these patients anticipated that psychological distress due to their recent CRC would be greatly reactivated when genetic testing was discussed years after. Now they could cope with their CRC and a possible hereditary predisposition for Lynch syndrome all at once which enabled them to finish this chapter to a large extent. These findings are in line with studies among recently diagnosed breast cancer patients for whom no additional burden was imposed by actively approaching them for genetic counseling and testing [11, 12]. In fact, the majority of these recently diagnosed breast cancer patients stated that the offer for genetic counseling and testing should take place at primary treatment or even earlier, immediately after breast cancer diagnosis [11, 12].
It may be that patients cannot immediately overlook the ultimate consequences of MIPA-testing. To be clear, MSI-testing is not a conclusive diagnostic test. A MIPA-positive test result refers to a possibly high genetic cancer risk but may also be due to non-hereditary, somatic hypermethylation of for example the MLH1-promoter. Therefore, to pinpoint the exact cause of the microsatellite instability, further genetic testing by DNA-analysis must take place and will take place only after comprehensive genetic counseling. Notwithstanding this fact, the current findings on psychological distress are contrary to assumptions about the potentially negative impact of offering and performing genetic risk assessment immediately after cancer diagnoses [13] at a time one would expect patients to be more psychologically vulnerable [14-16]. Patients with breast cancer who have not yet reached a decision about definitive surgical cancer treatment may benefit from genetic risk assessment [17]. In general subtotal colectomy seems to be the preferred treatment for CRC in young patients with Lynch syndrome [18].

**Distress delay**

High general distress and high cancer specific distress in recently diagnosed patients with CRC (chapter 5) were 18% and 40%, respectively. High cancer specific distress was present in 24% of the patients diagnosed with CRC less than 1 year ago. This high distress percentage was less than in patients diagnosed with CRC between 12-36 months ago (39%) or diagnosed longer than 36 months ago (35%) (chapter 3). An explanation might be that contemplation and consideration of the cancer is more likely to occur once active treatment for cancer in the hospital is over. A previous study showed that 15% of patients with breast cancer became distressed not until after end of treatment, in the reentry phase [19]. In line with this it was found that informational and support needs are most present between 2 till 5 years after cancer diagnosis [20]. This could indicate that distress levels may become higher when time goes by. In view of this, it has been demonstrated that distress fluctuates over a 5-year period following BRCA genetic test disclosure due to the continuous integration process of carriership in daily life [21].

**Psychological impact of CRC**

Our review demonstrated that decreased social and emotional functioning could persist up to one year after primary treatment for CRC, especially in patients younger than 60 years and in those with a stoma. Our MIPAPS pilot study revealed that the CRC diagnosis and subsequent treatment dominated patients' psychological well-being and not MIPA-testing (chapter 4). Many other studies
have found that a CRC diagnosis leads to significant changes in people’s lives. Patients with CRC are at risk of experiencing poor quality of life [22, 23], fatigue and altered bowel habits [24-26], continual fear of recurrence [27], future concerns [26, 28] and struggle to adapt living with a stoma [29, 30]. Sexual identities of patients with CRC were disrupted as a result of their surgery or having to live with a temporary or permanent stoma [31, 32]. Professional identities were lost due to an inability to meet social expectations about professional behaviour within a work context [32]. Our MIPAPS study revealed that neither TNM-stage, nor adjuvant treatment or MSI-test result were related to general distress or to cancer specific distress. To conclude, multiple factors such as demographic characteristics of the person, their social environment, the way they appraise the illness and only to some extent medical factors influence how well patients psychologically adjust to a new CRC diagnosis [33].

Patients most vulnerable to psychological distress

The results of our MIPAPS study (chapter 5) did not confirm our hypothesis that MSI-testing in recently diagnosed patients with CRC is followed by high psychological distress. Moreover, neither TNM-stage nor adjuvant treatment were associated with high levels of psychological distress. Our studies however indicated that instead of cancer related or genetic risk factors patients’ characteristics are predominant in reported psychological distress. High psychological distress in patients previously diagnosed with CRC was related to female gender, religiousness and family communication difficulties (chapter 3). In recently diagnosed patients with CRC psychological distress was associated with female gender, low social support and high cancer risk perception (chapter 5). Below an overview is given of the main risk factors associated with high psychological distress in patients with CRC.

Age

Our review showed that patients diagnosed with CRC below the age of 50 were most vulnerable to genetic testing related psychological distress. A study on the demands of illness in patients with CRC revealed that especially the youngest age group (26-45 years) was most susceptible to disruption by their diagnosis and treatment of CRC, which can be explained by the developmental tasks associated with this age group, i.e. marital adjustment, child rearing and career development [34]. MIPA-testing mostly concerns relatively young patients with CRC, often below the age of 50 years. Therefore, professionals caring for CRC patients who
may be at high risk for Lynch syndrome should be aware of the fact that especially younger patients may experience intense illness-related problems and thus should apply appropriate interventions [34].

**Gender**

Both in our literature review (chapter 2), our traditionally MSI-testing study (chapter 3) and in our MIPAPS study (chapter 5), women appeared to be most prone to psychological distress. Studies showed that in general women in contrast to men are responsible for managing more roles inside and outside of the family, are involved in more interpersonal relationships, assume more care giving roles and are more responsive to the events affecting other people’s lives [35] and hence experience more distress when illness occurs [33].

**Social support**

Social support in the context of genetic testing involves the nuclear family with partner and children and the broader family including parents, sibs and second degree relatives such as uncles and aunts. Both our traditionally MSI-testing study and the MIPAPS study show that patients with low social support are vulnerable to high psychological distress. This is consistent with findings from studies among testing for hereditary cancer in which those with a perceived lack of social support reported heightened levels of distress and worries [36].

**Partners**

It was previously found that patients with cancer are more distressed and need more social support when having a highly distressed partner [12, 37]. There is a considerable impact of the CRC diagnosis on partners’ before and 3 months after surgery [38]. In the MIPAPS study, perceived distress by informal care giving of the total partner group indicated overload at a mean of 5 months after their partner’s CRC diagnosis. In a study among partners of patients with another form of hereditary colorectal cancer, i.e. familial adenomatous polyposis (FAP), approximately one-quarter of the sample reported clinically relevant levels of distress [39]. Partner’s often observe the patient’s suffering but are unsure how to help [40], feel unprepared for dealing with their partner’s reactions and often assume the role of caregiver with little support from others [41]. Partners of patients with CRC are strongly affected by the disease with female caregivers reporting more distress, more role problems and less marital satisfaction than male caregivers [33]. Social support may function as a buffer between stressful
situations and psychological distress [42]. This suggests that professionals caring for CRC patients should include distress-assessment of the patient’s partner. Our MIPAPS study did not reveal a relation between caregiver experiences and gender, probably due to small sample size.

**Family**

Being at increased risk for Lynch syndrome is a family affair. Social support from relatives may be essential not only to adapt to the cancer diagnosis but also to cope with being the first in the family in whom a for Lynch syndrome predisposing mutation could be detected. The patients of our MIPAPS-pilot study were apprehensive about having to discuss a hereditary disposition for cancer with their family [43] and in our study among previously diagnosed patients with CRC who were offered MSI-testing psychological distress was significantly related to family communication difficulties [44]. Our and other studies [45, 46] show that family communication problems not only inhibits adequate dissemination of genetic risks in the family but is also related to psychological distress of the index patient. It has been found that the effect of a less open family communication style on psychological distress may maintain for years [21]. Therefore, it seems worth considering that the discussion of family communication with the patient at high risk for hereditary CRC should not only focus on dissemination of genetic risks results but also on sources of social support offered by relatives.

**Part ii  Summary of the main findings**

The key findings of the studies described in the second part of this thesis are:

1) Following an educational-support group nearly all BRCA-mutation carriers proceed with their initial choice for breast cancer surveillance or prophylactic bilateral mastectomy (PBM). Educational-support group participants decide to undergo prophylactic mastectomy earlier than non-attendees (chapter 6).

2) Following an educational-support group female BRCA-mutation carriers are able to make cancer risk management decisions. These women still report high levels of emotional distress and their communication with parents and sibs is diminished (chapter 7).
In this chapter above key findings and their implications will be addressed. First, breast cancer risk management decisions in the context of an educational-support group will be evaluated. Subsequently, the focus will be on meeting informational needs, emotional distress and family communication of female BRCA-mutation carriers following an educational-support group. Below the educational-support groups for BRCA-mutation carriers will be referred to as BRCA-groups.

Breast cancer risk management decisions
For more than ten years social workers of the family cancer clinic of the Radboud University Nijmegen Medical Centre in the Netherlands, have organized BRCA-groups. Since a core-goal of a BRCA-group is assisting women in making well-informed decisions on reducing breast cancer risk, the first study on these groups focused on breast cancer risk management choices (chapter 6). The aims of this study were to determine to what extent the initial preference for breast cancer surveillance or prophylactic bilateral mastectomy (PBM) was proceeded at a median of 2 years after first breast cancer surveillance visit and to explore the effect of a BRCA-group on the realization of risk management preference. We found that female mutation carriers with a preference for PBM are more likely to participate in a BRCA-group. This seems reasonable since the decision to opt for surgery is more complex, radical and irreversible compared to opting for surveillance so these women can use some guidance. Moreover, we found that nearly all BRCA-mutation carriers proceed with their initial choice for breast cancer surveillance or PBM. Our finding is in line with other studies which showed that the choice to undergo PBM is largely determined by a woman’s prior preference to PBM before or just after BRCA-test disclosure [47, 48]. Next, we found presumptive evidence that BRCA-group participants decide to undergo PBM earlier than non-attendees. It was previously found that more women with a prior preference to PBM opt for a PBM after a positive MRI or mammography than women without such prior intention [47]. All together, these data suggest that in case female BRCA-mutation carriers with a prior preference for PBM are well-informed and well-prepared, the step to undergo PBM is more easily set compared to women who do not participate a BRCA-group. It can be concluded that by providing comprehensive PBM related information, these women feel empowered to reach well-informed breast cancer risk management decisions.
Informational needs, emotional distress and family communication

The aim of the study described in chapter 7 was to evaluate overall BRCA-related aspects following participation in a BRCA-group. The results of this study indicate that following a BRCA-group, women were able to make cancer risk management decisions but still reported high levels of emotional distress while family communication appeared diminished. In this study response rate was low and an explanation is that group support simply does not meet the needs of every BRCA-mutation carrier [49, 50]. Informational needs were met since still 19% of BRCA-related information could be added and women reported to be well-informed to reach breast cancer risk decisions. The need to be well-informed to make personally suitable cancer risk reducing decisions is known from more studies. A majority of female BRCA-mutation carriers who underwent prophylactic bilateral salpingo-oophorectomy (PBSO) wished more information regarding the impact of this surgery on their sex life, the availability of sex counseling and the risk of coronary heart disease [51]. Proper and sufficient information about the PBM procedure and its possible aftermaths is one of the common and important factors related to satisfaction with the (cosmetic) outcome as well as the alterations on the sexual relationship and will lead to enhanced adaptation [52, 53]. So it may be concluded that these BRCA-groups meet informational needs of BRCA-mutation carriers.

It warrants attention that emotional distress of the women in our sample did not diminish after following group participation. This finding is in line with a study in which attendance at a retreat for BRCA-families did not significantly impact psychological distress, although the opportunity to meet others dealing with similar issues and a place to obtain both information and receive emotional support were highly appreciated [54]. It is therefore proposed to give more explicit focus on coping with emotional distress during following BRCA-meetings.

Finally, it was found that communicating BRCA-related issues with parents and sibs was diminished following group participation. Decreased family communication may be an unintended side effect of group participation and it is therefore proposed to give more direct attention to family communication during following BRCA-educational meetings. Medical confidentiality prohibits clinicians from directly contacting relatives of his or her patient about a genetic disease in the family [45]. Therefore, family communication of genetic cancer risks is of major importance to achieve the necessary transmission of information to relatives. Adequate family communication is essential if relatives are to have access to cancer prevention and surveillance programs and might therefore be life-saving.
The study comprised an evaluation of clinical practice. As a result it is not sure whether diminished family communication is a group effect or simply a time effect. Perhaps, over time also non-attendees discuss BRCA-related issues with their relatives less. After all, it is not necessary to discuss BRCA-related issues with your relatives repeatedly. It is likely that communication relating to hereditary cancer confirms to the rules and patterns that govern communication generally in families [56]. Moreover, it is likely that the specific and detailed information regarding for example PBM is shared more easily with women facing the same choices, e.g. group participants, compared to relatives who are either not-tested yet, proven non-carrier or without any intention towards preventive surgery.

**Implications for clinical practice**

**Applicability of MIPA-testing**
We found that shorter time interval between cancer diagnosis and genetic prescreening for Lynch syndrome was not related to higher psychological distress (chapter 2). MIPAPS-pilot study patients indicated that the advantages of early genetic prescreening for Lynch syndrome according to the MIPA-method outweighed the disadvantages (chapter 3). The MIPAPS study showed that MIPA-testing is not followed by clinically elevated psychological distress in either the MIPA-positive or the MIPA-negative group. Also caregiver experiences of their partners were unrelated to the MIPA-test result. (chapter 4). Notwithstanding the fact that low response rate of our MIPAPS-study may have biased our results all data point in the same direction namely that prescreening for Lynch syndrome by MSI-testing in recently diagnosed patients with CRC is applicable from a psychological point of view.

**Psychological distress**
It warrants clinical attention that a subgroup of recently diagnosed patients with CRC reported high distress which remained stable over time. Since short-term distress is a strong predictor for long-term distress it is of utmost importance to detect this highly distressed group and to offer them early psychosocial intervention. Adjustment to cancer is a family affair. Professional support needs to be directed toward both the patient and his or her immediate social environment in which the impact of parental cancer on children should not be overlooked [57, 58]. To avoid or reduce long-term distress, psychosocial assessment and if indicated
subsequent professional support should start early after the (hereditary) CRC diagnosis and should also be partner, family and socially focused. A screening tool for use in cancer genetics is currently being developed (Bleiker et al., Dutch Cancer Society, project grant NKI 2008-4016).

**Information and support for patients at genetic risk for cancer**

The overall conclusion regarding the BRCA-groups as described in this thesis is that they contribute to well-founded cancer risk management decisions. Because emotional distress did not diminish after participating in an BRCA-group, we consider separating the offer of BRCA-related information from the offer of psychosocial support. According to our results, BRCA-related informational meetings should focus on ways of coping with emotional distress, family communication and on the choice between breast cancer surveillance and PBM. As an alternative to the BRCA-support sessions, we believe that a more effective strategy may be to offer individual psychosocial support to women with high emotional distress. Patients at risk for Lynch syndrome do not face complex cancer risk management decisions. However, it might be worth investigating overall Lynch syndrome related needs and to explore whether informational meetings might meet those needs.

In society in general and also in the area of clinical genetics there is a growing interest in tailored websites, internet-based interventions and online guided self-help. Studies have shown that online guided self-help and face-to-face interventions can have comparable effects [59-63]. Online services have not been incorporated into existing genetic testing protocols. Although people are interested in services to support the ongoing integration of genetic information into daily life these are generally not available yet [64]. Given the profile of the majority of patients involved in genetic testing for hereditary cancer, namely relatively young, often having (small) children, being employed and sometimes with feelings of stigmatization, it is worth investigating the need for tailored online information and support for patients at risk for hereditary cancer.

**Limitations and future directions**

To our knowledge we were the first to study psychological distress following MSI-testing in recently diagnosed patients with CRC. This nationwide prospective study has given a first understanding in the psychological reactions to MIPA-testing of both patients and their partners. However, we did not achieve a high response rate and all patients were Dutch natives. Therefore, larger and international studies are needed to confirm our results.
Both from our as from other studies it is becoming increasingly clear that gender and social support are main aspects in adaption to potentially distressing events such as a cancer diagnosis or genetic testing for hereditary cancer. In future studies it is worth investigating patients’ specific strengths and needs regarding these aspects to offer customized care.

The ultimate medical preventive benefit of genetic testing for hereditary cancer depends on adequate dissemination of genetic test results and its consequences in the family. Future studies are needed to investigate how family communication barriers can be addressed adequately.

In the nearby future next generation sequencing including whole exome sequencing will provoke more genetic knowledge on multiple genes involved in complex and common diseases like cancer, heart disease, diabetes and mental illness. Individual risk assessments can be made based on the set of genes and individuals can be confronted with many genetic-based risks at the same time. In view of these future developments more studies regarding the impact of genetic health risks are needed on both health behavior, on related psychosocial well-being and on ways to support the ongoing integration of genetic information into daily life.
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Summary

The first part of this thesis addressed psychological distress after prescreening for Lynch syndrome by microsatellite instability (MSI)-testing in relatively young and recently diagnosed patients with colorectal cancer (CRC). Lynch syndrome is the most frequent form of hereditary colorectal cancer. To improve the recognition of Lynch syndrome among patients with CRC, the MIPA-strategy was developed according to which prescreening for Lynch syndrome by MSI-testing takes place immediately after tumor resection in a selection of patients: diagnosed with CRC below age 50 years or with a second CRC below age 70 years. The next step of the MIPA-method is discussion of the MSI-test result and referral to genetic counseling with a patient with an MSI-positive tumor by the treating physician. From 2008 onwards, MIPA-testing is included in the Dutch Guideline Hereditary Colorectal Cancer. It implies a striking difference compared to former practice in which MSI-testing takes place only after comprehensive genetic counseling of the patient. As a result of MIPA-testing patients are almost simultaneously confronted with a diagnosis of and treatment for CRC and a possibly hereditary predisposition for Lynch syndrome. CRC is in itself already responsible for considerable physical and psychosocial morbidity. The question is to what extent MIPA-testing is followed by high levels of psychological distress.

The second part of this thesis focused on educational-support groups for female BRCA-mutation carriers. Due to a high breast cancer risk, female BRCA-mutation carriers face a complex choice between breast cancer surveillance and prophylactic bilateral removal of their breasts. The decision is usually not a medical urgent one. Women can take time to process all information to make a well-informed decision. An important goal of so-called BRCA-groups as organized at the hereditary cancer clinic of the Radboud University Nijmegen Medical Centre in the Netherlands is assisting women in making informed choices regarding cancer risk management. Another goal is to address overall psychosocial related issues related to BRCA-carriership.

Part 1: Psychological impact of prescreening for Lynch syndrome in new colorectal cancer patients

Many studies have focused on the psychological impact of presymptomatic genetic testing for Lynch syndrome, i.e. in unaffected individuals. Also extended work has
been accomplished on familial cancer in general, including patients with CRC tested for Lynch syndrome. However, very few studies addressed the psychological impact of genetic testing for Lynch syndrome in recently diagnosed patients with CRC. The first step in this project was to perform a literature review to understand what was already known about psychological distress of patients in their first year following CRC diagnosis and about the psychological impact of symptomatic genetic testing for Lynch syndrome, i.e. in patients affected with CRC. This study is presented in Chapter 2. We reviewed reports published between January 1997 and October 2007. Searches took place in the electronic databases of PubMed, PsychInfo, Embase and the Cochrane Library. Only a limited number of relevant studies could be identified. Studies on the psychological impact of genetic testing in newly diagnosed patients were not available. What we did find was that reduced emotional and social functioning continues up to 1 year after CRC treatment, especially in patients with a stoma or diagnosed before age 60. In addition it was shown that most vulnerable to Lynch syndrome genetic testing related distress are female patients in general and male patients diagnosed before age 50.

In case of an MSI-positive tumor, the patient is at high risk for Lynch syndrome. Blood DNA-analysis must follow to detect its underlying cause. Studies on the psychological impact of genetic testing for Lynch syndrome generally focused on this period of blood DNA-analysis, not on the period of MSI-testing. Given our questions regarding the psychological impact of MIPA-testing, it was obviously important to know the impact of MSI-testing in former practice, i.e. after genetic counseling for Lynch syndrome. In Chapter 3 the focus was on the psychological impact of MSI-testing in former clinical genetics practice. We assessed whether high levels of psychological distress are present during MSI-testing and whether distress levels are related to the time between CRC diagnosis and MSI-testing. In 89 patients with a history of CRC, data were collected during MSI-testing just after genetic counseling. The median time between CRC diagnosis and MSI-testing was 24 months. General psychological distress (SCL-90) was low but more than one third of these patients reported high cancer specific distress (IES>26). Time between CRC diagnosis and MSI-testing was not significantly related to general distress nor to cancer specific distress. High cancer specific distress was reported by 25% of the patients diagnosed with CRC less than 12 months ago versus 39% and 35% by those diagnosed between 12 and 35 months and more than 36 months ago, respectively. Psychological distress following MSI-testing was related to female gender, religiousness, low social support and family communication difficulties.
The first step to understand the psychological impact of MIPA-testing was to explore the overall reactions of patients who had been confronted with this new Lynch syndrome detection method. In Chapter 4 a pilot study is described in which we investigated the experiences of 8 patients who were recently confronted with MIPA-testing. Patients were interviewed at home using a self-administered questionnaire based on the multicausal model of problem analysis adapted for hereditary CRC. Three themes emerged: 1) a changed life after CRC, 2) warning for the future and 3) family communication barriers. In this early stage after diagnosis coping with the treatment for CRC mainly determined the reactions. These few patients were of the opinion that as a result of MIPA-testing the preventive medical value especially for their children greatly outweighed possible family communication barriers.

The final step was to assess patients’ psychological distress in a larger sample at both short-term and longer term and to investigate caregiver experiences of their partners. Chapter 5 comprises the MIPAPS-study in which we prospectively determined psychological distress in recently diagnosed patients with CRC immediately following MSI-testing and 6 months later. From March 2007 until September 2009, 400 Dutch patients with a new CRC and their partners were approached by their treating surgeon to participate in our study. Levels of general distress (SCL-90) and cancer specific distress (IES) were moderate. In the MSI-positive patient group (high risk Lynch syndrome), high general distress (SCL-90>160) decreased after 6 months from 27% to 18%, while remaining stable in the MSI-negative group (low risk Lynch syndrome), from 14% to 18%. High cancer specific distress (IES>26) decreased in the MSI-positive group and remained stable in the MSI-negative group, from 39% to 27% and from 38% to 36%, respectively. Female patients were most prone to high levels of psychological distress as were patients with low social support or a high cancer risk perception. The partners of both the patients at low and at high risk for Lynch syndrome showed moderate to high levels of caregiver esteem (CRA-D) while in both groups perceived distress by caring (EDIZ) decreased over time.

Conclusions
Identification of Lynch syndrome is important because surveillance reduces CRC mortality in healthy relatives. Prescreening for Lynch syndrome by MIPA-testing implies a striking difference for patients compared to former clinical genetics practice. Relatively young and recently diagnosed patients with CRC are confronted with a possibly hereditary predisposition of their CRC during active treatment for
their CRC. Our findings indicate that time between CRC-diagnosis and MSI-testing is not related to general distress or cancer specific distress. Moreover, MIPA-testing is not followed by high levels of distress in general. Perceived distress by their partners is not related to MIPA-test result either. However, a subgroup of these patients report high psychological distress. Female patients with CRC are most vulnerable to distress as are patients with low social support or with high cancer risk perception. These patients need customized psychosocial care.

Part 2: Educational-support groups for female BRCA-mutation carriers

The second part of this thesis addressed educational-support groups in the area of hereditary breast and ovarian cancer. In this thesis two studies are described which evaluated such groups for recently proven female BRCA-mutation carriers, the so-called BRCA-groups. Healthy female BRCA-mutation carriers face a complex choice between intensive breast cancer surveillance and prophylactic bilateral mastectomy (PBM). A BRCA-group aims at assisting women in making a well-informed decision. However, it was unknown whether in fact participating in a BRCA-group changed the initial intention of surveillance into PBM. To be clear, this would be considered an unintended side-effect of group participation. In Chapter 6 we determined breast risk management preferences of 163 recently proven female BRCA-mutation carriers shortly after genetic test disclosure and their mastectomy status after a median observation period of 2 years. We additionally explored the effect of a BRCA-group on the realization of women’s breast cancer risk management preferences. Of the total sample, 27% had a preference for PBM and after two years 30% had actually undergone PBM. Female BRCA-mutation carriers with a preference for PBM are significantly more likely to participate in a BRCA-group compared to women with a preference for breast cancer surveillance. The number of women with a preference for PBM who actually had a mastectomy performed was significantly higher in the group that attended a BRCA-group compared to those who did not, 89% and 63%, respectively. Of the women with a preference for breast cancer surveillance, 90% of the BRCA-group attendees and 88% of the other mutation carriers were still under surveillance. We concluded that nearly all BRCA-mutation carriers proceed with their initial preference for surveillance or prophylactic mastectomy expressed during first surveillance visit after genetic test disclosure while participating in a BRCA-group group seems to strengthen the initial expressed intention to undergo PBM.
Above mentioned study did not answer the question whether women were more capable of coping with BRCA-mutation carriership in daily life after participating in a BRCA-group. In Chapter 7 we assessed informational needs, emotional distress and family communication of female BRCA-mutation carriers just before (T1) and after following BRCA-groups (T2). All 34 women indicated that group participation highly met their need for BRCA-relation information to support their decision-making process regarding breast cancer risk management. Mean levels of depression, anger, fatigue and tension were high and remained high at T2. Also cancer risk perception and frequency of cancer thoughts were high at both T1 and T2. Family communication with parents, brothers and sisters was significantly reduced at T2 compared to T1. This study showed that after following a BRCA-group these women were very capable of making cancer risk management decisions. However, these women still reported high levels of emotional distress and communicated with their family less after group participation.

Conclusions
Female BRCA-mutation carriers may opt between intensive breast cancer surveillance and prophylactic removal of their breasts with or without breast reconstruction. So-called BRCA-groups aim at assisting these women in making well informed and the most suitable BRCA-related choices. Female BRCA-mutation carriers with an intention towards prophylactic surgery are most likely to participate in a BRCA-group. Participating in a BRCA-group does not change the choice for breast cancer surveillance or prophylactic surgery but reinforces women to take action on prophylactic surgery. A BRCA-group contributes to well-informed decision-making but emotional distress does not improve and BRCA-related family communication with parents and sibs is diminished following a BRCA-group. A topic for future research and a challenge for clinical practice is to continuously improve our understanding of what is required to adequately meet the specific needs of these women.

In view of the studies described in this thesis it is concluded that the majority of people who are confronted with (a predisposition to) hereditary cancer gets through it without major psychological problems. However, a subgroup reports serious and more or less stable psychological complaints including adaptation problems, depressive symptoms and continuous fear of cancer. In contrast to what one may expect these complaints are not related to the medical or genetic context but to more stable characteristics such as age and gender, to social characteristics such as social support and family communication and to cancer risk perception. It is desirable to trace these people and to offer customized support.
Samenvatting

Het eerste deel van dit proefschrift richt zich op psychische klachten na het pre-screenen voor Lynch syndroom door het testen van microsatelliet instabiliteit (MSI) in tumoren van relatief jonge en recent gediagnosticeerde patiënten met dikke darmkanker. Lynch syndroom is de meest voorkomende vorm van erfelijke darmkanker. Om de herkenning van Lynch syndroom in patiënten met dikke darmkanker te vergroten is een aanvullende strategie ontwikkeld. Volgens deze zogenaamde MIPA-strategie vraagt de patholoog een MSI-test aan voor alle patiënten met dikke darmkanker onder de 50 jaar of met een tweede tumor horend bij Lynch syndroom onder de 70 jaar. MIPA staat voor MSI-test op indicatie van een patholoog. Patiënten met een MSI-positieve tumor hebben een verhoogd risico op Lynch syndroom. Zij kunnen vervolgens door hun behandelend arts verwezen worden voor erfelijkheidsadvisering in een klinisch genetisch centrum. Vanaf 2008 is MIPA-testen opgenomen in de Nederlandse Richtlijn Erfelijke Darmkanker. Deze methode betekent een voor patiënten belangrijk verschil in vergelijking met de tot dan toe gangbare klinisch genetische praktijk waarin een MSI-test pas wordt ingezet na uitgebreide genetische counseling van de patiënt. Door MIPA-testen worden patiënten bijna gelijktijdig geconfronteerd met een diagnose van en behandeling voor dikke darmkanker én met een mogelijk erfelijke aanleg voor Lynch syndroom. Dikke darmkanker alleen kan al ernstige lichamelijke en psychosociale morbiditeit tot gevolg hebben en de vraag is in hoeverre MIPA-testen zal leiden tot ernstige psychische klachten.

In het tweede deel van dit proefschrift staan informatie-support groepen voor vrouwen met een BRCA-mutatie centraal. Door hun hoge borstkankerrisico staan vrouwelijke BRCA-mutatie draagsters voor een complexe keuze tussen intensieve borstcontroles en preventieve borstverwijdering. Over het algemeen hebben deze vrouwen de tijd om alle informatie hieromtrent te verwerken en een weloverwogen besluit te nemen. Een belangrijk doel van de BRCA-groepen van de Polikliniek Familiaire Tumoren van het UMC St Radboud in Nijmegen is om deze vrouwen te ondersteunen bij het maken van weloverwogen keuzes. Een ander doel van deze groepsbijeenkomsten is het bevorderen van de integratie van BRCA-dragerschap in het dagelijkse leven.
Deel 1: Psychologische invloed van pre screenen voor Lynch Syndroom in nieuwe patiënten met dikke darmkanker

Er is inmiddels veel onderzoek gedaan naar de psychologische gevolgen van erfelijkheidsonderzoek naar Lynch syndroom bij zowel patiënten met dikke darmkanker als bij hun vaak nog gezonde familieleden. Echter weinig studies betroffen de psychologische invloed van erfelijkheidsonderzoek naar Lynch syndroom in recent gediagnosticeerde patiënten met dikke darmkanker.

De eerste stap in dit project was het uitvoeren van een literatuuronderzoek. Het doel was om te achterhalen wat er al bekend was over psychische klachten bij patiënten gedurende het eerste jaar na een diagnose dikke darmkanker en van de psychologische impact van genetisch testen in patiënten met dikke darmkanker. Dit literatuuronderzoek wordt beschreven in Hoofdstuk 2. We zochten in de elektronische databases van PubMed, PsychInfo, Embase en de Cochrane Library naar studies die gepubliceerd waren tussen Januari 1997 en Oktober 2007. Slechts een beperkt aantal relevante studies kon worden geïdentificeerd. We vonden geen onderzoeken naar de psychologische impact van genetisch testen in recent gediagnosticeerde patiënten met dikke darmkanker. Uit de gevonden studies bleek dat beperkt emotioneel en sociaal functioneren kon blijven bestaan tot een jaar na de dikke darmkanker diagnose, met name bij patiënten met een stoma en bij patiënten onder de 60 jaar. Verder bleek dat vrouwen in het algemeen en mannen met een diagnose onder de 50 jaar het meest kwetsbaar zijn voor psychische klachten gerelateerd aan de periode rondom erfelijkheidsonderzoek naar Lynch syndroom.

In het geval van een microsatelliet instabiele (= MSI-positieve) tumor heeft de patiënt een verhoogd risico op Lynch syndroom. DNA-analyse in bloed kan vervolgens uitwijzen wat de precieze oorzaak is van de MSI in het tumorweefsel. Onderzoeken naar de psychologische impact van genetisch testen voor Lynch syndroom richtte zich meestal op de periode rondom DNA-analyse en niet op de periode daarvoor, die van de MSI-test. In Hoofdstuk 3 beschrijven wij de mate van psychologische klachten na MSI-testen van 89 patiënten met een geschiedenis van darmkanker in de gangbare klinisch genetische praktijk dus na uitgebreide genetische counseling. We onderzochten daarbij de invloed van timing van de MSI-test door te bekijken of de mate van psychische klachten gerelateerd was aan de tijd tussen dikke darmkanker diagnose en het inzetten van de MSI-test. De
mediane tijd tussen de dikke darmkanker diagnose en het inzetten van de MSI-test bedroeg 24 maanden. Het algemene psychische klachten niveau was laag maar meer dan een derde van deze patiënten rapporteerde ernstige verwerkingsklachten. Er werd geen relatie gevonden betreffende de tijd tussen de diagnose van dikke darmkanker en MSI-test en de mate van algemene psychische klachten noch met verwerkingsklachten. Ernstige verwerkingsklachten werden gerapporteerd door 25% van de patiënten die minder dan een jaar geleden werden gediagnosticeerd met dikke darmkanker. Dit percentage was aanzienlijk lager dan de gerapporteerde percentages van 39% en 35% van respectievelijk patiënten met een diagnose tussen de 12 en 35 maanden en die van langer dan 36 maanden geleden. Vrouwen, gelovige patiënten en patiënten met problemen ten aanzien van erfelijke darmkanker relateerde familiecommunicatie waren het meest kwetsbaar voor psychische klachten.

Om een eerste indruk en inzicht te krijgen in mogelijke psychologische reacties op MIPA-testen verrichtten wij een kwalitatieve studie in recent gediagnosticeerde patiënten met een aan Lynch gerelateerde kanker. In Hoofdstuk 4 beschrijven we deze pilotstudie waarin we de ervaringen onderzochten van 8 MIPA-positieve patiënten, dus met een verhoogd risico op Lynch syndroom. Deze patiënten werden thuis geïnterviewd met behulp van een vragenlijst gebaseerd op het multicausale model van probleemanalyse en aangepast voor erfelijke darmkanker. Uit de data werden drie overkoepelende thema’s zichtbaar: 1) een veranderd leven na dikke darmkanker, 2) waarschuwing voor de toekomst en 3) familiecommunicatie problemen. In dit vroege stadium na de diagnose waren de diagnose van kankeren de bijbehorende behandeling dominant aanwezig in de beschrijving van hun ervaringen met MIPA-testen. Deze patiënten waren allen van mening dat door de vroege opsporing van Lynch syndroom de preventieve medische waarde voor met name hun kinderen toenemt en daardoor opwoog tegen eventuele familiecommunicatie problemen over erfelijke kanker.

De laatste stap was om de mate van psychische klachten op zowel korte als langere termijn te bepalen in een grote groep patiënten en om tevens de ervaringen van de partners te onderzoeken. Hoofdstuk 5 omvat de MIPAPS-studie waarin we prospectief psychische klachten onderzochten in recent gediagnosticeerde patiënten met dikke darmkanker onmiddellijk na MSI-testen (T1) en 6 maanden later (T2). Van Maart 2007 tot September 2009, werden 400 Nederlandse patiënten met een recente dikke darmkanker en hun partners benaderd door hun
behandelend arts (chirurg of MDL-arts) voor deelname aan onze studie. Het gemiddelde algemene psychische klachten niveau (SCL-90) en dat van de verwerkingsklachten (IES) waren matig. Door 27% van de MSI-positieve patiënten (hoog risico Lynch syndroom), werden ernstige psychische klachten (SCL>160) gerapporteerd op T1; na 6 maanden (T2) was dit afgenomen naar 18%. In de MSI-negatieve groep (laag risico Lynch syndroom) bleef dit percentage stabiel, van 14% op T1 naar 18% op T2. Het percentage van patiënten met ernstige verwerkingsklachten nam in de MSI-positieve groep af van 39% naar 27% en bleef stabiel in de MSI-negatieve groep van 38% naar 36%. Vrouwelijke patiënten bleken het meest kwetsbaar voor ernstige psychische klachten, evenals patiënten met weinig sociale steun en patiënten met een hoge kanker risicoperceptie. De partners van zowel de patiënten met een hoog en laag risico op Lynch syndroom rapporteerden een matig tot hoog gevoel van eigenwaarde door het verlenen van zorg terwijl de ervaren druk door het geven van zorg in beide groepen partners na 6 maanden was afgenomen.

Conclusies
Deel 2: Informatie-support groepen voor vrouwen met een BRCA-mutatie

Het tweede deel van dit proefschrift betreft informatie-support groepen voor vrouwen met een BRCA-mutatie. Gezonde vrouwelijke BRCA-mutatie draagsters staan voor een complexe keuze tussen intensieve borstcontroles en preventieve verwijdering van de borsten. Een BRCA-groep heeft tot doel om deze vrouwen te ondersteunen bij het nemen van een bij hen passende en weloverwogen beslissing waarbij de ene keuze niet beter is dan de andere. De aanleiding voor het eerste onderzoek naar deze groepen was de indruk die in de klinische praktijk was ontstaan dat vrouwen na deelname aan een BRCA-groep vaker en sneller overgingen tot preventieve borstverwijdering. Een ongewenst neveneffect van de groep zou zijn dat vrouwen zich voelden overgehaald tot preventieve borstverwijdering door de uitgebreide aandacht hiervoor gedurende de bijeenkomsten. In Hoofdstuk 6 bepaalden we de voorkeur van de vrouwen ten aanzien van borstkanker risicoreducerende maatregelen tijdens het eerste consult bij de internist, vlak na de BRCA testuitslag. Vervolgens keken we na twee jaar hoeveel vrouwen preventief hun borsten hadden laten verwijderen en wie van deze vrouwen hadden deelgenomen aan een BRCA-groep. Uit de data bleek dat van de totale onderzoeksgroep 27% een voorkeur had voor preventieve borstverwijdering. Na twee jaar had 30% van de totale groep daadwerkelijk de stap van preventieve chirurgie gezet. Significant meer vrouwen met een voorkeur voor preventieve borstverwijdering kwamen naar een BRCA-groep, vergeleken met vrouwen met een voorkeur voor borstcontroles. Vrouwen met een voorkeur voor preventieve chirurgie die aan een BRCA-groep hadden deelgenomen hadden significant vaker hun borsten laten verwijderen dan vrouwen die net als zij in eerste instantie hun borsten wilden laten verwijderen, maar niet aan een BRCA-groep hadden deelgenomen, 89% versus 63%. Na twee jaar was van de vrouwen met een voorkeur voor borstcontroles de meerderheid nog onder controle, 90% van de BRCA-groep deelnemers en 88% van de andere BRCA-mutatie draagsters. We kunnen concluderen dat bijna alle vrouwen met een BRCA-mutatie standvastig zijn in het volgen van hun eerste voorkeur ten aanzien van borstkanker-reducerende maatregelen. Een andere belangrijke conclusie is dat groepsdeelname de keuze van deze vrouwen niet verandert, maar het naleven van hun oorspronkelijke voorkeur lijkt te versnellen. Vrouwen met een voorkeur voor preventieve chirurgie zetten die stap namelijk eerder wanneer zij deelnemen aan een groep.
Bovenstaande studie gaf nog geen antwoord op de vraag of deze vrouwen na een \textit{BRCA}-groep beter in staat waren om met de gevolgen van het \textit{BRCA}-mutatie dragerschap om te gaan in hun dagelijks leven. In \textbf{Hoofdstuk 7} onderzochten we daarom de mate van emotionele klachten en familiecommunicatie vlak voor aanvang van (T1) en meteen na groepsdeelname (T2). Alle 34 vrouwen gaven aan dat groepsdeelname in hoge mate tegemoet kwam aan hun behoefte aan informatie ter ondersteuning van hun keuze voor borstkankerreducerende maatregelen. Het gemiddelde niveau van zowel depressie, boosheid, vermoeidheid als spanning was hoog en dat bleef zo op T2. Ook kanker risicoperceptie en de frequentie van gedachten aan kanker waren hoog op zowel T1 als T2. De familie-communicatie met ouders, broers en zussen was significant afgenomen op T2 vergeleken met T1. Dit onderzoek toont aan dat na groepsdeelname vrouwen goed in staat zijn te beslissen over de bij hen passende kankerreducerende maatregelen. Echter, deze vrouwen rapporteren nog veel emotionele klachten en praten na groepsdeelname significant minder over \textit{BRCA}-gerelateerde zaken met hun ouders, broers en zussen dan daarvoor.

\textbf{Conclusies}

Vrouwelijke \textit{BRCA}-mutatie draagsters staan voor de complexe keuze tussen intensieve borstcontroles en preventieve borstverwijdering met of zonder borstreconstructie. Het doel van een \textit{BRCA}-groep is het ondersteunen van deze vrouwen bij het maken van weloverwogen keuzes. Vrouwen met een voorkeur voor preventieve borstverwijdering blijken vaker aan een groep deel te nemen dan vrouwen met een voorkeur voor borstcontroles. Groepsdeelname verandert de voorkeur niet maar versnelt de keuze voor het laten verwijderen van de borsten. Onze beide onderzoeken tonen aan dat een \textit{BRCA}-groep bijdraagt tot het versterken van keuzes ten aanzien van borstkankerreducerende maatregelen. Er treedt echter geen verbetering op in de mate van emotionele klachten en \textit{BRCA}-gerelateerde familiecommunicatie met ouders, broers en zussen blijkt af te nemen na groepsdeelname. Een onderwerp voor verder onderzoek en een uitdaging voor de klinische praktijk is om steeds beter te begrijpen wat nodig is om adequaat aan de specifieke behoeftes van deze vrouwen tegemoet te komen.

Uit de in dit proefschrift beschreven studies wordt geconcludeerd dat de meerderheid van de mensen die geconfronteerd wordt met (een aanleg voor) erfelijke kanker hiermee zonder ernstige psychische klachten om kan gaan. De
Basale psychosociale zorg die geboden wordt in de huidige oncogenetische praktijk lijkt voor hen voldoende. Echter een subgroep rapporteert ernstige en min of meer stabiele psychische klachten waaronder verwerkingsproblemen, depressieve gevoelens en een continue angst voor kanker. In tegenstelling tot wat men zou kunnen verwachten, zijn deze klachten niet gerelateerd aan de medische of genetische context maar aan demografische kenmerken zoals leeftijd en geslacht, aan sociale kenmerken zoals sociale steun en familiecommunicatie en aan kanker risicoperceptie. Het is wenselijk om deze kwetsbare mensen tijdig op te sporen en de zorg te bieden die nodig is.
List of Publications


Landsbergen KM, Prins JB, Kamm YJL, Brunner HG, Hoogerbrugge, N. Female BRCA-mutation carriers with a preference for prophylactic mastectomy are more likely to participate an educational-support group and to proceed with the preferred intervention within two years. Fam Cancer 2010; 9(2):213-20.


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