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Risk-reducing surgery

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Risk-reducing surgery

Uptake & menopausal consequences

Catheleine Margje Geerte van Driel

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Uptake & menopausal consequences

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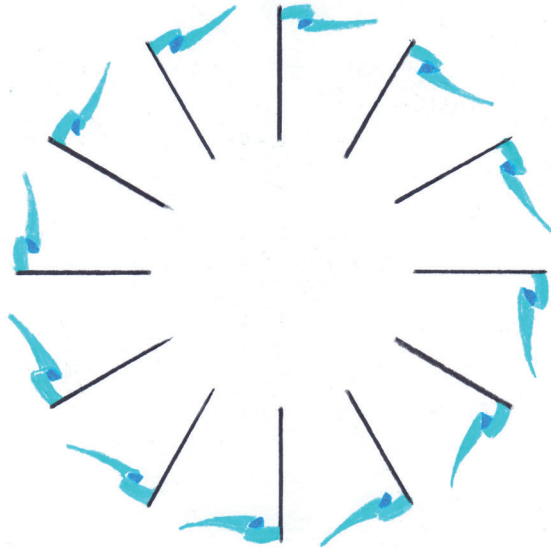
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Chapter 1

General introduction



Introduction

Chapter 1 starts with discussing mutations on the *BRCA1/2* genes in relation to the development of breast and ovarian cancer, followed by a discussion of the genetic counseling process relevant to women with a suspected genetic predisposition. Next, the risk management options available to women with an elevated risk of breast and ovarian cancer are studied. Then, an overview of currently known and possible predictors of the uptake of risk management options is given. Lastly, current interventions to alleviate sequelae following risk-reducing salpingo-oophorectomy (RRSO) are summarized and opportunities for future research are described. Chapter 1 concludes with an outline of this thesis.

Breast and ovarian cancer and genetic susceptibility

Pathogenic mutations in the *BRCA1* or *BRCA2* gene have been found to account for the majority of hereditary breast and ovarian cancer cases¹⁻³. *BRCA1* and *BRCA2* genes are tumor suppressor genes that have a function in ensuring genomic integrity by its roles in the DNA double-strand break repair process⁴. Pathogenic mutations in these genes can interfere with their role in this DNA repair process^{1,2,4}. The discovery of these genes in 1994 and 1995 has made genetic testing and the assessment of the risk of breast or ovarian cancer in individual women and their relatives possible^{1,2}. The inheritance pattern of a *BRCA1/2* mutation is autosomal dominant. It is estimated that approximately 7% of all breast cancer cases and 10% of all ovarian cancer cases are in women with a *BRCA1* or *BRCA2* gene mutation^{5,6}.

***BRCA1/2* associated breast cancer risk**

In a recent large prospective cohort study it was estimated that women who carry a *BRCA1* or *BRCA2* mutation have a cumulative breast cancer risk to the age of 80 years of 72% (95% confidence interval (CI), 65%-79%) and 69% (95%CI, 61%-77%), respectively⁷. Breast cancer incidence starts to rise between the ages of 21 and 30 years in both *BRCA1* and *BRCA2* mutation carriers. Peak incidence is reached between 41 and 50 years of age in *BRCA1* mutation carriers and between 51 and 60 years of age in *BRCA2* mutation carriers⁷.

***BRCA1/2* associated ovarian cancer risk**

In the same cohort study it was estimated that *BRCA1* and *BRCA2* mutation carriers have a cumulative ovarian cancer risk at the age 80 years of 44% (95% CI, 36%-53%) and 17% (95% CI, 11%-25%), respectively⁷. Ovarian cancer incidence starts to rise between the ages of 41 and 50 years in *BRCA1* mutation carriers and between the ages of 51 and 60 years in *BRCA2* mutation carriers⁷. In the Northern Netherlands an even earlier rise has

been observed in *BRCA1* mutation carriers, starting in their late thirties⁸. Peak incidence is reached between 61 and 70 years of age in both *BRCA1* and *BRCA2* mutation carriers⁷.

Table 1: Indications for referral to a clinical geneticist for women according to the most recent Dutch guidelines for breast cancer^{9,10} and hereditary and familial ovarian cancer^{9,10}.

For women with ovarian/fallopian tube cancer
<ul style="list-style-type: none"> • Woman with ovarian/fallopian tube cancer, regardless of family history, age at diagnosis and histological type
For women with breast cancer
<ul style="list-style-type: none"> • Woman with breast cancer and first or second degree relatives with ovarian/fallopian tube cancer, regardless of age at diagnosis • Woman with breast cancer and a relative with <i>BRCA1/2</i> mutation • Woman with breast cancer < 40 years • Woman with bilateral breast cancer with first case < 50 years • Woman with ≥ 2 primary breast cancer cases in ipsilateral breast, first case < 50 years • Woman with triple negative breast cancer < 60 years • Woman with breast cancer < 50 years and ≥ 1 first degree relatives with breast cancer < 50 years • Woman with breast cancer < 50 years and first degree relative with prostate cancer < 60 years • Woman with breast cancer and ≥ 2 first and second degree relatives with breast cancer, at least 1 case < 50 years, all on the same side of the family
For women without ovarian/fallopian tube cancer or breast cancer*
<ul style="list-style-type: none"> • First degree relative with ovarian or fallopian tube cancer, regardless of age at diagnosis • First or second degree relative with <i>BRCA1/2</i> mutation • First degree female relative with breast cancer < 40 years • First degree female relative with bilateral breast cancer, first case < 50 years • First degree female relative with ≥ 2 primary breast cancer cases in ipsilateral breast, first case < 50 years • First degree female relative with triple negative breast cancer < 60 years • First degree male relative with breast cancer • First degree female relative with breast cancer < 50 years and a first degree relative with prostate cancer < 60 years, both on same side of family. • ≥ 2 first degree relatives with breast cancer < 50 years • ≥ 3 first and second degree relatives with breast cancer, at least 1 case < 50 years, all on the same side of the family <p>* there is a strong preference to refer the affected family member for clinical genetic assessment because DNA testing will start with this person. Advice for the family members of the affected person will follow based on the DNA testing and family history.</p>

Genetic counseling and risk-management options for hereditary breast and ovarian cancer

When breast and/or ovarian cancer cluster in a family, affected members of this family should be referred to the clinical geneticist to investigate if they carry a *BRCA1/2* mutation. As specified in the Dutch national guidelines, every women with ovarian cancer should be offered genetic testing, regardless of age at diagnosis, histological type of cancer and family history⁹. The most up-to-date indications for referral have been specified in the recent update of the current national guideline on breast cancer and the national guideline for hereditary and familial ovarian cancer (Table 1)^{9,10}. Based on a detailed medical history

of breast and ovarian cancer and family history of breast, ovarian and prostate cancer, the clinical geneticist assesses whether gene panel testing including (but not limited to) *BRCA1* and *BRCA2* genes is indicated. If an indication is present, women receive extensive counseling on the personal and familial implications of DNA testing¹¹.

Risk-management options

Several risk-management options exist in case a woman is proven to be a *BRCA1/2* mutation carrier. Regarding breast cancer risk, *BRCA1/2* mutation carriers can either opt for breast cancer screening or for risk-reducing mastectomy (RRM) with or without breast reconstruction¹². With respect to ovarian cancer, risk-reducing salpingo-oophorectomy (RRSO) is currently the only proven option to effectively reduce the risk of dying of ovarian cancer, because screening was found to be ineffective for early detection of ovarian cancer^{13–15}. In the Netherlands, women are extensively counseled on the optimal timing, effectiveness and consequences of breast and ovarian cancer risk management options by a multidisciplinary team consisting of clinical geneticists, surgical oncologists, gynecological oncologists, oncology nurses, psychologists, plastic surgeons and radiologists^{11,16}.

Effectiveness of breast cancer screening & RRM

BRCA1/2 mutation carriers can opt for an intensive breast cancer screening program. The screening recommendations have been specified in current national guidelines¹⁰. For *BRCA1* mutation carriers this starts at the age of 25 years with annual MRI and from the age of 40 years adding mammography once every two years. The intensive screening program for *BRCA2* mutation carriers starts at the age of 25 years with annual MRI and from the age of 30 years adding annual mammography. From the age of 60 to 75 years, *BRCA1* and *BRCA2* mutation carriers are screened annually with mammography only, unless the breast tissue is heterogeneous or extremely dense, in which case alternating annual MRI and mammography is advised. The evidence on the benefit of clinical breast examination in addition to imaging is limited. There is a study showing that the addition of clinical breast examination to mammography increased breast cancer detection¹⁷. However, in another study in women screened using MRI, the benefit of clinical breast examination was found to be minimal or none at all¹⁸.

The alternative, RRM, is offered as an option to women from the age of 25 years and after comprehensive counseling on the arguments for and against¹². A recent review reported that the breast cancer risk reduction by RRM ranges from 90% to 100%¹⁹. Model-based analyses suggest that RRM at the age of 25 years combined with RRSO at the age of 40 years results in only slightly better survival compared to intensive breast cancer screening due to the already high survival in the breast cancer screening programme²⁰. However, empirical evidence on the comparative effectiveness on survival of intensive screening

versus RRM is lacking and a definite answer on this question remains unknown. As will be discussed in the next paragraph, survival is not the only important factor to take into account in decision making, because from the patients' perspective, having to face burdensome cancer treatments or having to deal with the stress of false positive screening results are highly relevant as well.

Consequences of breast cancer screening & RRM

The choice between RRM and intensive breast cancer screening is complex because it is not only based on the comparative effectiveness of both options in terms of cancer prevention, but also a matter of weighing the other consequences either options have for these women. For example, as all screening tests have a specificity of less than 100%, women who choose breast cancer screening can be faced with false positive results, anxiety and subsequent additional investigation. Studies have found that women who are given an all-clear result and are placed on the routine recall do not experience high levels of anxiety due to screening^{21,22}. However, women who do need additional investigation experience a temporary increase in anxiety levels²¹⁻²⁵.

In case of RRM, women can experience a decrease in general and cancer-related anxiety²⁶⁻²⁸. However, in several studies women report a decline in sexual functioning and a persistently lower body image after RRM with or without reconstruction when compared to before the procedure²⁶⁻³⁰. Women who opted for RRM with breast reconstruction did report higher levels of satisfaction with body shape and appearance than women who did not.³⁰ However, after breast reconstruction following RRM, women can be faced with a lack of sensation in the reconstructed breasts and surgical complications during the reconstruction process^{29,31,32}.

Effectiveness of RRSO

RRSO is recommended at an age, before the incidence of ovarian cancer starts rising, i.e. between 35 and 40 years of age for *BRCA1* mutation carriers and between 40 and 45 years of age for *BRCA2* mutation carriers, provided that childbearing has been completed^{9,33-36}. When performed within the recommended age range, RRSO reduces the risk of ovarian cancer up to 96%³⁷⁻⁴⁰. In earlier studies RRSO was also associated with approximately a 50% reduction of breast cancer risk in *BRCA1/2* mutation carriers, however more recent studies suggest that this protective effect is much less pronounced than previously thought^{40,41}.

Consequences of RRSO

What makes the uptake and timing of RRSO complex for *BRCA1/2* mutation carriers is that these women are often young, at premenopausal age and that RRSO induces acute surgical menopause. Frequently mentioned menopausal symptoms after RRSO are hot flashes, night sweats, loss of sexual desire and vaginal dryness^{32,42,51-53,43-50}. Menopausal

symptoms occur not only earlier, but also more severely after acute surgical menopause in comparison to natural menopause^{54,55}. Furthermore, these symptoms can persist many years after RRSO⁴³. Regarding sexual difficulties after RRSO, the prevalence of sexual dysfunction and hypoactive sexual desire disorder has been found to be 74% (95% CI: 66–81%) and 73% (95% CI: 64–80%), respectively. The most commonly experienced sexual symptoms after surgical menopause are: reduced libido, vaginal dryness, pain during intercourse, reduced sexual satisfaction and reduced ability to achieve an orgasm^{53,56}. Women who experience a high level of relationship satisfaction more often continue to have regular sexual activity, even when facing vaginal menopausal symptoms^{53,57}. Hormone replacement therapy (HRT) reduces vasomotor and sexual symptoms after RRSO, however not to the premenopausal situation⁵⁸.

In conclusion, although RRM and RRSO are very effective procedures to reduce the risk of breast and ovarian cancer, they have a profound impact on quality of life of the women involved. This thesis focusses on factors associated with the decision for preventive surgery in *BRCA1* and *BRCA2* mutation carriers (Part I) and on possible psychological interventions to mitigate the menopausal and sexual side effects after RRSO (Part II).

Part I:

Factors associated with the uptake of risk-reducing surgery

The decision whether or not to choose risk-reducing surgery (i.e. RRM and/or RRSO) is a complex process. Possible factors that may influence the decision process are personal or family history of cancer (e.g. having first degree relatives with breast/ovarian cancer), demographic characteristics (e.g. age, parity), psychological factors (e.g. perceived risk, cancer worry, cancer anxiety, effectiveness) and actual cancer risk^{7,59,68–77,60–67}. Optimal decisional support integrates all these factors to ensure individualized and medically adequate decisions and optimal support of patients in terms of psychological well-being and decisional satisfaction. In order to address all relevant factors during counseling and provide adequate support it is important to further identify which factors influence the decision to undergo risk-reducing surgery.

Socio-demographic characteristics, family history and personal history of cancer are the most commonly studied factors. Several studies have reported that a higher level of education, being married, having children, a personal history of breast cancer, unilateral therapeutic mastectomy and having relatives with breast and/or ovarian cancer were associated with the decision for RRM^{59–68}. Likewise, having children, a higher level of education, a personal history of breast cancer, a family history of breast and/or ovarian cancer have been reported to be associated with the decision to undergo RRSO^{65,69–73}.

As described above, risk-reducing surgeries can best be performed *before* a certain age for optimal effectiveness and *from* a certain age in order to prevent side effects at too young an age. This is especially true for RRSO which is advised before the age the incidence of ovarian cancer starts to rise until a few years thereafter, as there are no effective screening alternatives and ovarian cancer has a high mortality rate^{7,78}. Therefore, factors that influence the timing of risk-reducing surgery after DNA test results disclosure also need to be understood. These factors help understand what constitutes the “right time” to choose risk-reducing surgery for women^{74,75}. This understanding can be beneficial to health care providers during counseling on uptake and timing of risk-reducing surgery. Until now, most studies are limited to investigating the uptake of risk-reducing surgery, but not its timing i.e. the age at which risk-reducing surgery is performed.

A limitation of previous research is that the impact of changes in guidelines in recent years, such as stopping ovarian cancer screening, on uptake and timing of risk-reducing surgery has yet to be determined⁶⁹. Lastly, the impact of only few psychological factors has been thoroughly investigated. Among these factors, high cancer risk perception, anxiety and worry are repeatedly reported to be associated with the uptake of RRM and RRSO^{60,63,69,73,76,77}. Other psychological factors (e.g. affect, perceived personal control) are likely to be at play, but have at best been sparsely investigated⁷⁴.

Part II:

Psychological interventions alleviating menopausal symptoms after RRSO

Hormone replacement therapy

The use of systemic HRT in young premenopausal women after RRSO is a balancing act between the effects of HRT on menopausal symptoms (e.g. hot flushes, vaginal dryness), sexual functioning, bone and cardiovascular health on the one hand and on breast cancer risk on the other^{42,79}. The Dutch national guideline on hereditary and familial ovarian cancer advises to prescribe HRT after RRSO to women without a history of breast cancer until the age of 50 years⁹.

Women who have had breast cancer or are older than 50 years at the time of RRSO are advised not to start HRT as the use of HRT in postmenopausal women is associated with increased breast cancer risk and contraindicated in breast cancer survivors⁹. The amount of studies on the safety of short-term use of topical vaginal estrogens in breast cancer survivors is limited. However, it is known that estrogen serum levels remain low during the use of topical vaginal estrogens^{80–82}. Therefore it is likely that also in breast cancer survivors the benefits of short-term use of topical vaginal estrogens outweighs the risks^{9,82–84}. Reported HRT use after RRSO ranges from 44 to 71% in young *BRCA1/2* mutation carriers

without a history of breast cancer^{42,48,49,85–87}. The main reason women cite for not using HRT after premenopausal RRSO is anxiety about increasing their risk of breast cancer⁴².

Effectiveness of HRT

The use of HRT after RRSO is associated with a decrease of frequency and severity of vasomotor symptoms, but HRT does not decrease these symptoms to the pre-surgical situation^{42,48,49,54,86,88}. The findings concerning the effect of HRT on sexual complaints are more mixed. Although sexual symptoms, such as vaginal dryness, vaginal discomfort and pain during intercourse decrease, they are not completely alleviated with the use of HRT⁴⁹. Other sexual symptoms after RRSO such as a decrease in sexual desire and sexual satisfaction do not improve with the use of HRT^{45,48,49,53,86,88}. Topical vaginal estrogen is effective in improving vaginal dryness and improving sexual functioning in case of vaginal symptoms, but has no direct effect on sexual desire⁵³.

HRT safety

Preliminary findings concerning the safety of systemic HRT indicate that short-term HRT use until the age of 50 years does not increase breast cancer risk in women who underwent RRSO. However, the use of HRT after menopausal age is associated with an increased breast cancer risk. HRT is contraindicated in breast cancer survivors, due to an increased risk of breast cancer recurrence^{89,90}. More studies are needed on the safety of longer term HRT use in *BRCA1/2* mutation carriers after RRSO^{42,54,91–97}.

Alternative interventions

As HRT does not alleviate menopausal and sexual symptoms completely and is advised against in breast cancer survivors and after the age of 50 years, a search commenced for alternative treatment options for these symptoms. In this search a myriad of modalities such as topical hormone therapy, transdermal testosterone, non-hormonal medication, complementary or alternative treatments, lifestyle/physical exercise and psychological interventions have been suggested⁹⁴. Psychological interventions have recently gained more interest due to their favorable characteristics when compared to hormonal interventions.

The main advantages of psychological interventions, such as mindfulness or cognitive based interventions, is firstly that they have no impact on cancer incidence or recurrence and secondly that they might impact frequency and perceived burden of symptoms (i.e. perceived bother) simultaneously⁹⁸. Moreover, although no randomized trials have been performed in the RRSO population, psychological therapies seem to be beneficial in other populations, such as natural menopausal women, breast cancer survivors, women suffering from hypoactive sexual desire disorder or female sexual arousal disorder and women suffering from sexual complaints after gynecological cancer^{98–104}.

Chapter outline

The research presented in this thesis aims to improve our understanding of factors associated with the timing and uptake of risk-reducing surgery in women with a *BRCA1/2* mutation and to investigate a non-hormonal alternative to HRT to mitigate the menopausal and sexual symptoms after surgical menopause, especially after RRSO in breast cancer survivors

Part I: Factors associated with the uptake of risk-reducing surgery

Several factors are presumed to be associated with choosing RRM and RRSO in *BRCA1/2* mutation carriers. In **chapter 2**, the socio-demographic, medical and family characteristics possibly associated with the early timing of RRM in *BRCA1/2* mutation carriers after DNA test disclosure were analyzed. Next to the above-mentioned factors, other psychological factors, such as emotional state, influence the decision for RRM. That is why in **chapter 3**, the psychological factors associated with the intention to choose RRM were analyzed. This approach confirmed that the counsellor should pay attention to women's perceived control and emotional state when counseling to women that are confronted with decision whether or not to choose RRM.

Several studies reported that ovarian cancer screening lacked effectiveness for early detection of ovarian cancer, after which ovarian cancer screening was no longer offered. From that time onwards, the only ovarian cancer risk management option offered to *BRCA1/2* mutation carriers is timely RRSO. In **chapter 4**, the effects of no longer offering ovarian cancer screening on the uptake and timing of RRSO was studied. In addition, other factors possibly associated with choosing RRSO were investigated.

When taken together, the topics addressed in **chapter 2, 3 and 4** help understand the uptake and timing of RRM and RRSO in women with a *BRCA1/2* mutation and provide valuable insight in the topics that need to be addressed during counseling.

Part II: Psychological interventions alleviating menopausal symptoms after RRSO

The duration of menopausal symptoms after RRSO and what factors influence the severity and duration of these symptoms are currently not well known. To alleviate menopausal symptoms after RRSO, HRT is the most effective and most frequently offered option. Unfortunately, HRT is contraindicated in breast cancer survivors. Furthermore, HRT does not alleviate menopausal complaints and sexual sequelae to the premenopausal level. Therefore an alternative to HRT is necessary.

Chapter 5 describes a cross-sectional study on factors associated with the severity and duration of menopausal symptoms in previously premenopausal women at a mean of

7.9 years after RRSO. In **chapter 6**, a systematic literature review on the effectiveness of psychological interventions in reducing symptoms associated with menopause in natural or treatment-induced menopausal women is described. As there is a paucity of evidence on effectiveness with long-term follow-up of psychological interventions to alleviate menopausal and sexual complaints after RRSO, a randomized controlled trial was performed which is described in **chapter 7**. This randomized controlled trial aimed to investigate the short-term and long-term benefits of mindfulness-based stress reduction on the menopausal quality of life, sexual functioning and sexual distress in women after RRSO. The research described in **chapter 6 and 7**, provides a basis for the implementation of psychological interventions in a clinical setting after RRSO. Lastly, it provides suggestions towards future research on interventions alleviating sexual complaints after RRSO. **Chapter 8** summarizes the main findings of this thesis in the context of current literature, addresses strengths and weaknesses and provides directions for further research on the topics of the abovementioned chapters.

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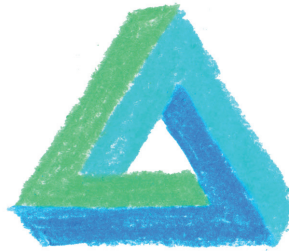
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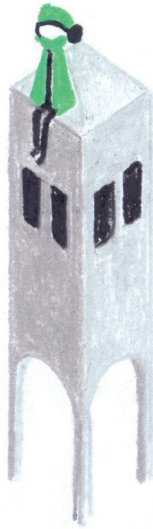
Part 1

factors associated with the uptake of risk-reducing surgery



Chapter 2

Risk-reducing mastectomy in BRCA1/2 mutation carriers:
factors influencing uptake and timing



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Introduction: Strategies in case of high risk of breast cancer in BRCA1/2 mutation carriers are either intensive breast cancer screening or risk-reducing mastectomy (RRM). Both options have a high physical and psychosexual impact. The aim of this study is to investigate who chooses when to undergo RRM.

Methods: BRCA1/2 mutation carriers have been prospectively registered at the family cancer clinic between 1994 and 2011. Analyses were performed to assess the relation between characteristics of the BRCA1/2 mutation carriers and an earlier decision for RRM.

Results: A cumulative percentage of 35.6% of all women chose to undergo RRM within the first five years after disclosure of DNA test results. Women needed less time to choose for RRM measured from the first visit, if they were younger than 50 years of age (hazard ratio (HR)=2.67, 95% confidence interval (CI)=1.30-5.48) or had a mother who had had breast cancer (HR=1.51 95% CI=1.04-2.18). Also, women needed less time to choose for RRM in case of a previous breast cancer (HR=2.25, 95% CI=1.55-3.27). After a previous unilateral therapeutic mastectomy as a treatment for breast cancer, women needed less time to choose for RRM of the contralateral breast (HR=2.69, 95% CI=1.29-5.62) compared to women who had had breast-conserving therapy.

Conclusion: BRCA1/2 mutation carriers aged under 50, having a mother with breast cancer, who had previous unilateral breast cancer and previous unilateral therapeutic mastectomy chose more often and earlier for RRM.

Introduction

Women with a *BRCA1* or *BRCA2* mutation have a significantly higher lifetime risk of developing breast cancer and are diagnosed at a younger age compared to the general population¹⁻⁴. The lifetime risk at the age of 70 years for breast cancer was found to be 57-65% for *BRCA1* and 45-49% for *BRCA2* mutation carriers^{1,2}.

BRCA1/2 mutation carriers have to make major decisions regarding the medical management of their increased breast cancer risk. To reduce the risk of death due to breast cancer, women can choose for risk-reducing mastectomy (RRM) or they can opt for intensive breast cancer screening aiming at early detection^{5,6}. When performed at a young age, before the cancer risk is rising, RRM is associated with an actual breast cancer risk reduction of 90-95%⁷. However RRM has been associated with a negative impact on body image⁸.

A review including 43 published articles identified three main types of factors that influence high-risk women's decisions about risk-reducing strategies: a) medical and physical factors, b) psychological factors and c) social context factors. How these factors operate in women's lives over time remained unknown⁹.

The purpose of this study was to identify baseline characteristics of *BRCA1/2* carriers that opt for RRM early on following the disclosure of DNA test results. Identifying which characteristics influence the (early) decision for RRM can indicate important topics to be discussed during counselling.

Methods

Patients

Women with an increased risk of carrying a *BRCA1/2* mutation are referred to the clinical genetic department of the University Medical Centre Groningen for genetic risk assessment. Those that have a high cancer risk are followed-up at the Family Cancer Clinic (FCC) with a multidisciplinary team including clinical geneticists, surgical oncologists, gynaecological oncologists, plastic surgeons, social workers, nurse practitioners and a psychologist¹⁰. When visiting the FCC women were asked to give informed consent for entering their data into a prospectively maintained password protected FCC database. Protection of the patients' identity was guaranteed by assigning study-specific, unique patient numbers. According to Dutch law no further Institutional Review Board approval was needed for this study.

Data collection

Women were included in this study if they were proven *BRCA1/2* mutation carriers and had visited the FCC between April 1994 and November 2011 at least once. As according to Dutch guidelines RRM should preferably be offered to women from the age of 25 years, only women ≥ 25 years of age were included in this study. We considered the disclosure date of the *BRCA1/2* mutation to the patient as the first moment of contact and the last visit was considered to be the most recent visit to the FCC or the most recent visit to the FCC before RRM. The date of first contact and the date of the last visit were extracted from the (digital) patient files and used to calculate follow up times. For this study, characteristics concerning the patient as well as her family were collected. Patient characteristics concerned: age, mutation status and medical history. The medical history concerned previous breast and/or ovarian cancer, related treatment and risk reducing strategies. Patient characteristics were retrieved from the prospectively maintained FCC database. Family characteristics concerned: number and age of children and breast and/or ovarian cancer within the family, both at the time of the first visit to the FCC. Family characteristics were derived from non-electronic clinical genetics records

Statistical analysis

Survival analysis was chosen to demonstrate the course of decision making over time, since this method adjusts for variable follow-up time. Univariate and multivariate survival analyses were performed over the total group of women (women opting for RMM as well as opting for intensive breast cancer screening), in order to calculate the cumulative percentage of women undergoing RRM over time, hazard ratios (HR) and the 95% confidence intervals (CI) of the baseline characteristics where the timing of the decision to undergo RRM was considered dependent.

The disclosure date of the *BRCA1/2* mutation to the patient was considered as the first moment of contact. The last moment of contact was considered to be the most recent visit or the most recent visit to the FCC before RRM. All tests were performed in SPSS Statistics 20 package and all p-values were two-tailed and considered significant if $p \leq 0.05$.

Results

Description of the population

From April 1994 until November 2011, 508 *BRCA1/2* carriers ≥ 25 years of age had visited the FCC (Figure 2.1). Women were excluded if a RRM was performed before the first visit to the FCC ($n=10$), if they had had bilateral breast cancer or disseminated disease ($n=38$) and if their clinical files were not available ($n=21$) or were incomplete ($n=30$). Two women were excluded due to mild mental retardation and inability to make their own decisions ($n=2$). The number of women included in the analysis was 407. Patient characteristics are given in Table 2.1.

Table 2.1: Characteristics of the study population at the time of DNA test disclosure and the uptake of RRM within 5 years of follow up (N=407).

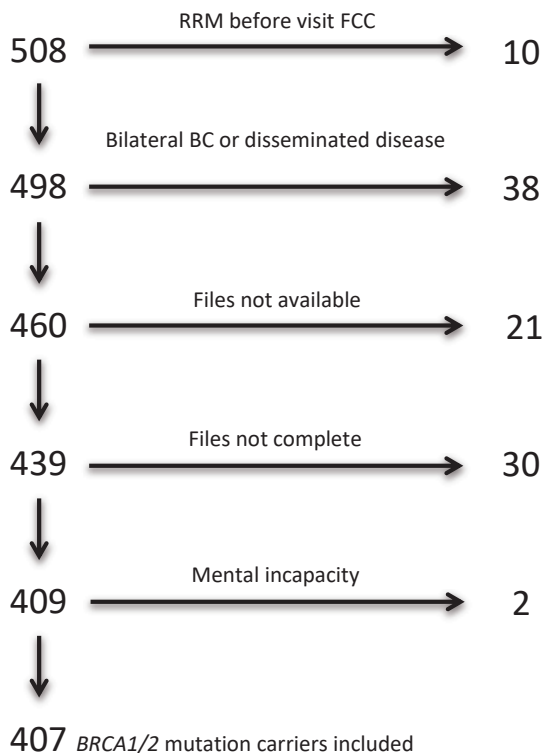
Patient characteristic	Frequencies at the time of DNA disclosure	Cumulative uptake of RRM after 5 years	Cumulative deferral of RRM after 5 years
Overall	N.A.	35.6%	64.4%
Age			
<50	335/407 (82.3%)	38.4%	61.6%
≥50	72/407 (17.7%)	20.7%	79.3%
Mutation status			
<i>BRCA1</i>	255/407 (62.7%)	40.9%	59.1%
<i>BRCA2</i>	152/407 (37.3%)	25.8%	74.2%
Children			
No	97/402 (24.1%)	27.9%	72.1%
Yes	305/402 (75.9%)	38.1%	61.9%
Age youngest child			
<18	219/301 (72.8%)	43.5%	56.5%
≥18	82/301 (27.2%)	25.1%	74.9%
Mother with BC			
No	246/398 (61.8%)	30.6%	69.4%
Yes	152/398 (38.2%)	44.2%	55.8%
Sister with BC			
No	300/399 (75.2%)	33.4%	66.6%
Yes	99/399 (24.8%)	41.2%	58.8%
Mother with OC			
No	316/402 (78.6%)	38.7%	61.3%
Yes	86/402 (21.4%)	24.6%	75.4%
Sister with OC			
No	357/395 (90.4%)	36.5%	63.5%
Yes	38/395 (9.6%)	28.7%	71.3%
BC* in history			
No	291/407 (71.5%)	26.3%	73.7%
Yes	116/407 (28.5%)	61.3%	38.7%
Number of BC*			
1	107/116 (92.2%)	61.8%	38.2%
>1	9/116 (7.8%)	100.0%	0.0%
Therapy of first BC*			
Lumpectomy	45/112 (40.2%)	31.4%	68.6%
Mastectomy**	67/112 (59.8%)	74.5%	25.5%
OC in history			
No	391/407 (96.1%)	36.2%	63.8%
Yes	16/407 (3.9%)	19.6%	80.4%

N.A. not applicable, BC: breast cancer, OC: ovarian cancer, RRSO: risk reducing salpingo-oophorectomy, RRM: risk reducing mastectomy.

* This concerns unilateral breast cancer, RRM of the contralateral breast remained medical management option.

** Unilateral therapeutic mastectomy

Figure 2.1: Population flowchart. All *BRCA1/2* mutation carriers ≥ 25 years old entered in the FCC database at November 2011 ((n=508) from April 1994 – November 2011)



Determinants of the timing of the decision to undergo RRM

Within the first five years after disclosure of DNA test results a cumulative percentage 35.6% women chose to undergo RRM (Table 2.1). In Table 2.2 it is shown that in the multivariate survival analysis, women younger than 50 years needed less time after counselling to decide for RRM than women > 50 years of age (HR=2.87 95% CI=1.40-5.92, $p=0.0042$). Furthermore women who had a mother with breast cancer needed less time to decide for RRM (HR=1.51 95% CI=1.04-2.18, $p=0.031$). Women previously diagnosed with unilateral breast cancer decided earlier for RRM of the contralateral breast than women without a breast cancer history (HR=2.54, 95% CI=1.74-3.70, $p<0.001$). Of the women with previous breast cancer, those who underwent therapeutic mastectomy as a therapy for a unilateral breast cancer needed less time to choose for RRM of the contralateral breast (HR=2.69, 95% CI=1.29-5.62, $p=0.008$) compared to women who had breast conserving therapy (Table 2.3).

Table 2.2: Analysis of the determinants of the timing of the decision for RRM (uni- and multivariate survival analysis) (N=407)

Patient characteristic	Univariate HR (95% CI) p-value	Multivariate HR (95% CI) p-value
Age		
<50	2.67 (1.30-5.48) 0.007	2.87 (1.40-5.92) 0.004
≥50	1	1
Mutation status		
<i>BRCA1</i>	1.76 (1.16-2.67) 0.008	
<i>BRCA2</i>	1	
Has children		
No	1	
Yes	1.26 (0.81-1.97) 0.30	
Age youngest child		
<18	2.18 (1.21-3.92) 0.01	
≥18	1	
Mother with BC		
No	1	1
Yes	1.52 (1.05-2.20) 0.03	1.51 (1.04-2.18) 0.03
Sister with BC		
No	1	
Yes	1.35 (0.90-2.03) 0.15	
Mother with OC		
No	1	
Yes	0.66 (0.41-1.07) 0.09	
Sister with OC		
No	1	
Yes	0.74 (0.36-1.52) 0.42	
BC* in history		
No	1	1
Yes	2.25 (1.55-3.27) <0.001	2.54 (1.74-3.70) <0.001
OC in history		
No	1.15 (0.42-3.12) 0.79	
Yes	1	
RRSO		
No	1	
Yes	1.20 (0.79-1.84) 0.39	

BC: breast cancer, OC: ovarian cancer, RRSO: risk reducing salpingo-oophorectomy

*This concerns unilateral breast cancer, RRM of the contralateral breast remained medical management option. Result significant when $p < 0.05$.



Table 2.3: Analysis of the determinants of the timing of the decision for RRM in the subgroup of BRCA1/2 carriers with previous breast cancer (N=116).*

Patient characteristic	Univariate HR (95% CI) p-value
Age	
<50	3.20 (1.15-8.92) 0.03
≥50	1
Mutation Status	
BRCA1	1.57 (0.76-3.25) 0.22
BRCA2	1
Has children	
No	1.23 (0.64-2.38) 0.54
Yes	1
Age youngest child	
<18	4.00 (1.55-10.33) 0.004
≥18	1
Mother with BC	
No	1
Yes	1.62 (0.90-2.91) 0.11
Sister with BC	
No	1
Yes	1.04 (0.56-1.92) 0.90
Mother with OC	
No	1
Yes	0.60 (0.25-1.41) 0.24
Sister with OC	
No	1
Yes	0.34 (0.08-1.42) 0.14
Number of BC**	
1	2.72 (0.37-19.89) 0.32
>1	1
Therapy of first BC*	
Lumpectomy	1
Mastectomy***	2.69 (1.29-5.62) 0.008
OC in history	
No	1
Yes	0.85 (0.20-3.50) 0.82
RRSO	
No	1
Yes	1.84 (0.95-3.58) 0.07

BC: breast cancer, OC: ovarian cancer, RRSO: risk reducing salpingo-oophorectomy

* As in the multivariate results only therapy of first BC contributed, only univariate results are presented

** This concerns unilateral breast cancer, RRM of the contralateral breast remained medical management option.

*** Unilateral therapeutic mastectomy

Result significant when $p < 0.05$.

Discussion

Women needed less time to choose for RRM if they were younger than 50 years of age (HR=2.87 95% CI=1.40-5.92), had a mother with breast cancer (HR=1.51 95% CI=1.04-2.18), had previous unilateral breast cancer (HR=2.54, 95% CI=1.74-3.70) and had a previous unilateral therapeutic mastectomy as a treatment for breast cancer (HR=2.69, 95% CI=1.29-5.62). Contrarily to women who needed less time to decide for RRM, women who deferred RRM were older than 50 years of age, did not have a mother with breast cancer, did not have a previous unilateral breast cancer and had a previous unilateral lumpectomy as a treatment for breast cancer.

Previous studies showed that being a mother¹¹⁻¹³, a previous breast cancer diagnosis^{13,14}, previous mastectomy¹⁵, family history of breast cancer¹⁶⁻¹⁸ and younger age¹⁹ are associated with the decision for RRM. However, how these factors influence the timing of RRM remains unknown⁹.

Lodder et al. found it unresolved whether 'young age' or 'having children' is explanatory for the decision for RRM¹². In our study having children or the age of the youngest child are not statistically significantly associated with an earlier decision to undergo RRM in the multivariate model, whereas an age < 50 years predisposes for RRM (HR=2.87 95% CI=1.40-5.92). This can be explained by the fact that we specifically take time to decision into account. A study that also took the time to the decision for RRM into account found similar results; younger than 60 years (HR=1.8, p=0.04) was associated with earlier RRM²⁰. In this study, women aged 50 years or over are less likely to choose for RRM than younger women. One of the reasons might be that these women are counselled differently (doctors' factor) counselling concerning RRM than younger women, because of a declining life expectancy gain from RRM with increasing age²¹. Another explanation could be that these women take their declining risk of breast cancer into account (patient's factor).

Metcalf et al. found that *BRCA1/2* mutation carriers who underwent therapeutic mastectomy as the initial surgery for breast cancer were more likely to undergo contralateral RRM (p < 0.0001)²². In another study a statistically significant relation between breast conserving therapy and the decision to undergo contralateral RRM within 1 year of treatment for a primary unilateral breast cancer was found (OR = 1.7, 95% CI=1.21-2.36, p=0.0002)¹⁷. The authors explained this as a relation between failed breast-conserving therapy, followed by RRM.

Yi et al. found that there was an association between having one or more relatives with breast cancer and the decision for RRM (OR= 1.57; 95% CI = 1.19-2.09)¹⁸. King et al. also reported the association between having one or more relatives with breast cancer and the

decision for RRM (OR = 2.91, 95% CI = 2.33-3.63, $p < 0.0001$)¹⁷. Metcalfe et al. differentiated between different types of relatives (sister, mother). They found that women who had a sister with breast cancer were more likely to undergo RRM (OR=2.4, $p=0.003$). Women who had a mother with breast cancer also showed a higher uptake of RRM, although this was not statistically significant (OR=1.7, $p=0.07$)¹⁶. In our study experience with cancer, whether this is personal experience or experience with affected family members, seem to be a factor closely related to the choice for RRM. It could be that these experiences increase the cancer specific worries²³, which could make women more inclined to choose for RRM to avoid cancer. Another explanation for the relation between experiences with cancer and an earlier decision for RRM is that women are already familiar with the treatment options for breast cancer such as therapeutic mastectomy, thus making the step to RRM easier.

The strength of our study is that the analysis was performed in a large consecutive series of proven *BRCA1* or *BRCA2* mutation carriers, who were counselled in a similar protocolled way by members of one multidisciplinary team. Furthermore the majority of the data has been collected prospectively and the timing of the decision to undergo RRM is taken into account when analysing the determinants. Lastly, univariate and multivariate analyses were performed. The fact that this study is quantitative in nature is next to strength, also a limitation because qualitative information on underlying motives for RRM is not included. Another limitation is that some data had to be gathered retrospectively when they were missing in the prospective database.

In conclusion, age younger than 50 years, having had a previous breast cancer or having affected family member seem to be factors in an (early) decision for RRM. Therefore it is advisable to discuss these factors during counselling. The speculations about the underlying motives of women who choose for RRM need to be clarified by longitudinal and qualitative research.

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Chapter 3

Psychological factors associated with the intention to choose risk-reducing mastectomy in family cancer clinic attendees



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Objectives: Women seeking counseling because of familial breast cancer occurrence face difficult decisions, such as whether and when to opt for risk-reducing mastectomy (RRM) in case of *BRCA1/2* mutation. Only limited research has been done to identify the psychological factors associated with the decision for RRM. This study investigated which psychological factors are related to the intention to choose for RRM.

Methods: A cohort of 486 cancer-unaffected women with a family history of breast cancer completed the following questionnaires prior to genetic counseling: the Cancer Worry Scale, Positive And Negative Affect Scale, Perceived Personal Control Scale, Hospital Anxiety and Depression Scale and State Anxiety Scale and questions regarding socio-demographic characteristics, family history, risk perception and RRM intention. Multivariate logistic regression was used to analyse the relation between psychological factors and women's intention to choose for RRM.

Results: Factors associated with RRM intention were high positive affect (OR = 1.86, 95%CI = 1.12-3.08), high negative affect (OR = 2.52, 95%CI = 1.44-4.43), high cancer worry (OR = 1.65, 95%CI = 1.00-2.72), high perceived personal control (OR = 3.58, 95%CI = 2.18-5.89), high risk-perception (OR = 1.85, 95%CI = 1.15-2.95) and having children (OR = 2.06, 95%CI = 1.21-3.50).

Conclusion: Negative and positive affects play an important role in the intention for RRM. Furthermore, perceived personal control over the situation is associated with an intention for RRM. In addition to focusing on accurate risk communication, counseling should pay attention to the influence of perceived control and emotions to facilitate decision-making.

Introduction

Women who carry a *BRCA1* or *BRCA2* mutation have a significantly higher risk of developing breast cancer and ovarian cancer and a higher risk to develop cancer earlier in life, compared to the general population¹⁻⁵. *BRCA1/2* mutation carriers have to decide between the two main risk management options to cope with the increased breast cancer risk: breast cancer surveillance aimed at the early detection of breast cancer, and risk-reducing mastectomy (RRM) aimed at preventing breast cancer^{6,7}.

RRM results in an actual breast cancer risk reduction of about 90%^{8,9} and a decrease of general and breast cancer specific distress¹⁰, but is also associated with a negative impact on the sexual relationship, sexual satisfaction and body image¹⁰⁻¹². Previously, sociodemographic (e.g. age, having children) and medical factors (e.g. mutation status, previous breast or ovarian cancer) have been found to influence the RRM decision-making process¹³. However, only limited research has been done to identify the psychological factors associated with the decision for RRM. So far, this research has primarily focused on perceived risk, anxiety & worry¹³.

Specifically, a higher perceived cancer risk has been associated with uptake of, or intention to choose for RRM¹⁴⁻²². Furthermore, increased cancer-related distress, (cancer specific) anxiety and cancer worry are associated with a preference for RRM^{17,19,21-23}.

As several studies have emphasized the role of emotions and underlying affect on medical decision-making²⁴⁻²⁷, it is very plausible that more psychological factors, such as affect, influence the decision to undergo RRM. Identifying these factors is important for health care professionals providing decisional support and permits improved shared decision-making. This study specifically investigated which psychological factors are related to the intention to choose for RRM.

Methods

Population

The population of the current study was recruited in the context of the Breast Cancer Risk Communication (BRISC) study, which is a prospective study carried out in three academic familial cancer clinics in the Netherlands, i.e. University Medical Center Groningen, VU University Medical Center Amsterdam and Leiden University Medical Center²⁸. Included in the BRISC study were women with a family history of breast cancer who sought first time genetic counseling concerning their breast cancer risk. A family history of breast cancer was defined as having at least one first-degree- and/or paternal second-degree family member with breast cancer. Women were not eligible to participate in this study

if they were younger than 18 years of age, suffered from evident psychiatric illness, were terminally ill or had a personal history of breast and/or ovarian cancer.

Protection of the patients' identity was guaranteed by assigning study-specific, unique patient numbers. The Medical Ethics Committees of all three centers approved the BRISC study protocol in 2005.

Data collection

All the data used in this paper was collected as part of the BRISC study of which recruitment took place between December 2005 and November 2007. Various questionnaires were completed at multiple time points. The questionnaires and administration procedure are described in more detail in the BRISC study protocol²⁸. The questionnaires analyzed in the current study were filled out prior to intake consultation and concerned questions regarding sociodemographic factors (age, level of education, having children, relationship status, religiousness), family breast cancer history (first degree relatives with breast cancer), psychological scales (Cancer Worry Scale (CWS)²⁹, Positive And Negative Affect Scales (PANAS-PA and PANAS-NA)³⁰, State-Trait Anxiety Inventory-state (STAI-state)³¹, Hospital Anxiety and Depression Scales (HADS-A and HADS-D)³² and Perceived Personal Control (PPC)³³, risk perception and RRM intention.

To determine risk perception, women's appraisal of perceived breast cancer risk was assessed independently of actual risk that was going to be determined and communicated after intake. Women were asked to appraise their perceived breast cancer risk independent of their actual risk. Women could select an answer on a 7-point scale, the options ranging from "very small" (1) to "very large" (7). Women were considered to have a high risk-perception if they selected "large" or "very large" as the answer.

To determine RRM intention, women answered the following question: "If you would be a proven *BRCA1/2* mutation carrier, would you choose for RRM?". Women could select an answer on a 7-point Likert-type scale, with options ranging from "No, definitely not" to "yes, definitely". Women were considered to have the intention to choose for RRM if they selected "probably yes", "yes" or "yes, definitely" as the answer.

Statistical analysis

All questionnaires were scored in accordance with the commonly used scoring manuals. Mean imputation was used when questionnaires were incomplete but at least half of the items were completed. If this criterion was not met, the case was deleted from the analysis. Dichotomization of each measure was done in order to compare the highest scoring subgroup to the lowest scoring subgroup. The CWS, PANAS and HADS were dichotomized using cut-off points as previously defined in literature. The CWS score was considered low

if ≤ 13 , and high if ≥ 14 ³⁴. The PANAS-PA score was considered low if ≤ 35 and high if ≥ 36 . The PANAS-NA score was considered low if ≤ 17 and high if ≥ 18 ³⁵. Both the HADS-A and HADS-D scores were considered low if ≤ 7 and high if ≥ 8 ³⁶. The remaining questionnaires were dichotomized using the median value to create equally sized groups.

To investigate the association between the baseline characteristics and the intention to choose for RRM a univariate and multivariate logistical regression was done to calculate the odds ratios (OR) and the 95% confidence intervals (95% CI), where intention to choose for RRM was considered dependent.

All tests were performed in SPSS Statistics 20 package and all p-values were two-tailed and considered significant if $p < 0.05$.

Results

Description of the population

The analyses included 486 women and population characteristics are given in Table 3.1. Of these women, 125 (25.7%) women had an intention to choose for RRM when indicated and 260 (54.5%) women perceived their breast cancer risk as high (Table 3.1).

Predictors of the intention to choose for RRM

In the univariate analysis, having children (OR = 2.21, 95%CI = 1.35-3.60), not being highly educated (OR = 1.59, 95%CI = 1.03-2.45), a high perceived risk (OR = 1.89, 95%CI = 1.25-2.88), experiencing high cancer worry (OR = 2.20, 95%CI = 1.45-3.32), a high negative affect (OR = 1.88, 95%CI = 1.20-2.95) and a high perceived personal control (OR = 3.41, 95%CI = 2.16-5.36) were all statistically significantly associated with the intention to choose for RRM (Table 3.2).

In the multivariate analysis, women who had children (OR = 2.06, 95%CI = 1.21-3.50), had a high perceived-risk (OR = 1.85, 95%CI = 1.15-2.95), experienced high cancer worry (OR = 1.65, 95%CI = 1.00-2.72), had a high positive affect (OR = 1.86, 95%CI = 1.12-3.08), had a high negative affect (OR = 2.52, 95%CI = 1.44-4.43) and had high perceived personal control (OR = 3.58, 95%CI = 2.18-5.89) had statistically significant greater intention to choose for RRM (Table 3.3).

Table 3.1: Patient characteristics prior to genetic counseling in women with and without intention to choose for RRM (N=486)

Patient characteristics	(N=486)* n (%)	Intention for RRM	
		Yes (N=125, 25.7%) n (%)	No (N=361, 74.3%) n (%)
Age (years)			
< 40	240 (49.4)	54 (22.5)	186 (77.5)
≥ 40	246 (50.6)	71 (28.9)	175 (71.1)
Having children			
No	153 (31.5)	25 (16.3)	128 (83.7)
Yes	332 (68.5)	100 (30.1)	232 (69.9)
Has first degree relative with BC			
No	107 (28.9)	28 (26.2)	79 (73.8)
Yes	263 (71.1)	59 (22.4)	204 (77.6)
Highly educated ²			
No	282 (59.1)	82 (29.1)	200 (70.9)
Yes	195 (40.9)	40 (20.5)	155 (79.5)
Married or cohabiting			
No	98 (20.2)	21 (21.4)	77 (78.6)
Yes	387 (79.8)	104 (26.9)	283 (73.1)
Actively religious			
No	348 (72.2)	90 (25.9)	258 (74.1)
Yes	134 (27.8)	34 (25.4)	100 (74.6)
Perceived risk			
Low	217 (45.5)	43 (19.8)	174 (80.2)
High	260 (54.5)	81 (31.2)	179 (68.8)
Cancer worry [^]			
Low	286 (59.1)	56 (19.6)	230 (80.4)
High	198 (40.9)	69 (34.8)	129 (65.2)
Positive affect [^]			
Low	254 (54.2)	55 (21.7)	199 (78.3)
High	215 (45.8)	63 (29.3)	152 (70.7)
Negative affect [^]			
Low	344 (73.3)	75 (21.8)	269 (78.2)
High	125 (26.7)	43 (34.4)	82 (65.6)
State anxiety ⁺			
Low	244 (50.7)	56 (23.0)	188 (77.0)
High	237 (49.3)	66 (27.8)	171 (72.2)
Hospital anxiety [^]			
Low	403 (82.1)	97 (24.1)	306 (75.9)
High	83 (17.9)	28 (33.7)	55 (66.3)
Hospital depression [^]			
Low	436 (89.9)	109 (25.0)	327 (75.0)
High	49(10.1)	16 (32.7)	33 (67.3)
Perceived personal control ⁺			
Low	226 (47.2)	32 (14.2)	194 (85.8)
High	253 (52.8)	91 (36.0)	162 (64.0)

RRM=risk-reducing mastectomy.

BC=breast cancer

1: Based on risk estimate provided by genetic risk counselor at intake consultation.

2: Yes: Vocational or research university

#: Some variables have missing cases, therefore the cases of some variables do not add up to 486.

+: Cut-off point based on median/equal group sizes.

^: Cut-off point based on a previously defined score from literature.

Table 3.2: Univariate logistic regression of the predictors of RRM intention, prior to genetic counseling (N=486)

Patient characteristics	Univariate logistical regression	
	OR	95% CI
Age (years)		
< 40	1	
≥ 40	1.40	0.93-2.11
Having children		
No	1	
Yes	2.21**	1.35-3.60
Has first degree relative with BC		
No	1.25	0.73-2.06
Yes	1	
Highly educated ²		
No	1.59*	1.03-2.45
Yes	1	
Married or cohabiting		
No	1	
Yes	1.35	0.79-2.29
Actively religious		
No	1.03	0.65-1.62
Yes	1	
Perceived risk ⁺		
Low	1	
High	1.89**	1.25-2.88
Cancer worry [^]		
Low	1	
High	2.20**	1.45-3.32
Positive affect [^]		
Low	1	
High	1.50	0.99-2.28
Negative affect [^]		
Low	1	
High	1.88**	1.20-2.95
State anxiety ⁺		
Low	1	
High	1.30	0.86-1.96
Hospital anxiety [^]		
Low	1	
High	1.61	0.97-2.67
Hospital depression [^]		
Low	1	
High	1.45	0.77-2.75
Perceived personal control ⁺		
Low	1	
High	3.41**	2.16-5.36

RRM=risk-reducing mastectomy.

BC=breast cancer

1: Based on risk estimate provided by genetic risk counselor after intake consultation.

2: Yes: Vocational or research university

*: p<0.05

** : p<0.01

+ : Cut-off point based on median/equal group sizes.

^ : Cut-off point based on a previously defined score from literature.

Table 3.3: Multivariate logistic regression of the predictors of RRM intention, prior to genetic counseling (N=453)

Patient characteristics	Univariate logistical regression	
	OR	95% CI
Having children		
No	1	
Yes	2.06**	1.21-3.50
Risk perception		
Low	1	
High	1.85*	1.15-2.95
Cancer worry [^]		
Low	1	
High	1.65*	1.00-2.72
Positive affect [^]		
Low	1	
High	1.86*	1.12-3.08
Negative affect [^]		
Low	1	
High	2.52**	1.44-4.43
Perceived personal control ⁺		
Low	1	
High	3.58**	2.18-5.89

RRM=Risk-reducing mastectomy.

*: $p < 0.05$

** : $p < 0.01$

+ : Cut-off point based on median/equal group sizes.

[^] : Cut-off point based on a previously defined score from literature.

Discussion

The objective of this study was to identify psychological factors associated with the intention to choose for RRM, as research so far has mainly been limited to sociodemographic and medical factors.

Of the participants 25.7% had an intention to choose for RRM if indicated due to a *BRCA1/2* mutation. Next to having children, the following psychological factors were associated with the intention to choose for RRM: high positive and high negative affect, experiencing a high level of personal control, experiencing a high level of cancer worry and high cancer risk-perception.

A novel finding of this study is that higher levels of negative affect, characterized by feelings of distress and higher levels of positive affect, characterized by feelings of energy and self-esteem, being distinctive dimensions, both play an important role in the intention to choose for RRM. Slovic et al. introduced the theoretical framework of the affect heuristic, which describes the importance of affect in guiding judgments and decisions³⁷. This

framework asserts that mental representation of events become “tagged” with an affective meaning constructed of people’s positive and/or negative previous experiences with this event. Thereby, relying on affect can be a very quick and efficient way to weigh the pros and cons of a situation, especially in case of a very complex and uncertain situation³⁷. The situation of having a *BRCA1/2* mutation and having to decide on whether or not to choose for RRM can very well be characterized as a complex and uncertain situation and therefore the role of affect becomes more apparent in this decision-making process. A review on affect and cancer risk perception concluded that communicating factual risk information not only improves counselees’ factual knowledge but also elicits an affective reaction, or in other words an emotional meaning is assigned to the presented factual information³⁸. This emotional reaction can be more influential in medical decision-making than factual knowledge³⁸.

The second novel finding of this study is that an increased perceived personal control is positively correlated with the intention to choose for RRM. The fact that perceived personal control over a situation might induce a stronger intention to undertake corresponding actions is described by the theory of planned behavior³⁹. This theory asserts that the intention to engage in behavior is determined by a person’s attitude toward the behavior, perception of social norms and perceived control³⁹ and is widely used to explain the decision-making process⁴⁰. Perceived personal control is fundamental to adequate coping with health issues such as genetic susceptibility to breast cancer⁴¹.

This study corroborates the findings of several previously performed studies concerning predictors of RRM (Table 3.4). Firstly, the psychological factors associated with RRM intention that are corroborated by this study are high perceived-risk^{14–21,42–44} and cancer worry^{17,19,43} are associated with an intention to choose for RRM. These findings suggest that apart from actual risk, the way women perceive their risk influences their intention to choose for RRM. This is underpinned by the fact that people tend to base their decisions on their interpretation of literal information in addition to basing it on the literal information itself²⁶. This interpretation is shaped, among other things, by emotions such as worry^{26,45}. Secondly, our study found that the socio-demographic factor having children was associated with the intention to choose for RRM. Multiple previous studies have shown that women who have children are more inclined to choose for RRM^{18,20,46–50}.

The RRM intention percentage found in this study is comparable to the percentages of 19% and 23% found in previous studies on the pre-genetic counseling intention for RRM in women with an increased breast cancer risk^{21,22}.

Table 3.4. Recent* studies on predictors of RRM in high risk populations

Author & year	Study population <i>n</i> , BC (un)affected, eligible ^a for genetic counseling or tested.	Outcome type of RRM - RRM intention or uptake & contralateral of bilateral - Assessment of predictors and RRM before or after genetic counseling - Type of analysis	Predictors statistically significantly associated with RRM
Tong et al., 2015 ²¹	696 BC affected and unaffected women eligible for genetic counseling.	- Contra/bilateral RRM intention - Prior to genetic counseling - Multivariate logistic regression	- Younger age - Higher education - Greater perceived BC risk - Greater distress
Portnoy et al., 2015 ⁴³	BC affected and unaffected <i>BRCA</i> mutation carriers	- Contra/bilateral RRM uptake - After genetic counseling - Multivariate logistic regression	- Greater perceived BC risk - Greater BC worry
Elsayegh et al., 2014 ⁵³	165 women with DCIS eligible for genetic counseling	- Contralateral RRM uptake - After genetic counseling - Multivariate logistic regression	- Younger age - Having relatives with OC - Having <i>BRCA</i> mutation
van Driel et al., 2014 ⁵⁴	407 BC affected and unaffected <i>BRCA</i> mutation carriers	- Contra/bilateral RRM uptake - After genetic counseling - Multivariate cox regression	- Younger age - Having a mother with BC - Previous BC - Therapeutic unilateral mastectomy
Singh et al., 2013 ⁵⁵	136 BC unaffected <i>BRCA</i> mutation carriers	- Bilateral RRM uptake - After genetic counseling - Multivariate logistic regression	- 1 st and 2 nd family BC death - Having children - More recent genetic testing
King et al., 2013 ⁴⁴	284 women ≤ 50y with BC eligible for genetic counseling	- Contralateral RRM intention - Prior to genetic counseling - Multivariate linear regression	- Higher neuroticism - Greater perceived new BC risk - Higher risk of <i>BRCA</i> mutation - Any surgical recommendation - Lower lumpectomy preference
Schwartz et al., 2012 ²³	108 BC affected and unaffected <i>BRCA</i> mutation carriers	- Contra/bilateral RRM uptake - Predictors prior to genetic counseling - RRM uptake after genetic counseling. - Multivariate logistic regression	- Intact ovaries - Greater anxiety
Haroun et al., 2011 ⁴²	246 BC unaffected <i>BRCA</i> mutation carriers	- Bilateral RRM uptake - After genetic counseling - <i>T</i> -test and chi-squared test	- Younger age - Greater perceived BC risk
Julian-Reynier et al., 2010 ⁵⁰	244 BC unaffected <i>BRCA</i> mutation carriers	- Bilateral RRM uptake - Predictors prior to & after genetic counseling - RRM uptake after genetic counseling. - Multivariate cox regression	Prior to genetic testing: - Having children < 15 y at testing - Having FDR with BC < 50 years - RRM intention before <i>BRCA</i> disclosure After genetic testing: - Impact of <i>BRCA</i> disclosure
Skytte et al., 2010 ⁴⁹	306 BC unaffected <i>BRCA</i> mutation carriers	- Bilateral RRM uptake - After genetic testing - Multivariate cox regression	- Younger age - Having children

Kiely et al., 2010 ⁵⁶	1018 BC affected women with a BC family history, included tested <i>BRCA</i> mutation carriers and untested women.	- Contralateral RRM uptake - Before and after genetic counseling† - Multivariate cox regression	- Younger age at BC diagnosis - BC diagnosis more recent - Therapeutic unilateral mastectomy - Underwent RRSO
Evans et al., 2009 ⁵⁷	211 BC unaffected <i>BRCA</i> mutation carriers and 3,515 women at >25% lifetime risk of breast cancer without known mutations.	- Bilateral RRM uptake - After genetic counseling - Univariate cox regression	- <i>BRCA</i> mutation - Younger age at testing (in <i>BRCA</i> mutation carriers)
Beattie et al., 2009 ⁵⁸	237 BC affected and unaffected <i>BRCA</i> mutation carriers	- Contra/bilateral RRM uptake - After genetic counseling - Univariate cox regression	- Younger age - Previous BC - RRSO

* Since publication of Howard et al., Women's decision-making about risk-reducing strategies in the context of hereditary breast and ovarian cancer: a systematic review. *J Genet Couns* 2009, 18: 578–97. 10.1007/s10897-009-9245-9. Influential factors identified in this narrative review: having children, perceived cancer risk, cancer-related distress, anxiety, worry & family history of BC/OC. #: Eligibility criteria differed per study (e.g. based on family history, risk of carrying *BRCA* mutation, age of first breast cancer etc.), †: Population was partly untested, BC: breast cancer, DCIS: ductal carcinoma in situ, OC: ovarian cancer, FDR: first degree relative, RRSO: risk-reducing salpingo-oophorectomy.

Strengths of this study are that the analyses were done in a large sample of women, making it possible to identify multiple independent associations. Next to that, a large range of psychological factors and questionnaires were taken into account.

It could not be studied whether psychological factors associated with the intention to undergo RRM and actual RRM uptake change after genetic counseling. However, previous studies have shown that the intention whether or not to choose for RRM prior to genetic testing predicts actual uptake of RRM^{51,52}. Furthermore, previous studies show that if a woman prefers RRM, this preference remains stable over time. Lastly, the data of this study has been collected between 2005 and 2007. It could be that the factors influencing the decision for RRM have evolved in recent years.

The results of this study signify that the intention to choose for RRM is influenced, amongst other factors, by psychological factors i.e. cognitive and affective factors.

With regard to affect, next to supplying precise and literal risk information in order to achieve accurate risk-perception, counseling should include the clarification of counsees' affective response, ensuring it fits the intended message goals, either by routine discussion or specific interventions. Furthermore, counselors' awareness of the influence of perceived control on the decision making process incites focus on specific topics and informational needs that enhance counsees' sense of control and thereby coping capabilities.

Supplying decisional support that integrates the role of affect and perceived control in the decision-making process ensures medically adequate decisions and the optimal support of counselees in other respects such as psychological wellbeing and satisfaction, thereby facilitating meaningful shared decision-making.

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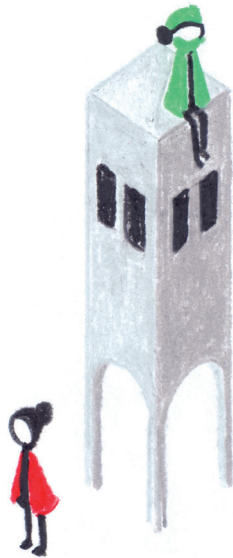
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Chapter 4

Stopping ovarian cancer screening in BRCA1/2 mutation carriers:
effects on risk management decisions & outcome of
risk-reducing salpingo-oophorectomy specimens



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Introduction: Ovarian cancer screening (OCS) for *BRCA1/2* mutation carriers was stopped in our family cancer clinic in 2009 because of its ineffectiveness. The study objective was to investigate the effect of stopping OCS on the timing and uptake of risk-reducing salpingo-oophorectomy (RRSO) and on the percentage of occult cancers in the specimens.

Methods: 419 *BRCA1/2* mutation carriers were recruited between January 1999 and June 2013. Uptake, timing and the outcome of the RRSO specimens before stopping OCS (period I) were compared to those after stopping OCS (period II).

Results: The percentage of women undergoing RRSO within the recommended age range increased from 81% to 95%. Receiving DNA test results in period II independently predicted a shorter time interval to RRSO (hazard ratio: 2.48, 95% confidence interval: 1.81-3.39). The incidence of detecting occult cancers in RRSO specimens before and after stopping OCS was 1.3% and 1.8% respectively and was not statistically significantly different.

Conclusion: The presentation of risk management options to women may influence their decision. The increased patient awareness of the ineffectiveness of OCS could have led to a higher percentage of women undergoing RRSO and doing so more often within the recommended age range.

Introduction

Women who carry a *BRCA1/2* mutation have a high lifetime risk of developing ovarian cancer. A recent prospective study estimated a lifetime risk for ovarian cancer in *BRCA1* and *BRCA2* mutation carriers of 59% (95% Confidence interval (CI) = 43-76%) and 16.5% (95% CI = 7.5-34%), respectively¹. Since 2007, the perspective on optimal risk management for ovarian cancer in *BRCA1/2* mutation carriers has changed in response to studies which reported that ovarian cancer screening (OCS) lacked effectiveness for early detection of ovarian cancer in these mutation carriers²⁻⁵. In light of these findings and in advance of national guideline changes, our family cancer clinic stopped offering OCS in October 2009. From that time onwards, the only ovarian cancer risk management option offered to *BRCA1/2* mutation carriers is risk-reducing salpingo-oophorectomy (RRSO). RRSO is recommended for patients younger than the age at which the ovarian cancer incidence rises, 35 to 40 years for *BRCA1* mutation carriers and 40 to 45 years for *BRCA2* mutation carriers, provided that the patients have completed their childbearing⁶⁻⁸. RRSO reduces the risk of ovarian cancer with 80-90% when performed within the recommended age range⁹⁻¹⁴. Moreover, RRSO may also reduce the risk of breast cancer in premenopausal women⁹⁻¹⁴. However, RRSO is also associated with adverse effects in premenopausal women due to acute surgical menopause¹⁵⁻¹⁷.

Both younger age and nulliparity at the time of receiving the DNA test result were factors related to a longer interval between receiving DNA test results and RRSO¹⁸⁻²¹. In the aforementioned studies *BRCA1/2* mutation carriers could choose between OCS and RRSO. Our objective was to investigate the effect of stopping OCS on the timing and uptake of RRSO and on the percentage of occult cancers found in the RRSO specimens.

Methods

Study design and patients

A prospective cohort design was used to investigate the effect of stopping OCS on the timing and uptake of RRSO and on the percentage of occult cancers found in the RRSO specimens. This study was performed in *BRCA1/2* mutation carriers who visited the family cancer clinic at least once between 1999 and June 2013. All the women who visited the family cancer clinic in this time period were asked for informed consent before entering their data into the prospectively maintained, password protected family cancer clinic database. Protection of the patient's identity was guaranteed by assigning study-specific, unique patient numbers. According to Dutch law, no further Institutional Review Board approval was needed for our study.

Setting

Women at increased risk for hereditary ovarian and/or breast cancer are referred to the family cancer clinic of the University Medical Center Groningen for genetic risk assessment²². Proven *BRCA1/2* mutation carriers are then followed-up at the family cancer clinic, which consists of a multidisciplinary team including gynecological oncologists, surgical oncologists, clinical geneticists, plastic surgeons, nurse practitioners and psychologists who offer integrated care²².

Change in ovarian risk managing protocol

All *BRCA1/2* mutation carriers receive standardized counseling about the increased ovarian cancer risk, first from a clinical geneticist in the course of DNA testing, and subsequently from a gynecological oncologist at the family cancer clinic²². Before October 1, 2009 (period I) women were offered OCS (consisting of an annual gynecological exam, transvaginal ultrasound and CA125 testing from the age of 35 years onwards) or RRSO from the age of 35 to 40 years for *BRCA1* mutation carriers and 40 to 45 years *BRCA2* mutation carriers, given that they had completed their child-bearing^{22,23}. Starting October 1, 2009 (period II) our family cancer clinic stopped offering OCS because of its proven ineffectiveness in reducing morbidity and mortality of ovarian cancer²⁻⁵. In period II, RRSO was the only risk management option advised for all *BRCA1/2* mutation carriers^{22,23}, advice that was combined with information addressing the consequences of acute menopause after RRSO²². The waiting time for surgery remained stable during the follow-up time of this study, approximately three to six weeks.

Data collection

The following data were collected for each patient: date of birth, number of children, personal history of breast cancer, mother and/or sisters with breast and/or ovarian cancer, mutation status (*BRCA1* or 2), date on which DNA test results were received by the patient, chosen ovarian cancer risk management option (RRSO or no RRSO), date of RRSO and outcome of the RRSO specimen. Age, mutation status and medical history were retrieved from the prospectively maintained family cancer clinic database. When the aforementioned variables were missing in the family cancer clinic database, they were retrieved from the patient's medical records. Family history, number of children and date on which DNA test results were received were always retrieved from the patient's medical records. Data was retrieved from the prospective family cancer clinic database and patient medical records in July 2013. The number of children was grouped into one child or less and two or more children to ensure equal group sizes. Age at the time of DNA test result disclosure was stratified on the basis of whether a woman had or had not reached the recommended age for RRSO. The recommended age range was defined as 35 to 40 years for *BRCA1* mutation carriers and 40 to 45 years for *BRCA2* mutation carriers.

Statistical analysis

Follow-up time was calculated as the time interval between DNA test result disclosure and the date at the last follow-up or, in the case of RRSO, date of surgery. Women who received their DNA test results in period I were compared to women who received their DNA test results in period II in terms of cumulative uptake of RRSO.

Multivariable survival analyses were performed to estimate hazard ratios (HRs) and related 95% confidence intervals (95% CIs) that could be used to assess if the period in which patients received their DNA test results (i.e. period I or period II) was independently associated with the interval between DNA test result disclosure and RRSO. All tests were performed in SPSS Statistics 20 package and all p-values were two-tailed and considered statistically significant if $p \leq 0.05$.

Results

Population

Between January 1999 and June 2013, 541 *BRCA1/2* mutation carriers visited the family cancer clinic at least once. Of these, 24 (4.4%) women had already undergone bilateral salpingo-oophorectomy (for any reason) and 12 (2.2%) women had developed ovarian cancer before the date of receiving DNA test results. In total, 84 (15.5%) patient files were either unavailable ($n=38$, 7.0%) or incomplete ($n=46$, 8.5%). Two (0.4%) women were unable to make their own decisions due to a mental incapacity and were excluded from the analysis. A final total of 419 (77.5%) women were included in our analyses. The women excluded did not statistically significantly differ from the women included in the study in terms of mutation status (*BRCA1* or *BRCA2*) or having a personal history of breast cancer.

A total of 319 women received their DNA result in period I and 100 women received it in period II (Table 4.1). In period I, 35% ($N=113$) of the women had a *BRCA2* mutation, whereas in period II, 55% ($N=55$) of the women had *BRCA2* mutation.

The follow-up time (time from receiving DNA test results to RRSO or last follow-up) ranged from zero to 174 months, with a median follow up time of six months. In period I, the follow up time ranged from zero to 174 months (median eight months) with a median time to RRSO of eight months. In period II, the follow up time ranged from zero to 37 months (median three months) with a median time to RRSO of four months.

Table 4.1. Characteristics of the study population at the time they received DNA test results in period I and period II (n=419)

Patient characteristics	Frequencies or mean values	
	Period I [#] (n = 319)	Period II [#] (n = 100)
Age, mean (SD) (range)	39.2 (10.5) (19-71)	39.4 (10.0) (23-60)
Mutation status, n (%)		
BRCA1	206 (65)	45 (45)
BRCA2	113 (35)	55 (55)
Number of children, n (%)		
0-1	124 (39)	43 (43)
≥ 2	195 (61)	57 (57)
Mother with BC*, n (%)		
No	206 (65)	62 (62)
Yes	113 (35)	38 (38)
Sister with BC*, n (%)		
No	237 (74)	84 (84)
Yes	82 (26)	16 (16)
Mother with OC**, n (%)		
No	260 (82)	85 (85)
Yes	59 (18)	15 (15)
Sister with OC**, n (%)		
No	293 (92)	97 (97)
Yes	26 (8)	3 (3)
Personal history of BC*, n (%)		
No	233 (73)	81 (81)
Yes	86 (27)	19 (19)
Follow-up time in months, median (range)	8 (0-174)	3 (0-37)

* BC: breast cancer **OC: ovarian cancer

#: Period I: Before 1/10/2009, (OCS offered),

Period II: After or at 1/10/2009. (OCS not offered any more)

Uptake of RRSO

In period I, the overall cumulative uptake of RRSO within 12 months after DNA test result disclosure was 53% and this increased to 85% in period II (Table 4.2). The cumulative uptake for women with two children or more increased from 66% to 97% and the uptake for women who reached the recommended age increased from 77% to 91%.

Timing of RRSO

Out of the 419 women in this study, 322 women had either not yet reached the recommended age range for RRSO or were already past this age at the time they received their DNA test result. The remaining 97 women were under follow-up during the recommended age range for RRSO. Out of these women, 81% (61/75) underwent RRSO within the recommended age range in period I. This percentage increased to 95% (21/22) in period II (Table 4.3).

Table 4.2. Cumulative uptake of RRSO 12 months after DNA test result disclosure for two groups: women who received their DNA test results in period I or in period II (n=419)

Patient characteristics	Cumulative uptake of RRSO 12 months after receiving DNA test results	
	Period I# (%)	Period II# (%)
Overall	53	85
Reached recommended age ^x		
No	13	56
Yes	77	91
Mutation status		
BRCA1	51	79
BRCA2	59	89
Number of children		
0-1	31	59
≥ 2	66	97
Mother with BC*		
No	59	91
Yes	45	72
Sister with BC*		
No	45	83
Yes	75	91
Mother with OC**		
No	55	85
Yes	49	81
Sister with OC**		
No	51	84
Yes	81	100
Personal history of BC*		
No	49	83
Yes	67	91

^x: The recommended age range for BRCA1 and BRCA2 mutation carriers is from 35 to 40 years and from 40 to 45 years, respectively.

[#]: Period I: Before 1/10/2009, (OCS offered),
Period II: On or after 1/10/2009, (OCS no longer offered)

* BC: breast cancer **OC: ovarian cancer

A shorter interval between receiving DNA test results and RRSO was independently associated with receiving DNA test results in period II (HR = 2.48, 95%CI = 1.81-3.39), with having reached the recommended age for RRSO (HR = 4.27, 95%CI = 3.12-5.84) and with having two or more children (HR = 2.00, 95%CI = 1.51-2.65) (Table 4.4). Mutation status, a mother with breast or ovarian cancer, a sister with breast or ovarian cancer, and a personal history of breast cancer were not independently statistically significantly associated with a shorter interval between receiving DNA test results and RRSO in the multivariable analysis.

Table 4.3. Uptake of RRSO within the recommended age range^x in women who were under follow-up within the recommended age range in period I and II (N=97)

	Period I [#] (n=75)	Period II [#] (n=22)
RRSO within recommended age range ^x , n (%)		
No	14 (19)	1 (5)
Yes	61 (81)	21 (95)

^x: The recommended age range for *BRCA1* and *BRCA2* mutation carriers is from 35 to 40 years and from 40 to 45 years, respectively.

[#]: Period I: Before 1/10/2009, (OCS and RRSO offered),
Period II: On or after 1/10/2009. (OCS no longer offered)

Table 4.4. Analysis of the predictors of the time interval between receiving DNA test results and the date of RRSO (multivariable survival analysis) (N=419)

	Multivariable survival analysis	
	HR	95% CI
Reached recommended age ^x		
No	1	
Yes	4.27+	3.12-5.84
Number of children		
0-1	1	
≥ 2	2.00+	1.51-2.65
Period of receiving DNA test results		
Period I [#]	1	
Period II [#]	2.48+	1.81-3.39

^x: The recommended age range for *BRCA1* and *BRCA2* mutation carriers is from 35 to 40 years and from 40 to 45 years, respectively.

⁺: p<0.01;

[#]: Period I: Before 1/10/2009, (OCS and RRSO offered),
Period II: On or after 1/10/2009. (OCS no longer offered)

Outcomes of RRSO specimens

During period I, three occult cancers were recorded in 220 RRSO specimens (1.3%) (Table 4.5). All cases concerned *BRCA1* mutation carriers ranging from 41 to 60 years of age. After staging, two ovarian cancer cases, FIGO stage IIC and IIIB and one fallopian tube cancer case, FIGO stage IC were found. During period II, one occult cancer was recorded in 54 RRSO specimens (1.8%). This case concerned a serous tubal intraepithelial carcinoma (STIC) in a *BRCA2* mutation carrier aged 57 years.

Discussion

The objective of this study was to investigate the effect of stopping OCS on the timing and uptake of RRSO and on the percentage of occult cancers found in the RRSO specimens. We found that after stopping OCS the percentage of women who underwent RRSO within the recommended age range increased from 81 to 95%. Only one woman did not perform RRSO within the recommended age range in period II. This concerned a *BRCA1* mutation

Table 4.5. Outcomes of RRSO specimen (n = 274/419†)

	Frequencies or mean values	
	Period I# (n = 220/319‡)	Period II# (n = 54/100‡)
Histopathology, n (%)		
Benign	217 (98.7)	53 (98.2)
Malignant	3 (1.3)	1 (1.8)
FIGO stage, age, mutation	- IC, 60y, <i>BRCA1</i> - IIIB, 44y, <i>BRCA1</i> - IIC, 41y, <i>BRCA1</i>	- STIC*, 57y, <i>BRCA2</i>

†: Out of 419 cases, 274 women chose RRSO. The number of RRSOs divided by the total population in each period does not give the same percentages as mentioned in table 4.2, because table 4.2 shows cumulative percentages. Furthermore, the number of RRSOs is lower in period II due to a shorter follow-up time.

#: Period I: Before 1/10/2009, (OCS and RRSO were offered),

Period II: On or after 1/10/2009. (OCS no longer offered)

*: STIC: Serous Tubal Intraepithelial Carcinoma

carrier who received her DNA test results at the age of 39 years and performed RRSO two years later at the age of 41 years. Before stopping OCS, the overall cumulative uptake of RRSO of all *BRCA1/2* mutation carriers (before, at and beyond the recommended age range) within one year after receiving DNA test results was 53%. This is in agreement with the reported range of RRSO uptake that varies internationally between 34.9% and 73.5%²⁴. After stopping OCS, the overall cumulative uptake of all *BRCA1/2* mutation carriers within one year after DNA test result disclosure increased to 85%, which signifies a very high acceptance of RRSO as a risk management option in our total *BRCA1/2* mutation carrier population.

Furthermore, our findings suggest that stopping OCS was related to a shorter interval between DNA test result disclosure and RRSO. This association was found to be independent of the known associations with age and/or having children^{18–21}. It is plausible that the increased uptake and more adequate timing of RRSO in period II is caused by the unequivocal advice by clinicians in favor of RRSO and the increased awareness of OCS ineffectiveness in our *BRCA1/2* mutation carrier population. This is supported by a qualitative study that found that clinicians' advice was a key factor in the decision to undergo RRSO and that awareness of OCS ineffectiveness was a secondary factor in this decision²⁵. This was also previously suggested by others who indicated that worries about effectiveness of OCS was a factor in the decision for RRSO^{26,27}.

The reported data on the outcomes of the RRSO specimens is an extension of an earlier dataset used in a study concerning the histopathology of RRSO specimens at our family cancer clinic till March 2012²⁸. We report one additional occult cancer case. Our current study analyzed the percentage of occult cancers in *BRCA1/2* mutation carriers before and after stopping OCS, which was 1.3% and 1.8% respectively. The percentages were

not statistically significantly different and remains low in our centre compared to other studies which reported occult cancer percentages from 2% to 12%^{5,29,30}.

In addition to stopping OCS, having reached the recommended age for RRSO and having two or more children were also related to a shorter interval between receiving DNA test results and RRSO. This is in agreement with four time-to-event studies that also found having children and/or age as related factors¹⁸⁻²¹. One study found an independent association between a personal history of breast cancer and a shorter time between receiving DNA test results and RRSO¹⁸, an association that we were unable to confirm. A possible explanation for the different outcome of this study could be that it was conducted in a population of high-risk women with only 26% proven *BRCA1/2* mutation carriers¹⁸. The motivations for undergoing RRSO may differ in a non-proven high-risk population.

Another time-to-event study in a population of proven *BRCA1/2* mutation carriers also found no association between a personal history of breast cancer and a shorter time between receiving DNA test results and RRSO²¹. In agreement with our study, this study also found no association between a family history of breast and/or ovarian cancer and a shorter interval between receiving DNA test results and RRSO²¹.

To the best of our knowledge our study is the first to investigate the effect of stopping OCS on the timing and uptake of RRSO and outcomes of RRSO specimens in a large consecutive series of proven *BRCA1/2* mutation carriers from one family cancer clinic. Furthermore, the majority of the data has been collected prospectively and our study has the longest follow-up period compared to other time-to-event studies.

Our study does not account for other possible changes in factors influencing the uptake and timing of RRSO. For example, a factor that could have influenced the timing of RRSO is the waiting time for surgery. However, the waiting time remained stable during the follow-up period of our study. The fact that our study is quantitative in nature is both a strength and a limitation, because qualitative information on patients' underlying motives for RRSO is not included.

When changing a clinical guideline it is important to establish its effect on clinical practice. Increasing the uptake of RRSO as soon as possible after receiving DNA test results is not an end in itself, however undergoing RRSO within the recommended age range is vital for its effectiveness in preventing *BRCA1/2*-mutation-related ovarian cancer¹². The way in which risk-management options were presented to women and the increased patient awareness of the ineffectiveness of OCS may have influenced the decision making process. It is a reassuring finding that after stopping OCS we did not find a deferral of surgery. Contrarily, a larger percentage of women chose to undergo RRSO within the recommended age range.

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Part II

Psychological interventions alleviating menopausal symptoms after RRSO



Chapter 5

Severity and duration of menopausal symptoms
after risk-reducing salpingo-oophorectomy



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Introduction: To reduce the risk of ovarian cancer, women with BRCA1/2 mutations are advised to undergo risk-reducing salpingo-oophorectomy (RRSO) at premenopausal age. Premenopausal RRSO results in acute menopause and is associated with various menopausal symptoms. This study investigates the severity and duration of subjective menopausal symptoms after premenopausal RRSO and associated factors.

Methods: We included 199 women who underwent RRSO before age 52 in this cross-sectional study. The Menopause Rating Scale (MRS) was used to measure the level of psychological, somato-vegetative and urogenital symptoms (no/little, mild, moderate, or severe). Uni- and multivariate logistic regression were performed to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for having moderate or severe symptoms as compared to having no or mild symptoms. Duration of symptoms was investigated by calculating the time since RRSO.

Results: Sixty-nine percent (137/199) of the included women reported moderate or severe symptoms on the MRS, 7.9 years (mean) after RRSO. Fifty-seven percent (94/137) of the women reported severe urogenital symptoms, and about one quarter reported severe psychological and/or somato-vegetative symptoms. Only psychological symptoms tended to improve over time (≥ 10 years). A personal history of breast cancer was independently associated with having moderate or severe menopausal symptoms (OR=3.4; 95%CI=1.6-7.1).

Conclusion: The majority of women report moderate or severe menopausal symptoms, even 10 years after surgical menopause, in particular breast cancer survivors. To improve quality of life, follow-up care after RRSO should focus on these symptoms and be accessible for many years after RRSO.

Introduction

The lifetime risk for women with a *BRCA1* mutation to develop ovarian cancer by age 70 has been estimated at 59% (95%CI = 43-76%) and for women with a *BRCA2* mutation at 16.5% (95%CI = 7.5-34%)¹. These risks are considerably higher than the lifetime risk of 1.4% in the general population². In addition, the prognosis of ovarian cancer is poor, with a 5-year survival rate of 46.2%². Ovarian screening is not effective in detecting cancer in an early and curable stage³, and at present risk-reducing salpingo-oophorectomy (RRSO) is considered the only effective option to reduce the risk of dying from ovarian cancer⁴. If performed within the recommended age ranges, RRSO can reduce ovarian cancer mortality with 95% and overall mortality with 76%^{5,6}.

Women with a *BRCA1* mutation are offered RRSO at the age of 35-40 years and those with a *BRCA2* mutation at 40-45 years, provided child wish is fulfilled⁷. These age-ranges are ascertained from European and American guidelines and were identified as such because the incidence of ovarian cancer is expected to rise after those ages^{3,4}. RRSO at premenopausal age will result in acute menopause and is likely to be associated with vasomotor and sexual symptoms, such as hot flashes, night sweats, vaginal dryness, loss of sexual interest and dyspareunia, which may lead to a decrease in quality of life⁸⁻¹¹. Hormone replacement therapy (HRT) can alleviate the severity of menopausal symptoms, although it seems to have a modest effect on sexual symptoms and vasomotor symptom levels remain above a premenopausal level¹².

There is a large variety in reported severity and duration of menopausal symptoms, and literature on predictors are scarce, especially regarding surgical menopause¹³. The aim of this study was to evaluate the severity and duration of menopausal symptoms in women after premenopausal RRSO and to find factors associated with the severity and duration of these symptoms. With this knowledge, we aim to improve individual pre- and post-surgery counselling regarding expected severity and duration of menopausal symptoms for women who opt for RRSO. Furthermore, to improve quality of life, we will be able to target additional interventions at women who are expected to experience severe menopausal symptoms after RRSO.

Methods

Post-RRSO guidelines in the Netherlands

In accordance with the Dutch national guideline, women in the Netherlands are offered RRSO without hysterectomy⁷. Hormone replacement therapy is prescribed to all women who are premenopausal at the time of RRSO, preferably tibolone, because this does not increase mammographic breast density. Women who have had a preventive mastectomy

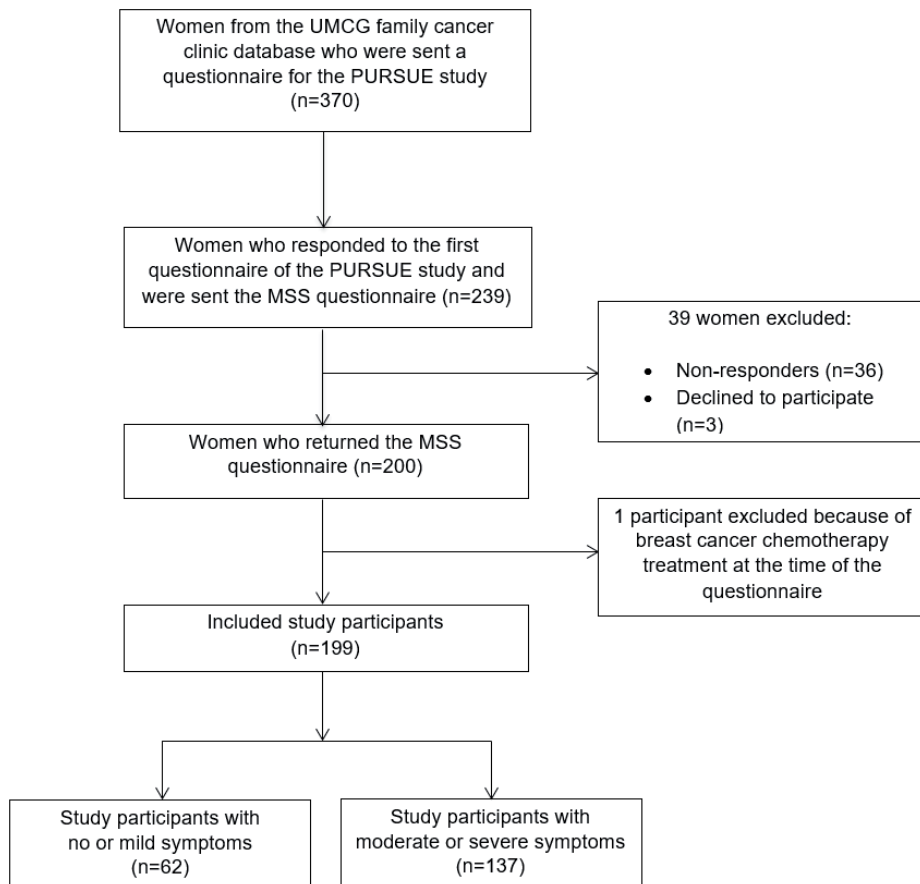
are offered continuously combined hormone replacement therapy. If women suffer from vaginal symptoms, vaginal estriol is prescribed, which may be combined with tibolone in some occasions. For reducing hot flushes in breast cancer survivors, venlafaxine and clonidine are prescribed, which are moderately effective¹⁴, and vaginal estriol is prescribed to these women for vaginal symptoms⁷.

Study design and population

Women included in this cross-sectional study had undergone RRSO, for which they were counseled or treated in the UMCG¹⁵. These women were recruited in the baseline assessment of the PURSUE study (psychosexual consequences of risk reducing salpingo-oophorectomy), a study investigating the effect of mindfulness-based stress reduction training on the experienced severity of menopausal symptoms [NCT02372864]. Women invited to participate in the PURSUE study had undergone RRSO and were younger than 52 years at the time of RRSO. Women were excluded if they suffered from severe psychiatric illness or active cancer at the time of inclusion (current cancer treatment or diagnostic signs of cancer), if they had insufficient understanding of the Dutch language or if they were younger than 18 years. We did not exclude women with a history of breast cancer, nor did we exclude women using HRT or women who had undergone a hysterectomy.

For the PURSUE study, eligible women were sent an information letter, a purpose-designed screening questionnaire about the severity and frequency of menopausal symptoms and an informed consent form. Women were asked to return the questionnaire on menopausal symptoms, regardless of their willingness to participate in the randomized controlled PURSUE trial. All women who returned the PURSUE questionnaire on menopausal symptoms, were asked to participate in the current study. For the current study, an additional Menopausal Symptoms Study (MSS) questionnaire and consent form were sent. There was no advantage for women who returned the questionnaire, which reduced the influence of non-response bias.

Recruitment for the current study took place from November 2015 until December 2016. A number of 239 women from the UMCG family cancer clinic returned the first PURSUE questionnaire and received the additional MSS questionnaire and consent form. Of those women, 200 returned the MSS questionnaire and 199 were included in the analyses of this study. A patient inclusion flow chart is presented in Figure 5.1. The Medical Ethical Committee of the University Medical Center Groningen accepted the protocol for the PURSUE study and the amendment to include the current study. Protection of the patients' identity was guaranteed by assigning study-specific, unique patient numbers.

Figure 5.1: Flowchart of study participants**Data collection**

Information on current age, date of RRSO, menopausal status at the time of RRSO, *BRCA1/2* mutation status and breast cancer history was collected from the screening-questionnaire of the PURSUE study. Menopausal status at the time of RRSO was asked because menopausal status could have changed due to breast cancer treatment.

The additional MSS questionnaire contained questions regarding current length and weight, smoking/drinking habits, physical activity and the use of menopausal medication. Additionally, the Menopause Rating Scale (MRS) was included in the questionnaire to measure the level of menopausal symptoms, which has good reliability and validity, excellent applicability and sufficient repeatability^{16,17}.

The MRS lists eleven symptoms that can be rated on a five-point Likert-type scale. The questionnaire consists of three subscales: psychological symptoms, somato-vegetative symptoms and urogenital symptoms. In the *psychological subscale*, depressive mood, irritability, anxiety and physical and mental exhaustion are rated. In the *somato-vegetative subscale*, hot flushes and sweating, heart discomfort, sleep problems and joint and muscular discomfort are rated. In the *urogenital subscale*, sexual problems, bladder problems and vaginal dryness are rated. Symptoms can be rated from 0 (no symptoms) to 4 (severe symptoms), leading to a maximum score of 44 points. The measured level of menopausal symptoms overall and the level of psychological, somato-vegetative and urogenital symptoms can be described as no/little, mild, moderate or severe. The allocation of scores per subscale is presented in Table 5.1.

Data on breast cancer treatment (chemotherapy, hormone therapy, radiotherapy and immunotherapy) was collected retrospectively from patient files. Data on duration of menopausal symptoms was analyzed by calculating time since RRSO.

Table 5.1: The symptom severity scores of the MRS: subscales and total

Symptom severity	Psychological subscale (4 items)	Somato-vegetative subscale (4 items)	Urogenital subscale (3 items)	MRS total (11 items)
No, little	0-1	0-2	0	0-4
Mild	2-3	3-4	1	5-8
Moderate	4-6	5-8	2-3	9-16
Severe	≥7	≥9	≥4	≥17
Maximum total	16	16	12	44

Statistical analysis

Characteristics were described for all women, and separately for women with no or mild symptoms (≤ 8 points on the MRS) and moderate or severe symptoms (≥ 9 points on the MRS)¹⁸. Being physically active was defined as exercising 5 days a week for 30 minutes or more, which is derived from the Dutch advice on physical activity and in line with international recommendations^{19,20}. The questionnaire was generally well completed, with fewer than 0.5% missing data. Missing values were replaced by mean imputation. The highest percentage of missing data was 18% per questionnaire (2/11 questions) and 4.5% per question (9/199 questionnaires). To describe the duration of menopausal symptoms, the proportion of women reporting no/little, mild, moderate or severe symptoms was calculated at different time points after RRSO (0-1 year, 2-3 years, 4-5 years, 6-10 years and ≥ 10 years).

Univariate logistic regression and multivariate logistic regression analyses were performed to identify factors associated with having moderate or severe symptoms as compared to having no or mild symptoms. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs), with the severity of menopausal symptoms overall (no or mild versus moderate or severe symptoms) considered as the dependent variable. A sensitivity analysis was performed in which all current HRT-users were excluded from the analysis. All analyses were performed with IBM SPSS version 23 (IBM Corp., Armonk, NY, USA). P-values were considered significant if $p < 0.05$.

Results

Patient characteristics

In Table 5.2 the patient characteristics are displayed. The mean age at the time of filling in the questionnaire was 50.5 years \pm 6.7. A total of 68/199 (34.2%) women had a personal history of breast cancer. Eighty-one (40.7%) women had a history of HRT use and 48 (24.5%) women were current HRT users at the time of filling in the questionnaire.

Severity of menopausal symptoms per subscale

In Table 5.3 the level of menopausal symptoms is displayed per subscale. According to the MRS scores, 27 women (13.6%) experienced no/little symptoms, 35 (17.6%) mild symptoms, 76 (38.2%) moderate symptoms and 61 (30.7%) severe symptoms after a mean of 7.9 years \pm 4.8 after RRSO (median 7.9 years, range 0.4-20.2). Severe symptoms were reported mostly in the urogenital domain, by 103 women (51.8%).

Table 5.2: Patient characteristics

Characteristics	All women	Women reporting no or mild symptoms (MRS total ≤8)	Women reporting moderate or severe symptoms (MRS total ≥9)
Number of women	N = 199	N = 62	N= 137
Current age in years, mean (SD)	50.5 (6.7)	50.9 (6.3)	50.3 (6.8)
Age at time of RRSO in years, mean (SD)	42.5 (4.9)	42.8 (4.8)	42.4 (5.0)
Time since RRSO at time of MRS in years, mean (SD)	7.9 (4.8)	8.0 (5.3)	7.9 (4.6)
Mutation status, n (% of total)			
<i>BRCA1</i>	102 (51.3)	37 (59.7)	65 (47.4)
<i>BRCA2</i>	66 (33.2)	18 (29.0)	48 (35.0)
Unknown	31 (15.6)	7 (11.3)	24 (17.5)
Menopausal status at time of RRSO, n (% of total)			
Premenopausal	134 (67.7)	48 (75.0)	86 (64.2)
Postmenopausal	35 (17.7)	10 (15.6)	25 (18.7)
Unknown	29 (14.6)	6 (9.4)	23 (17.2)
Ever HRT use, n (% of total)	81 (40.7)	29 (46.8)	52 (38.0)
Current HRT use, n (% of total)	48 (24.5)	22 (35.5)	26 (19.4)
Breast cancer history, n (% of total)	68 (34.2)	10 (16.1)	58 (42.3)
Time since last BC diagnosis, mean (SD) (n=68)	10.5 (7.3)	8.4 (4.7)	10.9 (7.7)
Breast cancer treatment, n (% of total) (n=68)			
Chemotherapy	47 (23.6)	8 (12.9)	39 (28.5)
Radiotherapy	41 (20.6)	9 (14.5)	32 (23.4)
Endocrine therapy	22 (11.1)	3 (4.8)	19 (13.9)
Body Mass Index, n (% of total)			
BMI ≤ 20	3 (1.5)	1 (1.7)	2 (1.5)
BMI 20-25	111 (56.6)	35 (58.3)	76 (55.9)
BMI ≥ 25	82 (41.89)	24 (40.0)	58 (42.6)
Physical activity: > 30 minutes a day active, n (% of total)			
0-4 days a week	76 (38.4)	22 (35.5)	54 (39.7)
≥ 5 days a week	122 (61.6)	40 (64.5)	82 (60.3)
Alcohol consumption, n (% of total)			
0-6 glasses a week	178 (89.9)	53 (86.9)	125 (91.2)
≥ 7 glasses a week	20 (10.1)	8 (13.1)	12 (8.8)
Smoking, n (% of total)			
No	173 (87.4)	56 (90.3)	117 (86.0)
Yes	25 (12.6)	6 (9.7)	19 (14.0)
Hours of work outside the house per week, n (% of total)			
0	36 (18.1)	10 (16.1)	26 (19.0)
1-23	60 (30.2)	19 (30.6)	41 (29.9)
24-40	103 (51.7)	33 (53.2)	70 (51.1)

BC: Breast cancer

HRT: Hormone replacement therapy

MRS: Menopause rating scale

RRSO: Risk reducing salpingo-oophorectomy

* Numbers do not add up to the total number of women due to missing data

Table 5.3: Frequency of menopausal symptoms per domain of the MRS (n=199)

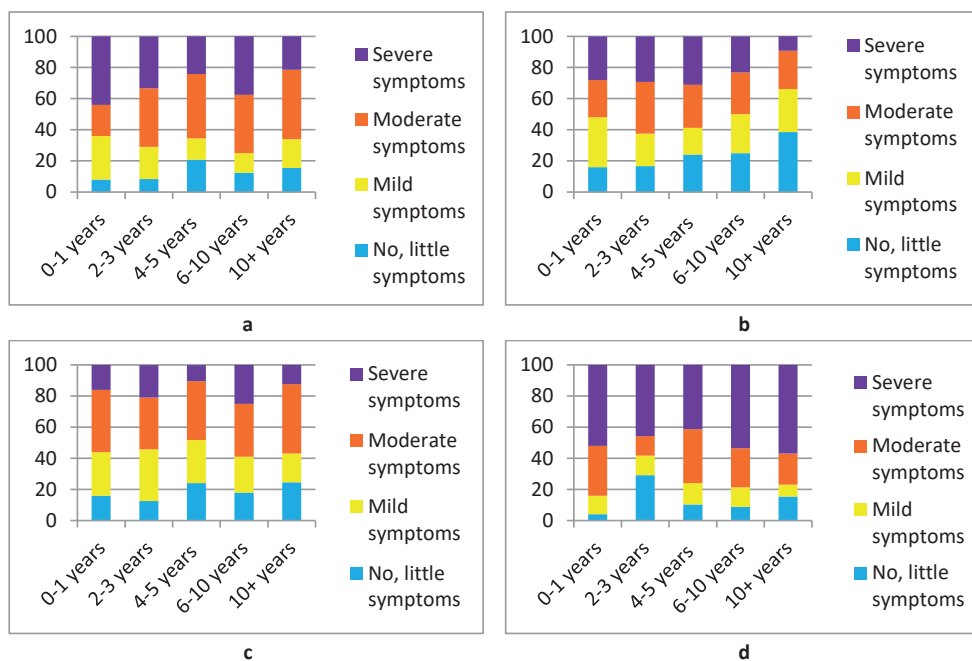
Domain	Frequency, % of total (n) (n=199)	Frequency of women with no or mild symptoms (n=62)	Frequency of women with moderate or severe symptoms (n=137)
Total MRS score			
No, little (0-4)	13.6 (27)	43.5 (27)	0 (0)
Mild (5-8)	17.6 (35)	56.5 (35)	0 (0)
Moderate (9-16)	38.2 (76)	0 (0)	55.5 (76)
Severe (≥ 17)	30.7 (61)	0 (0)	44.5 (61)
Psychological domain			
No, little (0-1)	27.1 (54)	62.9 (39)	10.9 (15)
Mild (2-3)	25.1 (50)	33.9 (21)	21.2 (29)
Moderate (4-6)	26.6 (53)	3.2 (2)	37.2 (51)
Severe (≥ 7)	21.1 (42)	0 (0)	30.7 (42)
Somato-vegetative domain			
No, little (0-2)	20.1 (40)	51.6 (32)	5.8 (8)
Mild (3-4)	24.1 (48)	37.1 (23)	18.2 (25)
Moderate (5-8)	38.7 (77)	11.4 (7)	51.1 (70)
Severe (≥ 9)	17.1 (34)	0 (0)	24.8 (34)
Urogenital domain			
No, little (0)	13.1 (26)	33.9 (21)	3.6 (5)
Mild (1)	11.1 (22)	21.0 (13)	6.6 (9)
Moderate (2-3)	24.1 (48)	30.6 (19)	21.2 (29)
Severe (≥ 4)	51.8 (103)	14.5 (9)	68.6 (94)

Duration and type of menopausal symptoms after RRSO

In Figure 5.2 the distribution of symptom levels at different time points in different domains is displayed. Twenty-five women filled in the questionnaire 0-1 year after RRSO, 24 women 2-3 years after RRSO, 29 women 4-5 years after RRSO, 56 women 6-10 years after RRSO and 65 women ≥ 10 years after RRSO. Overall symptom severity levels and somato-vegetative symptom levels were reported at similar levels by women at different time points after RRSO. Sixty-four percent of the women who had undergone RRSO 0-1 year ago reported moderate or severe menopausal symptoms, of the women who had undergone RRSO ≥ 10 years ago this was 66%. Psychological symptoms were reported more severe by women who had undergone RRSO more recently: 52% of the women who had undergone RRSO 0-1 year ago reported moderate or severe symptoms, for the women who had undergone RRSO ≥ 10 this was 39%. Urogenital symptoms were reported more severe by women who had undergone RRSO longer ago: at 0-1 years after RRSO 84% reported moderate or severe symptoms, and at ≥ 10 years after RRSO this was 87%.

Figure 5.2: Severity of symptoms at different time points after RRSO in total and per subdomain, expressed as the percentage of all women per time point ($n_{0-1\text{year}}=25$, $n_{2-3\text{years}}=24$, $n_{4-5\text{years}}=29$, $n_{6-10\text{years}}=56$, $n_{10+\text{years}}=65$)

a) The total score of the MRS (Severe symptoms: ≥ 17 points, Moderate symptoms: 9-16 points, Mild symptoms: 5-8 points, No, little symptoms: 0-4 points). b) Psychological subscale (Severe symptoms: ≥ 7 points, Moderate symptoms: 4-6 points, Mild symptoms: 2-3 points, No, little symptoms: 0-1 point). c) Somato-vegetative subscale (Severe symptoms: ≥ 9 points, Moderate symptoms: 5-8 points, Mild symptoms: 3-4 points, No, little symptoms: 0-2 points). d) Urogenital subscale (Severe symptoms: ≥ 4 points, Moderate symptoms: 2-3 points, Mild symptoms: 1 point, No, little symptoms: 0 points)



Uni- and multivariate logistic regression analyses of factors associated with moderate or severe menopausal symptoms

In Table 5.4 the univariate logistic regression analysis of factors associated with moderate or severe menopausal symptoms is displayed. In the univariate analysis, a personal history of breast cancer (OR = 3.8, 95% CI = 1.8-8.0) and having received breast cancer chemotherapy (OR = 2.8, 95% CI = 1.2-6.4) were statistically significantly associated with experiencing moderate or severe menopausal symptoms after RRSO. Current HRT-use was statistically significantly associated with experiencing no or mild menopausal symptoms (OR = 0.4, 95% CI = 0.2-0.8). When current HRT-users were excluded from the analysis, a personal history of breast cancer remained statistically significantly associated with moderate to severe symptoms after RRSO (OR = 3.0, 95% CI = 1.4-6.7). Chemotherapy was not statistically significantly associated with moderate or severe symptoms in this analysis. In the multivariate analysis, only a personal history of breast cancer was statistically significantly associated with experiencing moderate or severe menopausal symptoms after RRSO (OR = 3.4, 95% CI = 1.6-7.1, $p = 0.001$).

Table 5.4: Univariate logistic regression analysis of factors associated with the severity of menopausal symptoms after RRSO (n=199)

Variable	Odds ratio, all women (n=199) (95% CI)	P-value	Odds ratio, women using HRT excluded (n=118) (95% CI)	P-value
Time since RRSO				
≤ 2 years	1		1	
2-5 years	1.3 (0.4-3.8)	0.66	3.0 (0.6-15.4)	0.20
≥ 5 years	1.3 (0.5-3.1)	0.58	1.5 (0.5-4.7)	0.51
Menopausal status at RRSO				
Premenopausal				
Postmenopausal	1		1	
History of BC	1.3 (0.6-3.0)	0.52	1.2 (0.5-3.0)	0.63
No				
Yes	1		1	
BC chemotherapy	3.8 (1.8-8.0)	0.001 [^]	3.0 (1.4-6.7)	0.008 [^]
No				
Yes	1		1	
BC radiotherapy	2.8 (1.2-6.4)	0.015 [^]	2.1 (0.9-5.1)	0.09
No				
Yes	1		1	
HRT, current	1.9 (0.8-4.2)	0.13	1.5 (0.6-3.5)	0.36
No				
Yes	1		1	
Smoking, current	0.4 (0.2-0.8)	0.006 [^]		
No				
Yes	1		1	
BMI	1.5 (0.6-4.0)	0.40	1.1 (0.4-3.3)	0.84
< 25				
≥ 25	1		1	
Alcohol consumption	1.4 (0.7-2.5)	0.32	1.2 (0.6-2.6)	0.55
< 6 units per week				
≥ 6 units per week	1		1	
Physical activity, > 30 min. per day	0.6 (0.3-1.7)	0.35	1	
< 5 days per week			0.6 (0.1-2.9)	0.54
≥ 5 days per week	1		1	
Time since last BC diagnosis (n=63)	0.8 (0.5-1.6)	0.57	0.7 (0.3-1.5)	0.38
> 10 years				
≥ 10 years	1		1	
	0.5 (0.1-2.1)	0.35	0.5 (0.1-2.2)	0.32

BC: Breast cancer

BMI: Body mass index

HRT: Hormone replacement therapy

RRSO: Risk reducing salpingo-oophorectomy

[^] significant p-value

Discussion

This cross-sectional study including 199 women after RRSO at premenopausal age showed that a majority report moderate or severe menopausal symptoms, after a mean of 7.9 years after RRSO. A personal history of breast cancer was independently associated with moderate or severe menopausal symptoms after RRSO.

Roughly half of the women reported severe urogenital symptoms, such as dysuria, vaginal dryness, itching, burning and dyspareunia, caused by chronic estrogen deprivation after menopause¹⁸. However, the proportion, severity and duration we observed after surgical menopause was much higher than has been observed in natural induced menopausal women²¹. In a study investigating the severity of symptoms in natural induced menopausal women, only 29.3% of the women reported urogenital symptoms, of which 40.8% rated it as a moderate and 11.2% as a severe problem²². A study investigating changes in severity of menopausal symptoms in natural induced menopausal women showed that vaginal symptoms increase with time. In this study, 4% of the early perimenopausal women experienced vaginal dryness, compared to 47% of the women three years after menopause²³.

Psychological symptoms tended to decrease with time, as women reported more severe symptoms directly after RRSO compared to ≥ 10 years after RRSO. This is in agreement with findings from longitudinal studies in natural menopausal women^{24,25}. However, other authors did not find a decrease in psychological symptoms after (surgical) menopause, although they were unable to control for the effect of ageing^{26,27}. The exact explanation for these differences in findings remains unclear, although it is suggested that psychological symptoms might not be related to changing estrogen levels, rather to ageing, health status and social factors²⁸.

Hormone replacement therapy was not an independent determinant of severity of symptoms after RRSO in this study, which indicates that the symptom-reducing effect of HRT might be limited for some symptoms¹¹. In a study by Tucker et al., no differences were found in rates of female sexual dysfunction and hypoactive sexual desire disorder between groups who did and who did not use HRT²⁹. However, symptoms of dyspareunia and the overall severity of sexual symptoms could be improved with HRT. This corresponds with a study by Madalinska et al.¹¹, in which women who used HRT reported the same level of sexual symptoms compared to women who did not use HRT, specifically symptoms of vaginal dryness and dyspareunia.

In our study, an association was found between a history of breast cancer and the severity of menopausal symptoms after RRSO. Finch et al.⁹ could not find a significant difference

between breast cancer history and the level of vasomotor symptoms after surgery, although there was a significant difference in symptom levels before surgery. Nonetheless, women in their study were less likely to be sexually active before and after RRSO if they had a previous diagnosis of breast cancer. Therefore, it seems likely that a personal history of breast cancer may be associated with the overall severity of menopausal symptoms and the severity of sexual symptoms after RRSO, but that the level of vasomotor symptoms after RRSO may be unrelated to breast cancer history.

We found a univariate association between breast cancer chemotherapy and the experience of moderate or severe menopausal symptoms after RRSO. Other studies have shown that chemotherapy and adjuvant endocrine therapy for breast cancer (LHRH analogues, tamoxifen, aromatase inhibitors) can cause or worsen menopausal symptoms^{30,31}. Breast cancer chemotherapy may cause permanent or transient ovarian failure, dependent on age at treatment, dose and type of chemotherapy³². Additionally, adjuvant endocrine cancer therapy can cause or worsen menopausal and sexual symptoms as a side effect, although cessation of therapy leads to a reversal of complaints³⁰. In the current study we excluded women who were currently treated for cancer, therefore, only long-term effects of past endocrine and chemotherapy use could be tested, which were not independently associated with severity of menopausal symptoms after RRSO.

To the best of our knowledge, this is the first study to investigate the severity and duration of menopausal symptoms after premenopausal RRSO in different domains and at different time points with a follow-up and sample size this large. The main strengths of this study are the widely used and validated questionnaire with a reliable scoring system for menopausal symptoms, the long-term follow-up and the high response rate of 83%. A possible limitation of this study is that women who did not respond to the invitation for the PURSUE study, were not included in our sample. Women experiencing no or moderate symptoms might be less willing to fill in the questionnaire, which could have influenced our results. Another possible limitation of this study is that about 10% of the women included in our study were also included in the mindfulness arm of the PURSUE study, who had completed a mindfulness training before filling in the MSS. Therefore, the level of menopausal symptoms in our study might be underestimated. Another limitation is that causality and the development of symptoms over time cannot be established due to our cross-sectional design.

In conclusion, menopausal symptoms after surgical menopause by premenopausal RRSO are often moderate or severe and of long duration. Especially urogenital symptoms seem to be severe, and do not diminish over the years. Breast cancer survivors are at higher risk to experience moderate or severe menopausal symptoms after premenopausal RRSO. The results of this study indicate that follow-up care and interventions to alleviate menopausal

symptoms after RRSO should be accessible for more than 10 years after RRSO, particularly for breast cancer survivors. Further research is needed to investigate safe interventions targeted at women with severe menopausal symptoms who have a contraindication to use HRT.

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Chapter 6

Mindfulness, cognitive-behavioral and behavioral-based therapy
for natural and treatment-induced menopausal symptoms:
a systematic review and meta-analysis



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Introduction: During menopause women experience vasomotor and psychosexual symptoms that cannot entirely be alleviated with hormone replacement therapy (HRT). Besides, HRT is contraindicated after breast cancer. The aim was to review the evidence on the effectiveness of psychological interventions in reducing symptoms associated with menopause in natural or treatment-induced menopausal women.

Methods: Medline/Pubmed, PsycINFO, EMBASE and AMED were searched until June, 2017. Randomized controlled trials (RCTs) concerning natural or treatment-induced menopause, investigating mindfulness or (cognitive-)behavioral-based therapy were selected. Main outcomes were frequency of hot flushes, experienced bother by hot flushes, other menopausal symptoms and sexual functioning. Study selection and data extraction were performed by two independent researchers. A meta-analysis was done to calculate the standardized mean difference (SMD).

Results: Twelve RCTs were included. Short-term (<20wk) effects of psychological interventions in comparison to no treatment or control were observed for hot flush bother (SMD: -0.54, 95%CI: -0.74 to -0.35, $p < 0.001$, $I^2 = 18\%$) and menopausal symptoms (SMD: -0.34, 95%CI: -0.52 to -0.15, $p < 0.001$, $I^2 = 0\%$). Medium-term (≥ 20 wk) effects were observed for hot flush bother (SMD: -0.38, 95%CI: -0.58 to -0.18, $p < 0.001$, $I^2 = 16\%$). In the subgroup treatment-induced menopause, consisting of exclusively breast cancer populations, as well as in the subgroup natural menopause hot flush bother was reduced by psychological interventions. Too few studies reported on sexual functioning to perform a meta-analysis.

Conclusion: Psychological interventions reduced hot flush bother on the short and medium-term and menopausal symptoms on the short-term. These results are especially relevant for breast cancer survivors in whom HRT is contraindicated. There was a lack of studies reporting on the influence on sexual functioning.

Introduction

Menopause can occur either naturally or can be induced by treatments such as pelvic radiation, oophorectomy, endocrine therapy or chemotherapy^{1,2}. Menopausal symptoms are experienced frequently with up to 85% of menopausal women reporting vasomotor symptoms (i.e. hot flushes and night sweats), up to 60% reporting vaginal discomfort (i.e. vaginal dryness and/or dyspareunia), and up to 87% reporting sexual dysfunction (e.g. lack of sexual desire and difficulty reaching orgasm)³⁻⁵. Moreover, women who experience treatment-induced menopause report more severe symptom levels than women experiencing natural menopause^{6,7}.

To reduce the aforementioned symptoms, hormone replacement therapy (HRT) is currently the most effective option^{8,9}. However, the use of HRT in postmenopausal women is associated with increased breast cancer risk and contraindicated in breast cancer survivors^{10,11}. Furthermore, HRT only partially relieves symptoms, symptom levels remain higher than in premenopausal women and especially sexual discomfort is not alleviated¹². Therefore, safe non-hormonal alternatives to HRT are needed, in particular for breast cancer survivors such as young *BRCA1/2* mutation carriers after breast cancer and risk-reducing salpingo-oophorectomy.

Non-hormonal options to decrease the frequency and bother of hot flushes include stress-reducing psychological interventions such as cognitive behavioral therapy (CBT), behavioral therapy (BT) and mindfulness-based therapies (MBT)¹³. The possible mechanism of action of these interventions is that they reduce stress. Stress is thought to lower the threshold for heat dissipation responses^{14,15} and therefore can potentiate a hot flush¹⁶. It is proposed that CBT, BT and MBT diminish this trigger by reducing stress, thus reducing the frequency of hot flushes. An additional mechanism of action of the abovementioned interventions might be that by modifying cognitive appraisals of hot flushes, the bother caused by hot flushes can be decreased¹³.

Several large randomized controlled trials that were recently published have investigated the effect of CBT, MBT and BT on hot flushes and other menopausal symptoms¹⁷⁻²⁰. The aim of this systematic review and meta-analysis is to add a quantitative examination of the existing evidence on the effectiveness of psychological interventions in reducing symptoms associated with menopause in natural or treatment-induced menopausal women.

Methods

The conduct and reporting of this systematic literature review and meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement²¹. Firstly, studies were screened for eligibility based on their titles and abstract. Full texts of possibly eligible studies were retrieved after the initial screening for more detailed evaluation. Secondly, two review authors (CD and AS) independently performed a final selection of studies, assessed the risk of bias and extracted data from the full-text papers using a pre-specified form. The following data was extracted with the use of these forms: population (e.g. sample size, natural or treatment-induced menopause), intervention (e.g. type of intervention, duration, length of program), control group, co-interventions and outcomes (e.g. frequency and both of hot flushes, menopausal symptoms, sexual functioning and adverse effects). Of the outcomes the time points of measurement and results such as means and measure of variance were extracted.

Menopausal symptoms were defined as the combined level of burden by a broad range of symptoms related to menopause such as psychosocial symptoms (e.g. irritability, forgetfulness), physical symptoms (e.g. joint pain, headaches), genital symptoms (e.g. dryness, itching), sexual dysfunction and vasomotor symptoms.

Electronic databases that were searched are Medline/Pubmed, EMBASE, PsycINFO and AMED. Other search methods used were reference checking of selected studies and of existing reviews on adjacent topics. The initial search was conducted in February 2016 and an updated search was performed in June 2017.

Risk of bias was assessed with the risk of bias tool from the Cochrane collaboration²². Disagreements on inclusion of studies, extracted data or risk of bias assessments was solved by consensus between the two review authors (CD and AS). If consensus was not reached the other authors were consulted (GB, MS & MM). The protocol of this systematic literature review and meta-analysis is registered in the PROSPERO database (CRD42016038135).

Eligibility criteria

Studies considered eligible were RCTs with a published full-text in English evaluating the effect of CBT, BT or MBT on either naturally occurring or treatment-induced hot flushes, menopausal symptoms or sexual functioning as compared to a waiting list or to “care as usual” (e.g. lifestyle advice, breast cancer follow-up). Menopause did not have to be formally established (e.g. by amenorrhea > 12 months or laboratory tests), but could be based on patient-reported signs and symptoms of menopause. The intervention could either consist of group or individual therapy and could be a general program or could

be specifically tailored to symptoms associated with menopause. Only patient-reported outcomes were included.

Studies were excluded if interventions were limited to yoga, hypnosis, exercise, meditation, awareness training or breathing techniques as a stand-alone therapy, because these interventions were either not based on a stress-reducing mechanism of action or were not based on widely used protocolled standards. Studies were also excluded if there was no face-to-face therapeutic contact with a therapist or trainer during the study (e.g. web-based interventions). Use of HRT in the intervention and/or control group was allowed. However, studies that specifically aimed to use HRT as the control condition were excluded. Lastly, studies were excluded if the outcomes were physical measures (e.g. sternal skin conductance) only. The rationale behind favoring patient-reported outcomes over physical measures was that patient-reported hot flush frequency could be more closely related to actual inconvenience caused by hot flushes as patient-reported hot flush frequency measures the perceptual aspect, whereas physical measures assess the physiological aspect of the hot flush construct²³. Therefore we deemed patient-reported outcomes of more interest for clinical practice.

Statistical analysis

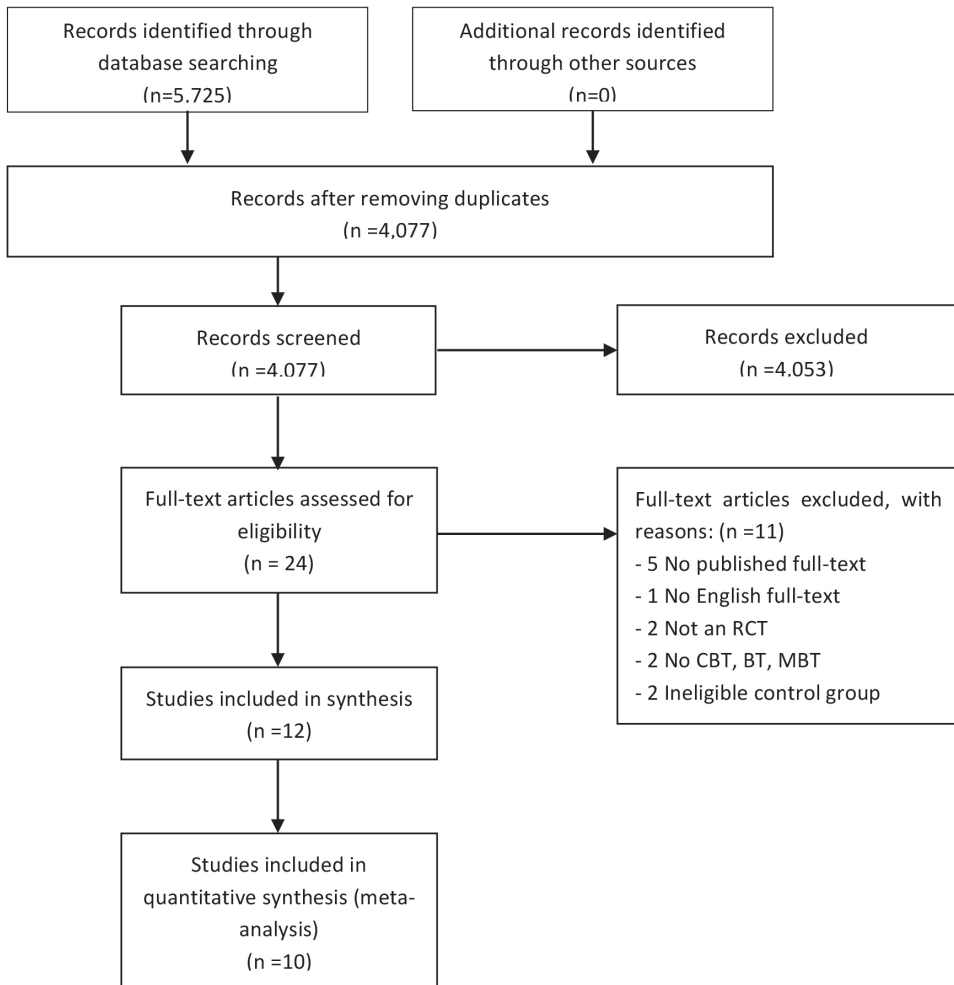
The following outcomes were considered at short-term (<20 weeks post randomization) and at medium-term (≥ 20 weeks post randomization): frequency and bother of hot flushes, menopausal symptoms and sexual functioning. A random effects meta-analysis using inverse variance method was performed. Using mean endpoints and standard deviations (SDs), per study a standardized mean difference (SMD) with a 95% confidence interval (CI) was calculated for all outcomes. Effect sizes were defined as small (0.2); medium (0.5) or large (0.8)²⁴. Heterogeneity was assessed per outcome with I^2 , χ^2 and p-value. Funnel plots were made to assess publication bias. Asymmetrical funnel plots indicate a higher risk of publication bias²². Asymmetry was assessed using Egger's test which was interpreted using a cut-off value of 0.10²⁵. As the effect of the interventions could differ for treatment-induced and natural menopausal symptoms, a subgroup analysis was performed for natural menopause versus treatment-induced menopause when two or more studies were available per subgroup for an outcome. All analyses were performed using Review manager (RevMan version 5.3.5.).

Results

Selection of studies

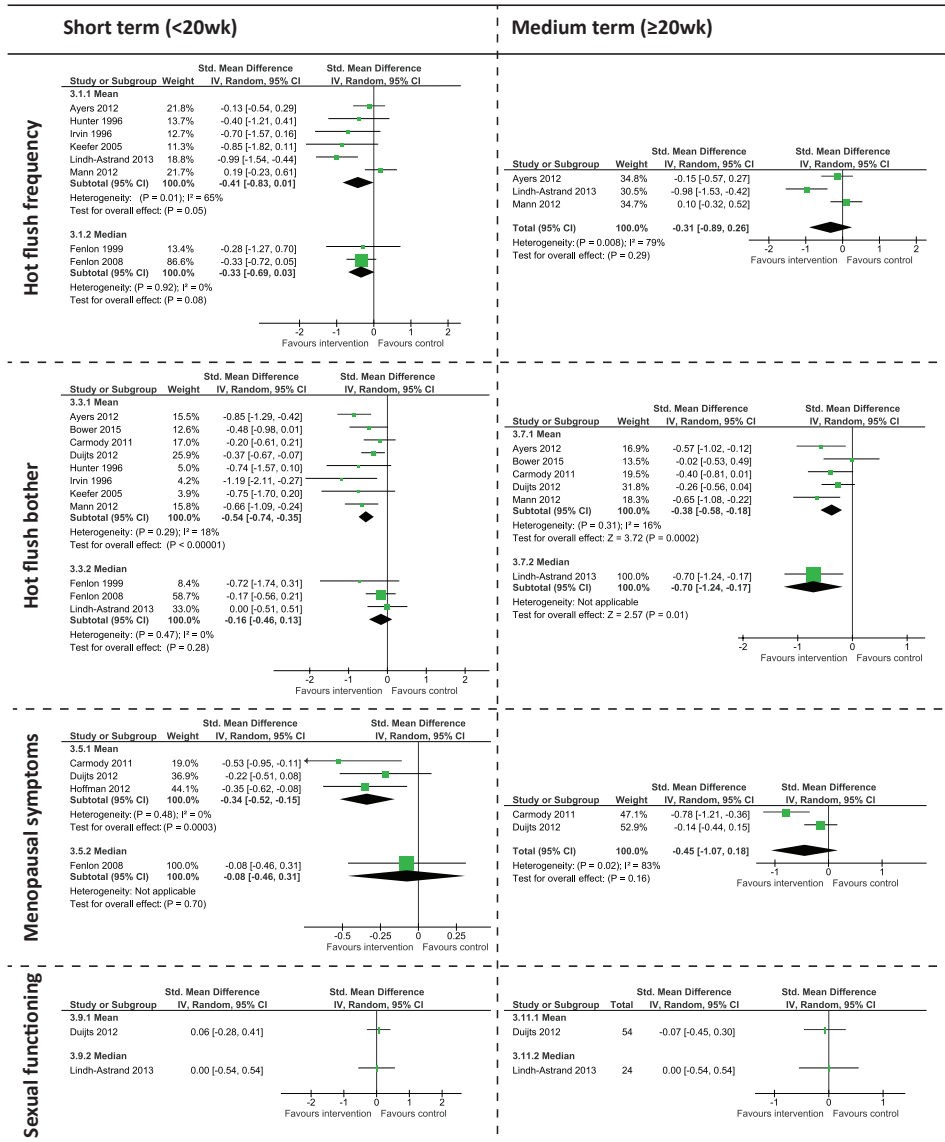
A flow diagram of the study selection is shown in Figure 6.1. Based on the title and abstract screening, 24 records were eligible for full-text assessment of which twelve records did not meet the eligibility criteria. So, the final number of included studies in the qualitative

Figure 6.1: Flow diagram of study selection



synthesis was twelve. Of the included studies, ten studies could be included in the main quantitative synthesis (meta-analysis), as two studies only reported medians because of possible skewness of the data^{26,27}. An overview of studies reporting medians compared to studies in the main meta-analysis is shown in Figure 6.2.

Figure 6.2: Forrest plot of hot flush frequency, hot flush bother, menopausal symptoms and sexual functioning for both short-term (<20 wk) and medium-term (≥20 wk) results, split for mean and median outcomes.



Std: standardized, SD: standard deviation, IV: inverse variance, CI: confidence interval

Characteristics of included studies

The total size of study population per study varied from 16 to 214 women (Table 6.1). The combined sample size of all studies consisting of participants in the control and intervention groups was 1,016 women. Six of the twelve included studies involved women whose symptoms were treatment-induced, all of which concerned breast cancer survivors^{17,19,26–29}. Three studies investigated the effect of MBT^{19,28,30}, five studies investigated CBT^{17,18,29,31,32} and four studies investigated BT^{20,26,27,33}. All studies, except three had a waiting list control group^{27,29,33}. One study had a “care as usual” control group²⁹ which consisted of breast cancer survivors during follow up with lifestyle advice on coping with hot flushes by a nurse specialist. The second study had a population of women experiencing natural menopause and had an active control group. The placebo activity in this case was individual leisure reading³³. The third study was conducted in breast cancer survivors and had an attention control group. The attention consisted of a general discussion of menopausal complaints with a nurse²⁷.

To measure hot flush frequency, the frequency subscale of the hot flush rating scale (HFRS scale) or similar diaries were used. Hot flush bother was most often measured by the HFRS subscale that measures bother by hot flushes (problem-rating, distress and interference). Menopausal symptoms were measured using the Functional Assessment of Cancer Therapy – Endocrine Therapy Scale (FACT-ES) and the Menopausal Quality of life scale (MENQOL). Both questionnaires contain psychosocial, physical, vaginal, sexual and vasomotor related items. Sexual activity was measured by the habit subscale of the Sexual Activity Questionnaire (SAQ) and sexual behavior subscale of the Women’s Health Questionnaire (WHQ).

Assessment of risk of bias

A high risk of performance bias was present for all studies, because blinding of CBT, BT and MBT-based interventions is not feasible. Consequently, the risk of detection bias was high as outcomes were patient-reported.

Meta-analysis of overall effect

A statistically significant benefit from psychological interventions was seen on short-term hot flush bother (SMD: -0.54, 95% CI: -0.74 to -0.35, $p < 0.001$), short-term menopausal symptoms (SMD: -0.34, 95% CI: -0.52 to -0.15, $p < 0.001$) and medium-term hot flush bother (SMD: -0.38, 95% CI: -0.58 to -0.18, $p < 0.001$) (Table 6.2). No statistically significant benefit from psychological interventions was seen on short-term hot flush frequency (SMD: -0.41, 95% CI: -0.83 to 0.01, $p = 0.05$) or medium-term hot flush frequency (SMD: -0.21, 95% CI: -0.89 to 0.26, $p = 0.29$). Heterogeneity was high for most outcomes. A meta-analysis of sexual functioning was not feasible because only two studies reported on this outcome^{17,20}.

Table 6.1: Table of study characteristics

Study author, year, study design, country	Population largest N analyzed, population type, mean age.	Intervention Type, Group or individual, program length, population tailored or general	Comparison	Outcomes measured concept, scale
Mindfulness-based intervention				
Bower et al., 2015. RCT	65, BC survivors Mean age: 47	MAP, Group 6x2hr, wkly Tailored	WLC	- HF/NS severity
Hoffman et al., 2012. RCT	214, BC survivors Mean age: 50	MBSR, Group 8x2hr, wkly + 2h General	WCL	- Menopausal symptoms
Carmody et al., 2011. RCT	92, peri/post-menopausal Mean age: 53	MBSR, Group 8x2.5hr, wkly General	WCL	- HF bother - HF intensity - Menopausal symptoms
Cognitive behavioral-based interventions				
Duijts et al., 2012. RCT	173, BC survivors Mean age: 48	CBT, Group 6x1.5hr, wkly Tailored	WLC	- Menopausal symptoms - HF/NS bother - sex. freq. change
Ayers et al., 2012. RCT	129, peri/post-menopausal mean age: 53	CBT, Group 4x2hr, wkly Tailored	WLC	- HF/NS problem rating - HF/NS frequency
Mann et al., 2012. RCT	88, BC survivors mean age: 54	CBT, Group 6x1.5hr, wkly Tailored	CAU (BCFU)	- HF/NS problem rating - HF/NS frequency
Keefer et al., 2005. RCT	19, perimenopausal Mean age: 51	CBT, Group 8x1.5hr, wkly Tailored	WLC	- HF frequency/2wk - HF/NS problem rating
Hunter et al., 1996. RCT	24, menopausal Mean age: 52	CBT, Individual 4x1hr / 6-8 wk Tailored	WLC	- HF/NS problem rating - HF/NS frequency
Behavioral-based interventions				
Lindh-Åstrand et al., 2013. RCT	59, post-menopausal Mean age 54.9	BT, Group 10x1hr / 12 wk Tailored	WLC	- HF frequency/24 hrs - VM symptoms and sexual behavior
Fenlon et al., 2008. RCT	104, BC survivors Median age: 55	BT, individual 1x1 hr General	Att. C	- HF frequency/wk - HF severity - HF/NS problem rating - Menopausal symptoms
Fenlon et al., 1999. RCT	16, BC survivors Mean age: 48	BT, Individual 2 wkly. General.	WLC	- HF frequency/24h - HF/NS problem rating
Irvin et al., 1996. RCT	33, post-menopausal Mean age 50.8	BT, Individual 1x1h General	Act. C	- HF frequency/24h - HF intensity

Abbreviations

Act. C: active control group
Att. C: attention control group
BC: breast cancer
BT: behavioral therapy (relaxation)
CAU: care as usual

CBT: cognitive behavioral
therapy
HF: hot flush
hr: hour
MAP: mindfulness awareness
program

MBSR: mindfulness based stress
reduction
N: number
NS: night sweats
VM: vasomotor
wk: week

Table 6.2: Meta-analysis for hot flush frequency, hot flush bother and menopausal symptoms (short and medium-term)

Outcome	Number of studies	N total	SMD (95%CI)	P (overall effect)	I ² /X ² /P (heterogeneity)
Short-term (<20wks)					
HF frequency	6	300	-0.41 [-0.83, 0.01]	0.05	65%/14.19/0.01
HF bother	7	568	-0.63 [-0.80, -0.46]	<0.001*	0%/6.49/0.48
Menopausal symptoms	3	474	-0.34 [-0.52, -0.15]	<0.001*	0%/1.46/0.48
Medium-term (≥20wks)					
HF frequency	3	234	-0.31 [-0.89, 0.26]	0.29	79%/9.55/0.008
HF bother	5	486	-0.49 [-0.80, -0.19]	0.002*	63%/10.75/0.03
Menopausal symptoms	2	264	-0.45 [-1.07, 0.18]	0.16	83%/5.82/0.02

SDM: standardized mean, HF: hot flushes, wks: weeks.

* statistically significant (<0.05%)

low: 0-24%, moderate: 25-49%, substantial: 50-74%, significant 75-100%²².

Publication bias

The Egger test result was >0.10 for all studies indicating no proof of statistically significant publication bias. However the funnel plots showed some asymmetry, indicating that this result could be due to a limited number of studies per outcome (data not shown).

Subgroup analysis

A beneficial effect of psychological interventions was seen on short-term hot flush bother in the subgroup treatment-induced menopause (SMD: -0.47, 95% CI: -0.69 to -0.25, $p < 0.001$) as well as in the subgroup natural menopause (SMD: -0.85, 95% CI: -1.11 to -0.59, $p < 0.001$). Benefit of psychological interventions was also seen on medium-term hot flush bother for both the natural menopause subgroup (SMD: -0.77, 95% CI: -1.16 to -0.39, $p < 0.001$) as well as in the treatment-induced menopause subgroup (SMD: -0.32, 95% CI: -0.64 to 0.00, $p = 0.05$).

Adverse effects

Four studies reported on adverse effects of CBT, MBT and BT and did not encounter any adverse effects^{18,20,28,29}.

Discussion

Main findings

A small to moderate reduction of short- and medium-term hot flush bother and short-term menopausal symptoms by psychological interventions (i.e. CBT, BT and MBT) was found in the meta-analysis. Hot flush frequency however, was not statistically significantly reduced by psychological interventions. Furthermore, the short and medium term hot flush bother was reduced by psychological interventions in the breast cancer survivor

subgroup and the natural menopause subgroup. However, medium term hot flush bother reduction was bordering on statistical significance in the breast cancer survivor subgroup. No adverse effects caused by psychological interventions were reported.

Strengths and limitations

This systematic literature review and meta-analysis is the first to investigate and quantify the efficacy of CBT, BT and MBT on menopausal symptoms in both naturally occurring and treatment-induced menopause in survivors of breast cancer with inclusion of recently published studies and novel mindfulness interventions. Furthermore, a large number of RCTs were included and subgroup analyses were possible for natural and treatment-induced subgroups for most outcomes. An important aspect of this systematic literature review and meta-analysis is that only patient-reported outcomes were included, which reflect the actual inconvenience caused by hot flushes²³. A high level of heterogeneity was found in the meta-analysis, likely because of the differences in populations (natural vs. treatment-induced) and possibly due to differences between interventions (e.g. type, duration). The level of heterogeneity was not of great concern because the aim of this systematic literature review and meta-analysis was to answer the wider question about the effectiveness of psychological interventions as a whole, as they are all based on the similar principal of stressor impact reduction, in all menopausal women regardless of cause. Other limitations were the fact that some of the included RCTs were small (i.e. five of the twelve studies consisted of <60 participants in total) and possible presence of publication bias.

Interpretation

Hot flush bother versus hot flush frequency

As reduction of hot flush *bother* was greater than the reduction of hot flush *frequency* it could be that the main mechanism of action of psychological interventions is to modify cognitive appraisal of hot flushes, thereby increasing coping skills to reduce the impact of hot flushes¹³. In the general population, women who report a low frequency of hot flushes can still experience substantial bother by hot flushes and vice versa³⁴. Frequency of hot flushes has been identified as being associated with bother by hot flushes³⁴. However, they were not interchangeable as other factors such as affect, symptom sensitivity, general health, and sleep problems are also associated with the level of bother by hot flushes³⁴. So, reduction of bother by hot flushes might be the most appropriate measure of improved quality of life in women suffering from vasomotor symptoms^{34,35}.

Effectiveness in breast cancer survivors

Psychological interventions could be a valid strategy to reduce hot flush bother in breast cancer survivors. This is an important finding of the meta-analysis as breast cancer

survivors are contraindicated to use HRT, but report more frequent, more severe, more distressing and a longer duration of hot flashes compared to age-matched controls or naturally menopausal women^{6,36–38}.

Lack of long-term outcomes

No studies reported on long-term (≥ 52 weeks) outcomes. The effect of a booster session on maintaining the effect of the intervention warrants further investigation. This could not be evaluated properly in the meta-analysis because only two studies incorporated a booster session and did so within the short-term period^{17,27}.

Lack of sexual outcomes

Only two of the 12 included studies reported on sexual outcomes^{17,20}. The lack of sexual outcomes in current research stands in stark contrast to the fact that sexual functioning is shown to be severely impaired during menopause with 76% of menopausal women reporting sexual dysfunction^{5,39–41}. A recent one-armed pilot study aimed at improving sexual functioning in surgical menopausal women investigated the effect of an intervention combining MBT and sexual health education and found statistically significant improvement of sexual functioning⁴². This suggests that psychological therapy could be an effective intervention to improving sexual functioning in menopause. Indeed, a review by Al-Azzawi et al., concludes that non-pharmacological approaches, including psychological therapy, should be the first step in treating postmenopausal sexual dysfunction, before moving on to pharmacological options⁴³.

Other causes of treatment-induced menopause

Lastly, breast cancer treatment was the only cause for treatment-induced menopause that was investigated in the included studies. However, there are more causes for treatment-induced menopause such as risk-reducing salpingo-oophorectomy in women with high risk for ovarian cancer (e.g. *BRCA1/2* mutation carriers). Risk-reducing salpingo-oophorectomy in *BRCA1/2* mutation carriers has become a widely applied procedure causing early surgical menopause^{44–47}. Next to an increased risk for developing ovarian cancer, *BRCA1/2* mutation carriers also have an increased risk to develop breast cancer^{48–52}. About one third of *BRCA1/2* mutation carriers who experience surgical menopause have had breast cancer and therefore have a contraindication for using HRT⁵³. This signifies the need for a safe, non-hormonal alternative for alleviating menopausal symptoms in groups with different causes of treatment-induced menopause.

Conclusion

The need for non-hormonal alternatives to HRT has been firmly established following the publication of the Women's Health Initiative¹⁰ and considering the contra-indication of HRT in breast cancer survivors. The results of this review suggest that psychological

interventions could be a safe and effective treatment that reduce bother by hot flushes in all women experiencing symptoms associated with menopause, including breast cancer survivors. These findings support healthcare providers in offering psychological interventions to women who suffer from hot flushes and menopausal complaints, especially for women who will not be using HRT.

However, larger trials with a longer follow-up time are needed to confirm the (long-term) effectiveness of psychological therapies. Furthermore, RCTs investigating the comparative effectiveness of CBT, BT, and MBT are needed, as studies on this topic are scarce.

The staggering lack of sexual outcomes in current research in conjunction with the fact that sexual functioning is severely impacted during menopause, emphasizes that future research should focus on the effect of psychological interventions on sexual outcomes.

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Chapter 7

Mindfulness-based stress reduction for menopausal symptoms
after risk-reducing salpingo-oophorectomy (PURSUE study):
a randomized controlled trial



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Introduction: The aim of this study was to assess the short- and long-term effects of mindfulness-based stress reduction (MBSR) on the resulting quality of life, sexual functioning, and sexual distress after risk-reducing salpingo-oophorectomy (RRSO).

Methods: A randomized controlled trial was performed in a specialized family cancer clinic of the university medical center Groningen. 66 women carriers of the *BRCA1/2* mutation who developed at least two moderate-to-severe menopausal symptoms after RRSO were included. Women were randomized to an 8 week MBSR training or care as usual (CAU). The main outcome measures were the change in the Menopause-Specific Quality of Life Questionnaire (MENQOL), the Female Sexual Function Index, and the Female Sexual Distress Scale administered from baseline at 3, 6, and 12 months. Linear mixed modeling was applied to compare the effect of MBSR with CAU over time.

Results: At 3 and 12 months there were statistically significant improvements in the MENQOL for the MBSR group compared with the CAU group (both $p = 0.04$). At 3 months, the mean MENQOL scores were 3.5 (95% confidence interval [95%CI], 3.0–3.9) and 3.8 (95%CI, 3.3–4.2) for the MBSR and CAU groups, respectively; at 12 months, the corresponding values were 3.6 (95%CI, 3.1–4.0) and 3.9 (95%CI, 3.5–4.4). No significant differences were found between the MBSR and CAU groups in the other scores.

Conclusion: MBSR was effective at improving quality of life in the short- and long-term for patients with menopausal symptoms after RRSO. However, it was not associated with improvement in sexual functioning or distress.

Introduction

Women carrying a *BRCA1* or *BRCA2* mutation have an increased lifetime risk of developing breast and ovarian cancer compared with the general population¹⁻⁴. At present, because ovarian cancer screening is ineffective for early detection, offering risk-reducing salpingo-oophorectomy (RRSO) is standard practice to reduce the incidence of ovarian cancer in these women⁵⁻⁸. RRSO is recommended at the ages of 35 to 40 years for *BRCA1* mutation carriers and at 40 to 45 years for *BRCA2* mutation carriers, provided there is no desire to have more children⁹⁻¹³. There is good evidence that the procedure reduces the risk of ovarian cancer by up to 96% when performed within these age ranges¹⁴⁻¹⁷.

The acute surgical menopause induced by RRSO is associated with sequelae, of which hot flashes, (night) sweats, vaginal dryness, loss of sexual desire, and pain during intercourse are the most frequent¹⁸⁻²⁷. Moreover, it is reported that menopausal symptoms are more severe after acute surgical menopause than after natural menopause²⁸. Although hormone replacement therapy (HRT) can alleviate the symptoms, they only do so partially, and symptom levels remain above those of premenopausal women²². Confounding this issue is the fact that one-third of *BRCA1/2* mutation carriers who undergo RRSO have had breast cancer, contraindicating HRT use^{29,30}. Therefore, non-hormonal methods are needed to alleviate menopausal symptoms induced by RRSO in breast cancer survivors.

A possible non-hormonal alternative could be a psychological intervention that targets perception and acceptance, such as mindfulness-based training. The goal of such training is to help the patient pay full attention to the present moment in a non-judgmental, accepting way³¹. Specifically, the mindfulness-based stress reduction (MBSR) method achieves this through a well-described, protocol-based training program over an eight-week period. The program consists of meditation, gentle yoga poses, and body awareness exercises. In studies carried out in women experiencing menopausal symptoms after breast cancer treatment or natural menopause, MBSR has shown promise for both reducing difficulty with hot flashes and improving menopause-specific quality of life³²⁻³⁵. However, these studies were not carried out in women with RRSO-induced menopause, and they were either uncontrolled or had short follow-up periods.

In the present study, we aimed to investigate the short- and long-term effects of MBSR compared to care as usual (CAU) in *BRCA1/2* mutation carriers after RRSO. Specifically, we were interested in the effects on menopause-specific quality of life (primary outcome) and on sexual functioning and sexual distress (secondary outcomes).

Methods

Study Design

The randomized controlled trial, “Psychosexual consequences of Risk-reducing Salpingo-oophorectomy in *BRCA1/2* mutation carriers” (PURSUE) study is an open label trial and was approved by the Medical Ethical Committee of the University Medical Center Groningen on November 14, 2014 (registration number NL46796.042.14). It was conducted in accordance with the principles of the Declaration of Helsinki (as amended in 2013) and the relevant Dutch legislation (the Medical Research Involving Human Subjects Act). The ClinicalTrials.gov Identifier for the trial is NCT02372864. Women were recruited for participation from January 2015 to October 2015, and were followed for one year after randomization. Patients were not involved in the development of the study.

Participants

The clinical data for women referred to the Family Cancer Clinic of the University Medical Center Groningen at increased risk of developing breast or ovarian cancer, including *BRCA1/2* mutation carriers, have been prospectively recorded in a database since 1994³⁶. We contacted *BRCA1/2* mutation carriers who underwent RRSO at an age younger than 52 years by letter detailing the possibility of receiving MBSR training aimed at alleviating menopausal symptoms after RRSO. The letter included a purpose-designed questionnaire (see Appendix S1) about the presence and severity of menopausal symptoms. Cancer history and current psychiatric and cancer treatment were recorded on the questionnaire. Women were eligible for participation if they had undergone RRSO before the age of 52 years and reported at least two moderate-to-severe menopausal symptoms in the two preceding weeks. We excluded the following groups: those who were undergoing cancer treatment at the time of inclusion, apart from those receiving adjuvant hormonal or immune therapy; those who were receiving psychiatric care; and those who had insufficient understanding of the Dutch language to complete questionnaires. We did not exclude women using HRT, non-hormonal medications (e.g. clonidine), or dietary or herbal remedies (e.g. soy, black cohosh), or those with a history of breast cancer. All eligible women were invited for an intake visit, and after giving written informed consent, were randomized to an intervention or a control group. The intervention group received an eight-week MBSR training course, plus CAU, whereas the control group received only CAU.

Interventions

Participants in the MBSR group received an eight-week MBSR training course (Appendix S2). This comprised weekly sessions lasting two and half hours each, a silent retreat evening lasting four hours, and a commitment to performing mindfulness exercises at home for 30–45 minutes on six days of the week using instructions on a provided MP3 player³¹. The

MBSR training was a standard training program and not specifically adapted to focus on menopausal symptoms. In total, six MBSR training classes were organized, each with four to seven study participants only. Training classes took place at three locations in the north of the Netherlands to reduce travel time for participants, and all were led by one of three certified and experienced MBSR trainers.

Care as Usual

CAU consisted of information provided by a specialist nurse during the intake visit. This covered lifestyle advice for hot flashes, night sweats, vaginal dryness, sexual functioning, cardiovascular health, and bone health. An information booklet summarizing this information was provided to participants in both groups. Approximately 12 weeks after randomization, all participants were offered a repeat appointment with the nurse to address any remaining issues.

Randomization

We used block randomization stratified by HRT use. Randomization was done by the independent trial coordination center of the University Medical Center Groningen via a web-application, using a computerized random number generator. After randomization, an e-mail was automatically sent to the research nurse and researchers detailing the group allocation of that particular study participant. The participants were informed about their allocation group by the research nurse.

Assessments

Questionnaires were sent by mail at randomization (T0, baseline), and at three (T1), six (T2) and twelve (T3) months thereafter. If participants did not respond, a second request was sent after four weeks and a third request after eight weeks. If no response was received after twelve weeks, or the data was unclear, the participant was contacted by e-mail and/or phone by a researcher.

Baseline Descriptive Measures

The following baseline characteristics were collected: age, weight, height, marital or cohabitating status, parity, number of children living at home, highest completed education, employment, smoking history, alcohol consumption, exercise behavior, breast cancer history, mastectomy history, and HRT use. In addition, anxiety and depression were screened for using the Generalized Anxiety Disorder 7 (GAD-7) questionnaire³⁷ and the Patient Health Questionnaire-2 (PHQ-2)³⁸, respectively.

Primary Outcome Measure

The primary outcome of interest was menopause-specific quality of life, as measured by the Menopause-specific Quality of Life questionnaire (MENQOL). The MENQOL is a self-

administered 29-item questionnaire that assesses quality of life in menopausal women over the preceding four weeks³⁹. It records the presence and the severity of menopausal symptoms as the degree of perceived burden (or bother) women experience from menopausal symptoms, using seven-point scales per item. It consists of four domains: vasomotor (three items), psychosocial (seven items), physical (16 items), and sexual (three items). The domain scores range from one to eight, with one reflecting an absence of symptoms and eight reflecting extremely bothersome symptoms. A cut-off score is not available.

Secondary Outcome Measures

The Female Sexual Function Index questionnaire (FSFI) consists of 19 items on six sub-domains: desire, arousal, lubrication, orgasm, satisfaction, and pain⁴⁰. Each domain is scored on a Likert-type scale from zero to five. Higher scores indicate better sexual functioning in the prior four weeks, and a score <26.55 indicates sexual dysfunction⁴¹.

Sexual distress was determined using the Female Sexual Distress Scale questionnaire (FSDS) for the preceding four weeks. The FSDS consists of 12 items scored on a five-point Likert scale from zero (no distress) to four (always experiencing distress)⁴². A score of 11 or higher indicates sexual distress⁴³.

Sample Size Calculation

The minimum sample size was calculated as 64 with and 60 without correcting for 10% attrition based on a minimal clinically relevant difference of 1.0 on the MENQOL, a standard deviation of 1.36 based on a previous RCT that compared the change in MENQOL score between a MBSR intervention group and a waiting list control group at 20 weeks in naturally post and perimenopausal women³³, a statistical power of 80% and an α of 0.05³³.

Quality Control

To improve consistency and uniformity of the MBSR training sessions, three meetings were organized with the trainers under the supervision of an experienced MBSR trainer (MS), and adherence to the protocol was assessed by audio recordings of 6/48 (12.5%) of all training sessions. Protocol adherence was defined as the weighted average of agreement between the specified and actual exercise duration. Participant attendance was recorded by trainers at start of each session, and participants were asked to report the frequency and duration of daily home exercises on weekly evaluation forms during the intervention period.

Statistical Analysis

In case of missing items in the questionnaires, scores were calculated using mean imputation if at least 80% of the answers had been given. Baseline characteristics were described for each treatment arm using means and standard deviations for continuous variables and using frequencies for categorical variables. The primary and secondary outcomes were analyzed by linear mixed modeling to allow for the inclusion of women with missing time points for longitudinal data. The scores on the MENQOL, FSDS, FSFI, and their sub-domains at T0, T1, T2, and T3 were modeled as a function of the treatment arm, the time moment, and the interaction between the treatment arm and the time moment. An unstructured data matrix was assumed because the data did not indicate another correlation structure. All analyses were performed on an intention-to-treat basis. The normality of the outcome measures was determined by visual inspection of a Q-Q plot.

We used IBM SPSS version 23 (IBM Corp., Armonk, NY, USA) for all analyses. All p-values were two-tailed and considered significant if $p < 0.05$.

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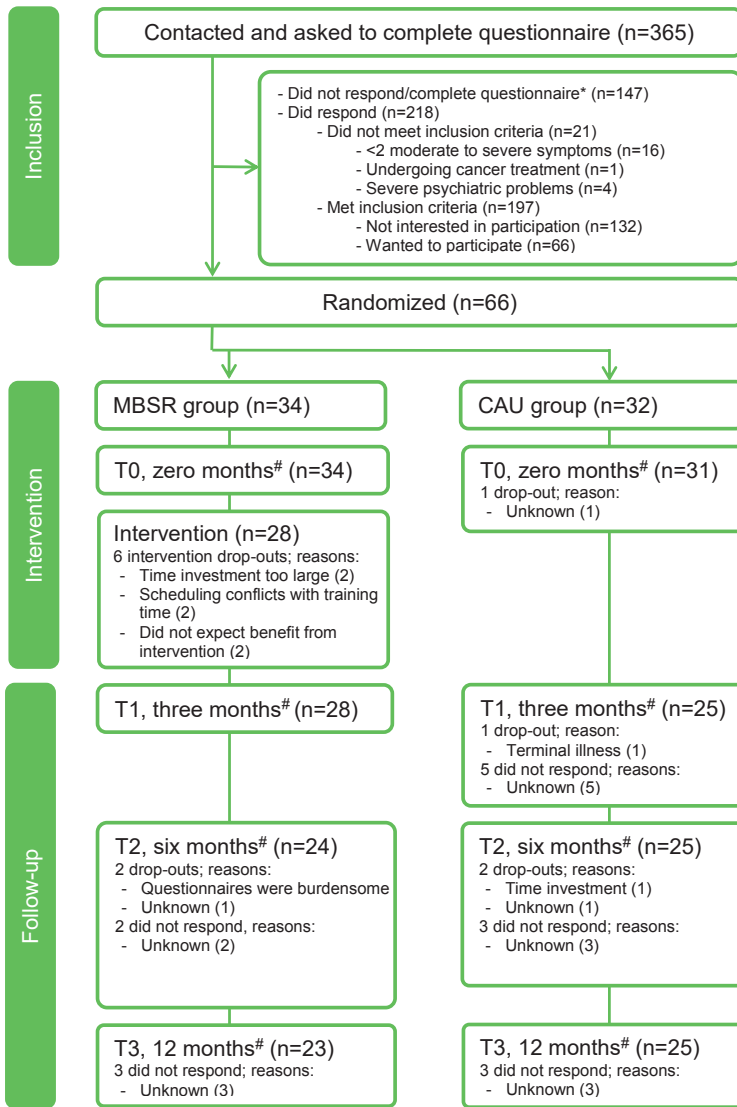
Results

Recruitment and Attrition

Of the 365 women informed about the study, 218 women completed and returned the questionnaires on the presence and severity of menopausal symptoms (Figure 7.1); of these, 197 met the inclusion criteria and 66 agreed to participate and be randomized to the MBSR ($n = 34$) and CAU ($n = 32$) groups. One participant in the CAU group did not return the questionnaire at T0 or at subsequent time points for unknown reasons, so baseline data were available for 65 participants (34 MBSR, 31 CAU). At inclusion, the average age of the participants was 47.7 ± 5.2 years, and 19 out of 65 (29%) women used HRT (Table 7.1). Furthermore, 17 out of 65 women (26%) had a history of breast cancer.

Six participants did not complete the intervention, with two citing scheduling conflicts, two citing that it was too time consuming, and two citing that they were not expecting a benefit. At each time point, at least 70% of participants returned their questionnaires, and the reasons for non-response are shown in Figure 7.1. In total, 53 women completed the MENQOL questionnaire at T1 resulting in a statistical power of 76%.

Figure 7.1: Population flowchart



*: 39 women responded they had no interest in participating in the study without filling in the rest of the questionnaire

#: The T0, T1, T2 and T3 questionnaires were sent zero, three, six and 12 months after randomization respectively

Table 7.1: Baseline characteristics

Variable	Total (N = 65)	MBSR (N = 34)	CAU (N = 31)
Age, mean (SD)	47.7 (5.2)	47.0 (5.0)	48.5 (5.4)
BMI, mean (SD)	26.4 (4.9)	26.6 (4.0)	26.2 (5.8)
Married or cohabiting, n (%)			
No	7 (10.8)	1 (2.9)	6 (19.4)
Yes	58 (89.2)	33 (97.1)	25 (80.6)
Children, n (%)			
No	10 (15.4)	2 (5.9)	8 (25.8)
Yes	55 (84.6)	32 (94.1)	23 (74.2)
Children at home, n (%)			
No	16 (24.6)	4 (11.8)	12 (38.7)
Yes	49 (75.4)	30 (88.2)	19 (61.3)
Higher education [#] , n (%)			
No	37 (56.9)	23 (67.6)	14 (45.2)
Yes	28 (43.1)	11 (32.4)	17 (54.8)
Employment status, n (%)			
Unemployed	10 (15.4)	6 (17.6)	4 (12.9)
Part-time	39 (60.0)	19 (55.9)	20 (64.5)
Full-time	16 (24.6)	9 (26.5)	7 (22.6)
Smoker, n (%)			
No	56 (86.2)	31 (91.2)	25 (80.6)
Yes	9 (13.8)	3 (8.8)	6 (19.4)
Alcohol consumption, n (%)			
0-1 unit / wk	36 (55.4)	17 (50.0)	19 (61.3)
2-5 units /wk	24 (36.9)	16 (47.1)	8 (25.8)
>6 units / wk	5 (7.7)	1 (2.9)	4 (12.9)
Exercise behavior, n (%)			
< 150 min / wk	12 (18.5)	8 (23.5)	4 (12.9)
≥ 150 min / wk	53 (81.5)	26 (76.5)	27 (87.1)
Underwent RRM, n (%)			
No	34 (52.3)	15 (44.1)	19 (61.3)
Yes	31 (47.7)	19 (55.9)	12 (38.7)
Had BC, n (%)			
No	48 (73.8)	25 (73.5)	23 (74.2)
Yes	17 (26.2)	9 (26.5)	8 (25.8)
Current HRT use, n (%)			
No	46 (70.8)	23 (67.6)	23 (74.2)
Yes	19 (29.2)	11 (32.4)	8 (25.8)
PHQ-2, mean (SD)	1.3 (1.3)	1.4 (1.4)	1.1 (1.1)
GAD-7, mean (SD)	5.5 (4.5)	5.0 (3.5)	5.9 (5.3)

n = 65, One participant did not return the questionnaire at T0 or at subsequent time points, so baseline data were available for 65 participants. [#]: Higher education = (applied) university or higher. Abbreviations: SD, standard deviation; BMI, body mass index; RRM, risk-reducing mastectomy; BC, breast cancer; HRT, hormone replacement therapy; PHQ-2, Patient Health Questionnaire-2; GAD-7, Generalized Anxiety Disorder-7; MBSR, mindfulness-based stress reduction; CAU, care as usual.

Quality Control

Adherence by the trainers to the MBSR protocol, based on the audio recordings of several training sessions, was 80%. Participants receiving MBSR attended 79% of the MBSR sessions. The patient-reported adherence to daily homework was 75% during the intervention period, with participants reporting practicing for 33 minutes on average per day.

Primary and Secondary Outcomes

Table 7.2 summarizes the results of linear mixed modeling of the primary and secondary outcomes as a function of time, treatment, and interaction between time and treatment. Figure 7.2 visualizes the primary outcome estimates per time point and arm.

At randomization (T0), 63% (41/65) of participants reported five or more complaints with a bother score of six or higher (scale one to eight, data not shown). Statistically significant differences in improvements were found for the MENQOL total score (T1: 0.56, $p = 0.04$, T3: 0.56, $p = 0.04$) and the vasomotor (T1: 0.93, $p = 0.04$, T3: 0.98, $p = 0.02$) and physical (T1: 0.65, $p = 0.01$, T3: 0.69, $p = 0.03$) subscales in the MBSR group compared with the CAU group at three and 12 months after the start of the intervention (Table 7.2).

Figure 7.2: MENQOL score estimates per time point and arm. The error bar represents the standard error.

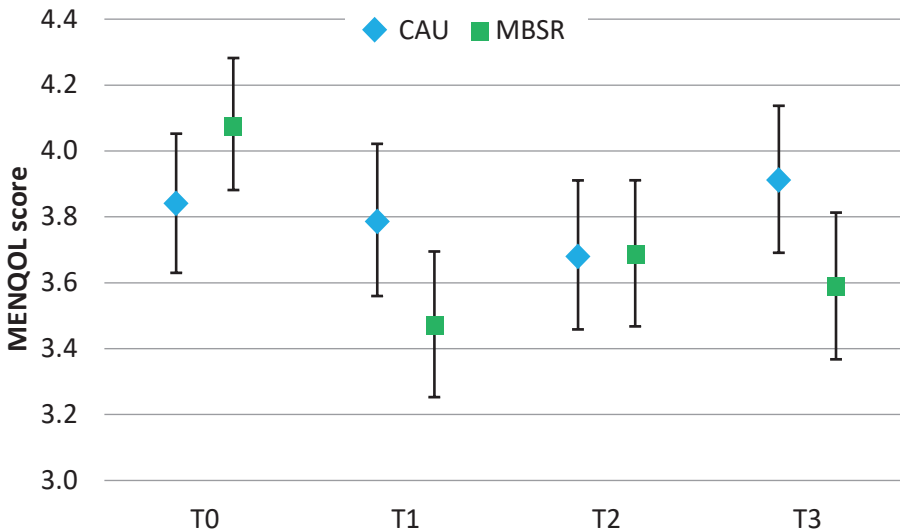


Table 7.2: Linear mixed modeling of the primary and secondary outcomes as a function of time, treatment, and interaction

		T0	T1	T2	T3
MENQOL	Total score				
	CAU	3.8 (3.4–4.3)	3.8 (3.3–4.3)	3.7 (3.2–4.1)	3.9 (3.5–4.4)
	MBSR	4.1 (3.7–4.5)	3.5 (3.0–3.9)	3.7 (3.2–4.1)	3.6 (3.1–4.0)
	p		0.04*	0.31	0.04*
	Vasomotor subscale				
	CAU	4.2 (3.6–4.8)	4.1 (3.5–4.8)	4.2 (3.5–4.8)	4.3 (3.7–4.9)
	MBSR	4.5 (4.0–5.1)	3.5 (2.9–4.1)	3.8 (3.1–4.4)	3.6 (3.0–4.2)
	p		0.04*	0.09	0.02*
	Psychosocial subscale				
	CAU	3.7 (3.2–4.2)	3.6 (3.0–4.1)	3.6 (3.0–4.2)	3.8 (3.3–4.4)
	MBSR	3.8 (3.3–4.3)	3.4 (2.8–3.9)	3.6 (3.0–4.2)	3.7 (3.1–4.3)
	p		0.31	0.95	0.50
	Physical subscale				
	CAU	3.5 (3.1–3.9)	3.6 (3.2–4.0)	3.5 (3.0–3.9)	3.8 (3.3–4.2)
MBSR	3.5 (3.2–3.9)	3.0 (2.6–3.4)	3.3 (2.9–3.7)	3.2 (2.7–3.6)	
p		0.01*	0.32	0.03*	
Sexual subscale					
CAU	4.0 (3.1–4.8)	3.9 (3.0–4.7)	3.5 (2.7–4.3)	3.7 (2.9–4.4)	
MBSR	4.4 (3.6–5.2)	4.1 (3.3–4.9)	4.2 (3.4–5.0)	4.0 (3.2–4.8)	
p		0.66	0.39	0.77	
FSDS	Total score				
	CAU	14.7 (10.7–18.7)	15.6 (10.7–20.4)	12.2 (7.8–16.6)	12.4 (7.5–17.2)
	MBSR	16.9 (13.1–20.8)	16.7 (12.0–21.3)	17.2 (12.9–21.5)	17.6 (12.8–22.5)
p		0.65	0.17	0.26	
FSFI	Total score				
	CAU	15.0 (11.9–18.1)	14.6 (11.3–17.8)	14.7 (11.3–18.2)	16.3 (13.0–19.6)
	MBSR	14.8 (11.9–17.8)	15.7 (12.6–18.8)	14.4 (11.0–17.8)	16.8 (13.5–20.0)
	p		0.40	0.92	0.75
	Desire subscale				
	CAU	2.7 (2.3–3.1)	2.7 (2.3–3.1)	2.6 (2.2–3.1)	2.7 (2.2–3.1)
	MBSR	2.7 (2.3–3.1)	2.5 (2.1–3.0)	2.5 (2.0–2.9)	2.7 (2.2–3.1)
	p		0.63	0.66	0.97
	Arousal subscale				
	CAU	2.8 (2.1–3.6)	2.8 (2.0–3.6)	2.8 (2.0–3.5)	3.2 (2.5–3.9)
	MBSR	3.0 (2.3–3.7)	3.2 (2.5–3.9)	2.8 (2.1–3.6)	3.2 (2.5–4.0)
	p		0.71	0.75	0.69
	Lubrication subscale				
	CAU	2.9 (2.1–3.7)	2.7 (1.9–3.6)	3.0 (2.1–3.9)	3.0 (2.2–3.9)
	MBSR	2.8 (2.1–3.6)	3.1 (2.3–3.9)	2.9 (2.1–3.8)	3.8 (2.9–4.7)
	p		0.29	0.94	0.14
	Orgasm subscale				
	CAU	3.0 (2.2–3.8)	2.8 (2.0–3.7)	2.8 (1.9–3.7)	3.4 (2.5–4.2)
	MBSR	2.9 (2.1–3.7)	3.3 (2.5–4.1)	3.1 (2.2–4.0)	3.7 (2.8–4.6)
	p		0.16	0.41	0.39
Satisfaction subscale					
CAU	3.6 (3.0–4.1)	3.6 (3.0–4.2)	3.7 (3.1–4.4)	3.9 (3.3–4.6)	
MBSR	3.3 (2.7–3.8)	3.3 (2.7–3.9)	3.2 (2.6–3.9)	3.3 (2.7–3.9)	
p		1.00	0.71	0.38	
Pain subscale					
CAU	2.8 (1.8–3.7)	2.7 (1.7–3.7)	2.6 (1.6–3.6)	3.2 (2.3–4.1)	
MBSR	2.9 (2.0–3.8)	3.1 (2.2–4.0)	2.4 (1.5–3.4)	3.2 (2.2–4.1)	
p		0.51	0.53	0.75	

Results are presented as means and 95% confidence intervals. n = 65, one participant did not return the questionnaire at T0 or at subsequent time points, resulting in baseline data being available for 65 participants. Reported p-values are reported for the group x time interactions in contrast to T0 in a linear mixed model. A p-value<0.05 (*) corresponds to a statistically significantly difference in the outcome measure between the MBSR and CAU groups from T0. Abbreviations: MENQOL, Menopause-Specific Quality of Life; FSDS, Female Sexual Distress Scale; FSFI, Female Sexual Functioning Index; CAU, care as usual; MBSR, mindfulness-based stress reduction.



At six months, there was a non-significant trend for improvement in the MBSR group compared with the CAU group ($p = 0.31$), but there were no statistically significant differences in the psychosocial and sexual subscales of the MENQOL between the MBSR and CAU groups at any assessment point. A statistically non-significant but clinically relevant improvement (≥ 1 improvement in MENQOL total score) was also seen in 28.6% of the MBSR group compared with 16.7% of the CAU group at T1.

Regarding the secondary outcomes, 94% (61/65) of participants reported clinically relevant sexual dysfunction and 65% (42/65) reported clinically relevant sexual distress at randomization (T0; data not shown). However, no statistically significant differences were observed between the MBSR and CAU groups for the FSDS and FSFI total scores or subscales at any assessment point (Table 7.2).

After visual inspection of their respective Q-Q plots, the MENOL and FSDS could be considered to be normally distributed, but some non-normality could be observed in the distribution of FSFI scores at baseline (data not shown).

Discussion

Main Findings

In this randomized study, we showed that MBSR improved menopause-specific quality of life over both the short- and long-term in women with at least two moderate-to-severe menopausal symptoms after RRSO. However, MBSR did not improve sexual functioning or sexual distress.

Strengths and Limitations

The main strengths of this study are its randomized controlled design, the long-term follow-up over 12 months and that MBSR was conducted by certified trainers with high protocol adherence. Furthermore, this study is the first RCT to test a psychological intervention for alleviating menopausal complaints after RRSO, and is among the first to test the effect of that intervention on sexual symptoms associated with menopause.

The CAU group did not receive a blinded placebo intervention because it was impossible to blind participants to treatment allocation, which could induce a placebo effect. The use of a non-active control group receiving CAU and no other attention during the intervention period means that there was no control for the non-specific effects of MBSR (e.g., repeated contact with MBSR trainers and other group participants). Although no adverse effects were reported during the intervention, this was not routinely monitored or recorded, so cannot be excluded as a possibility. The FSFI questionnaire was observed to have some non-normality which could have resulted in an optimistic p-value estimation.

Since the FSFI was not found to be statistically significantly more improved in the MBSR arm compared to the CAU arm this would not impact the conclusions of the study. Finally, only one third of the eligible women chose to participate in this study, therefore a self-selection bias is plausible which could have caused an overestimation of the intervention effect.

Interpretation

This is the first study reporting the long-term effects of MBSR in women with menopausal symptoms after RRSO. Consistent with previous studies, we showed short-term improvement at three months (T1)^{32,33}. However, our study is the first to report a persisting effect after one year, with improvement in menopause-specific quality of life at 12 months (T3) in the MBSR group compared with the CAU group. Although there was improvement from baseline in the MBSR group compared with the CAU group at the intermediate period of six months (T2), this was not statistically significant. Given that the change in effect at six months (T2) is small but in the same direction as the short- and long-term significant effect, it is likely that this is merely due to a statistical issue that could be solved with a larger sample size.

On the interpretation of the MENQOL score, no specific studies have been published. However, the authors of the MENQOL questionnaire have suggested that a relevant clinical difference in MENQOL score could be 0.5 point change³⁹. This suggestion was based on previous publications that compared patient-rated relevant change in symptoms with the corresponding change on a 7-point scale in other disease-specific QOL questionnaires (similar to the MENQOL questionnaire)^{44,45}. A change of 0.5 or of 1.0 was equivalent to patients reporting their symptoms to be 'A little better' and 'Moderately better', respectively^{44,45}.

In the current study the improvement in the total MENQOL score was mainly due to the improvement in the subscales of vasomotor symptoms (i.e. burden caused by hot flushes, night sweats and sweating in general) and physical symptoms (e.g. burden caused by stamina reduction, aches, urination frequency). The average difference on a 7-point scale in the vasomotor subscale and the physical subscale was 0.93 and 0.65 points, respectively. Therefore clinicians and patients could expect a modest to moderate reduction of perceived burden (i.e. bother) by vasomotor and physical symptoms of approximately 13% and 9% respectively.

Clinicians and patients might want to be able to interpret the clinical impact of MBSR in terms of symptom frequency reduction. The MENQOL questionnaire only measures bother by menopausal symptoms, not frequency of menopausal symptoms. However some direction on the relationship between bother by and frequency of menopausal symptoms

can be given. In an earlier RCT that recorded both the change in hot flush frequency and change in MENQOL score, an improvement of approximately one point in the MENQOL score was found together with a 45% reduction of the hot flush frequency (an estimated reduction of approximately four hot flushes per day). However, the conclusion that one point change in MENQOL score represents the aforementioned reduction in hot flushes is too simplified. Changes in the other symptom domains or other (unknown) factors influence the total MENQOL score as well and therefore the relation between MENQOL score and hot flush frequency could be different in other circumstances.

The baseline level of sexual dysfunction was very high in this study, comparable to that reported after RRSO in other research, but much higher than that reported in the general population^{27,46}. Unfortunately, our MBSR intervention did not improve this sexual dysfunction or distress. In contrast to this, previous controlled studies of mindfulness-based therapy for low sexual desire and arousal have found significant improvements in sexual functioning after the intervention^{47,48}. Differences in study populations could explain the results, because the sexual problems in previous studies were of a psychological nature (e.g., lack of desire or low arousability), whereas the problems in the current population may have been of a mixed psychological and physiological nature (e.g., vaginal discomfort and loss of desire due to estrogen deprivation)^{47,48}. However, consistent with our study, the earlier research also failed to show any improvement in sexual distress^{47,48}. In a single-armed pilot study, mindfulness-based therapy did improve sexual functioning after RRSO, but that study used an intervention specifically targeting sexual difficulties, rather than a general MBSR protocol as we used in this study⁴⁹.

It has been proposed that mindfulness facilitates a more accepting, even-tempered state of being that helps decrease reactivity to stimuli⁵⁰. Therefore, MBSR could work by reducing the degree to which vasomotor and physical symptoms are experienced as problematic or bothersome; in other words, by dampening the perceived severity of symptoms⁵¹. Indeed, it might be that MBSR also primarily affects the psychological aspects of sexual problems by improving cognitive appraisal rather than by altering the actual physiological symptoms. This would explain why a previous study on the effect of MBSR on physiological arousal, as measured by vaginal photoplethysmography, did not find an improvement⁴⁷. However, another hypothesis is that by decreasing stress, MBSR could diminish the frequency of hot flushes at a physiological level, because stress is thought to lower the threshold for heat dissipation responses^{51,52}. Moreover, the effect of MBSR on the physiological stress response has been suggested by preliminary research indicating that it produces statistically significant reductions in cortisol levels and non-significant improvements in dehydroepiandrosterone-sulfate levels^{53,54}.

Conclusion

This study indicates that MBSR improves short- and long-term menopause-specific quality of life in women with menopausal complaints after surgical menopause induced by RRSO. We recommend that healthcare providers advocate MBSR in conjunction with HRT. However, MBSR may be especially relevant for breast cancer survivors or in other settings when HRT is contraindicated.

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Chapter 8

Summary and general discussion



Introduction

This thesis aims to increase understanding of the factors that influence the uptake and timing of risk-reducing surgery in *BRCA1/2* mutation carriers (Part I) and to investigate the effectiveness of psychological interventions in alleviating menopausal complaints after risk-reducing salpingo-oophorectomy (RRSO) (Part II). Firstly, this chapter will give a brief summary of the findings presented in the previous research chapters. Then, the findings of the two parts of the thesis are placed into the context of current literature, the methodology is reconsidered and the implications for practice and future research are discussed.

Summary

Part I: Factors associated with the uptake of risk-reducing surgery

As described in the general introduction (chapter 1), more knowledge on the factors that influence the complex decision on whether or not to undergo risk-reducing surgery is needed. These factors are relevant during counseling and in providing optimal decisional support. Next to identifying sociodemographic factors, this thesis aimed to study the influence of additional psychological factors and stopping with offering ovarian cancer screening on the uptake and timing of risk-reducing surgery.

In **chapter 2**, it was analyzed which patient characteristics are associated with an earlier decision for risk-reducing mastectomy (RRM) in a consecutive series of 407 *BRCA1/2* mutation carriers who visited our family cancer clinic between 1994 and 2011. It was found that a cumulative percentage of 36% of all women chose to undergo RRM within the first five years after disclosure of their DNA test results. Earlier uptake of RRM was associated with women being younger than 50 years of age, having had previous unilateral breast cancer, having a mother with breast cancer and having undergone unilateral therapeutic mastectomy instead of lumpectomy (in case of previous unilateral breast cancer). These results suggest that women with a personal or familial history with cancer seem to choose RRM earlier in comparison to women who do not have this experience. We hypothesized that these first-hand experiences with the impact of breast cancer, resulting in an increase of cancer specific worry¹, speed up the uptake of RMM.

Chapter 3 is focused on exploring the possible association of psychological factors, such as affect, with the intention to choose RRM. A cohort of 486 cancer-unaffected women with a family history of breast cancer filled out questionnaires concerning their breast cancer risk, prior to their intake consultation with a clinical geneticist. The battery of questionnaires consisted of the cancer worry scale, positive and negative affect scale, perceived personal control scale, hospital anxiety and depression scale and state anxiety scale and questions

regarding socio-demographic characteristics, family history, risk perception and RRM intention. We found that psychological factors associated with intention to undergo RRM were high positive affect, high negative affect, high cancer worry, high perceived personal control and high risk-perception. It is likely that affect plays a role in decision-making, as it provides means to make quick and efficient decisions in complex situations^{2,3}. The hypothesis behind this is that women process risk information in two ways, namely by deliberating the risk in a cognitive and literal manner and by understanding the risk in an intuitive manner. The intuitive understanding of risk is often derived from experiences with similar events in the past (e.g. a family member with breast cancer) that have become “tagged” with affective meaning. This affective tag can be used as an intuitive shortcut to reach a decision².

In **chapter 4**, the effect of stopping ovarian cancer screening on the timing and uptake of RRSO was explored. A higher percentage of women underwent RRSO and did so more often within the recommended age range. Other factors that led to an earlier uptake of RRSO were having two or more children and having reached the recommended age range for RRSO. The findings of this study closely reflect the effect of a change in counselling by health care providers. Women who are counseled unambiguously that RRSO is the only effective risk-reducing strategy and is best performed within a certain age range after completing childbearing will follow this advice more often. Furthermore, from the patient’s perspective, being a mother also means having the responsibility to care for children. This factor might also make women more inclined to choose RRSO within the recommended age range.

Part II: Psychological interventions alleviating menopausal symptoms after RRSO

In the second part of this thesis the consequences of surgical menopause after RRSO at premenopausal age are discussed. Firstly, we reported that the severity and the duration of symptoms is an often overlooked topic. Subsequently, this thesis aimed to investigate the effectiveness of psychological therapies on menopausal and sexual complaints in women after surgical menopause following RRSO. This is especially relevant as hormone replacement therapy (HRT) was found not to eliminate menopausal symptoms to a premenopausal level in women after RRSO and is contraindicated in breast cancer survivors^{4,5}.

Chapter 5 describes a cross-sectional study on the severity and duration of menopausal symptoms in previously premenopausal women. At a mean follow-up time of 7.9 years after RRSO, 69% (137/199) of the included women reported moderate to severe symptoms on the menopause rating scale. Of these symptoms, urogenital symptoms (e.g. dysuria, vaginal dryness, itching, burning and dyspareunia) were most frequently mentioned, followed by psychological symptoms (e.g. depressive mood, irritability,

anxiety). Furthermore, being a breast cancer survivor was associated with moderate to severe menopausal symptoms after RRSO.

In **chapter 6**, a systematic literature review and meta-analysis is described on the existing evidence on the effectiveness of psychological interventions in reducing symptoms associated with menopause in natural or treatment-induced menopausal women. Psychological interventions were found to be effective as an alternative or an addition to HRT in reducing natural and breast cancer treatment-induced menopausal complaints. The work described in this chapter is a step towards clinical implementation of psychological treatment of menopausal symptoms. However, lacking were studies investigating the long-term effects of psychological interventions on menopausal symptoms and the effectiveness of psychological interventions in other populations such as women with menopausal complaints after RRSO.

This led to the conception of the last study of this thesis, which is described in **chapter 7**. This study is a randomized controlled trial investigating the short and long-term effects of mindfulness-based stress reduction (MBSR) on menopausal quality of life, sexual functioning and sexual distress after RRSO. Our results showed that MBSR did indeed improve short- and long-term menopause specific quality of life when compared to care as usual, even after one year. However, MBSR did not improve sexual functioning or sexual distress. From this we concluded that in the case of non-sexual menopausal complaints, MBSR can be advised by healthcare providers as an alternative or addition to HRT, especially in breast cancer survivors.

Context of other literature

Part I: Factors associated with the uptake of risk-reducing surgery

In part I of this thesis we aimed to identify the factors that influence (the timing of) decisions about risk-reducing surgeries in women with an elevated risk for breast and ovarian cancer. To understand the findings of part I of this thesis it is necessary to place them into the context of literature on decision-making in the field of risk-reducing surgery. In the following paragraph we will approach this matter from two perspectives, namely: the patient's and the physician's perspective and their role in shared decision-making.

Shared decision-making on risk-reducing surgery

Shared decision-making in risk-reducing surgery aims to foster the patient's self-determination and autonomy. In literature, the approach is described as a clinician sharing the available medical information on risk-reducing options and their differences with the patient and a patient sharing information on her personal circumstances, values

and preferences⁶. The goal is reached by ensuring the patient is well-informed and receives support in deliberating on the advantages and disadvantages of several options in the context of their own life^{6,7}. From this description of shared decision-making it becomes clear that in order to reach a shared decision, two perspectives need to be taken into account, namely the physician's and the patient's perspective. These two perspectives combined lead to the preferred risk management option with regard to reducing the risk of developing or dying from cancer.

Uptake of risk-reducing surgery; patients' perspectives

The physician's perspective in decision-making consists of biomedical information, such as expected benefits and harms of risk-reducing options in terms of survival, and the patient's perspective consists of personal circumstances, values and preferences. This perspective is often shaped by previous experiences to which an affective meaning is assigned (**chapter 2 & 3**). Specifically, when deciding on risk-reducing surgery in case of hereditary breast and ovarian cancer risk, previous experiences with cancer gain importance in the decision-making process. In line with our results that women with a personal or family history of cancer choose RRM more often (**chapter 2**), a qualitative study conducted in 20 women at high risk for hereditary breast cancer, found that family experiences were important in how information about RRM was processed⁸. Also, women's perception of their own cancer risk, perception of the consequences of developing breast cancer and their risk-reducing strategy decisions were influenced by their experiences with cancer in their family⁸.

As described in the summary of **chapter 3**, our hypothesis was that patients process the information on risk in a cognitive, literal manner, as well as in an intuitive, affective manner. The context of women's family cancer history relates more to the intuitive manner of interpreting risk. This is substantiated by a qualitative study interviewing 36 unaffected women from high-risk breast cancer families. From this study it is clear, that although women's cognitive understanding of their risk is accurate, this understanding of risk information is of secondary importance in their decision-making process². Instead, it was found that risk perception and subsequent decision-making about risk-management options, are primarily driven by an intuitive understanding of their risk. This intuitive understanding of risk is closely linked with affective meaning elicited by past experiences, such as breast cancer in family members².

The fact that the affective understanding of risks plays an important role in decision-making from the patient's perspective, makes miscommunication between the patient and her physician more likely. Especially when the physician is not aware of the importance of the affective understanding of risks. The physician aims to provide facts and figures to explain the medical situation to the patient, however in light of

contextual factors a patient might intuitively interpret this risk to be much higher or lower than what the physician intended to bring across. From the physician's perspective, this could lead to under- or overutilization of risk-management options when left unaddressed. Moreover, a certain risk could be undesirable from a biomedical standpoint, but acceptable from the patient's perspective in the context of her life and vice versa. Lastly, medical decision-making is often complicated by the fact that more than one type of risk is relevant for the patient and/or the physician. Such as the risks of surgery, the risk of developing a disease and/or the risk of dying from a disease. Time-dependent factors further complicate this decision as cancer risks change throughout the patient's life as well as the impact developing cancer or risk-reducing strategies have in different life stages (e.g. before completing childbearing, while having young children).

Uptake of risk-reducing surgery; physician's perspective

After discussing the patient's perspective, this paragraph will describe the influence of the physician's perspective on risk-management decision-making. By stopping ovarian cancer screening in *BRCA1/2* mutation carriers in 2009, the physicians of our family cancer clinic (FCC) aimed to prevent ovarian cancer by subsequent underutilization of RRSO as a result of a false sense of security. The strategy in our FCC was twofold, namely by communicating biomedical information (e.g. ovarian cancer screening does not detect cancer in an early and curable stage, timely RRSO is currently the only effective option for preventing death due to ovarian cancer), but also by jointly discussing the affective interpretation assigned to this situation and what this means to the patient in the context of their life. Using this strategy, a best course of action was determined jointly by the patient and the physician. We observed that after stopping ovarian cancer screening, the uptake of RRSO within the recommended age range increased (**chapter 4**). We hypothesized that this two-fold strategy increased patients' knowledge on the ineffectiveness of ovarian cancer screening and supported patients to make value-consistent decisions. This is in line with findings from the study of Pai et al., who found that choosing RRSO over ovarian cancer screening was related to an increased awareness of the ineffectiveness of ovarian cancer screening⁹.

Traditionally, the focus of physicians and researchers has been on communicating the physician's perspective (e.g. biomedical facts and figures) and checking whether this perspective was communicated correctly in terms of for example the correct recall of risk information¹⁰⁻¹². Part I of this thesis makes a case for incorporating the patient's perspective in the shared decision-making process. By doing so, this may improve patient-physician communication, increase patients' understanding and empower patients to make decisions that are optimal given the individual circumstances of the patient.

Part II: Psychological interventions alleviating menopausal symptoms after RRSO

In part II of this thesis severity and duration of menopausal symptoms after RRSO and possible interventions to alleviate these symptoms are investigated. A common thread in part II is *sexual health after (surgical) menopause*. The findings of part II of this thesis will be discussed and placed in the context of adjacent literature concerning sexual health after (surgical) menopause. The rationale behind high-lighting specifically this theme is that sexual health or lack thereof has a large impact on women's lives, but nonetheless is often overlooked.

Sexual health after (surgical) menopause

After RRSO, urogenital symptoms such as vaginal dryness and dyspareunia do not seem to diminish with time (**chapter 5**) and sexual dysfunction and sexual distress after RRSO were reported by a large majority of women in the RCT presented in this thesis (**chapter 7**). This high proportion of women reporting sexual dysfunction and sexual distress could in part be due to selection bias, however a cross-sectional study also found a high prevalence of sexual dysfunction in women after RRSO⁴. In women with a personal history of breast cancer, sexual symptoms after RRSO seem to be even more pronounced (**chapter 5**), although mixed results in literature have been reported^{4,13-15}.

A study in women who underwent RRSO reports that most women were merely counseled on menopausal symptoms, such as experiencing hot flashes after RRSO¹⁶. However, a large majority of women were at no point (i.e. pre or post-surgery) counseled on the impact of RRSO on their sex life by their physician¹⁶. Retrospectively, a majority of women would have liked a more thorough discussion on the impact of RRSO on their sexual health and more information on interventions to maintain or improve their sexual health¹⁶. Furthermore, sexual outcomes in intervention studies aimed at alleviating menopausal symptoms seem to be lacking (**chapter 6**). Although physicians subscribe to the view that the impact on sexuality should be routinely discussed, many reported lack of time and uncertainty on which member of the multidisciplinary team should take responsibility for this discussion^{17,18}. The lack of discussing expectations about the impact on sexual functioning creates the impression that barriers to discuss sexual health might be present.

Barriers to discussing sexual health after (surgical) menopause

A narrative review on sexual health communication during cancer care identified three types of barriers from the physician's perspective, namely: patient characteristics, physician characteristics and system issues¹⁷. Based on certain patient characteristics, such as: gender, age, sexual orientation and relationship status, physicians may make incorrect assumptions about the patient's wishes regarding discussing sexual health^{17,19}. Physician characteristics that have repeatedly been associated with lack of routine discussion of

sexual health are a lack of knowledge, skills and experience concerning discussing sexual health issues^{17,20}. To bridge this gap, initial steps in offering unexperienced physicians practical guidelines already have been made^{17,21}. Lastly, system issues such as time constraints and issues with the availability of effective interventions were indicated as barriers to discuss sexual health with women during cancer care.

One of the difficulties of finding effective interventions for women with sexual health issues is that these issues are often a mix of physiological issues such as vaginal dryness and psychological complaints such as a lack of sexual arousal and sexual satisfaction^{4,13}. Therefore, it is not surprising that the simple use of a pharmacological option such as HRT was not found to be a predictor of the severity of symptoms after RRSO (**chapter 5**). This corresponds with several studies that found that HRT does not entirely ameliorate menopausal symptoms after RRSO to a premenopausal level^{4,22,23}. A study by Tucker et al., that specifically investigated sexual function after RRSO, found that HRT use after RRSO was associated with lower rates of dyspareunia and less severe complaints of vaginal dryness, when compared to no HRT use after RRSO. However HRT use had no effect on orgasm, desire, arousal or satisfaction levels²⁴.

By incorporating psychological interventions, this thesis aimed to identify an effective intervention to resolve sexual health problems after RRSO (**chapter 6 & 7**). An effective intervention was not yet found, however the field of psychological interventions to resolve sexual health issues is promising^{25,26}. For this reason, the search for an effective intervention continues, as will be discussed in the paragraph *“future research directions”* below. However, the success of an intervention does not only depend on the availability of effective options, but equally on whether the intervention is delivered to the right women at the right time. Sexual health issues need to be routinely discussed before and after surgery in order to manage women’s expectations more sufficiently.

Methodological considerations

Part I: Factors associated with the uptake of risk-reducing surgery

In part I of this thesis we used prospectively gathered databases to identify predictors of choosing risk-reducing surgery. It is important to consider the underlying methodology of the research conducted in this part to be better able to interpret its conclusions.

The University Medical Center of Groningen (UMCG) is the only university hospital in the Northern Netherlands and has a very large referral area. The FCC of the UMCG is a center of expertise on hereditary cancer and has gathered data on all hereditary breast and ovarian cancer cases prospectively since 1994, using a localized electronic patient record system. This system ensured the prospective data gathering for research purposes with high data quality when compared to retrospective data collection. Only for a small portion of the cases the data had to be completed retrospectively and this is also apparent from the low amount of missing data. The data gathered in the FCC lays the foundation of the research described in **chapter 2** and **4**.

When analyzing the uptake of risk-reducing surgeries, the follow-up time is often different between patients and between different studies. Women with a longer follow-up time have more opportunity to choose risk-reducing surgery. Therefore, having a long or short follow-up can lead to an over- or underestimation of the percentage of women choosing risk-reducing surgery. However, most women who underwent risk-reducing surgery did so after having reached the recommended age, which reduces the dependency on duration of follow-up. In other words, the time in follow-up after having reached the recommended age is an important predictor for uptake. A time-to-event analysis (i.e. Cox regression), which was performed in this thesis, takes follow-up time into account by correcting for differences in duration of follow-up between women. For this type of analysis it is necessary that not only the uptake of risk-reducing surgery is recorded, but also its timing since entering the FCC. Another advantage of our FCC database is that this could be determined reliably.

Furthermore, the FCC database, which has been prospectively including women for over 20 years, is based on a large catchment area and has a long follow-up. This has resulted in large sample sizes, which allowed for the identification of independent predictors of the uptake of risk reducing surgery using multivariate statistical analyses. The long period of patient recruitment could potentially lead to a more heterogeneous sample which is not entirely representative of patients today. For example, over the years there have been changes in the guidelines for recommending risk-management options and the guidelines regarding DNA testing. However, the inclusion criteria were kept constant to reduce this source of heterogeneity. Furthermore, due to the high quality of data

registration and adherence to the counselling guidelines, the effect of a change in RRSO counselling guidelines could be studied in detail in **chapter 4** of this thesis.

It is important to note that the predictors considered in **chapter 2** and **4** were only recorded at baseline. Therefore some of these characteristics may have changed during follow-up, which could have influenced the results. For example, it was found that having a mother with breast cancer was a predictor for undergoing RRM. Women whose mother developed breast cancer during follow-up would have been recorded as having a mother unaffected by breast cancer. However, the fact that a family member has developed cancer could have influenced the decision-making process. This could have led to a slight underestimation of the predictors at the time the decision was made. Furthermore, all family cancer history data relied to some degree on the accurate reporting of patients themselves.

Lastly, the majority of the studies in this thesis had actually 'choosing and undergoing risk-reducing surgery' as their outcome measure, however one study had the 'intention to undergo risk-reducing surgery' as reported by women as an outcome (**chapter 3**). This intention was recorded prior to receiving their DNA test results. While the intention to undergo RRM and undergoing RRM in the case of a proven *BRCA1/2* mutation is likely to be strongly correlated, they cannot be assumed to be identical. Therefore, the found predictors of the intention to undergo RRM could be slightly different from the predictors to actually undergo RRM.

Part II: Psychological interventions alleviating menopausal symptoms after RRSO

Part II of this thesis largely focused on psychological interventions to improve menopause-related quality of life. This was done firstly by analyzing RCTs in the context of a systematic literature review and meta-analysis and secondly through conducting an RCT specifically for the target population of this thesis. In general, certain methodological issues are known to affect the quality of RCTs, such as: random assignment of subjects to treatment groups, concealment of allocation, blinding of researchers and subjects to allocation etcetera. However when investigating psychological interventions such as a mindfulness-based intervention, certain specific methodological difficulties are encountered²⁷. Many studies do not report the participant's attendance, participant's homework adherence or the trainer's adherence to the protocol of the intervention. In these studies it is unclear whether the intervention was delivered in the intended intensity (i.e. "dosage"). Therefore an underestimation of the effect of the intervention could have occurred. Furthermore, many studies do not have an active control group to ascertain the influence of non-specific effects (e.g. peer support)²⁷⁻²⁹.

In the RCT described in **chapter 7**, specific measures were taken to avoid the above mentioned methodological difficulties. To ascertain whether the intervention was offered as intended, the intervention was delivered according to a detailed protocol, adherence to the protocol by the trainers was assessed using audio recordings, and participants' attendance and homework compliance was recorded. A strength of this study was the long duration of follow-up in order to assess the long term effect of the intervention, beyond the intervention itself. Long-term follow-up was not present in most other RCT's concerning effectiveness of psychological intervention on menopausal symptoms (**chapter 6**).

The RCT was designed as a pragmatic trial. The control condition was not an active comparator condition but consisted of care-as-usual. Although factors such as the effect of being in a group setting and having contact with peers and trainers were not controlled for in this design, it does give an estimation of the effectiveness of the intervention in daily clinical practice. This also holds true for potential self-selection bias as this could in part be present in clinical practice as well.

Clinical implications

Part I: Factors associated with the uptake of risk-reducing surgery

Based on the research in part I of this thesis we have a better understanding of which factors influence the uptake and timing of risk-reducing surgery. In the clinic, this understanding can be incorporated into the counseling of women who are at high risk for developing breast and ovarian cancer. Besides, the findings of this thesis could be used to encourage physicians who still offer ovarian cancer screening to discontinue this ineffective practice and instead offer timely RRSO.

As described earlier, shared decision-making is an approach in which a clinician shares medical information (i.e. physician's perspective) and a patient shares her personal circumstances, context, family history, values and preferences (i.e. the patient's perspective). The patient and the clinician jointly consider, deliberate and decide on (the timing of) the most appropriate risk-management strategy for this particular patient³⁰. The focus traditionally has been on conveying the most precise risk percentages to patients and evaluating the quality of counseling based on the accuracy of patients' literal recall. However, this insufficiently incorporates the patient's personal context and perspective. This thesis emphasizes that psychological factors such as affect, cancer worry and perceived personal control may be the most influential factors in the decision-making process from the patient's perspective. To empower women to reach a fully informed decision that is both medically adequate as well as consistent with values from their own perspective, these factors should be addressed and weighted during counselling.

Patients might very well have a sufficient cognitive understanding of the information on risks, but when exploring the affective meaning patients attach to this information, an incongruence in risk-interpretation could still be present that needs to be resolved. As mentioned before, it is vital that healthcare provider's counseling incorporates both the doctor's and patient's perspectives. The doctor's perspective can be incorporated through the discussion of accurate and objective biomedical information on age-related cancer risks and effective preventive strategies (**chapter 4**). The patient's perspective can be incorporated through a thorough discussion of influential factors such as affective meaning high-risk women assign to their situation or the impact of first-hand experience with cancer (**chapter 2 & 3**). The alignment of these perspectives is an implementation of shared decision-making and optimal decisional support.

Part II: Psychological interventions alleviating menopausal symptoms after RRSO

In this thesis psychological interventions were shown to have a moderate effect on hot flush bother, menopausal symptoms and menopause-specific quality of life (**chapter 6 & 7**). As such, psychological therapies could be one of the options offered to women suffering from menopausal complaints, either in conjunction with HRT or as an alternative to HRT when contraindicated such as in breast cancer survivors. Furthermore, breast cancer survivors often experience more severe complaints for a longer duration of time after RRSO (**chapter 5**) and therefore could especially be in need for an alternative to HRT.

In deciding for which women this psychological intervention could be most beneficial, a few matters can be taken into consideration. Firstly, only *bother* by hot flushes, not *frequency*, decreased after psychological intervention as shown in **chapter 6**. When offering this type of intervention this should be communicated to the patient to manage realistic expectations. When selecting women for these types of interventions, the level of bother by hot flushes and not the frequency should be leading. This might also be a logical criterion in light of the fact that *bother* by hot flushes might be the most appropriate measure of quality of life in women suffering from vasomotor symptoms^{31,32}. Secondly, there is a lack of data on the effect of psychological therapies on sexual outcomes, so no conclusions could be drawn concerning this outcome in **chapter 6**. Unfortunately, the general MBSR program did not improve sexual functioning or sexual distress in **chapter 7**. Therefore, it is concluded that current psychological therapies are best recommended to women with non-sexual menopausal complaints after RRSO.

Future research directions

Part I: Factors associated with the uptake of risk-reducing surgery

It is important that healthcare providers are aware of both the physician's and the patient's perspectives. A more formal way to incorporate the physician's perspective (i.e. medical/

factual considerations) and the patient's perspective (i.e. personal circumstances, values and preferences) is by using a decision support tool in conjunction with conventional counselling. Decision support tools for high-risk women that are currently available mostly focus on providing information about cancer risks, risk-reduction options and attaching values to the pros and cons of (timing of) certain risk-reducing options. Current tools do not or only slightly focus on congruence between patients' values stemming from the broader context of their life, such as past experiences and future aspirations or personality characteristics³³. If these decision support tools are upgraded to include the patient's perspective, they could be beneficial in aligning the cognitive and affective parts of the decision-making process.

To develop these types of tools in full, more insight into the decision-making process is needed. Especially the role of psychological factors such as emotions, personality characteristics and social factors, such as caregiver role and social support, is needed to further personalize counseling to improve the decision-making process. Quantitative research could lay a basis for identifying the type of patients' factors that are associated with the decision-making process, building on current research such as presented in this thesis. In-depth qualitative research is needed to give insight into the different aspects of the women's perspective on how these factors influence their decisions.

Furthermore, prospective longitudinal research on the relation between choosing certain risk-reducing options on physical, psychological and social outcomes should be incorporated into these decision tools. This improvement could lead to more specific counseling on the broader consequences of a certain decision, which are not only confined to medical pros and cons. A last consideration for future research is that, to the best of our knowledge, the role of the partner in the decision-making process regarding risk-reducing surgery has not been investigated. As studies on decision-making about breast reconstruction after cancer show that the partner has a consultative role, research on optimal shared decision-making concerning risk-reducing surgery should investigate the involvement of the partner in this process³⁴.

Part II: Psychological interventions alleviating menopausal symptoms after RRSO

What remains unclear and could be the focus of future research is the effectiveness of mindfulness, cognitive-behavioral and behavior-based interventions in alleviating menopausal complaints after RRSO. This type of research could answer questions such as which type of intervention is most effective and what moderates this effect (e.g. what type of patient benefits most from a certain type of intervention). Furthermore, new research should aim to investigate long-term outcomes, include populations with other causes of menopausal symptoms and include active control groups to control for the non-specific effects (e.g. contact with peers).

Sexual functioning is an important aspect of quality of life. At this moment we have no definite answer on how to treat sexual symptoms after RRSO. This is in part because randomized controlled trials investigating the effect of psychological therapies in menopausal women rarely report sexual outcomes. Also, HRT does not ameliorate sexual symptoms entirely and is contraindicated in breast cancer survivors, who are prevalent among *BRCA1/2* mutation carriers. What is more, the mindfulness based stress reduction intervention tested in this thesis was not effective in alleviating sexual dysfunction and sexual distress after RRSO. Seeing that a large proportion of women experience severe and persistent sexual complaints after RRSO makes it imperative that the search for an effective intervention must continue. A few general suggestions for future research can be made. Firstly, involving the partner of women suffering from menopausal complaints could lead to a more effective intervention, as relationship satisfaction is an important predictor of sexual functioning⁴. Secondly, it could be beneficial to combine treatment modalities such as psychological and pharmacological treatments, as sexuality has psychological as well as physical aspects³⁵. Lastly, HRT does not improve the domains of sexuality concerning sexual pleasure (e.g. desire and satisfaction)^{4,22-24,36,37}. Therefore, it is recommended that future research should not merely focus on improving the physical response (e.g. vaginal lubrication), but on designing psychological interventions that are effective in improving all domains of female sexual functioning³⁸.

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Appendices



Nederlandse Samenvatting

Vrouwen met een *BRCA1/2* genmutatie hebben een verhoogd risico op het ontwikkelen van borst- en eierstokkanker. Vrouwen met deze erfelijke aanleg voor borst- en eierstokkanker wordt aangeraden om hun borsten regelmatig te laten controleren op borstkanker of om hun borsten preventief te laten verwijderen. Met betrekking tot de eierstokken wordt geadviseerd deze preventief weg te laten halen, omdat controle van de eierstokken niet effectief is gebleken in het vroegtijdig opsporen van eierstokkanker. Het wel of niet preventief laten verwijderen van de borsten en/of eierstokken is een erg ingrijpende keuze. Bij de keuze om de borsten preventief te laten verwijderen speelt enerzijds mee dat na een preventieve borstverwijdering de kans op borstkanker erg klein is, maar anderzijds het kan een negatieve invloed hebben op de lichaamsbeleving en seksualiteit. Vrouwen die kiezen om hun eierstokken te laten verwijderen hebben eveneens een erg kleine kans om alsnog eierstokkanker te ontwikkelen. Echter komen deze vrouwen als gevolg van de eierstokverwijdering direct in de overgang terecht. Dit proefschrift richt zich op welke factoren van invloed zijn op het al dan niet preventief laten verwijderen van borsten en/of eierstokken en op welke gevolgen het verwijderen van de eierstokken heeft. Hieronder volgt een korte samenvatting van de verschillende hoofdstukken in deze thesis.

DEEL I:

FACTOREN DIE DE KEUZE BEÏNVLOEDEN OM BORSTEN EN/OF EIERSTOKKEN PREVENTIEF TE VERWIJDEREN

Om vrouwen te ondersteunen bij hun keuze om wel of niet hun borsten en/of eierstokken te laten verwijderen is het belangrijk om te weten welke factoren hun keuze beïnvloeden. Tijdens de gesprekken met de behandelend arts kan dan extra aandacht aan deze factoren worden besteed. In **hoofdstuk 2** is onderzocht wat de karakteristieken waren van vrouwen die sneller kozen voor een preventieve borstverwijdering na het bekend worden van hun *BRCA1/2* genmutatie. Dit is onderzocht in een groep van 407 vrouwen en uit dit onderzoek bleek allereerst dat ongeveer 36% van alle vrouwen hun borsten binnen vijf jaar preventief liet verwijderen nadat ze hoorden dat ze een *BRCA1/2* genmutatie hadden. Verder kozen vrouwen sneller voor een preventieve borstverwijdering als ze jonger dan 50 jaar waren, een moeder hadden met borstkanker, al eens borstkanker aan de andere borst hadden gehad en wanneer ze als behandeling van een eerdere borstkanker al een van hun borsten hadden laten verwijderen. Hieruit kunnen we afleiden dat vrouwen met een persoonlijke ervaring met kanker of een ervaring met kanker in hun familie eerder kiezen voor een preventieve borstverwijdering dan vrouwen die dit niet hebben. We verwachten dat dit komt door dat vrouwen met een dergelijke ervaring zich meer zorgen maken over het krijgen van kanker en daarom sneller hun borsten laten verwijderen.

Hoofdstuk 3 richt zich op de psychologische factoren die de keuze voor wel of niet preventieve borstverwijdering beïnvloeden. Deze factoren zijn onderzocht in een groep van 486 vrouwen die zelf nog nooit kanker hadden gehad, maar wel familieleden hebben die borstkanker hebben gehad. Voor ze getest werden op een genetische aanleg voor borst- en eierstokkanker vulden deze vrouwen een vragenlijst in met daarin de vraag of ze preventieve borstverwijdering zouden kiezen als blijkt dat ze inderdaad een *BRCA1/2* genmutatie hebben. Ook vulden ze vragen in over psychologische factoren zoals hoeveel zorgen ze zich maken over het krijgen van kanker, hun gemoedstoestand, het ervaren van controle over hun persoonlijke situatie, angstigheid en depressie. Hieruit bleek dat vrouwen met een zeer negatieve of juist een zeer positieve gemoedstoestand vaker de intentie uitspraken om hun borsten te laten verwijderen indien er sprake zou zijn van een *BRCA1/2* genmutatie. Daarnaast hadden vrouwen vaker de intentie om hun borsten te laten verwijderen als zij zich veel zorgen maken over het krijgen van kanker, zij de kans hoog inschatten om kanker te krijgen en wanneer zij een hoge mate van controle ervaren over hun persoonlijke situatie.

De gemoedstoestand die iemand ervaart wanneer zij worden geconfronteerd met een bepaalde complexe situatie kan helpen om in een dergelijke situatie toch een snelle en effectieve beslissing te kunnen nemen. Dit komt omdat vrouwen informatie over hun risico op kanker op twee manieren verwerken, namelijk door het risico op een verstandelijk niveau te begrijpen en door het risico tegelijkertijd op een intuïtieve manier te begrijpen. Dit intuïtieve begrip wordt waarschijnlijk gekleurd door ervaringen met vergelijkbare gebeurtenissen in het verleden (bijvoorbeeld een familielid met borstkanker). Deze gebeurtenissen dragen een bepaalde emotionele lading met zich mee, welke de gemoedstoestand beïnvloed en daarmee waarschijnlijk ook de beslissing om tot actie over te gaan.

Zoals eerder genoemd werd, is het met eierstokcontroles niet goed mogelijk om eierstokkanker in een vroeg stadium, wanneer de genezingskans nog hoog is, te ontdekken. Daarmee is eierstokcontrole weinig zinvol en wordt dit om die reden niet meer uitgevoerd in Universitair Medisch Centrum Groningen. In **hoofdstuk 4** werd onderzocht wat het effect is van het stoppen van eierstokcontroles op de keuzen om de eierstokken preventief te laten verwijderen. Er werd geconstateerd dat sinds eierstokcontroles niet meer worden uitgevoerd vrouwen vaker kiezen om hun eierstokken te verwijderen en dit vaker deden op een leeftijd voordat het risico op eierstokkanker sterk toeneemt. Vrouwen met twee of meer kinderen kozen het snelst voor risico reducerende eierstokverwijdering nadat het bekend werd dat zij een *BRCA1/2* mutatie hadden. Dit onderzoek toont aan dat vrouwen sneller overgaan tot preventieve eierstokverwijdering wanneer zij worden voorgelicht dat eierstokcontroles niet effectief zijn. Het feit dat vrouwen voor de leeftijd waarop het risico op eierstokkanker toeneemt deze keuze maken is gunstig. Blijkbaar is

er geen sprake van het “uit het oog raken” van vrouwen wanneer zij minder vaak contact hebben met hun behandelend arts vanwege het wegvallen van de periodieke controles.

DEEL II: PSYCHOLOGISCHE INTERVENTIES NA RISICO REDUCERENDE EIERSTOKVERWIJDERING.

Vrouwen die kiezen voor preventieve eierstokverwijdering komen vroegtijdig in de overgang omdat de hormoonproductie van de eierstokken abrupt wegvalt. Deze vrouwen hebben vaak last van klachten zoals opvliegers, nachtelijk zweten en vaginale droogheid. De ernst en duur van deze klachten worden vaak onderschat. Voor sommige vrouwen is het een optie om een hormoonbehandeling te krijgen om de ontbrekende hormonen weer aan te vullen. Voor vrouwen die borstkanker hebben gehad is dit geen optie, omdat hierdoor de kans om opnieuw borstkanker te krijgen stijgt. Omdat borstkanker vaker voorkomt bij vrouwen met een *BRCA1/2* mutatie is het van belang om te zoeken naar alternatieve behandelingen voor de overgangsklachten na preventieve eierstokverwijdering.

In **hoofdstuk 5** werden de ernst en duur van overgangsklachten gemeten in vrouwen die na een preventieve eierstokverwijdering in de overgang kwamen. Na gemiddeld 8 jaar had 70% van de vrouwen nog matige tot ernstige overgangsklachten. De klachten zoals pijn tijdens het plassen, een droge en/of jeukeyrige vagina en pijn tijdens seks kwamen het meeste voor. Ook werden psychologische klachten vaak genoemd (bijvoorbeeld depressiviteit, prikkelbaarheid, angstigheid). Vrouwen die in hun leven al eens borstkanker hadden gehad hadden meer overgangsklachten.

Zoals eerder gezegd, is het van belang om te zoeken naar alternatieve behandelingen voor de overgangsklachten na preventieve eierstokverwijdering. Een van de mogelijke alternatieven is een psychologische behandeling zoals (cognitieve)gedragstherapie of mindfulness training. Psychologische behandeling zou op twee manieren kunnen werken. Allereerst, zou het kunnen helpen door vrouwen technieken te leren waardoor zij beter om kunnen gaan met de klachten. Ten tweede kunnen psychologische behandelingen ook helpen stress te verlagen. Stress kan een trigger voor een opvlieger zijn en door stress te verlagen zou het kunnen dat een vrouw minder opvliegers heeft.

In **hoofdstuk 6** is op systematische wijze een overzicht gemaakt van al het eerder verrichte onderzoek naar de effectiviteit van psychologische behandelingen van overgangsklachten. Nadat de bevindingen van deze publicaties gecombineerd werden kon overkoepelend de conclusie worden getrokken dat psychologische behandelingen effectief waren in het verminderen van de ervaren last van opvliegers en andere overgangsklachten. Het aantal

opvliegers leek niet te verminderen onder invloed van psychologische behandelingen. Opvallend was dat er nauwelijks publicaties waren over het effect van psychologische behandelingen op seksuele problemen aangezien dit probleem wel vaak genoemd wordt door vrouwen na preventieve eierstokverwijdering.

In **hoofdstuk 7** wordt er een nieuwe studie beschreven die het effect van een stressverlagende mindfulness training op overgangsklachten onderzocht. Een verbetering ten opzichte van meeste eerdere studies is dat in deze studie ook het lange termijn effect onderzocht werd en daarnaast ook het effect op seksuele klachten in kaart werd gebracht. Uit deze studie bleek dat mindfulness training inderdaad de ervaren last van overgangsklachten verbeterde en dit effect was na een jaar nog steeds aanwezig. De seksuele klachten verbeteren niet onder invloed van de mindfulness training. De uitkomsten van dit onderzoek kunnen een eerste stap zijn in het vaker gebruik maken van psychologische behandelingen bij vrouwen na een preventieve eierstokverwijdering. Echter, er moet wel verder onderzoek verricht worden naar een veilige en effectieve behandeling van seksuele klachten na preventieve eierstokverwijdering.

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Curriculum Vitae

Catheleine van Driel is geboren op 1 maart 1989 te Zwolle. Zij heeft het tweetalig atheneum gedaan op de van der Capellen scholengemeenschap te Zwolle waar ze in 2007 haar diploma behaalde.

Hierop aansluitend startte ze haar studie Geneeskunde aan de Rijksuniversiteit Groningen waar ze diverse commissies deed, waaronder een bestuursjaar als voorzitter van de internationale geneeskunde studenten vereniging IFMSA-Groningen. Een proefproject van de junior scientific masterclass deed Catheleine onder de supervisie van prof. dr. G.H. de Bock. Dit proefproject vormde de basis voor een eerste publicatie en leidde in 2013 tot de start van een MD/PhD traject onder begeleiding van prof. dr. M.J.E. Mourits, prof. dr. G.H. de Bock en dr. J.C. Oosterwijk.

Naast het promotieonderzoek beschreven in deze thesis, deed Catheleine in deze periode haar senior co-schappen in het Röpcke-Zweers ziekenhuis in Hardenberg en het Isala in Zwolle waar ze in aanraking kwam met de psychiatrie. Voor haar semi-arts stage koos ze de polikliniek psychosen van het Universitair Centrum Psychiatrie te Groningen. Naast de klinische praktijk kwam ze hier in aanraking met het doen van onderzoek in deze populatie. Ze hoopt dit onderzoek in de toekomst voort te zetten. In 2018 startte zij de opleiding tot psychiater, tevens in het Universitair Centrum Psychiatrie te Groningen.

Catheleine woont samen met haar echtgenoot in Groningen.