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CONTENT

General introduction

1

Sexual functioning after breast cancer

Breast cancer (BC) is the most prevalent type of cancer in women, with an annual incidence of 14,765 in the Netherlands in 2017[1]. As a result of improved detection and treatment, survival rates have improved, resulting in more attention for the quality of life after BC, including sexual functioning. Sexual problems are a frequent, long-term consequence of BC and its treatment[2,3]. Between 45% and 77% of BC survivors report sexual problems after completion of treatment[4-6]. Frequently occurring sexual problems in BC survivors include decreased sexual desire, decreased sexual arousal and lubrication, dyspareunia, and vaginal dryness and atrophy[7-9].

The treatment of BC consists of a combination of surgery, chemotherapy, endocrine therapy, radiotherapy and immunotherapy[10]. Sexual problems after BC are mainly due to the effects of surgery, chemotherapy and endocrine therapy[7]. The results with regard to the effect of surgery on sexual functioning are mixed. Aerts and colleagues[11] reported worse sexual functioning among women who had undergone a mastectomy than those who had had breast conserving treatment (BCT). Howes et al.[12] reported similar results, and additionally found that the sexual wellbeing of women with BCT was lower than that of women with a breast reconstruction. Neto et al.[13] reported worse sexual functioning among women who had had a mastectomy alone compared to those who had undergone a breast reconstruction. Other studies failed to detect significant differences in sexual functioning between women treated with mastectomy versus BCT or mastectomy plus breast reconstruction[14,15]. Together, these results challenge the often held belief that less surgery will always result in better sexual functioning.

More consistent is the finding that women often report a decrease in body image after BC treatment[16,17] and that women who experience body image issues more often report sexual problems[6]. Studies have demonstrated that women who had a BCT experience better body image than women with a breast reconstruction[15,18] or mastectomy[15,19], and that women with a breast reconstruction have better body image than women with a mastectomy[18,19]. However, differences between surgical groups in body image may diminish in the longer-term[20]. Other surgery-related aspects that may play a role in sexuality and body image after BC include nipple preservation, which can result in better body image, higher satisfaction with nipple appearance, higher nipple sensitivity[21] and greater sexual well-being[22] than nipple reconstruction. Type of surgery can also affect the sensitivity of the breast, with women reporting more pleasure from breast caressing after BCT than after a breast reconstruction[14].

Chemotherapy can lead to premature ovarian failure, resulting in decreased systemic estrogen levels and abrupt temporary or permanent amenorrhea[23], which in turn can cause vaginal dryness and atrophy[24] and pain during intercourse[25]. Chemotherapy-related menopause is a significant risk factor for sexual dysfunction[26]. Similar sexual problems can occur as a result of endocrine treatment[27], which is used in patients with a hormone

receptor-positive BC[28-30] and which affects the working mechanism and production of estrogen. Although the findings regarding the effect of endocrine treatment on sexual functioning are somewhat mixed, studies show that tamoxifen and aromatase inhibitors can lead to sexual problems[6,27,31-33]. Women who experience a chemotherapy- or hormonal therapy-induced menopause report significantly lower sexual desire than women whose adjuvant treatment did not result in acute menopause[34].

Both surgery and radiotherapy can cause lymphedema in the arm[35]. Breast-cancer related lymphedema can contribute to sexual concerns, such as a compression garment hindering sexual intimacy or affecting feelings of one's attractiveness, or discomfort/pain caused by the lymphedema[36,37]. With regard to a direct relationship between radiotherapy and sexual functioning, Devulapalli et al.[38] reported that non-irradiated BC patients who underwent prosthetic or autologous breast construction had higher levels of sexual well-being than irradiated patients. Although the researchers did not provide an explanation for the observed association between radiotherapy and sexuality, it might be that women's sexual functioning is affected by the side effects of radiotherapy such as capsular contracture of the breast implant[39] or asymmetry of the breasts in women treated with breast conserving treatment[40]. To date, little is known about the effect of immunotherapy on sexual functioning after BC.

Other frequently reported consequences of BC treatment that may affect a woman's sexuality include fatigue[41], weight gain[5,42], hair loss[43,44], and fear of loss of fertility[45]. Although the diagnosis and treatment of any type of cancer can disturb sexual functioning, BC raises particular concerns because of the function of the breast as a source of erotic pleasure and stimulation[46]. The partner-relationship can also be affected by the distress surrounding diagnosis and treatment[47]. Not only the sexuality of BC survivors, but also that of their partners can be affected by BC and its treatment, which is reflected in the finding that as high as 75% of partners of BC survivors report that the onset and treatment of BC affected their sexual functioning and their sexual relationship[48].

Treatment of sexual dysfunction

Although the prevalence of sexual problems among BC survivors is relatively high, only a small proportion of women experience sexual problems that meet criteria for a diagnosis of sexual dysfunction according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV[49]), or the more recently published DSM-5[50]. Women with a DSM-IV dysfunction experience severe sexual problems that cause significant distress and that are not better accounted for by another psychological disorder, such as depression[49,50].

In general, sexual dysfunctions can be treated effectively with psychological interventions, such as sex therapy, sexual skills training and cognitive behavioral therapy (CBT)[51]. In their meta-analysis of psychological interventions for male and female sexual dysfunctions, Frühauf et al.[51] included 20 randomized controlled trials (RCTs) comparing a psychological

intervention to a waiting-list control group. The studies reviewed evaluated a range of psychological interventions, including sexual skills training, sex therapy, systematic desensitization, marital therapy, cognitive behavioral therapy (CBT) and educational interventions. The overall post-treatment effect size for reduction in symptom severity for men and women was d = .58. They concluded that psychological interventions are particularly effective in lowering the symptom severity of women experiencing hypoactive sexual desire disorder (d = .91) and orgasmic disorder (d = .46). No clear evidence was found for erectile dysfunction, premature ejaculation, vaginismus and mixed sexual dysfunctions. However, the authors emphasize that the non-significant treatment effects should be interpreted with caution, as some RCTs had small sample sizes and for certain types of sexual dysfunction few or no RCTs were available. Furthermore, the treatment types that were evaluated most frequently were sexual skills training and sex therapy. Frühauf et al.[51] emphasize the need for additional RCTs evaluating psychological therapies for sexual dysfunction, as evidence varied considerably across sexual dysfunctions, the studies varied in methodological quality and quality of reporting, for some dysfunctions the overall power of studies was low, and long-term effects of interventions were often not assessed.

Psychological therapies for sexual dysfunction often include elements of sex therapy, which is a treatment approach first outlined by Masters and Johnson[52]. Sex therapy typically consists of a combination of components that can be tailored to the needs of a patient or couple. An important element of sex therapy is sensate focus exercises, in which a couple performs a hierarchically structured program of sensual touching exercises with verbal and tactile feedback, starting with the body's non-erogenous zones. With the successful completion of each exercise, a subsequent exercise is introduced, with the aim of progressing to erogenous and genital touching and, eventually, sexual intercourse or other sexual activity. The goal of sensate focus exercises is to reduce anxiety and avoidance of sexual activity, to discover what feels pleasurable and to communicate this to the partner, and to be intimate without an exclusive focus on penile-vaginal penetration or orgasm.

Other components of psychological therapies for sexual dysfunction include increasing self-exploration and body awareness, improving partner communication, and improving skills of erotic stimulation. Psychosexual therapy can also include pelvic floor (relaxation) exercises, sexual fantasy training and exercises to reduce catastrophic fear of pain during sexual activity[53,54].

The behavioral components of psychosexual therapy aim to increase positive sexual experiences in order to develop a stronger motivation to engage in sexual activity. These behavioral components are often complemented with cognitive therapy, in which the goal is to identify and modify the patient's dysfunctional automatic cognitions, attributions or beliefs that hamper a pleasurable sexual experience or that inhibit sexual desire or arousal. Research has demonstrated the efficacy of CBT for several female sexual dysfunctions, including hypoactive sexual desire disorder[55-57], orgasmic disorder[58-60], sexual pain[61-63] and

vaginismus[64]. In their review of studies of the efficacy of CBT for female sexual dysfunctions, and consistent with the conclusion of Frühauf et al.[51], Ter Kuile et al.[53] conclude that evidence is strongest for hypoactive sexual desire disorder and orgasmic disorder. They argue that, despite its wide use in clinical practice, more research into the efficacy of CBTs for female sexual dysfunctions is warranted, as the majority of previous studies had methodological limitations[53], such as small sample sizes in many studies (e.g., varying between 10 to 38 participants per study arm[55,56,58,60,62]).

Psychosexual interventions for BC survivors

Several programs have been developed to alleviate sexual problems in BC survivors. In an RCT, Rowland et al.[65] evaluated a 6-week psycho-educational group intervention in improving the sexual well-being of BC survivors who reported moderately severe problems in body image, sexual function or partner communication. The program aimed to improve satisfaction with sexual functioning and the intimate relationship, with each session including a psycho-educational component, a communication-training component and a sex therapy-related component based on the principles of sensate focus therapy. As only 27% of women assigned to the intervention group actually attended at least one of the sessions, intention-to-treat (ITT) as well as as-treated and per-protocol (PP) analyses were performed. The results of the ITT analysis indicated that the intervention group reported a larger improvement in satisfaction with the sexual relationship, relationship adjustment and partner communication than the control group. However, the latter two outcomes were no longer statistically significant after adjustment for multiple testing. In the as-treated and PP analyses, the intervention group had a significantly larger improvement in relationship adjustment and partner communication. Although the results indicated that a psycho-educational group intervention has positive effects on sexual satisfaction and the partner relationship, no significant improvements were observed for sexual pain, satisfaction with the variety of sex or sexual comfort. Limitations of the study included use of non-validated sexuality measures, no reporting of effect sizes and high attrition from the intervention.

Scott et al.[66] compared three interventions to promote psychosocial adjustment in women with BC or gynaecological cancer. The interventions included medical information education (MI), individual patient coping training (PC) and couple-coping training (CanCOPE). MI consisted of five brief telephone calls in which education on cancer diagnosis and medical treatments was provided, but no psychological interventions. PC included the components of MI, with the addition of coping education and supportive counseling. The PC intervention consisted of four face-to-face sessions and two telephone calls. Topics included psychological reactions to cancer treatment, improving coping styles, identifying and challenging negative cancer-related cognitions, and counseling for self-confidence and body image. CanCOPE was similar to PC, but was couple-focused and contained an extra session focusing on mutual support and sexual counseling, including discussing the goals

of resumption of a mutually satisfying sex life, advice about sexual positions, and gradual introduction of sexual activity through sensate focus exercises. At 12-months follow-up, women in the CanCOPE group reported a sustained improvement in positive sexual self-schema ($d_{\text{CanCOPE vs. PC\&MI}} = .80$), sexual intimacy with the partner ($d_{\text{CanCOPE vs. MI}} = .91$) and perceptions of their partner's view of their body ($d_{\text{CanCOPE vs. MI}} = .44$) compared to the PC and MI groups. No effect on problems with sexual functioning was found, but the authors indicated that this might be a result of the low baseline level of sexual problems reported by the BC survivors, which was comparable to that of healthy women. Limitations of the study included use of a statistical approach that applies listwise deletion of participants with missing data, the relatively small sample size and the absence of a no-treatment control group.

In an RCT, Kalaitzi et al.[67] evaluated the efficacy of a 6-session psychosexual intervention for women who underwent a mastectomy without chemotherapy, endocrine therapy or radiotherapy, for in situ BC and their partners. The first session started during the women's hospitalization. The intervention included communication training, sensate focus exercises and exercises for body image issues, and was compared with a no-treatment control group. Women in the intervention group reported a decrease in depressive and anxiety symptoms, and an improvement in body image, relationship satisfaction, feelings of attractiveness, orgasm frequency and frequency of initiation of sex from pre-surgery to post-intervention. Limitations of the study include the small sample size (20 participants per study arm), no reporting of effect sizes, and the use of an inappropriate statistical approach with only separate within-group and no between-group analyses for each outcome. Also, the study sample was probably less affected sexually than other BC survivors in that they had undergone surgery alone, without any form of adjuvant treatment.

The studies of Rowland et al.[65], Scott et al.[66] and Kalaitzi et al.[67] had several methodological limitations. Additionally, these studies focused on BC survivors with less severe sexual problems (i.e., without a DSM-IV diagnosis of sexual dysfunction), which may have prevented the detection of positive effects in (a larger number of areas of) sexual functioning. This was, for example, the case in the sexual functioning scores of the study sample of Scott et al.[66]. BC survivors suffering from a DSM-IV sexual dysfunction might be in greater need of professional help. However, to date, no psychosexual intervention for BC survivors with a DSM-IV diagnosis has been developed and tested. Nonetheless, the previous studies in BC survivors demonstrated that psychosexual interventions are a promising intervention for improving the sexual well-being of this population.

Despite the availability of effective programs to treat sexual problems in BC survivors, there is a discrepancy between BC survivors' reported need for professional help and the actual uptake of care. Kedde et al.[4] reported that only 40% of BC survivors who felt a need for professional care actually consulted a health care professional. Hill et al.[68] reported that, although 42% of gynecological cancer and breast cancer survivors reported a need for

care, only 7% of these women actually sought such care. Not only BC survivors, but also health care professionals may be reluctant to discuss sexual health issues post-BC. Barriers for health care professionals include time constraints, embarrassment, lack of knowledge and experience in the area of sexual functioning in general, and after breast cancer in particular, and/or lack of referral options to provide support if needed[69].

Internet-based sex therapy

Internet-based CBT might be a welcome addition to the sexual health care that can be offered to BC survivors. Advantages of Internet-based therapy include a feeling of privacy, convenience and accessibility[70-72]; features that might be particularly attractive when discussing sexual functioning.

There is growing evidence that Internet-based CBT programs are an effective treatment method for a range of psychological problems, including depression[73], anxiety[74] and eating disorders[75]. Evidence is well-established for treatment of depression, social phobia and panic disorder[76]. Research has demonstrated that Internet-based CBT tends to be as effective as traditional face-to-face CBT[77], with an effect size (ES) that is quite similar to the average effect size of traditional face-to-face therapy (ES = .53)[78]. In an unguided Internet-based therapy program, participants complete a treatment protocol independently, without support of a therapist. Such a program consists primarily of psycho-educational information and instructions for exercises. In guided Internet-based therapy, a counselor is available, typically via email or telephone, to provide support in working through the treatment program. In general, guided Internet-based therapy appears to be more effective than unguided Internet-based interventions (ES_{guided} = 1.00 vs. $ES_{unguided}$ = .24/.26[74], or standardized mean difference = -.27, favoring guided therapy[79]).

Internet-based therapy programs for sexual dysfunctions have also been developed and tested, with most studies focusing on male sexual dysfunction[80-87]. More recently, Internet-based therapies for female sexual dysfunctions have been evaluated[88-93].

In an RCT, Jones and McCabe[88] evaluated a 10-week Internet-based CBT program in women from the general population with self-reported sexual problems. The therapy program consisted of five modules, including topics and interventions such as sensate focus exercises, discovering pleasurable bodily sensations, self-stimulation, communication exercises, experimenting and feeling comfortable with sexual intercourse, and exploring different intercourse positions. Weekly contact with a therapist took place via email. Women in the intervention group reported a larger improvement in sexual desire, sexual arousal, vaginal lubrication, orgasmic function, sexual satisfaction, genital pain and overall sexual functioning immediately post-CBT compared with the control group (partial η^2 = .18-.49). The intervention group also reported a larger improvement in communication with the partner, sexual intimacy and emotional intimacy as compared to the control group. All improvements were maintained during a three-month follow-up period. We would note

that there was some drop-out in completion of study assessments, and that Jones and McCabe[88] only included women in the analysis who were sexually active at baseline, resulting in further reduction of the already small sample size.

Hucker and McCabe[90] evaluated an online mindfulness-based CBT program in women with self-reported sexual difficulties, and evaluated the effect on relationship functioning. Biweekly online chat groups were integrated in the treatment as a platform for cognitive therapy and social support. The program included six online modules and unlimited email contact with a therapist. General mindfulness-based exercises as well as mindfulness during sensate focus exercises were part of treatment. The intervention group reported larger improvements in sexual intimacy (partial $\eta^2 = .26$), emotional intimacy (partial $\eta^2 = .08$) and partner communication (partial $\eta^2 = .08$) compared to the waiting-list control group. Improvements in emotional intimacy and communication were maintained after three months follow-up.

With regard to female cancer survivors, studies have been conducted in gynaecological cancer[91,92] and BC survivors[89]. In an RCT, Classen et al.[92] evaluated a 12-week online intervention for psychosexual issues in sexually distressed gynaecological cancer survivors. The program included psycho-educational information regarding the consequences of gynaecological cancer treatment on sexuality, and a professionally moderated forum with weekly discussions focusing on different, sexuality-specific topics. Women were encouraged to share their experiences in the discussion forum. The intervention group reported a larger reduction in sexual distress from pre- to post-intervention compared to the control group, albeit small ($d = .32$) and not statistically significant, with the latter probably as a result of the small sample size. Semi-structured interviews were conducted with women who received the intervention[91]. Women reported benefits from participating in the intervention, including receiving support from group members and forum moderators, increased emotional well-being, improved body image and sexuality and comfort in discussing sexuality online.

Schover et al.[89] evaluated a 12-week Internet-based intervention for sexual problems after treatment of breast cancer and gynaecological cancer. A group receiving Internet-based self-help was compared to a group receiving Internet-based self-help and three supplemental in-person counseling sessions. The Internet-based intervention included components such as psycho-education about the sexual and fertility consequences of cancer treatment, genital anatomy (including a vulvar self-portrait with pain and pleasure mapping), vaginal dryness and pain, sensate focus exercises, and communication exercises. The program included text, graphics, animations and videos. The guided self-help group reported increased overall sexual functioning at post-treatment, whereas only a trend of improvement was observed in the self-help group. The treatment gains were retained during a six-month follow-up period.

These first studies regarding BC-specific psychosexual interventions[65-67] and Internet-based sex interventions in cancer survivors[89,91,92] and the general population[88,90] indicate that these interventions are a feasible and potentially effective treatment method for female sexual dysfunction. However, the sample sizes of the studies were small[66,67,88-90,92], attrition from the intervention was high[65], drop-out from study assessments resulted in a small remaining sample size for analyses[88], no-treatment control groups were absent[66,89], effect sizes were not always reported[65,67,89], statistical approaches that use listwise deletion of participants with missing data were used[66], and only a minority of the studies included a CBT intervention[88,90], even though this is the most commonly used intervention for the treatment of sexual dysfunction in the clinical practice. Importantly, no previous studies developed and evaluated a therapy program for BC survivors with a formal diagnosis of sexual dysfunction according to the criteria of the DSM-IV, even though the need for treatment is high in this population given the severity of their sexual problems.

Objective of the thesis and research questions

In this thesis, we report on a randomized controlled trial evaluating the efficacy of an Internet-based CBT program in improving the sexual functioning of BC survivors with a sexual dysfunction according to the criteria of the DSM-IV[49]. The Internet-based CBT program offered in the RCT described in this thesis is a guided, Internet-delivered treatment, in which structured psycho-educational materials and exercises are offered via an Internet platform, with personal guidance of a therapist who provides support and feedback via email. The research questions investigated were:

1. Which patient-related and clinical factors are associated with BC survivors' sexual functioning and sexual distress, and with the sexual functioning of their partners?
2. What is the short-term efficacy of Internet-based CBT in improving the sexual functioning, sexual distress and other psychosocial outcomes in BC survivors with a DSM-IV sexual dysfunction?
3. What is the long-term effect of Internet-based CBT on the sexual functioning, sexual distress and other psychosocial outcomes in BC survivors with a DSM-IV sexual dysfunction?
4. What are the predictors of post-CBT sexual functioning and sexual distress of BC survivors with a DSM-IV sexual dysfunction who received Internet-based CBT?
5. What is the effect of Internet-based CBT on the sexual functioning and relationship satisfaction of partners of BC survivors with a DSM-IV sexual dysfunction?

Outline of this thesis

Chapter 2 describes the study design of the randomized controlled trial, in which the rationale and study methods are reported. **Chapter 3** describes the sexual functioning of BC

survivors with a DSM-IV sexual dysfunction and that of their partners. **Chapter 4** presents the effects of the randomized controlled trial evaluating the efficacy of an Internet-based CBT program for DSM-IV sexual dysfunctions in BC survivors on sexual functioning, sexual distress, body image, menopausal symptoms and other psychosocial outcomes. **Chapter 5** describes the long-term effects of the Internet-based CBT program on the sexual functioning, sexual distress and other psychosocial outcomes of BC survivors with a DSM-IV sexual dysfunction. **Chapter 6** describes the predictors of a positive outcome of the Internet-based CBT program. **Chapter 7** reports on the evaluation of the changes that occurred during the Internet-based CBT and during a follow-up period in partners of BC survivors with a sexual dysfunction. This thesis ends with a general discussion of the research and outcomes in **Chapter 8**, and an overall summary in **Chapter 9**.

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2

Internet-based cognitive behavioral therapy for sexual dysfunctions in women treated for breast cancer: design of a multicenter, randomized controlled trial

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ABSTRACT

Background

Sexual dysfunction is a prevalent, long-term complication of breast cancer and its treatment and can be treated effectively with face-to-face sexual counselling. However, relatively few women actually opt for face-to-face sex therapy, with many women indicating that it is too confronting. Internet-based interventions might be a less threatening and more acceptable approach, because of the convenience, accessibility and privacy it provides. Recent studies have demonstrated the efficacy of Internet-based programs for improving sexual functioning in the general population. The objective of the current study is to investigate the efficacy of an Internet-based cognitive behavioral therapy (CBT) program in alleviating problems with sexuality and intimacy in women who have been treated for breast cancer.

Methods/design

In a multicenter, randomized controlled trial we are evaluating the efficacy of an Internet-based CBT program in reducing problems with sexuality and intimacy in breast cancer survivors. Secondary outcomes include body image, marital functioning, psychological distress, menopausal symptoms, and health-related quality of life. We will recruit 160 breast cancer survivors (aged 18-65 years) with a formal DSM-IV diagnosis of sexual dysfunction from general and academic hospitals in the Netherlands. Women are randomized to either an intervention or waiting-list control group. Self-report questionnaires are completed by the intervention group at baseline (T0), ten weeks after start of therapy (T1), post-treatment (T2), 3 months post-treatment (T3), and 9 months post-treatment (T4). The control group completes questionnaires at T0, T1 and T2.

Discussion

There is a need for accessible and effective interventions for the treatment of sexual dysfunctions in breast cancer survivors. This study will provide evidence about the efficacy of an Internet-based approach to delivering a CBT intervention targeted specifically at these sexual health issues. If proven to be effective, Internet-based CBT for problems with sexuality and intimacy will be a welcome addition to the care offered to breast cancer survivors. Hopefully this therapy will lower the barrier to seeking help for these problems, resulting in improved quality of life after breast cancer.

INTRODUCTION

Breast cancer is the most common type of cancer among women in the Netherlands[1]. Improved breast cancer screening and treatment have resulted in increased survival rates[2]. Consequently, more interest and research has focused on the health-related quality of life (HRQL) of breast cancer survivors, including issues of sexuality and intimacy.

The prevalence rates for sexual dysfunctions as a result of breast cancer treatment vary between 30% and 100%[3-7]. Breast cancer survivors (BCS) experience worse sexual functioning compared to women without a history of cancer[8-10]. Frequently reported problems include decreased sexual desire (23-64%), decreased sexual arousal or vaginal lubrication (20-48%), anorgasmia (16-36%) and dyspareunia (35-38%)[3].

The different components of breast cancer treatment can all directly or indirectly affect sexual functioning[3]. Previous studies have shown that women who have received chemotherapy are at a higher risk of developing sexual dysfunctions than women who have not undergone this treatment[8,11-17], regardless of the type of surgery[14,18]. Chemotherapy can cause premature, abrupt menopause, leading to reduced sexual desire in some women[19]. It can also induce vaginal dryness and atrophy, which subsequently can affect sexual functioning[6,8,12,13,15,20]. Results with regard to endocrine treatment are somewhat mixed, but studies show that tamoxifen and aromatase inhibitors can lead to sexual problems[21-27]. The evidence pertaining to the effect of surgery on sexual functioning is mixed[28-30], with some studies showing that women who undergo a mastectomy report more problems in sexual functioning than women who receive breast conserving therapy[28,31,32], while other studies have not found an association between type of surgery and sexual functioning[18,29]. More consistent is the finding that mastectomy more often results in compromised body image than does breast conserving treatment[4,13,28]. Other common complaints after breast cancer treatment are concerns about sexual attractiveness and femininity, fatigue, anxiety and depression, fear of loss of fertility, and overall decreased HRQL[3,18,33,34]. Emotional well-being and the quality of the partner-relationship can also be affected by the distress surrounding diagnosis and treatment[35-37]. Although the diagnosis and treatment of any type of cancer can cause problems in sexual functioning[3], breast cancer raises particular concerns because of the importance of the breast in feminine sexuality and the breast as a source of erotic pleasure and stimulation[33].

Sexual dysfunctions can be treated effectively with face-to-face forms of sex therapy[38-41]. Sex therapy typically comprises a flexible treatment program including a number of elements that can be tailored to the needs of individuals and couples. It typically involves behavioral components derived from the sex therapy developed by Masters and Johnson[42], i.e. psycho-education about sexuality and sexual dysfunction, a temporary ban on intercourse, and sensate focus exercises. A ban on intercourse can break the vicious cycle of fear of sexual intercourse and subsequent negative experience and disappointment, and

offers the opportunity for positive experiences by eliminating or reducing performance demand[43]. Sensate focus exercises form a hierarchically structured exercise program, through which partners gradually reintroduce the consecutive phases of sexual contact. The exercises are targeted at becoming more comfortable with one's own body and achieving sexual intimacy with one's partner, both physically and emotionally. Other goals are to discover new approaches to sexual stimulation, and to encourage communication between partners about sexual experiences, sexual desires and sexual boundaries. These behavioral elements of sex therapy are usually combined with cognitive therapy[40,43]. Through cognitive therapy, therapist and client aim to detect and modify the client's dysfunctional, disturbing cognitions regarding sexuality that arise during exercises. Via the method of cognitive restructuring, the dysfunctional cognitions are replaced by more functional appraisals. Sex therapy is often delivered in a couple format, but individual applications and group therapy formats are also described in the literature[44,45].

The efficacy of different types of face-to-face therapy for female sexual dysfunction (FSD) has been demonstrated, including sexual desire and sexual arousal disorder[40,46,47], orgasmic disorder[48,49], sexual pain[50,51], and vaginismus[52,53]. Several modified treatment programs have been developed and evaluated for breast cancer survivors[44,54]. Interventions with stronger effects tend to be couple-focused and include treatment components that educate both partners about the woman's diagnosis and treatment, promote couples' mutual coping and support processes, and include treatment components that make use of specific sex therapy techniques addressing sexual and body image concerns[44,54].

Despite the availability of effective treatments for sexual dysfunctions, there is a significant discrepancy between the self-reported need for professional sexual health care in cancer survivors and the actual uptake of care[5,55]. Kedde et al.[5] reported that only 40% of BCS who felt a need for care actually consulted a health professional. Hill et al.[55] reported that, although over 40% of gynaecologic cancer and breast cancer survivors expressed interest in receiving professional care, only 7% had ever actually sought such care.

Although sexual functioning is an important issue, health care professionals may be reluctant to query breast cancer patients about sexual problems during medical consultations, due to time constraints, embarrassment, lack of knowledge and experience in this area, and/or lack of resources to provide support if needed[56,57]. It may also be difficult for patients to initiate discussion about their sexual difficulties with their health care professional[58-60]. It has been suggested that when reporting sensitive or potentially stigmatizing information, individuals may feel more comfortable undergoing assessment and treatment via the Internet[61,62]. This idea is supported by a survey[63] that was conducted in women who attended an informational meeting of a sexuality and breast cancer clinic, but who subsequently did not follow-up for an appointment for face-to-face counselling. While some women indicated that they did not consider treatment of their sexual problems to be necessary, others indicated that they did not wish to undergo such treatment in a

hospital-setting, or that the face-to-face setting of the counselling formed too great a barrier. Many respondents suggested that Internet-based therapy would be a less threatening and more acceptable approach. The advantages of Internet-based therapy include privacy, convenience and accessibility[64-66], all of which may be particularly attractive in the area of sexual problems.

There is growing evidence that Internet-based CBT is an effective method to treat a range of psychosocial problems[67-74]. More recently, Internet-based CBT programs for sexual dysfunctions have been developed and tested[45,66,75-78]. However, most of these online interventions have focused on male sexual dysfunctions[75,76,78-81]. Early trials have demonstrated the applicability and effectiveness of online CBT for FSD in the general population[77], and of an online intervention for sexual problems in breast cancer survivors[82]. However, the efficacy of an Internet-based CBT for sexual problems in BCS has not yet been researched.

In this article, we describe the design of a randomized, controlled, multicenter trial that evaluates the efficacy of an Internet-based CBT program for sexual dysfunctions in women who have been treated for breast cancer. We hypothesize that women in the Internet-based CBT group will report a significantly greater improvement in sexual functioning and intimacy than women in a waiting-list control group. Secondarily, we hypothesize that women who undergo the Internet-based CBT will report significantly less psychological distress and fewer menopausal symptoms, and a significantly greater improvement in body image, marital functioning and HRQL than women in the control group.

METHODS

In this study, patients are randomized to either an intervention group or a waiting-list control group. Women in the intervention group will undergo an Internet-based CBT aimed at alleviating problems with sexuality and intimacy. The design of the trial and the anticipated flow of participants are displayed in Figure 1. The trial has been approved by the Institutional Review Board of The Netherlands Cancer Institute (under number NL44153.031.13), as well as by all review boards of the hospitals from which patients are being recruited (for a list of the participating hospitals, see the Acknowledgements section). Patient recruitment and data collection started in September, 2013.

Study sample

The study sample will be composed of 160 women fulfilling the following inclusion criteria: (1) age 18 to 65 years (the upper limit of 65 years is not based on any assumption regarding the salience of sexuality with increasing age, but on the smaller chance of access to Internet in this age group); (2) a history of histologically confirmed breast cancer (stages: T1-T4, N0-N1 and M0); (3) a diagnosis of breast cancer six months to five years prior to

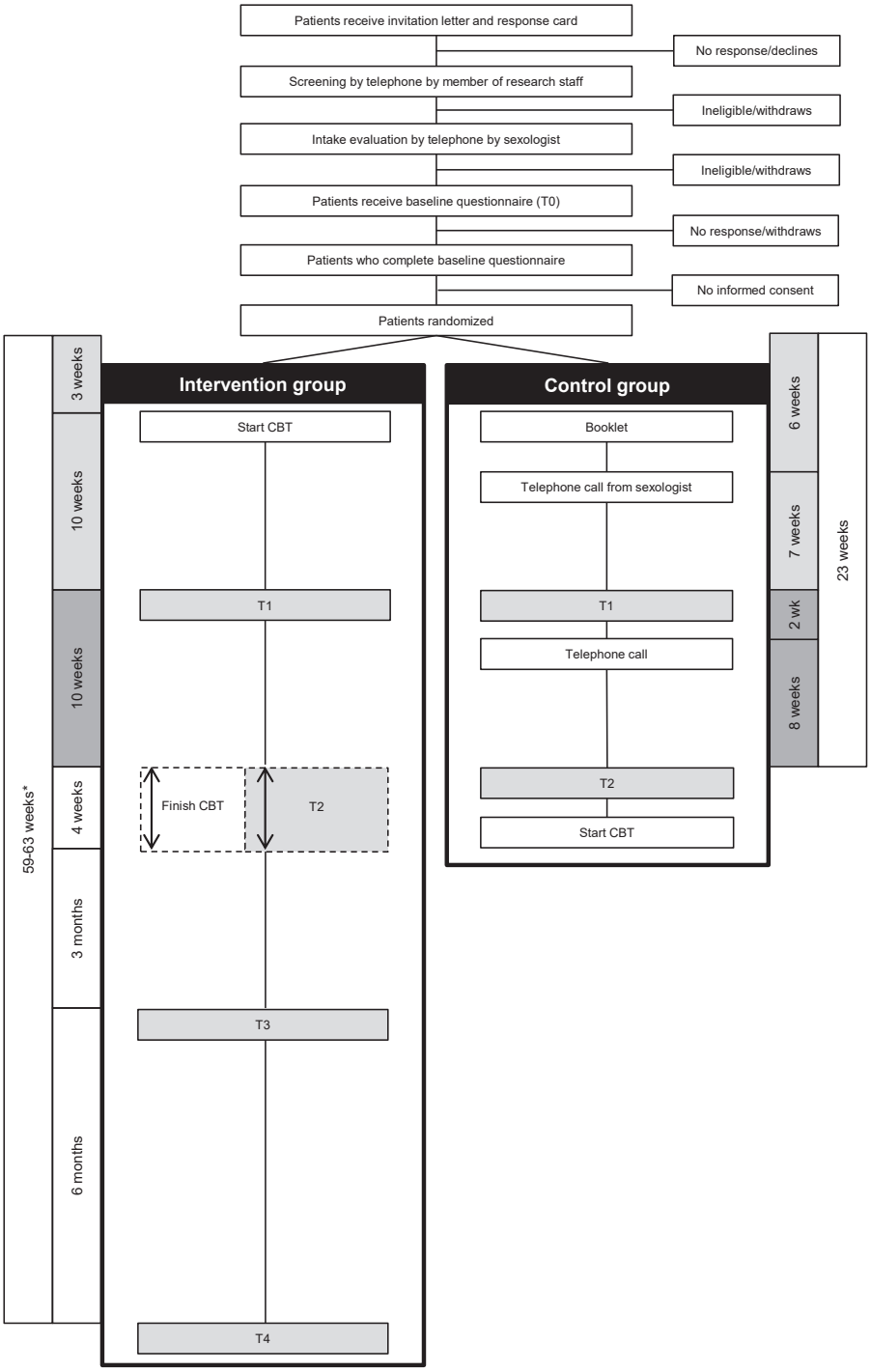

Figure 1. Overview of study procedures. *The total duration of study participation is dependent on the duration of the CBT.

study entry; (4) completion of breast cancer treatment (with the exception of endocrine therapy and immunotherapy); (5) disease-free at time of study entry; (6) a basic fluency in the Dutch language (for assessment and therapy purposes); and (7) a formal diagnosis of sexual dysfunction according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV[83] (to be established by an experienced sexologist during an intake interview). Single as well as partnered women can participate in the study. Sexual orientation is irrelevant for eligibility.

Exclusion criteria are: (1) no access to Internet; (2) serious cognitive or psychiatric problems (i.e., depression, alcohol dependency, or psychotic disorders) as determined on the basis of the Mini International Neuropsychiatric Interview[84]; (3) treatment for another type of cancer (with the exception of cervix carcinoma in situ and basal cell carcinoma); (4) presence of severe relationship problems for which the Internet-based program is not appropriate; (5) participation in a concurrent therapy program to alleviate problems with sexuality or intimacy; (6) participation in a concurrent CBT program for other psychological problems; and (7) participation in another trial investigating problems with sexuality/intimacy.

Recruitment and randomization

Patients are recruited from 10 community and university hospitals in the Netherlands and are identified through the hospital registries by their physician, or by means of the database of the Netherlands Cancer Registry. Selected patients are sent an invitation letter describing the study and Internet-based therapy, and are asked to return a response card to indicate if they are interested in participation. In case of no interest, women are asked to specify their reason(s) for this on the card. In the absence of a response, a reminder is sent three weeks after the first mailing. Women who are not interested in participation or who do not respond to the reminder are not contacted again.

Interested women are screened for eligibility twice: first by a member of the study staff and subsequently by a sexologist. In these interviews, more information about the study procedures and therapy is given and eligibility criteria are checked. The sexologist carries out a diagnostic interview to determine final eligibility of the woman, and the Mini International Neuropsychiatric Interview[84] is completed. All sexologists involved in the study are female, and have undergone special training in the application of the Internet-based CBT program.

Eligible women are sent a baseline questionnaire (T0) and an informed consent form. Study questionnaires can be completed online or in a paper-and-pencil format. The baseline questionnaire assesses sociodemographic and medical background variables, and the study outcomes. If the score of the marital adjustment subscale of the Maudsley Marital Questionnaire[85] (see 'Study measures' section) exceeds the cut-off score of 35, the eligibility of the participant is discussed once more with the sexologists to determine if the nature

and severity of the relationship problems would recommend treating these problems prior to tackling the sexual dysfunction, thus resulting in exclusion from study participation.

Consenting women are randomized to either an intervention group (n = 80) or a waiting-list control group (n = 80) using the minimization technique, with type of surgery (breast conserving therapy; mastectomy only; mastectomy with breast reconstructive surgery), current endocrine treatment for breast cancer (yes; no), time since breast cancer diagnosis (< 1 year; 1-3 yrs; 3-5 yrs), and menopausal status (premenopausal; postmenopausal) as stratification variables.

Study arms

Intervention group: Internet-based CBT program

Each woman is assigned a sexologist who guides her through the Internet-based CBT program. Contact with the therapist is web-based, via a secured, password-protected website. From a total of 10 modules, the sexologist selects four to five modules that best fit the sexual problems of the client. The Internet-based CBT program was originally developed for use in the general population at Virenze, a mental health center located in Utrecht, the Netherlands. The program was adapted for use specifically for breast cancer survivors. This involved editing and adding text related to the physical and psychosexual problems often experienced by women who have had breast cancer. The therapists are licensed psychologists and sexologists who have undergone additional training in issues relating to breast cancer, and in the use of the Internet program.

A description of the content of the different program modules is provided in Table 1. Each module contains several interventions, each of which comprises the following elements: (1) introduction, (2) psycho-education, (3) "homework" assignments (e.g., registration exercises; discuss intimacy with partner; sensate focus exercises) and (4) reporting back to the therapist and receiving feedback on the homework assignments. The modules can be used in varying order, leading to a tailored and flexible treatment program consisting of a maximum of 20 therapy sessions that are completed within a period of 24 weeks. A minimum of five sessions is considered the lower limit of sessions required in order to expect an effect. The average time investment for a participant is 90-120 minutes per week. Women are motivated by the sexologist to involve their partner in the treatment, but partner involvement is not mandatory. The time limit within which the therapist should respond to incoming messages from a client is set at five working days. Weekly contact between therapist and client is pursued. After 10 weeks of treatment, a mid-term evaluation is held to reflect on the progress so far, and to adjust goals, if necessary, for the remaining part of treatment. The Internet-based CBT program is provided at no cost to the woman.

Table 1. Description of therapy modules

Module 1: Put your problem into words
In this module the client describes her sexual problems, and learns how sexuality can be influenced by the treatment of breast cancer. The sexual response curve and female sexual dysfunctions are elaborated on. Furthermore, information is given about what intimacy is and how it interplays with sexuality. Women are encouraged to discuss their sexual problems with their partner.
Module 2: How is my relationship doing?
In this module the client explores the level of intimacy in her relationship, becomes aware of the amount of quality time spent with the partner, and receives psycho-education about sex and intimacy. The importance of open communication with the partner is discussed, and advice is given on how to improve communication with regard to intimacy and in particular sex. The couple evaluates how their relationship and sex life has been influenced by the diagnosis and treatment of breast cancer.
Module 3: Sex and my body
In this module sensate focus therapy is introduced. The first steps of the hierarchically structured exercise program are completed. An introduction is given with regard to the influence of thoughts and external stimuli on the experience of sex. Attention is also paid to possible tension in the pelvic floor and methods to relax this part of the body.
Module 4: Focus my attention
In this module the client receives task concentration training in order to learn to focus her attention on sexual experiences in such a way that it is beneficial to the client.
Module 5: Explore my body
In this module sensate focus therapy is elaborated on and the hierarchically structured exercise program is completed. The client reports on her experiences with the homework exercise within a cognitive behavioral framework.
Module 6: Discovering my sexual arousal feelings (version for male partners)
The topics of this module are similar to the female version (see module 7), but are written from a male perspective.
Module 7: Discovering my sexual arousal feelings (female version)
In this module psycho-education is provided about the female body and genitals, female sexual dysfunction, genital stimulation, sexual techniques, and the male body and genitals. Accompanying exercises are provided for each subject, including, for example, exposure exercises for sexual pain disorders. Attention is also paid to the importance of and ways to discuss sexual feelings and preferences with the partner.
Module 8: Change my thoughts
In this module the influence of thoughts on feelings and behavior is explained, and the client's dysfunctional cognitions with regard to sex and intimacy are identified. Via the method of cognitive restructuring these cognitions are replaced by more functional, adaptive thoughts.
Module 9: My sexual preferences
In this module the client's sexual development, sexual needs, myths and beliefs about sex are evaluated. The client is encouraged to talk about her sexual preferences with her partner, and an action plan for behavior change is created.
Module 10: Relapse prevention
In this module the client reflects on her former automatic behavior and possible risk factors for relapse. A plan of action is generated to use in the event of a relapse.

Waiting-list control group

Participants in the control group are asked to refrain from undergoing any psychological or medical interventions for sexual problems during their participation in the study. To increase the likelihood that women will remain in the study until they are offered the CBT program, they are provided with a booklet addressing questions about sexuality and cancer. Additionally, six weeks after randomization and upon completion of the second questionnaire, women in the control group are contacted by telephone to address any questions or comments that they may have about their participation in the study, and to reconfirm that they will be eligible for the Internet-based CBT program upon their completion of the study.

Data collection

Patients

Patients in both study arms complete a battery of self-report questionnaires at equivalent moments in time for the first three assessments (T0: baseline; T1: 10 weeks after start of therapy (intervention group) or 13 weeks after randomization (control group); and T2: post-treatment (intervention group) or 23 weeks after randomization (control group), see Figure 1). To achieve an equivalent average assessment time for both groups, women in the intervention group complete T2 post-treatment, but always between 20 and 24 weeks after start of therapy. Women who finish the CBT prior to 20 weeks complete T2 20 weeks after start of therapy. Women in the intervention group also complete questionnaires three months post-treatment (T3) and nine months post-treatment (T4). The control group is not asked to complete T3 or T4, but rather is given the opportunity to undergo the intervention following completion of T2. This was done because it was not deemed ethically acceptable to withhold the intervention from women in the control group for the prolonged period of time that would be required if they were to complete all follow-up questionnaires (i.e., approximately one year after study enrollment). To minimize respondent burden, the T4 questionnaire only includes the questionnaires assessing the primary outcome measures. In every questionnaire, women in both the intervention group and control group are asked if they pursued any other activities to reduce their sexual problems (e.g., use of vaginal lubricant, relaxation exercises). A reminder is sent to participants who do not complete and return the questionnaire within one week. If a woman does not complete the questionnaire in the week after the reminder, she is contacted by telephone.

Partners

Only partners of the women in the intervention group are asked to complete questionnaires regarding problems with sexuality and intimacy (male partner: IIEF[86], female partner: FSFI[87]), and relational functioning (PAIR Inventory[88], MMQ[85]) at the same points in time as the participants.

Study measures

Sociodemographic and clinical data

Sociodemographic data and clinical data are obtained during the screening interview and via the baseline questionnaire. Sociodemographic data include age, education, relational status, living situation and work status. Clinical data are collected from the medical records and via self-report, and include date of breast cancer diagnosis, treatment (type of surgery, chemotherapy, radiotherapy, endocrine therapy, immunotherapy), medication use and comorbidity.

Outcome measures

Detailed descriptions of the outcome measures are provided in Table 2. Briefly, the primary outcome measures include standardized self-report questionnaires assessing problems with sexuality and intimacy. These include the Sexual Activity Questionnaire[89,90], the Female Sexual Function Index[87,91], the Female Sexual Distress Scale-Revised[92] and the PAIR Inventory[88]. Secondary outcome measures include standardized self-report questionnaires assessing body image (EORTC QLQ-BR 23 Body image subscale[93]), menopausal symptoms (FACT-ES[94]), marital functioning (MMQ[85]), psychological distress (HADS[95,96]) and HRQL (SF-36[97,98]). The International Index of Erectile Function[86] is used to assess sexual functioning in male partners.

Compliance with the Internet-based CBT program

The level of compliance is established via a question that is posed to the sexologist at the completion of therapy: 'How many of the total number of therapy sessions that you considered to be optimal for this client has the client actually completed?'. This question is answered on a five-point scale, ranging from 'the client has done all of the sessions I deemed necessary (100%)' to 'the client has not/barely done the sessions I deemed necessary (less than 25%)'. Additionally, the actual number of completed modules and interventions are extracted from the client's records at the mental health center where the Internet program is housed. Additionally, at completion of therapy, both the client and the sexologist are asked to indicate the frequency with which homework assignments were completed on a five-point scale (always-frequently-occasionally-rarely-never), and to indicate the reasons for not completing all homework assignments, if applicable. Women who do not complete the Internet-based CBT program are asked to indicate their reason(s) for discontinuation (e.g., therapy was too intensive, online therapy was not suitable, illness). Every effort will be made to obtain all questionnaires of all participants, regardless of whether they do or do not complete their therapy.

Table 2. Study outcome measures and corresponding questionnaires

Variable	Questionnaire	Details
Primary outcomes		
Sexual functioning	SAQ[89,90]	• Assesses sexual functioning • 10 items; 4-point Likert scales • Subscales: pleasure; discomfort; habit • Subscale scores: pleasure 0-18; discomfort 0-6; habit 0-3; higher score indicates higher levels of pleasure; lower score indicates lower levels of discomfort; habit is a single item (0 'less sexual activity than usual' to 3 'much more sexual activity than usual') • Time frame: past month • Test retest kappa: 0.50-0.76
	FSFI[87,91]	• Assesses sexual functioning • 19 items; 5- and 6-point Likert scales • Subscales: desire; arousal; lubrication; orgasm; satisfaction; pain • Total score*: 2-36 / Subscale scores*: desire 1.2-6; arousal 0-6; lubrication 0-6; orgasm 0-6; satisfaction 0.8-6; pain 0-6; higher score indicates better sexual functioning • Time frame: past 4 weeks • Cronbach's alpha: > 0.82
	FSDS-R[92,99]	• Assesses distress related to sexual dysfunction • 13 items; 5-point Likert scale (0 'never' to 4 'always') • Total score: 0-52; higher score indicates higher level of sexual distress • Time frame: past 30 days • Cronbach's alpha: > 0.88
Intimacy	PAIR Inventory[88]	• 36 items; 5-point Likert scale (0 'strongly disagree' to 4 'strongly agree') • Subscales: emotional intimacy; social intimacy; sexual intimacy; intellectual intimacy; recreational intimacy; conventionality • Subscale score*: 0-96; higher score indicates higher levels of intimacy • Time frame: 'how the relationship is now' • Cronbach's alpha: 0.70-0.80
Secondary outcomes		
Body image	EORTC QLQ-BR23 Body Image subscale[93]	• 4 items; 4-point Likert scale (1 'not at all' to 4 'very much') • Score: 0-100; higher score indicates higher level of functioning • Time frame: past week • Cronbach's alpha: 0.69-0.91
Menopausal symptoms	FACT-ES[94]	• 18 items; 5-point Likert scale (0 'not at all' to 4 'very much') • Score range: 0-72; higher score indicates fewer menopausal symptoms • Time frame: past 7 days • Cronbach's alpha = 0.79

(Continued on next page)

Table 2. (*continued*)

Variable	Questionnaire	Details
Marital functioning	MMQ[85]	• 20 items; 9-point Likert scale (range 0-8) • Scales: marital adjustment (M); sexual adjustment (S); general life adjustment (GL) • Scale scores*: S + GL: 0-40; M: 0-80; higher score indicates greater dissatisfaction in the specific domain • Time frame: past 2 weeks • Cronbach's alpha in normal vs. distressed group: M = 0.88/0.87; S = 0.64/0.82; GL = 0.60/0.68
Psychological distress	HADS[95,96]	• 14 items; 4-point Likert scale (range 0-3) • Subscales: depression (HADS-D); anxiety (HADS-A) • Total score: 0-42 / Subscale scores: 0-21; higher score indicates more psychological distress • Time frame: past week • Cronbach's alpha: HADS-A: 0.68-0.93; HADS-D: 0.67-0.90
Health-related quality of life	SF-36[97,98]	• 36 items; dichotomous and 3- to 6-point Likert scales • Subscales: physical functioning; role limitations due to physical health problems; bodily pain; social functioning; general mental health; role limitations due to emotional problems; vitality; general health perceptions • Subscale score*: 0-100; higher score indicates higher levels of functioning/well-being • Time frame: past week • Cronbach's alpha = 0.66-0.93 (mean: 0.84)
Sexual functioning (male partners)	IIEF[86]	• 15 items; 5-/6-point Likert scale (0-5 or 1-5) • Subscales: erectile function (EF); orgasmic function (OF); sexual desire (SD); intercourse satisfaction (IS); overall satisfaction (OS) • Total score: 5-75 / Subscale scores: EF 1-30; OF 0-10; SD 2-10; IS 0-15; OS 2-10; higher score indicates a higher level of functioning in specific domain • Time frame: past 4 weeks • Cronbach's alpha: 0.73-0.99

*The score is calculated based on weighted items.
EORTC QLQ-BR23 = European Organisation of Research and Treatment of Cancer Breast Cancer-specific Quality of Life Questionnaire; FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; MMQ = Maudsley Marital Questionnaire; PAIR Inventory = Personal Assessment of Intimacy in Relationships Inventory; SAQ = Sexual Activity Questionnaire; SF-36 = 36-Item Short Form Health Survey.

Patients' evaluation of the intervention program

Upon completion of the CBT, women in the intervention group are asked to complete an evaluation questionnaire about the program. Questions are posed about their satisfaction with the program, the perceived efficacy of the program in alleviating sexual problems, their satisfaction with the choice of modules and exercises, the usability of the program, if they would recommend the treatment to other women experiencing similar problems, and if they would suggest any changes to the program. Women who discontinue the CBT program are asked the same questions.

A subset of women (approximately 15 from the intervention group) will be asked to participate in an evaluation interview by telephone. This semi-structured interview covers the same topic areas as addressed by the self-report evaluation questionnaire, allowing women to provide feedback in a more narrative form. Where applicable, women will also be asked if their partner would be willing to share his or her experience with the program.

Statistical issues

Power calculation

The SAQ, FSFI, FSDS-R and PAIR Inventory are the primary outcome measures on which sample size calculations are based. With a total sample of 130 women (65 per group), and under the assumption of no interaction, the study will have a 80% power to detect a 0.5 standard deviation difference (Cohen's effect size[100]) for the main effects of the Internet-based CBT program, with the *p* value set at 0.05 (two-sided test). A 0.5 standard deviation difference is considered to be indicative of clinically meaningful differences in self-reported symptom experience[100].

We will recruit 160 women into the study, to allow for an attrition rate of approximately 20% (i.e., women who discontinue participation in the study entirely, including failure to complete all follow-up questionnaires). Those women who discontinue the therapy but complete the follow-up assessments will be included in the intention-to-treat analysis.

Statistical analysis

First, Student's *t*-tests or appropriate non-parametric statistics will be used to evaluate the comparability of the intervention and control group at baseline in terms of sociodemographic and clinical characteristics. If, despite the stratified randomization procedure, the groups are not comparable on one or more background variables, those variables will be employed routinely as covariates in subsequent analyses.

Questionnaire scores will be calculated according to published scoring algorithms. Between-group differences over time in mean scores will be tested using multilevel analysis. Effect sizes will be calculated using standard statistical procedures. All analyses will, to as great an extent as possible, be conducted on an intention-to-treat basis. Per protocol

analyses will also be carried out (as a secondary analysis), comparing women who meet minimal compliance levels with the program with the control group. We will use correlation analyses to examine the relationship between degree of program adherence, partner involvement, and program effect. For the analysis of the secondary outcome measures, appropriate statistical (*p* value) adjustments will be made for multiple testing. The semi-structured interview data will be transcribed and content analyzed to extract narrative, qualitative information about the women's experience with the intervention.

DISCUSSION

A relatively large percentage of breast cancer survivors experience sexual problems as a consequence of their disease and its treatment. Studies show that CBT is an effective treatment method for alleviating sexual dysfunctions in the general population, when provided in a face-to-face setting. Recently, more attention has been paid to developing Internet-based interventions targeting sexual functioning. However, research into Internet-based interventions for FSDs is scarce, and even less is known about the efficacy of Internet-based CBT specifically targeted at breast cancer survivors. In the current trial, we are investigating the efficacy of an Internet-based CBT in reducing problems with sexuality and intimacy, psychological distress and menopausal symptoms, and in improving body image, marital functioning and health-related quality of life of breast cancer survivors.

This trial has several notable strengths, including: (1) the randomized trial design, (2) the multicenter nature of the trial, (3) the comparison of the intervention group with a waiting-list control group, (4) the use of intention-to-treat analyses, and (5) the long-term follow-up assessments of outcomes in women in the intervention group.

This trial also has several limitations. First, it would be valuable to compare the Internet-based CBT group not only with a control group, but also with a face-to-face CBT group. However, our previous experience in offering breast cancer survivors the opportunity to participate in face-to-face sexual therapy proved problematic[63]. Very few women were willing to take that step, indicating that they found the face-to-face setting too confronting. Thus, we anticipated that including a face-to-face therapy arm in the trial would result in substantial recruitment problems. Also, we consider it important to first establish the efficacy of the Internet-based CBT program. If the program proves to be efficacious, a subsequent step could be a comparative effectiveness study with face-to-face treatment[61]. Second, although as one of the conditions for participating in the trial, women are asked not to participate in any other programs targeted at their sexual problems, the possibility exists that some women (particularly in the control group) may do so. However, we do not expect any such activities to be as structured, tailored and targeted at sexual problems specifically after breast cancer treatment as our CBT program. In any case, at each assess-

ment point, women are asked to report any activities that they may have undertaken to alleviate their sexual problems. Third, the absence of T3 and T4 follow-up assessments for the control group precludes a longer-term between-group comparison of study outcomes. As noted earlier, this decision was based on both ethical and feasibility considerations. We (and the institutional review board) did not consider it appropriate to withhold therapy for an extended period of time, which would have been the case if women in the control group were required to complete all assessment points before having the opportunity to participate in the Internet-based CBT program. We also believed that such a long waiting list period would have a significant, negative effect on recruitment into the study.

In conclusion, given the high rates of sexual dysfunction in breast cancer survivors, there is a need for effective and accessible treatments for these problems. If proven to be effective, Internet-based CBT can be a valuable addition to the standard care offered to breast cancer survivors. Hopefully, this treatment will lower the barrier to seeking help, resulting in an improved quality of life after treatment of breast cancer.

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Factors associated with specific DSM-IV sexual dysfunctions in breast cancer survivors: a study of patients and their partners

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ABSTRACT

Background

Many women experience sexual problems after breast cancer (BC) treatment. Little is known about BC survivors with a DSM-IV sexual dysfunction and their partners, and the factors associated with their sexual functioning.

Aim

To evaluate 1) patient-related and clinical factors associated with a) specific DSM-IV sexual dysfunctions and b) level of sexual functioning and sexual distress as reported by BC survivors and 2) the association between the sexual functioning of BC survivors and that of their partners.

Methods

We analyzed baseline data from a study of the efficacy of online cognitive behavioral therapy for sexual dysfunction in BC survivors.

Outcomes

Women completed self-report questionnaires assessing sexual functioning, sexual distress, relationship intimacy, marital functioning, menopausal symptoms, body image, and psychological distress. Their partners completed questionnaires assessing sexual functioning.

Results

The study included 169 BC survivors and 67 partners. The most prevalent female sexual dysfunctions were hypoactive sexual desire disorder (HSDD; 83%), sexual arousal disorder (40%) and dyspareunia (33%). Endocrine therapy was associated with HSDD ($p = .003$), and immunotherapy was associated with dyspareunia ($p = .009$). Older age was associated with lower sexual distress ($p < .001$). Depressive symptoms were highest in women with sexual arousal disorder ($p = .004$). An indication for erectile disorder was present in two-thirds of the partners. Lower overall partner sexual satisfaction was associated with lower overall BC survivor sexual functioning ($p = .001$), lower female arousal ($p = .002$), and lower female sexual satisfaction ($p = .001$). Poorer male erectile function was related to higher female sexual pain ($p = .006$). Partners of women who underwent breast reconstruction reported marginally significantly better orgasmic functioning ($p = .012$) and overall sexual functioning ($p = .015$) than partners of women who had undergone breast conserving treatment.

Clinical implications

BC survivors and their partners experience sexual problems after BC treatment. This suggests that not only the BC survivor but also her partner could benefit from sexual counseling.

Strengths and limitations

This is the first study focusing on BC survivors with a DSM-IV sexual dysfunction and their partners. The results cannot necessarily be generalized to women experiencing milder sexual problems or who have no interest in receiving sexual counseling.

Conclusion

Endocrine therapy and immunotherapy are relevant risk factors for HSDD and dyspareunia in BC survivors. The sexual functioning of women and their partners is affected, underscoring the importance of involving both partners in sexual counseling after BC treatment.

INTRODUCTION

Sexual problems are a frequent, long-term effect of the treatment of breast cancer (BC)[1]. BC survivors report more sexual problems compared to healthy controls[2-5]. It has been estimated that 45% to 77% of BC survivors experience sexual problems after treatment[5,6].

In most studies of BC survivors, the presence of a sexual problem is defined as a score above a given threshold on a patient-reported outcome measure (PROM). This is in contrast to the procedure used in clinical practice, where a diagnosis of sexual dysfunction is typically based on a clinical interview by a trained therapist using the criteria of the Diagnostic and Statistical Manual of Psychiatric Disorders, Fourth edition (DSM-IV)[7] or, more recently, the DSM-5[8]. It is generally accepted that an interview is the optimal manner of generating an accurate diagnosis, because it allows the clinician to take factors into account that can affect the patient's sexual functioning, such as current general health, sexual experiences, the quality of the partner relationship, and the presence of adequate sexual stimuli[9]. The clinician also can evaluate whether the sexual problem is of sufficient severity that it causes marked distress, and if it does not primarily reflect another DSM disorder.

According to the biopsychosocial model[10], sexual dysfunction is the result of a disturbance in the biological, psychological and/or social aspects of an individual's sexual functioning. The relationship with the partner is an important social factor in the assessment and treatment of sexual problems[11]. The sexual functioning of couples is interrelated[12,13], and research has shown that the partner's sexuality and feelings of intimacy can be affected by the patient's disease and treatment[14]. Although past research on the sexual functioning of BC survivors has often involved the partner[14-18], these studies have not explicitly investigated the association between the women's and their partners' reports of sexual functioning. In this article we focus on an understudied population, BC survivors with a formal DSM-IV diagnosis of sexual dysfunction, and the factors associated with their and their partners' sexual functioning.

AIMS

Our specific focus was on BC survivors who were motivated to undergo Internet-based cognitive behavioral therapy (CBT) for their problems. We investigated the association between sociodemographic and clinical factors and 1) specific DSM-IV diagnoses of sexual dysfunction and 2) self-reported levels of sexual functioning and sexual distress of BC survivors. In addition, we investigated differences in levels of sexual distress, psychological distress, menopausal symptoms, body image, marital functioning, and relationship intimacy as a function of specific DSM-IV diagnoses of sexual dysfunction. We also evaluated the

association between the sexual functioning of BC survivors and that of their partners, and whether the partner's sexual functioning was associated with the woman's BC treatment.

METHODS

The present analysis was based on baseline data derived from an on-going randomized controlled trial (RCT) investigating the efficacy of an Internet-based CBT program for sexual dysfunctions among BC survivors. Patients were recruited from 10 community and university hospitals in the Netherlands. A detailed description of the design of the trial has been published previously[19]. The institutional review boards of The Netherlands Cancer Institute (Amsterdam, the Netherlands) and of all participating hospitals approved the study.

Study sample

Inclusion criteria for the trial were: age 18 to 65 years; a diagnosis of histologically confirmed BC six months to five years prior to study entry; completion of BC treatment (with the exception of maintenance endocrine therapy and immunotherapy); free of disease at time of study entry; sufficient command of the Dutch language; and a formal diagnosis of sexual dysfunction according to DSM-IV criteria, as determined by a psychologist/sexologist during an intake interview. Single as well as partnered women, and women with different sexual orientations were eligible for the trial.

The most important study exclusion criteria were serious cognitive or psychiatric problems (i.e., major depressive disorder, alcohol dependency, or psychotic disorders) as determined by the Mini International Neuropsychiatric Interview[20]; treatment for another type of cancer (with the exception of cervix carcinoma in situ and basal cell carcinoma); and presence of severe relationship problems that would pre-empt treatment of sexual problems.

The partners of those women who were randomized to the intervention group (as part of the RCT; see below) also were invited to complete study questionnaires.

Study design and procedures

As part of the RCT, women who met initial age and BC-related eligibility criteria were sent an invitation letter and a response card. Interested women were screened twice by telephone for further eligibility, first by a member of the study staff and subsequently by a psychologist/sexologist. The sexologist determined the presence of one or more DSM-IV sexual dysfunctions. Those women who met criteria were sent a baseline questionnaire and an informed consent form, either online or by regular mail. The partners of those women who were subsequently randomized to the intervention group and who provided informed consent also were sent a questionnaire.

Main outcome measures

The study questionnaire for the BC survivors assessed sociodemographic and medical background variables, and included two standardized patient-reported outcome measures (PROMs) assessing sexual functioning: the Female Sexual Function Index (FSFI[21,22]) and the Female Sexual Distress Scale-Revised (FSDS-R[23,24]). Women also completed measures of relationship intimacy (Personal Assessment of Intimacy in Relationships Inventory; PAIR Inventory[25]), marital functioning (Maudsley Marital Questionnaire; MMQ[26]), menopausal symptoms (Functional Assessment of Cancer Treatment-Endocrine Symptoms; FACT-ES[27]), body image (European Organisation for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire, body image subscale; QLQ-BR23 BI subscale[28]) and psychological distress (Hospital Anxiety and Depression Scale; HADS[29,30]). Partners completed the International Index of Erectile Function (IIEF[31,32]). Information about the questionnaires is presented in Table 1.

Statistical analysis

We calculated questionnaire scores according to published scoring algorithms. Missing values were replaced by the average score of the completed items in the same scale for each individual, provided that at least 50% of the items in that scale had been completed.

We used descriptive statistics to characterize the study sample. We used the chi-square statistic, Student's t-test or point-biserial correlation to investigate differences in the women's 1) sociodemographic characteristics, 2) clinical characteristics, and 3) scores on the various PROMs as a function of their specific DSM-IV diagnosis of sexual dysfunction (present vs. absent). The PROMs included in these analyses were the FSDS-R, the PAIR (all subscales), the MMQ (all subscales), the FACT-ES, the QLQ-BR23 BI and the HADS (depression and anxiety subscales).

Sociodemographic and clinical factors included age, employment status, educational level, menopausal status (pre- vs. postmenopausal, with postmenopausal status defined as the absence of menses for > 12 months), onset of menopause (natural vs. treatment-induced), time since BC diagnosis, type of surgery (mastectomy, breast conserving treatment (BCT), breast reconstruction (BR)), chemotherapy, endocrine therapy, radiotherapy, and immunotherapy (yes vs. no).

Associations between sociodemographic and clinical factors (independent variables), and the FSFI total score and FSDS-R score (dependent variables) were analyzed with the Pearson product-moment correlation, Student's t-test, and analysis of variance (ANOVA).

Pearson product-moment correlations were used to evaluate the association between the BC survivors' FSFI-scores and their partners' IIEF-scores. In these analyses, we only included the sexually active couples. Because the use of partial correlations, adjusting for the woman's age (which was highly correlated with the partner's age, $p < .001$, $r = .91$), showed similar results, we report the outcomes of the Pearson product-moment correlations.

Table 1. Study outcome measures and corresponding questionnaires

Variable	Questionnaire	Details
Sexual functioning	FSFI[21,22]	• Assesses sexual functioning • 19 items; 5- and 6-point Likert scales • Subscales: desire; arousal; lubrication; orgasm; satisfaction; pain • Total score*: 2-36 / Subscale scores*: desire 1.2-6; arousal 0-6; lubrication 0-6; orgasm 0-6; satisfaction 0.8-6; pain 0-6; higher score indicates better sexual functioning • Time frame: past 4 weeks • Cronbach's alpha: desire .84; arousal .93; lubrication .95; orgasm .95; satisfaction .64; pain .96
	FSDS-R[23,24]	• Assesses distress related to sexual dysfunction • 13 items; 5-point Likert scale (0 'never' to 4 'always') • Total score: 0-52; higher score indicates higher level of sexual distress • Time frame: past 30 days • Cronbach's alpha: .91
Intimacy	PAIR Inventory[25]	• 36 items; 5-point Likert scale (0 'strongly disagree' to 4 'strongly agree') • Subscales: emotional intimacy; social intimacy; sexual intimacy; intellectual intimacy; recreational intimacy; conventionality • Subscale score*: 0-96; higher score indicates higher levels of intimacy • Time frame: 'how the relationship is now' • Cronbach's alpha: emotional .84; social .72; sexual .66; intellectual .66; recreational .71; conventionality .78.
Body image	QLQ-BR23 Body Image subscale[28]	• 4 items; 4-point Likert scale (1 'not at all' to 4 'very much') • Score: 0-100; higher score indicates higher level of functioning • Time frame: past week • Cronbach's alpha: .88
Menopausal symptoms	FACT-ES[27]	• 18 items; 5-point Likert scale (0 'not at all' to 4 'very much') • Score range: 0-72; higher score indicates fewer menopausal symptoms • Time frame: past 7 days • Cronbach's alpha: .74
Marital functioning	MMQ[26]	• 20 items; 9-point Likert scale (range 0-8) • Scales: marital adjustment (M); sexual adjustment (S); general life adjustment (GL) • Scale scores*: S + GL: 0-40; M: 0-80; higher score indicates greater dissatisfaction in the specific domain • Time frame: past 2 weeks • Cronbach's alpha: M .87; S .56; GL .57

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Table 1. (*continued*)

Variable	Questionnaire	Details
Psychological distress	HADS[29,30]	• 14 items; 4-point Likert scale (range 0-3) • Subscales: depression (HADS-D); anxiety (HADS-A) • Total score: 0-42 / Subscale scores: 0-21; higher score indicates more psychological distress • Time frame: past week • Cronbach's alpha: HADS-A .83; HADS-D .77
Sexual functioning (male partners)	IIEF[31]	• 15 items; 5-/6-point Likert scale (0-5 or 1-5) • Subscales: erectile function (EF); orgasmic function (OF); sexual desire (SD); intercourse satisfaction (IS); overall satisfaction (OS) • Total score: 5-75 / Subscale scores: EF 1-30; OF 0-10; SD 2-10; IS 0-15; OS 2-10; higher score indicates a higher level of functioning in specific domain • Time frame: past 4 weeks • Cronbach's alpha: EF.92; OF .97; SD .76; IS .88; OS .95

*The score is calculated based on weighted items.
FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; MMQ = Maudsley Marital Questionnaire; PAIR Inventory = Personal Assessment of Intimacy in Relationships Inventory; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire of the European Organisation of Research and Treatment of Cancer.

We used analysis of covariance, with the partners' age as a covariate, to evaluate the association between the women's BC treatment (type of surgery, chemotherapy, endocrine therapy, radiotherapy, immunotherapy) and the partners' sexual functioning. In a subsequent, exploratory analysis, we used ANOVA to evaluate the association between type of surgery and the women's body image.

Where relevant, we calculated effect sizes and odds ratios. Effect sizes of 0.20 were considered small, 0.50 moderate and clinically relevant, and 0.80 large[33]. Odds ratios of 1.5 were considered small, 2 as medium, and 3 as large[34]. Correlation coefficients of 0.10 were considered low, 0.30 moderate, and of 0.50 high[33].

To adjust for multiple comparisons, results were considered statistically significant at a p value < .01. The p value for overall analysis of (co)variance models was set at .05 and for the specific contrasts at .01. Non-parametric tests were used to compare groups when the assumptions of parametric tests were violated. When results of the non-parametric tests were the same as those based on parametric tests, we report only the latter.

RESULTS

Recruitment and participant flow in the trial are reported in detail elsewhere[35]. Specific to the present analysis, 169 women were randomly assigned to the intervention group (n = 84) and the control group (n = 85). All but two women of the intervention group had a partner, of whom 69 agreed to complete the study questionnaires. The present results pertain to the 67 male partners. Figure 1 provides a more detailed description of the study flow.

Sociodemographic and clinical characteristics

Table 2 presents the subjects' sociodemographic and clinical characteristics. The mean age of women in the study sample was 51 years (standard deviation (SD) = 7), 95% was married or in a relationship, 82% had some post-high school education, and 79% was employed. The mean time since BC diagnosis was 38 months (SD = 16). Most women (66%) first experienced sexual problems during their BC treatment, 12% prior to the BC diagnosis, and 22% after completion of treatment. The large majority of women (85%) was postmenopausal, with about half having experienced treatment-induced menopause.

Slightly more than half of the women had undergone BCT, one fourth had a mastectomy with BR, and 20% a mastectomy without BR. The large majority of women had undergone chemotherapy (83%), radiotherapy (81%), and endocrine therapy (82%). Approximately 20% of women had been treated with immunotherapy.

The mean age of the male partners was 54 years (SD = 8), and 69% had post-high school education.

Diagnosis of specific DSM-IV-based sexual dysfunctions

Thirty-six percent of the women were diagnosed with one, 56% with two, and 8% with three or more DSM-IV sexual dysfunctions (Table 2). Hypoactive sexual desire disorder (HSDD) was the most prevalent dysfunction type (83%), followed by female sexual arousal disorder (40%), dyspareunia (33%), female orgasmic disorder (10%), sexual aversion disorder (4%), sexual dysfunction not otherwise specified (NOS; 2%), and vaginismus (1%).

Almost all women (94%) had an FSFI score ≤ 26.5, indicative of a sexual dysfunction[36] and an FSDS-R score ≥ 11 (96%), indicative of marked distress denoting sexual dysfunction[23]. Slightly more than two-thirds of the women indicated that they had been sexually active in the past month. This did not differ significantly between the various DSM-IV diagnostic groups.

Two-thirds of the partners (66%) had an IIEF erectile function subscale score of ≤ 25, indicative of erectile dysfunction (ED)[32]. One-third of the partners reported severe, 22% moderate, and 10% mild to moderate ED.

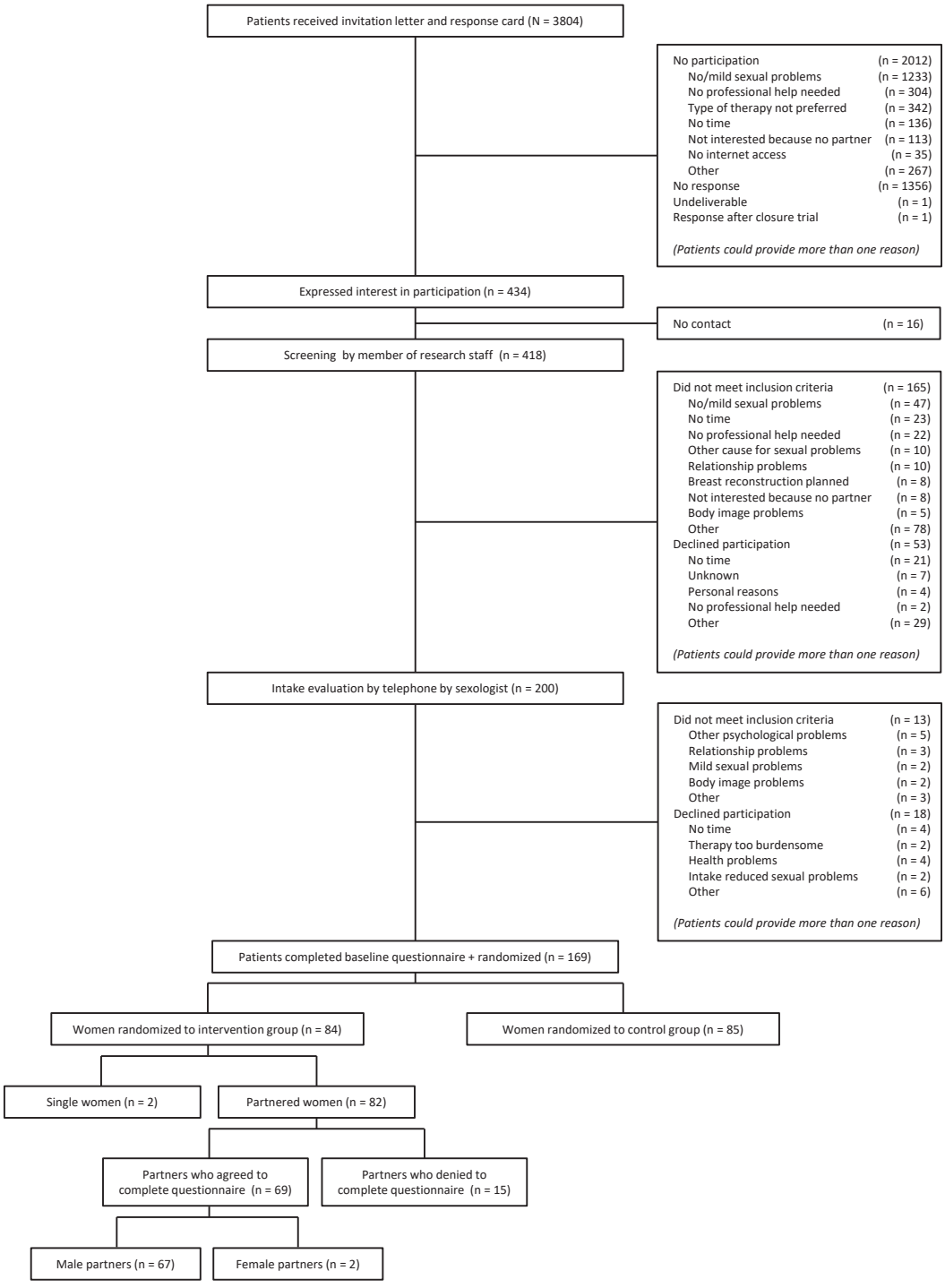

Figure 1. Participant flow and recruitment into the study

Sociodemographic and clinical factors associated with DSM-IV diagnosis, FSFI total scores and FSDS-R scores

Older age was associated with lower sexual distress (FSDS-R, $p < .001$, r = -.30). Endocrine therapy was associated with HSDD ($p = .003$, odds ratio = 3.67), and immunotherapy with dyspareunia ($p = .009$, odds ratio = 2.64). Because of its low prevalence in our sample, we did not include sexual aversion disorder, orgasmic disorder, vaginismus or sexual dysfunction NOS in these analyses. No other significant associations were observed between sociodemographic and clinical factors, and DSM-IV diagnosis, the FSFI total score, or the FSDS-R score (data not shown in tabular form).

Differences in PROMs as a function of specific DSM-IV sexual dysfunctions

Women with a sexual arousal disorder had significantly higher scores on the HADS depression subscale than women without a sexual arousal disorder ($p = .004$, ES = .47). No other significant associations were observed in PROM scores as a function of DSM-IV-diagnosis.

Association between sexual functioning of sexually active BC survivors and their partners

Total scores on the FSFI and IIEF showed a marginally significant correlation ($p = .037$, r = .29; Table 3). Lower overall sexual satisfaction of the partner was associated with lower overall female sexual functioning ($p = .001$, r = .44), lower female arousal ($p = .002$, r = .43), and lower female sexual satisfaction ($p = .001$, r = .45). Poorer male erectile function was related to higher female sexual pain ($p = .006$, r = .38).

Association between BC treatment and the partner's sexual functioning

There was a significant association observed between type of surgery and the partner's orgasmic functioning (IIEF orgasmic functioning subscale, $p = .041$) and overall sexual functioning (IIEF total score, $p = .05$). Post-hoc tests indicated that partners of women who had undergone a mastectomy with a BR reported marginally significantly better orgasmic functioning (r = .31, $p = .012$) and overall sexual functioning (r = .30, $p = .015$) than partners of women who had undergone BCT. The partner's age was not associated significantly with these outcomes. No other significant associations were observed between the woman's chemotherapy, endocrine therapy, radiotherapy or immunotherapy and her partner's sexual functioning (data not shown in tabular form). In a subsequent, exploratory analysis, we did not find a significant association between type of surgery and the women's body image.

Table 2. Baseline sociodemographic and clinical characteristics, and scores on patient-reported outcome measures

Characteristic	
Women	**Total (N = 169)**
Age, years (mean, (SD))	51.1 (7.2)
Education (n, (%))	
Primary education	1 (0.6)
Secondary education	29 (17.4)
Higher education	137 (82.0)
Unknown	2 (1.2)
Married/in a relationship (n, (%))	160 (94.7)
Part-time/fulltime job (n, (%))	134 (79.3)
Time since diagnosis, months (mean, (SD))	37.5 (16.3)
< 1 year	9 (5.3)
1-2 years	64 (37.9)
3-5 years	96 (56.8)
Menopausal status (n, (%))	
Premenopausal	26 (15.4)
Postmenopausal	143 (84.6)
Course of menopause (n = 143) (n, (%))	
Natural menopause	44 (26.0)
Treatment-induced menopause	89 (52.7)
Unclear	10 (5.9)
Surgery (n, (%))	169 (100)
Breast conserving treatment	95 (56.2)
Mastectomy with reconstruction	41 (24.3)
Mastectomy	33 (19.5)
Chemotherapy (n, (%))	141 (83.4)
Endocrine therapy (n, (%))	138 (81.7)
Radiotherapy (n, (%))	137 (81.1)
Immunotherapy (n, (%))	38 (22.5)
Sexually active (n, (%))	114 (67.5)
No. of diagnosed sexual dysfunctions (n, (%))	
1 sexual dysfunction	61 (36.1)
2 sexual dysfunctions	95 (56.2)
3 or 4 sexual dysfunctions	13 (7.7)
DSM-diagnosis (n, (%))	
HSDD	140 (82.8)
Sexual arousal disorder	67 (39.6)
Dyspareunia	55 (32.5)
Orgasmic disorder	16 (9.5)

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Table 2. (*continued*)

Characteristic			
Women		**Total (N = 169)**	
Sexual aversion disorder		7 (4.1)	
Vaginismus		2 (1.2)	
Sexual dysfunction NOS		4 (2.4)	
FSFI total score ≤ 26.5* (n, (%))[i]		158 (93.5)	
FSDS-R total score ≥ 11** (n, (%))		163 (96.4)	
Onset sexual problems (n, (%))			
Before BC treatment		21 (12.4)	
During BC treatment		111 (65.7)	
After BC treatment		37 (21.9)	
Male partners		**Total (N = 67)**	
Age, years (mean, (SD))		53.6 (8.4)	
Education (n, (%))			
Primary education		0 (0.0)	
Secondary education		21 (31.3)	
Higher education		46 (68.7)	
PROM scores women	**n**	**Mean (SD)**	**Range**
FSFI total[i]	163	13.5 (7.3)[i]	2.0-28.5
Desire	169	2.0 (0.9)	1.2-5.4
Arousal	169	2.1 (1.4)	0.0-5.4
Lubrication	169	2.2 (1.9)	0.0-6.0
Orgasm	169	2.4 (1.9)	0.0-6.0
Satisfaction[i]	163	2.7 (1.3)[i]	0.8-5.6
Pain	169	1.9 (2.1)	0.0-6.0
FSDS-R	169	24.9 (8.7)	0-52
PAIR Inventory¤	160		
Emotional	160	72.5 (20.4)	0.0-96.0
Social	160	62.8 (18.7)	8.0-96.0
Sexual	160	65.9 (18.2)	0.0-96.0
Intellectual	160	68.5 (16.3)	20.0-96.0
Recreational	160	76.2 (15.3)	20.0-96.0
Conventionality	160	62.9 (18.9)	16.0-96.0
MMQ¤			
Marital satisfaction	160	12.9 (9.1)	0.0-53.0
Sexual satisfaction	160	22.4 (7.3)	2.0-38.0
General Life satisfaction	160	9.1 (4.8)	0.0-21.0
QLQ-BR23 Body Image subscale	169	67.2 (26.1)	0.0-100
FACT-ES	169	51.6 (8.4)	27.0-72.0

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Table 2. (*continued*)

PROM scores women	**n**	**Mean (SD)**	**Range**
HADS	168	10.3 (6.3)	0.0-32.0
Anxiety	168	6.1 (3.9)	0.0-20.0
Anxiety score ≥ 11*** (n, (%))	168	22 (13.1)	
Depression	168	4.2 (3.1)	0.0-16.0
Depression score ≥ 11*** (n, (%))	168	7 (4.2)	
PROM scores partners	**n**	**Mean (SD)**	**Range**
IIEF total	67	38.0 (20.5)	7.0-72.0
Erectile function	67	16.7 (10.6)	2.0-30.0
Erectile function score ≤ 25**** (n, (%))	67	44 (65.7)	
Erectile function score ≤ 25 in partners of sexually active couples****‡ (n, (%))	51	28 (54.9)	
Orgasmic function	67	5.6 (4.5)	0.0-10.0
Sexual desire	67	6.9 (1.6)	2.0-10.0
Intercourse satisfaction	67	4.3 (4.6)	0.0-14.0
Overall satisfaction	67	4.6 (2.2)	2.0-10.0

Abbreviations: BC = breast cancer; FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; HSDD = hypoactive sexual desire disorder; IIEF = International Index of Erectile Function; MMQ = Maudsley Marital Questionnaire; NOS = not otherwise specified; PAIR Inventory = Personal Assessment of Intimacy in Relationships Inventory; PROM = patient-reported outcome measure; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire of the European Organisation of Research and Treatment of Cancer; SD = standard deviation.

*A score of ≤ 26.55 is indicative of a sexual dysfunction as defined by DSM-IV criteria.

**A score of ≥ 11 is indicative of sexual dysfunction.

***A score of ≥ 11 is indicative of a case of anxiety/depression.

**** A score of ≤ 25 is indicative of erectile dysfunction.

[i]This score is based on 163 women, as 6 of the 169 women could not coplete all FSFI questions, as they were single and had no regular sex partner.

¤All subscale scores are based on scores of 160 women, as only partnered women could complete questions.

‡As sexually inactive men are assigned a zero-score (i.e., the lowest score, indicating erectile dysfunction) on 5 of the 6 items of the erectile function subscale, we also report the percentage of men of sexually active couples that scored below the cut-off score.

Table 3. Pearson correlation between the FSFI and IIEF scores of sexually active women and partners

	IIEF domain											
	Total score		Erectile function		Orgasmic function		Sexual desire		Intercourse satisfaction		Overall satisfaction	
FSFI domain	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Total score	*0.29*	*0.037*	*0.29*	*0.037*	0.05	0.742	0.05	0.717	*0.28*	*0.050*	**0.44**	**0.001**
Desire	0.12	0.418	0.11	0.433	0.01	0.948	- 0.028	0.848	0.15	0.306	0.16	0.275
Arousal	0.12	0.419	0.06	0.688	0.03	0.854	0.06	0.668	0.08	0.574	**0.43**	**0.002**
Lubrication	0.20	0.170	0.25	0.081	0.01	0.955	- 0.126	0.377	0.18	0.220	0.23	0.108
Orgasm	0.18	0.205	0.18	0.220	0.08	0.602	0.26	0.069	0.09	0.544	0.25	0.080
Satisfaction	0.14	0.346	0.02	0.892	0.02	0.867	*0.31*	*0.029*	0.15	0.279	**0.45**	**0.001**
Pain	*0.32*	*0.024*	**0.38**	**0.006**	0.03	0.845	- 0.17	0.232	*0.36*	*0.010*	0.25	0.083

Bold font indicates statistically significant correlations. Italic font indicates marginally statistically significant correlations.
Abbreviations: FSFI = Female Sexual Function Index; IIEF = International Index of Erectile Function.
r = correlation coefficient rho.
Pearson correlation was performed on 51 sexually active couples. Sixty-nine partners completed study questionnaires, of whom two were female. The sexual activity status was based on a question included in the study questionnaire: 'How often did you engage in sexual activity this month?'.

DISCUSSION

HSDD, sexual arousal disorder and dyspareunia were the most prevalent sexual dysfunctions in our sample of BC survivors. These results are similar to those reported for the general population[37], but differ from those reported by Kedde et al.[5] in a previous Dutch study of BC survivors[5]. The second most prevalent sexual problem in that study was difficulty in having an orgasm (21%), while in our sample only 10% was diagnosed with an orgasmic disorder. The higher prevalence of orgasmic problems in the study of Kedde et al.[5] may be due to the fact that they relied on cut-off scores on PROMs to define sexual dysfunctions, while we employed interviewer-based DSM-IV criteria. The use of a PROM might be insufficient to distinguish between an orgasmic disorder and another more primary problem with, for example, sexual arousal.

Another difference in results between our study and that of Kedde et al. was with regard to the prevalence of HSDD, which was 83% in our sample as compared to only 5.7% in the Kedde et al. sample. It may be that HSDD is more common in BC survivors who are interested in undergoing sexual therapy, as was the case in our study. In addition, the mean age of the women in the study of Kedde et al. was 39 years, as compared to 51 years in our sample. As HSDD is more common in older, middle-aged women[38], this may also explain, in part, the differences observed in the prevalence of the sexual dysfunction between the two studies.

In our sample, women who were diagnosed with HSDD were more than three times more likely to have undergone endocrine therapy than those without HSDD. This is consistent with prior research that has shown that endocrine treatment negatively affects sexual functioning[39,40], but also suggests that endocrine therapy is a specific risk factor for the development of HSDD. We also observed that immunotherapy is a risk factor for dyspareunia. A previous study found an association between immunotherapy and menopausal symptoms, including vaginal dryness[41]. This could, in part, explain our finding of an association between immunotherapy and dyspareunia and deserves further investigation.

Although women with a sexual arousal disorder experienced more symptoms of depression than women without an arousal disorder, their mean HADS depression score was well below the cut-off score of ≥ 11 used to define clinically relevant levels of depressive symptoms[29,30]. This suggests that, although heightened, the level of depressive symptoms experienced by women with an arousal disorder is not necessarily of clinical concern.

We identified a smaller number of correlations between the self-reported sexual functioning of the women and that of their partners than has been reported in a non-clinical sample[12] and in a prostate cancer sample[42]. Nevertheless, the fact that 55% of the male partners in our sample reported moderate or severe erectile dysfunction underscores the importance of assessing the level of sexual functioning of both BC survivors and their partners.

Our finding that poorer male erectile function was associated with higher female sexual pain is in accordance with previous findings that female dyspareunia or vaginismus frequently precede non-organic erectile dysfunction (ED)[43,44]. Even in the presence of sexual problems, both partners may feel pressure to have sexual intercourse[45], and the male partner may fear that the woman will experience pain, leading to negative expectancies and a focus on non-erotic or task-irrelevant cues. This in turn could inhibit sexual excitement, resulting in erectile difficulties[46].

The partners of women who had undergone a BR reported better orgasmic and overall sexual functioning than those of women who had received BCT. A possible explanation for this finding could be that women with a BR may have a better body image than women with a BCT. This, in turn, could have a positive effect on women's sexuality and that of their partners. However, we did not observe a significant association between type of surgery and women's body image. Nonetheless, this does not rule out the possibility that the male partners experienced a reconstructed breast as more sexually attractive than is sometimes the case with a conserved breast (that nevertheless has been altered by the surgery).

The finding that the sexual functioning of partners of the women who had undergone BCT did not differ significantly from that of the partners of women who had had a mastectomy (without reconstruction) may, in part, reflect a less prominent role of the breast in the pre-illness sexual relationship of women who chose the more mutilating type of surgery.

In most cases, our sample of women with a DSM-IV diagnosis of sexual dysfunction also scored above the thresholds of the FSFI and the FSDS-R indicative of serious sexual problems. This suggests that PROMs assessing sexual functioning might be an efficient alternative to an extensive diagnostic interview for identifying BC survivors with a clinically relevant sexual problem. However, because our study sample did not also include women without a DSM-IV diagnosis of sexual dysfunction, it was not possible to adequately evaluate the screening properties of the FSFI or the FSDS-R, including sensitivity, specificity and positive predictor value. Additional studies are needed to evaluate the appropriateness of using these questionnaires as screeners in the BC survivorship setting.

Our study had several limitations. First, as noted earlier, our sample only included women who were diagnosed with a DSM-IV sexual dysfunction. Thus, we could investigate only associations among sociodemographic, clinical and psychosexual factors within this subpopulation. This affects the generalizability of our results. It would be of interest to investigate some of the issues explored in the current study in a sample of BC survivors experiencing milder sexual problems.

Second, women were excluded from the study if they had severe psychological problems that would take precedence (in a therapeutic sense) over sexual dysfunction. This may have introduced some sampling bias in that it excluded women with sexual dysfunction who had other psychiatric comorbidity. However, only a very small percentage (< 5%) of women was excluded from study participation for this reason.

Third, the study sample was recruited as part of an RCT of an Internet-based CBT intervention for sexual problems. Thus, women who agreed to participate in the trial were, by definition, those who were motivated to receive professional psychosexual help. Our results cannot necessarily be generalized to women with a sexual dysfunction who are not interested in receiving sexual counseling.

Our study also had several noteworthy strengths. To the best of our knowledge, it is the first investigation focusing on BC survivors with a DSM-IV sexual dysfunction where the diagnosis is based on formal diagnostic interviews rather than questionnaire data. The inclusion of partner data allowed us to investigate the interplay between the sexual functioning of BC survivors and their partners.

In conclusion, our study results indicate that endocrine therapy and immunotherapy are relevant risk factors for DSM-IV defined HSDD and dyspareunia. The results also underscore the importance of involving the partner in sex counseling after BC treatment. Our findings can contribute to a better understanding of the sexual problems and needs of BC survivors and their partners, and to the detection and timely treatment of this vulnerable population.

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4

Efficacy of Internet-based cognitive behavioral therapy in improving sexual functioning of breast cancer survivors: results of a randomized controlled trial

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ABSTRACT

Purpose

We evaluated the effect of Internet-based cognitive behavioral therapy (CBT) on sexual functioning, relationship intimacy (primary outcomes), body image, menopausal symptoms, marital functioning, psychological distress and health-related quality of life (HRQL) (secondary outcomes) in breast cancer survivors (BCSs) with a DSM-IV diagnosis of sexual dysfunction.

Methods

We randomly assigned 169 BCSs to either the Internet-based CBT or a waiting-list control group. The CBT consisted of weekly therapist-guided sessions and had a maximum duration of 24 weeks. Self-report questionnaires were completed by the intervention group at baseline (T0), mid-therapy (T1), and post-therapy (T2), and at equivalent times for the control group. We used a mixed-effect modeling approach to compare the groups over time.

Results

Compared with the control group, the intervention group showed a significant improvement over time in overall sexual functioning (effect size for T2 (ES_{T2}) = .43, p = .031), which was reflected in an increase in sexual desire (ES_{T1} = .48 and ES_{T2} = .72, $p < .001$), sexual arousal (ES_{T2} = .50, p = .008), and vaginal lubrication (ES_{T2} = .46, p = .013). The intervention group reported more improvement over time in sexual pleasure (ES_{T1} = .32 and ES_{T2} = .62, p = .001), less discomfort during sex (ES_{T1} = .49 and ES_{T2} = .66 p = .001), and less sexual distress (ES_{T2} = .59, p = .002) compared with the control group. The intervention group reported greater improvement in body image (ES_{T2} = .45, p = .009) and fewer menopausal symptoms (ES_{T1} = .39, p = .007) than the control group. No significant effects were observed for orgasmic function, sexual satisfaction, intercourse frequency, relationship intimacy, marital functioning, psychological distress or health-related quality of life.

Conclusion

Internet-based CBT has salutary effects on sexual functioning, body image, and menopausal symptoms in BCSs with a sexual dysfunction.

INTRODUCTION

Breast cancer (BC) and its treatment can have serious adverse effects on sexual functioning[1-7]. Treatment can lead to abrupt ovarian failure, vaginal atrophy and dryness, pain, and decreased sexual desire[8,9]. Body image and feelings of sexual attractiveness and femininity can also be negatively affected[10-12]. Recent studies have shown that 45% to 77% of women experience a sexual dysfunction after BC treatment[13,14], with decreased sexual desire, sexual arousal and vaginal lubrication, anorgasmia and dyspareunia as the most prevalent problems[13,15,16].

There is a range of effective psychological interventions for sexual dysfunctions[17-23], with face-to-face cognitive behavioral therapy (CBT) generally considered to be the gold standard[24]. There is growing evidence that Internet-based CBT is an effective method of treatment for a variety of psychological problems[25,26], including sexual dysfunctions[27-34]. Most studies of online sex therapy have focused on male sexual dysfunction[27-32]. However, several studies have evaluated the efficacy of online CBT for women's sexual dysfunctions[33] and problems with sexual intimacy[34]. Various BC-specific psychological interventions targeting sexuality have been developed and evaluated[35-39], including an online intervention[40]. However, these trials had a number of methodological limitations, including absence of a control group[40], high attrition from the intervention[37], and small sample size[35,38].

In our study, we investigated the efficacy of Internet-based CBT in improving sexual functioning in breast cancer survivors (BCSs) with a formal Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, (DSM-IV[41]) diagnosis of a sexual dysfunction. We hypothesized that women in the Internet-based CBT group would report greater improvement in sexual functioning and relationship intimacy than women in a waiting-list control group. Secondarily, we expected that women in the Internet-based CBT group would report less psychological distress, fewer menopausal symptoms, and greater improvement in body image, marital functioning and health-related quality of life (HRQL) than women in the control group.

PATIENTS AND METHODS

Research design and study sample

A detailed description of the design of this randomized controlled trial has been reported elsewhere[42]. Briefly, women with a history of BC and a diagnosis of sexual dysfunction were recruited from 10 hospitals in the Netherlands and were randomly assigned to either an intervention group or a waiting-list control group. Inclusion criteria were: age 18 to 65 years; diagnosis of histologically confirmed BC 6 months to 5 years prior to study entry; completion of BC treatment (with the exception of maintenance endocrine therapy and

immunotherapy); disease free at time of study entry; sufficient command of the Dutch language; and a DSM-IV-based diagnosis of a sexual dysfunction. Single as well as partnered women could participate. Sexual orientation was irrelevant for eligibility. Exclusion criteria were: no Internet access; serious psychiatric comorbidity (e.g., depressive disorder, alcohol dependency), because these problems often need to be treated first before addressing a sexual dysfunction[41]; treatment for another type of cancer (with the exception of cervix carcinoma in situ and basal cell carcinoma); presence of severe relationship problems; concurrent therapy to alleviate problems with sexuality or intimacy; concurrent CBT for other psychological problems; and participation in another trial investigating problems with sexuality or intimacy. The institutional review boards of all recruiting hospitals approved the trial.

Procedure

Figure 1 provides the CONSORT diagram of the study. Briefly, we identified potentially eligible patients via hospital databases and/or the Netherlands Cancer Registry. Patients received a letter describing the study and a postcard on which they could indicate their potential interest in participating in the study. Interested women were contacted by study staff to confirm basic eligibility and subsequently by a psychologist or sexologist to determine if they met DSM-IV criteria for a sexual dysfunction and whether the sexual problems were related to BC and its treatment.

Timing of assessments

After providing informed consent and completing the baseline questionnaire (T0) patients were randomly assigned to either the intervention group or control group using the minimization technique[43], with time since diagnosis, type of surgery, current use of endocrine therapy and menopausal status as stratification variables. Follow-up questionnaires were completed ten weeks after start of therapy (T1; mid-treatment) and post-therapy (T2), and at equivalent times for the control group. Participants received both email and telephone reminders to complete the questionnaires. Women in the intervention group completed two additional follow-up questionnaires 3 months and 9 months after completion of their therapy. Results of these latter two assessments will be reported in a later report. Upon completion of T2, women in the control group were given the opportunity to participate in the CBT program.

Intervention group

The content of the Internet-based CBT is described in detail in Table 1. In providing the CBT program to participants, we collaborated with Virenze, a mental health organization in Utrecht, the Netherlands.

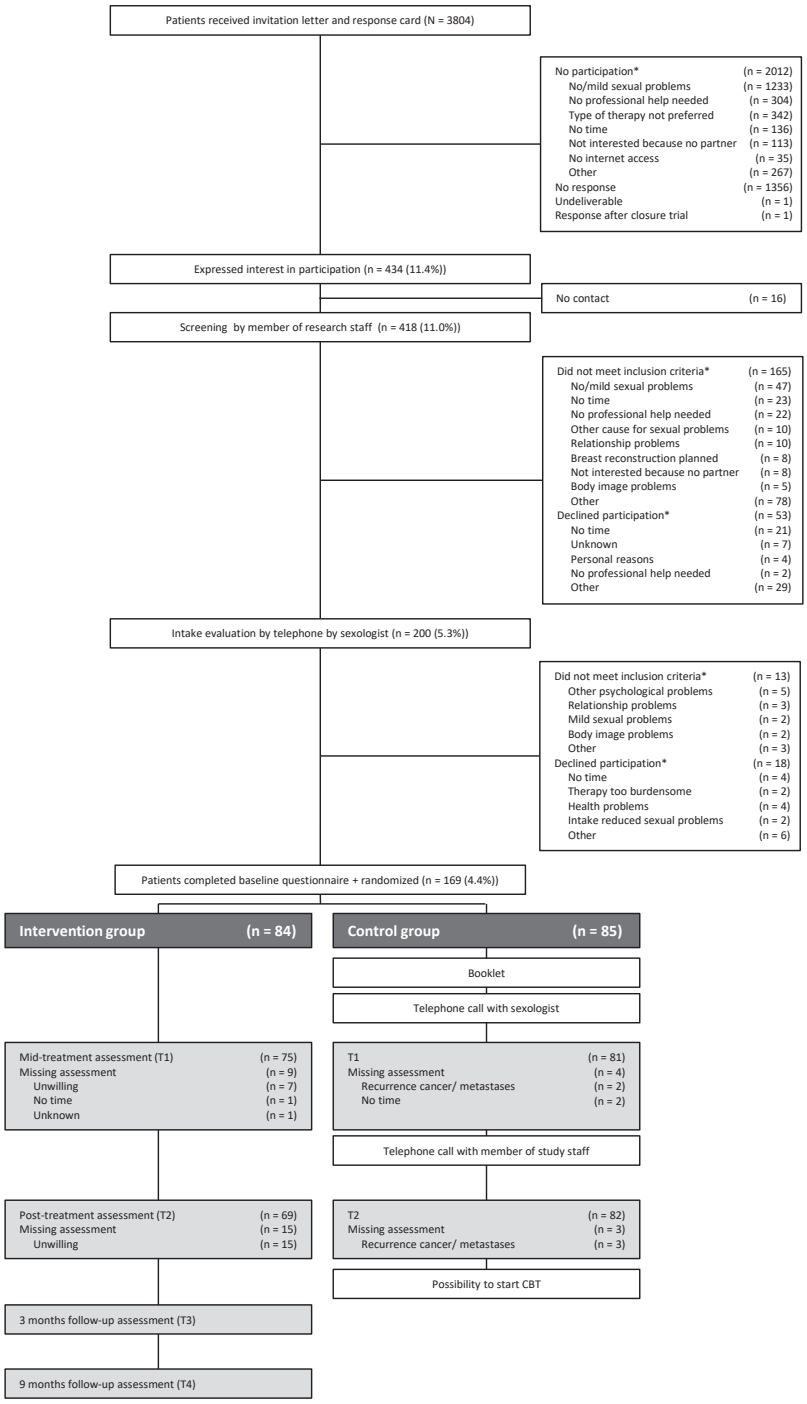

Figure 1. CONSORT diagram. CBT, cognitive behavioral therapy. T1, mid-therapy; T2, post-therapy; T3, 3 months after therapy; T4, 9 months after therapy. (*) Patients could provide more than one reason. No. of missing assessments at T1 and T2 were not necessarily cumulative.

Waiting-list control group

Women in the control group received an information booklet addressing sexuality issues after BC treatment. Six weeks after random assignment, the psychologist or sexologist telephoned the women to discuss briefly any questions that had arisen after reading the booklet. Two weeks after completion of T1, women were called by a member of the study staff. This was done to maintain contact and to reconfirm the possibility of participation in the CBT program after completion of T2.

Primary outcomes

Sociodemographic and basic clinical information was obtained during screening and via the baseline questionnaire. Sexual functioning was assessed with the Female Sexual Function Index (FSFI)[44-46] and the Sexual Activity Questionnaire (SAQ)[47,48], and sexual distress with the Female Sexual Distress Scale-Revised (FSDS-R)[45,49,50]. We used a slightly modified scoring procedure for the SAQ so that both sexually active and inactive women could complete the questionnaire. Relationship intimacy was measured with the Personal Assessment of Intimacy in Relationships Inventory (PAIR)[51].

Secondary outcomes

Secondary outcomes included body image (subscale of the European Organisation for Research and Treatment of Cancer Breast Cancer module; QLQ-BR23[52]), marital functioning (Maudsley Marital Questionnaire; MMQ[53]), menopausal symptoms (Functional Assessment of Cancer Treatment-Endocrine Symptoms; FACT-ES[54]), psychological distress (Hospital Anxiety and Depression Scale; HADS[55,56]), and HRQL (36-Item Short Form Health Survey; SF-36[57,58]). A detailed description of the outcome measures is provided in Appendix Table A1. Partners of women in the intervention group also completed self-report questionnaires from T0 to T4. These latter results will be reported separately.

Statistical analyses

With > 65 participants per group, the study had 80% power to detect an effect size (ES) of .50, with a two-tailed *p* value set at .05[60]. Baseline characteristics of the groups were compared using chi-square, Student's *t*-test or univariable analysis of variance. Questionnaire scores were calculated according to published scoring algorithms. Missing values were replaced by the average score of the completed items in the same scale for each individual, provided that ≥ 50% of the items in that scale had been completed.

Table 1. Description of the Internet-based CBT

General features of the Internet-based CBT
Therapists
• Four female psychologists/sexologists were involved in the study. • All psychologists had a Master of Science degree in Clinical Psychology, and had extensive experience with the treatment of sexual dysfunctions. Three of them were registered as a sexologist at the Dutch Scientific Association for Sexology. One of the psychologists was a registered health psychologist. • All psychologists/sexologists had undergone special training in the sexual issues of breast cancer survivors and the application of the Internet-based CBT program. • The sexologists met weekly to discuss therapeutic issues and to align procedures. As the therapists worked at two different locations, the therapists at one location met in person, and then a conference call between the two locations took place.
Structure of the CBT
• The Internet-based CBT was guided by a personal psychologist/sexologist. • Prior to the start of the CBT, the therapist and client formulated therapeutic goals, and these were included in the treatment plan. • The sexologist selected 4-5 modules that suited the sexual problems best. • Each module consisted of multiple interventions, varying between 4-8 interventions per module. • Each intervention consisted of standardized information texts, homework assignments, a report to the sexologist, and feedback from the sexologist. • The Internet-based CBT was composed of approximately 20 weekly sessions that had to be completed within a maximum period of 24 weeks. • The CBT was tailored to the needs of the individual, including the choice of modules and homework exercises, and the frequency of contact. • The sessions did not take place in real time, but rather consisted of an extensive reply (feedback, and additional questions and remarks) from the therapist in response to the completed homework assignment(s). The contact between therapist and participant took place via email. One 'session' could thus include a series of messages, but the main goal was to combine a response, additional questions/remarks, and a new homework assignment into one message. • There was room for the therapist and client to tailor the timing between sessions (e.g., if needed, the next session could be delayed). • Two evaluation interviews were scheduled by phone; one halfway and one at the end of therapy. During these interviews the therapist reviewed with the client the extent to which goals were achieved and set future goals (including maintenance of progress made after the end of therapy).
Therapy adherence
• Adherence to the intervention was one of the major, recurring items on the agenda for the weekly meetings of the psychologists/sexologists. • If a week passed without client activity, a reminder was sent via email by the therapist. If another week passed, the therapist telephoned the client. • To improve adherence to therapy, two motivational calls were scheduled by the therapist: once during the first half, and once during the second half of the CBT (note: these calls took place in addition to the telephonic evaluation interviews). • In the case of more serious problems with therapy adherence, the therapist telephoned the client to discuss the cause and possible solutions.
Involvement of the partner
• Involvement of the partner was desirable, but not mandatory. During the intake interview, the sexologist/psychologist discussed the potential importance and added value of partner involvement. After a woman was randomized into the intervention group, the sexologist/psychologist contacted her to plan the start of the CBT, and discussed the role that the partner would have. In each case, the therapist evaluated, together with the client, the possibilities, preferences and best approach with regard to partner involvement. Partners were involved in the homework assignments that focused on the client and her partner, and had the option to write their personal reports to the psychologist/sexologist (via separate response fields that were included in the homework assignments). Module 6 (see below) was included in the CBT program specifically for the male partners (female partners could complete Module 7 instead).

(Continued on next page)

Table 1. (*continued*)

General features of the Internet-based CBT
Internet platform
• The client had access to the therapy program using a personal account via a secured, password-protected website. • The clients had a personal page displaying the modules that had been selected. Only the modules that the client had completed and those on which she was currently working were accessible at any given point in time. Subsequent modules were not shown until access was given upon successful completion of each module. • Each module contained information texts and descriptions of homework assignments, including response fields for reports to the psychologist/sexologist. Separate response fields were available for partner reports. Additional contact between the therapist and client took place through an emailing/messaging system that was linked to the client's personal account. • Automatic emails were sent to notify the therapist and client when new messages were sent/received.
Costs of the CBT
• The CBT was provided at no cost to the women.
Description of modules
The content of the Internet-based CBT was based on published guidelines for CBT for sexual dysfunctions (see Ter Kuile et al.[24]). Below, we describe the more specific components of the Internet-based CBT under investigation. ***Module 1: Put your problem into words*** In this module the client describes her sexual problems, and learns how sexuality can be influenced by the treatment of breast cancer. The sexual response curve and female sexual dysfunctions are elaborated upon. Potential causes of and perpetuating factors for the sexual problems are evaluated in the light of the biopsychosocial model[59] of sexuality. Information is given about what intimacy is and how it interplays with sexuality. Women are encouraged to discuss their sexual problems with their partner; how do they deal with the sexual problem, what are their expectations and motives for having sex, does a difference in sexual needs exist? The module ends with an evaluation of the thoughts and feelings that interfere during sex. Examples of homework assignments: describe the problems with sexuality and intimacy; evaluate problem coping-style; evaluate the similarities and differences in sexual needs between the woman and her partner; create an outline of the own sexual response curve and evaluate it (and discuss it with her partner); evaluate stimulating and inhibiting thoughts and feelings that occur before, during and after sex. ***Module 2: How is my relationship doing?*** In this module the client explores the level of intimacy in her relationship, becomes aware of the amount of quality time spent with the partner, and receives psycho-education about sex and intimacy. The phases and types of intimacy (e.g., emotional, psychological, intellectual, social) are evaluated. The importance of open communication with the partner is discussed, and advice is given on how to improve communication with regard to intimacy and, in particular, sexual intimacy. The couple evaluates how their relationship and sex life has been influenced by the diagnosis and treatment of breast cancer. Couples learn that having sex and spending quality time need attention and planning, and that this will not necessarily happen naturally. Examples of homework assignments: evaluate balance between the quality time with partner and personal leisure time, and discuss with partner if this needs changing; create an action plan to increase amount of quality time and sexual/intimate moments; discover intimacy and passion in the relationship (how is the relationship evolving, what does the intimacy look like, how did the diagnosis and treatment of breast cancer change intimacy, what needs changing); have an open conversation with the partner about sex and intimacy, tell each other about own sexual wishes/preferences and boundaries; evaluate experienced 'myths' with regard to sex; learn to communicate more freely about sex, e.g. create a 'sex dictionary'. ***Module 3: Sex and my body*** In this module sensate focus therapy is introduced. The first steps of the hierarchically structured exercise program are completed. An introduction is given about to the influence of thoughts and external stimuli on the experience of sex. Attention is also paid to possible tension in the pelvic floor and methods to relax this part of the body. Examples of homework assignments: evaluate body through mirror-exercise; caress-exercise (individual); caress-exercise (couple), where the couple sits across from each other on the bed and starts with looking at each other's bodies, then caresses each other with the goal to rediscover what feels good; registration of sexual stimuli.

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Table 1. (*continued*)

General features of the Internet-based CBT
Module 4: Focus my attention
In this module the client receives task concentration training in order to learn to focus her attention on sexual experiences in such a way that it is beneficial to her. Examples of homework assignments: create an outline of own attention distribution during sex (situation, thoughts, feelings, response); concentration exercises (non-sexual and sexual).
Module 5: Explore my body
In this module sensate focus therapy is elaborated on and the hierarchically structured exercise program is completed. The client reports on her experiences with the homework exercise within a cognitive behavioral framework. Examples of homework assignments: sensate focus program with partner (non-genital zones to genital zones).
Module 6: Discovering my sexual arousal feelings (version for male partners)
The topics covered by this module are similar to the female version (see module 7), but are written from a male perspective.
Module 7: Discovering my sexual arousal feelings (female version)
In this module psycho-education is provided about the female body and genitals, female sexual dysfunction, genital stimulation, sexual techniques, and the male body and genitals. Accompanying exercises are provided for each subject, including, for example, exposure exercises for sexual pain disorders (with the goal of not avoiding sex, and with a focus on reducing fear of pain and reestablishing satisfying sexual functioning (e.g. non-penetrative sex). Goals include reducing the muscular tension in the pelvic floor and improving lubrication during sexual activity). Attention is also paid to the importance of and ways to discuss sexual feelings and preferences with the partner. Examples of homework assignments: examine own vulva and vagina, and evaluate thoughts and feelings; select and practice techniques that increase sexual arousal; gradual exposure for sexual pain disorders; conversation with partner about sexual wishes and boundaries.
Module 8: Change my thoughts
In this module the influence of thoughts on feelings and behavior is explained, and the client's dysfunctional cognitions with regard to sex and intimacy are identified. Via the method of cognitive restructuring these cognitions are replaced by more functional, adaptive thoughts. Examples of homework exercises: learn to distinguish between situation, thoughts and feelings; learn to detect own negative automatic thoughts, and formulate more balanced thoughts.
Module 9: My sexual preferences
In this module the client's sexual development, sexual needs, myths and beliefs about sex are evaluated. The client is encouraged to talk about her sexual preferences with her partner, and an action plan for behavior change is created. Examples of homework assignments: create a personal "Love Map" of sexual needs and development, sexual history, sexual myths, sexual norms and values, and discuss with partner.
Module 10: Relapse prevention
In this module the client reflects on her former automatic behavior and possible risk factors for relapse. A plan of action is generated to use in the event of a relapse.

Abbreviations: CBT = cognitive behavioral therapy.

We conducted baseline to follow-up analyses (T0 to T1 and T0 to T2) using mixed-effect models with a random intercept, a restricted maximum likelihood solution and an autoregressive covariance structure[61]. Within each mixed-effect model, the control group was the reference category. We entered group, time, and the interaction of group x time as independent variables into the model. The rate of missing T2 questionnaires was significantly different between groups, which suggested that the data were not missing completely at random. Therefore, we adjusted for non-ignorable drop-out[62]. This allowed evaluation of the contribution of missing data patterns to the outcome by adding the missing data pattern and its interaction with both group and time to the model (details provided in Appendix). We also adjusted for chemotherapy, because the study groups differed significantly on this variable (p = .035). Both adjustments led to better fitting models according to the Bayesian Information Criterion[63] and Akaike Information Criterion[64] (SPSS [Chicago, IL] syntax provided in Appendix).

As an additional approach to dealing with the differential drop-out in study assessments, we reanalyzed the data using Last Observation Carried Forward (LOCF)[65], where the participant's last available assessment is substituted for each of the missing assessments, and tipping point analysis[66], which estimates how much worse those with missing versus complete observations would have to score to yield negative rather than positive study outcomes, and whether this would be clinically plausible (see Appendix).

The p value for overall model effects was set at .05, and for specific contrasts at .01. Differences in change from baseline to follow-up between groups were accompanied by ESs. An ES of .20 was considered small, .50 moderate, and .80 large[60]. An ES of ≥ .50 was considered clinically relevant[67]. All analyses were conducted on an intention-to-treat basis.

In the absence of an exit DSM-IV interview at follow-up (T2), we calculated the Reliable Change Index (RCI)[68] by subtracting the pre-test score from the post-test score and dividing by the standard error of the difference (S_{diff}). The S_{diff} was based on data from a healthy Dutch control group[69]. An RCI > 1.96 was interpreted as an individual clinically meaningful change[68]. Chi-square tests, accompanied by odds ratios, were used to analyse the differences in improvement between the control group and the intervention group. Odds ratios of 1.5 were considered small, 2.0 moderate, and 3.0 large[70].

RESULTS

From September 2013 to May 2015, 3,804 women were invited to participate in the study, of whom 2,012 (52.9%) returned the response card indicating their reason(s) for not wanting to participate, and 1,356 (35.6%) patients did not respond. The reasons for non-participation are shown in Figure 1. Of the 434 women who expressed interest in study participation, 418 were screened for initial eligibility, and 200 of these were sub-

sequently referred for an intake interview with a psychologist or sexologist. On the basis of the intake interview, 187 women were deemed eligible for participation, 18 of whom ultimately declined participation. The remaining 169 women were randomly assigned to the intervention group (n = 84) or the control group (n = 85). T1 data were obtained from 156 women (92.3%) and T2 data from 151 women (89.3%). The percentage of available T2 data differed significantly between groups (82.1% vs. 96.5% for the intervention and control groups, respectively; p = .003).

The mean age of the study sample was 51.1 years and 94.7% had a partner. Slightly more than half of the women had undergone breast conserving treatment. The majority had received chemotherapy (83.4%), radiotherapy (81.1%), or endocrine therapy (81.7%). Most women (56.2%) were diagnosed with two sexual dysfunctions, the most prevalent being hypoactive sexual desire disorder (82.8%), sexual arousal disorder (39.6%), and dyspareunia (32.5%). Most women (65.7%) reported first having experienced sexual problems during their BC treatment. There were no significant between-group differences in previous attempts to reduce sexual problems. Except for chemotherapy rate, baseline characteristics were balanced across groups (Table 2).

The CBT was successfully completed (according to the judgment of the therapist) by 61.9% of women (mean duration CBT = 22.1 weeks; standard deviation (SD) = 4.5), 31.0% ended the CBT prematurely (mean duration CBT = 9.6 weeks; SD = 5.8), and 7.1% never started the CBT. The most common reasons for attrition were time constraints (25.6%), the intensity of the CBT (20.5%), and personal circumstances (12.8%) or relationship problems (7.7%).

Primary outcomes

Results of the analyses based on overall model effects indicated significant between-group differences over time favoring the intervention group for overall sexual functioning (FSFI total), sexual desire (FSFI desire subscale), sexual arousal (FSFI arousal subscale), vaginal lubrication (FSFI lubrication subscale), sexual pleasure (SAQ pleasure subscale), discomfort during sex (SAQ discomfort subscale), intercourse frequency (SAQ habit subscale), sexual distress (FSDS-R) and social intimacy (PAIR social subscale; Table 3).

Table 2. Baseline sociodemographic and clinical characteristics (N = 169)

Characteristic	No. (%)		
	All patients	Intervention group (n = 84)	Control group (n = 85)
Age, years			
Mean	51.1	51.6	50.5
SD	7.2	7.7	6.8
Education			
Primary education	1 (0.6)	1 (1.2)	0 (0.0)
Secondary education	29 (17.4)	18 (21.7)	11 (13.1)
Higher education	137 (82.0)	64 (77.1)	73 (86.9)
Unknown	2 (1.2)	1 (1.2)	1 (1.2)
Married/in a relationship	160 (94.7)	82 (97.6)	78 (91.8)
Part-time/fulltime job	134 (79.3)	65 (77.4)	69 (81.2)
Time since diagnosis, months			
Mean	37.5	38.1	37.0
SD	16.3	17.0	15.6
< 1 year	9 (5.3)	4 (4.8)	5 (4.5)
1-2 years	64 (37.9)	31 (36.9)	33 (38.8)
3-5 years	96 (56.8)	49 (58.3)	47 (55.3)
Menopausal status			
Premenopausal	26 (15.4)	13 (15.5)	13 (15.3)
Postmenopausal	143 (84.6)	71 (84.5)	72 (84.7)
Surgery	169 (100)		
BCT	95 (56.2)	49 (58.3)	46 (54.1)
Mastectomy with reconstruction	41 (24.3)	19 (22.6)	22 (25.9)
Mastectomy	33 (19.5)	16 (19.0)	17 (20.0)
Chemotherapy	141 (83.4)	65 (77.4)*	76 (89.4)*
Endocrine therapy	138 (81.7)	71 (84.5)	67 (78.8)
Endocrine therapy current	122 (72.2)	60 (71.4)	62 (72.9)
Radiotherapy	137 (81.1)	73 (86.9)	64 (75.3)
Immunotherapy	38 (22.5)	17 (20.2)	21 (24.7)
Immunotherapy current	6 (3.6)	2 (2.4)	4 (4.7)
Sexually active at baseline	114 (67.5)	62 (73.8)	52 (61.2)
DSM-diagnosis			
HSDD	140 (82.8)	69 (82.1)	71 (83.5)
Sexual arousal disorder	67 (39.6)	36 (42.9)	31 (36.5)
Dyspareunia	55 (32.5)	27 (32.1)	28 (32.9)
Orgasmic disorder	16 (9.5)	8 (9.5)	8 (9.4)
Sexual aversion disorder	7 (4.1)	5 (6.0)	2 (2.4)
Vaginismus	2 (1.2)	1 (1.2)	1 (1.2)
Sexual dysfunction NOS	4 (2.4)	4 (4.8)	0 (0.0)

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Table 2. (*continued*)

Characteristic	No. (%)		
	All patients	Intervention group (n = 84)	Control group (n = 85)
No. of diagnosed sexual dysfunctions			
1 sexual dysfunction	61 (36.1)	27 (32.1)	34 (40.0)
2 sexual dysfunctions	95 (56.2)	48 (57.1)	47 (55.3)
3 or 4 sexual dysfunctions	13 (7.7)	9 (10.7)	4 (4.7)
Onset sexual problems			
Before BC treatment	21 (12.4)	10 (11.9)	11 (12.9)
During BC treatment	111 (65.7)	57 (67.9)	54 (63.5)
After BC treatment	37 (21.9)	17 (20.2)	20 (23.5)
Previous activities to reduce sexual problems			
Psychologist/sexologist	4 (2.4)	1 (1.2)	3 (3.5)
Pelvic floor therapy	2 (1.2)	2 (2.4)	0 (0.0)
Lubricant	54 (32.0)	26 (31.0)	28 (32.9)
Vaginal moisturizer	13 (7.7)	6 (7.1)	7 (8.3)
Lidocaine cream	0 (0.0)	0 (0.0)	0 (0.0)
Estrogen cream	2 (1.2)	1 (1.2)	1 (1.2)
Relaxation exercises	7 (4.1)	4 (4.8)	3 (3.5)
Medication	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BCT = breast conserving treatment; HSDD = hypoactive sexual desire disorder; NOS = not otherwise specified; SD = standard deviation.
*p = .035. For all other variables there were no statistically significant differences between groups.

The specific contrasts indicated that, at T1, the intervention group reported a significantly greater increase in sexual desire (ES = .48) and pleasure (ES = .32), and decrease in discomfort during sex (ES = .49) compared with the control group. At T2, the intervention group reported greater improvement in overall sexual functioning compared with the control group (ES = .43), which was reflected in a significant improvement in sexual desire (ES = .72), sexual arousal (ES = .50), and vaginal lubrication (ES = .46). The intervention group also reported a significantly greater decrease in sexual distress (ES = .59) and in discomfort during sex (ES = .66), and greater increase in sexual pleasure (ES = .62) than the control group. Although the overall mixed-effect models for the SAQ habit subscale and PAIR social subscale were significant, specific contrasts did not reveal significant between-group differences at T1 or T2. No significant overall group differences were observed for other subscales of the FSFI or PAIR.

The RCI for the FSFI total score (Table 4) indicated that 63.2% of the intervention group experienced a clinically significant change in sexual functioning versus 32% of the control group, with the odds of improvement for the intervention group being 3.66 times greater than that of the control group ($p < .001$).

Table 3. Mean values at baseline, mid-treatment and post-treatment, and between-group differences for the mixed-effect models of the primary and secondary outcome measures

	T0*			T1*			T2*		
Outcome measure	**No. of patients**	**Mean**	**SD**	**No. of patients**	**Mean**	**SD**	**No. of patients**	**Mean**	**SD**
PRIMARY OUTCOMES									
Overall sexual functioning									
FSFI total									
Intervention	83†	13.76	6.92	72†	17.16	9.20	68†	19.15	9.53
Control§	80†	13.27	7.75	73†	15.46	8.29	75†	14.90	8.61
Sexual desire									
FSFI desire									
Intervention	84	2.03	0.84	74	2.63	1.08	69	2.82	1.02
Control§	85	1.96	0.90	80	2.05	0.83	81	2.08	1.00
Sexual arousal									
FSFI arousal									
Intervention	84	2.19	1.47	75	2.85	1.76	69	3.09	1.80
Control§	85	2.05	1.43	81	2.32	1.68	82	2.10	1.66
Vaginal lubrication									
FSFI lubrication									
Intervention	84	2.20	1.69	75	2.88	1.98	69	3.27	2.06
Control§	85	2.26	2.01	81	2.54	1.96	82	2.37	2.02
Orgasmic function									
FSFI orgasm									
Intervention	84	2.46	1.91	75	3.11	2.10	69	3.48	2.14
Control§	85	2.33	1.97	81	2.70	2.00	82	2.62	2.06
Sexual satisfaction									
FSFI satisfaction									
Intervention	83†	2.94	1.26	74†	3.71	1.56	68†	3.91	1.58
Control§	80†	2.54	1.26	75†	3.15	1.42	76†	3.12	1.43
Sexual pain									
FSFI pain									
Intervention	84	1.86	2.05	74	2.11	2.18	69	2.58	2.39
Control§	85	1.84	2.23	80	2.14	2.28	82	2.08	2.19
Sexual pleasure									
SAQ pleasure									
Intervention	83	4.50	3.06	74	6.82	4.21	69	7.43	4.35
Control§	85	4.21	2.86	79	5.65	3.68	81	4.86	3.52
Discomfort during sex									
SAQ discomfort									
Intervention	63‡	3.67	1.86	55‡	2.87	1.61	52‡	2.62	1.57
Control§	52‡	3.27	2.05	52‡	2.79	1.98	52‡	2.88	1.91
Intercourse frequency									
SAQ habit									
Intervention	84	0.55	0.90	74	0.89	1.07	69	1.13	1.00
Control§	84	0.45	0.77	80	0.45	0.67	82	0.60	0.81

	Between-group difference T0-T1				Between-group difference T0-T2			
***p* value overall model¤**	**Mean Change**	**SE**	***p***	**Effect size[i]**	**Mean Change**	**SE**	***p***	**Effect size[i]**
.031	2.09	1.30	.108	.20	**3.84**	**1.45**	**.009**	**.43**
<.001	**0.54**	**0.15**	**<.001**	**.48**	**0.66**	**0.15**	**<.001**	**.72**
.008	0.56	0.25	.028	.27	**0.88**	**0.29**	**.002**	**.50**
.013	0.57	0.32	.072	.23	**0.95**	**0.32**	**.004**	**.46**
.099	0.48	0.33	.153	.18	0.74	0.35	.035	.33
.193	0.35	0.23	.137	.19	0.42	0.25	.095	.27
.551	0.14	0.30	.642	.06	0.39	0.34	.254	.18
.001	**1.58**	**0.61**	**.010**	**.32**	**2.41**	**0.64**	**<.001**	**.62**
.001	**-0.87**	**0.28**	**.003**	**.49**	**-1.03**	**0.31**	**.001**	**.66**
.024	0.42	0.17	.015	.30	0.46	0.19	.017	.23

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Table 3. (*continued*)

Outcome measure	T0*			T1*			T2*		
	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD
Sexual distress									
FSDS-R									
Intervention	84	25.80	9.28	74	22.62	9.95	69	17.86	9.53
Control§	85	23.98	7.96	81	22.00	9.33	82	20.89	9.55
Emotional intimacy									
PAIR emotional intimacy									
Intervention	82†	75.61	17.21	74†	75.89	16.10	67†	77.19	16.40
Control§	78†	69.18	22.92	74†	70.05	22.61	76†	70.84	20.89
Social intimacy									
PAIR social intimacy									
Intervention	82†	61.95	18.62	74†	64.11	18.88	67†	65.76	18.69
Control§	78†	63.75	18.83	74†	64.38	18.80	76†	63.39	18.84
Sexual intimacy									
PAIR sexual intimacy									
Intervention	82†	67.95	17.44	74†	69.19	17.22	67†	71.70	16.74
Control§	78†	63.64	18.80	74†	64.54	19.57	76†	65.47	19.02
Intellectual intimacy									
PAIR intellectual intimacy									
Intervention	82†	69.80	15.13	74†	70.73	13.48	67†	77.97	17.13
Control§	78†	67.03	17.53	74†	66.81	19.97	76†	72.32	22.15
Recreational intimacy									
PAIR recreational intimacy									
Intervention	82†	75.22	12.78	73†	75.59	15.25	67†	76.00	13.73
Control§	78†	77.28	17.54	74†	74.70	18.39	76†	74.63	19.49
Conventionality									
PAIR conventionality									
Intervention	82†	64.85	16.90	74†	66.78	18.96	67†	67.37	20.02
Control§	78†	60.92	20.78	74†	58.86	20.48	76†	61.26	22.01
SECONDARY OUTCOMES									
Menopausal symptoms									
FACT-ES									
Intervention	84	50.26	8.46	75	53.09	9.27	69	53.55	9.05
Control§	85	52.94	8.20	81	52.45	7.99	82	54.04	7.61
Body image									
QLQ-BR23 body image									
Intervention	84	68.65	25.76	75	72.67	25.98	69	81.64	22.44
Control§	85	65.78	26.60	81	70.99	24.97	82	72.36	25.01

	Between-group difference T0-T1				Between-group difference T0-T2			
***p* value overall model¤**	**Mean Change**	**SE**	***p***	**Effect size[i]**	**Mean Change**	**SE**	***p***	**Effect size[i]**
.002	-2.12	1.26	.094	.21	**-5.00**	**1.39**	**<.001**	**.59**
.986	-0.15	2.21	.947	.01	-0.43	2.62	.868	.03
.044	2.09	1.90	.272	.15	4.41	1.76	.013	.42
.413	2.12	2.26	.349	.13	2.67	2.11	.207	.21
.650	0.73	2.29	.749	.04	2.33	2.58	.367	.14
.059	3.93	1.86	.036	.27	4.15	2.00	.040	.35
.233	3.92	2.30	.089	.22	2.55	2.47	.303	.17
.007	**3.26**	**1.02**	**.002**	**.39**	1.91	1.16	.103	.26
.009	1.52	2.70	.573	.07	**8.69**	**3.04**	**.005**	**.45**

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Table 3. (*continued*)

Outcome measure	T0*			T1*			T2*		
	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD
Marital functioning - Marital satisfaction									
MMQ marital									
Intervention	82†	11.84	7.77	74†	11.54	7.95	68†	12.03	9.75
Control§	78†	14.06	10.33	74†	14.73	11.13	76†	15.14	11.79
Marital sexual satisfaction									
MMQ sexual									
Intervention	82†	22.06	6.83	74†	18.89	9.09	68†	16.60	9.16
Control§	78†	22.73	7.74	74†	21.33	8.51	76†	20.66	8.64
Marital functioning - General Life satisfaction									
MMQ general life									
Intervention	82†	8.93	4.63	74†	9.43	5.06	67†	8.22	4.70
Control§	78†	9.32	4.92	74†	9.05	4.84	76†	8.53	4.65
Depression									
HADS depression									
Intervention	84	4.54	3.04	75	4.64	3.19	69	4.55	3.81
Control§	84	3.92	3.22	81	4.20	3.34	82	4.09	3.49
Anxiety									
HADS anxiety									
Intervention	84	6.15	3.41	75	6.49	3.45	69	6.02	3.46
Control§	84	6.01	4.31	81	6.02	4.14	82	5.85	3.91
Psychological distress									
HADS total									
Intervention	84	10.69	5.62	75	11.13	6.01	69	10.57	6.61
Control§	84	9.93	6.90	81	10.22	6.68	82	9.93	6.74
Physical functioning									
SF-36 physical functioning									
Intervention	84	79.40	18.36	75	78.09	21.04	69	79.64	19.35
Control§	85	82.10	14.16	81	81.23	17.62	82	82.87	16.65
Role limitations due to physical problems									
SF-36 role physical									
Intervention	83	68.98	35.48	75	68.67	38.58	69	73.91	37.48
Control§	85	62.94	40.75	81	66.36	41.68	82	70.12	40.72
Bodily pain									
SF-36 bodily pain									
Intervention	84	71.31	22.54	75	70.09	24.61	69	72.30	21.71
Control§	85	71.78	20.39	81	70.02	20.81	82	72.18	21.84

	Between-group difference T0-T1				Between-group difference T0-T2			
p value overall model¤	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
.455	-1.30	1.11	.241	.15	-1.38	1.31	.296	.17
.032	-2.68	1.19	.025	.28	-3.14	1.31	.018	.40
.810	0.38	0.64	.560	.08	0.03	0.66	.965	.01
.870	-0.20	0.38	.600	.06	-0.18	0.48	.707	.06
.720	0.16	0.41	.702	.05	-0.17	0.51	.738	.05
.896	-0.04	0.66	.946	.01	-0.35	0.88	.690	.04
.961	0.53	1.88	.778	.04	0.27	1.82	.881	.03
.988	-0.86	6.15	.889	.02	-0.13	7.07	.985	.00
.861	1.49	3.07	.629	.06	1.53	3.26	.639	.08

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Table 3. (*continued*)

Outcome measure	T0*			T1*			T2*		
	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD
General health perceptions									
SF-36 general health									
Intervention	84	65.24	20.55	75	64.13	20.37	69	63.01	22.18
Control§	85	67.52	22.29	81	64.17	23.37	82	65.96	23.01
Vitality									
SF-36 vitality									
Intervention	84	59.35	16.09	75	58.73	19.63	69	61.74	20.97
Control§	85	59.24	19.22	81	60.43	18.48	82	61.10	19.95
Social functioning									
SF-36 social functioning									
Intervention	84	79.61	19.09	75	76.50	22.60	69	79.71	23.59
Control§	85	81.18	20.74	81	80.40	18.95	82	80.79	20.05
Role limitations due to emotional problems									
SF-36 role emotional									
Intervention	83	86.35	29.47	75	81.78	33.91	69	81.16	34.53
Control§	85	75.69	36.87	81	76.95	36.38	82	77.64	37.06
General mental health									
SF-36 mental health									
Intervention	84	75.24	14.49	75	72.96	16.21	69	74.14	16.72
Control§	85	75.29	16.92	81	73.48	15.73	82	76.24	16.47

Note. Bold font indicates significant overall interaction effect between group and time, and significantly different contrast (T0-T1; T0-T2). Reported are the raw means and standard deviations. Models were adjusted for non-ignorable drop-out and chemotherapy treatment.

Abbreviations: FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; MMQ = Maudsley Marital Questionnaire; PAIR = Personal Assessment of Intimacy in Relationships Inventory; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire of the European Organisation of Research and Treatment of Cancer; SAQ = Sexual Activity Questionnaire; SD = standard deviation; SE = standard error; SF36 = 36-Item Short Form Health Survey.

*T0 = baseline; T1 = mid-treatment; T2 = post-treatment.

¤*p* value of the overall interaction effect between group and time.

ⁱEffect size was calculated based on the t-test statistic: (2*t)/(√degrees of freedom); (0.2 small, 0.5 moderate, 0.8 large).

†Scale was completed by less than total number of participants as only partnered participants could complete it.

‡Scale was completed by less than total number of participants as only participants who had had vaginal penetration could provide an answer.

§Control group is reference group.

		Between-group difference T0-T1				Between-group difference T0-T2			
	p value overall model¤	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	.578	1.91	2.25	.397	.11	-0.16	2.46	.949	.01
	.707	-1.80	2.58	.485	.08	-0.09	2.99	.976	.00
	.842	-1.50	3.44	.665	.05	0.40	3.68	.109	.02
	.348	-6.91	6.33	.276	.013	-9.90	7.04	.161	.22
	.542	0.45	2.27	.844	.02	-2.06	2.62	.433	.12

Table 4. Percentages and chi-square tests of participants with clinically meaningful improvement based on RCI of FSFI total score

	Non-imputed data				LOCF-imputed data			
	No. (%)				No. (%)			
Conclusion RCI*	Intervention group	Control group	*p* value†	OR‡	Intervention group	Control group	*p* value†	OR‡
Not improved	25 (36.8)	51 (68.0)	< .001	3.66	38 (45.8)	54 (69.2)	.003	2.66
Improved	43 (63.2)	24 (32.0)			45 (54.2)	24 (30.8)		
Total n§	68	75			83	78		

Abbreviations: FSFI= Female Sexual Function Index; LOCF= Last Observation Carried Forward; OR= odds ratio; RCI = Reliable Change Index.

*The RCI calculated per participant by subtracting the pre-test score (X_{T0}) from the post-test score (X_{T2}) and dividing by the standard error of the difference: $S_{diff}= \sqrt{2}(S_E)^2$, with $S_E= SD_{control}\sqrt{1-r_{xy\ control}}$, where $SD_{control}$ is the standard deviation and $r_{xy\ control}$ is the test-retest reliability of a healthy control group on the outcome measure.

†*p* value of the Pearson chi-square test.

‡Odds ratios of 1.5 were considered small, 2.0 as moderate, and 3.0 as large.

§The FSFI total score was calculated for less than the total number of participants as only participants with a regular sexual partner could provide an answer to all FSFI items.

Secondary outcomes

Significant group differences over time favoring the intervention group were observed for menopausal symptoms (FACT-ES), body image (QLQ-BR23 body image subscale) and marital sexual satisfaction (MMQ sexual satisfaction subscale; Table 3).

The specific contrasts indicated that the intervention group reported a significantly greater decrease in menopausal symptoms from T0 to T1 (ES = .39), and improvement in body image from T0 to T2 (ES = .45). Although the overall mixed-effect model for the MMQ sexual satisfaction subscale was significant, specific contrasts did not reveal significant between-group differences at T1 or T2. No significant overall group differences over time were observed for the other subscales of the MMQ or for HADS or SF-36 (Table 3).

LOCF and tipping point analysis

The analyses based on the LOCF-imputed data resulted in similar significance levels for nearly all outcome measures, with ESs decreasing between .03 and .15 points. The FSFI lubrication subscale was no longer significant (p = .051), which also affected the significance level of the FSFI total score (p = .106). The RCI results based on the LOCF-imputed data (Table 4) indicated that the odds of clinically significant improvement for the intervention group was 2.66 times greater than those of the control group (p = .003).

The results of the tipping point analyses indicated that the difference between scores of the women with missing outcome data and those with complete data would have to exceed a half a SD to tip the balance from significant to non-significant study outcomes, which we regarded as clinically implausible (see Appendix).

DISCUSSION

In this randomized controlled trial, an Internet-based CBT program had a positive, clinically relevant effect on sexual functioning of BC survivors with a DSM-IV diagnosis of a sexual dysfunction. This included a positive impact on sexual desire, sexual arousal, vaginal lubrication, sexual pleasure, discomfort during sex, and sexual distress. Additional positive effects were observed for body image and menopausal symptoms. No significant effects were found for orgasmic function, sexual satisfaction, intercourse frequency, relationship intimacy, marital functioning, psychological distress, or HRQL.

In contrast to earlier studies[33,34], we did not observe a significant effect on relationship intimacy. This may reflect the fact that previous intervention-based trials included specific, weekly partner communication exercises, whereas our CBT did not.

The positive effect that we observed on menopausal symptoms might reflect the fact that the FACT-ES includes three items relating to sexual functioning. When we repeated the analysis excluding these items, the results were no longer significant (p = .052), suggesting that the intervention impacted primarily on sex-related menopausal symptoms.

We did not observe a significant effect of the CBT program on psychological distress or marital functioning. This may reflect the fact that at baseline, relatively few women had clinically relevant levels of psychological distress (i.e., 13% and 4% scored above the HADS cut-off for anxiety and depression caseness, respectively) and that the presence of severe relationship problems was an exclusion criterion for trial participation. Thus there was relatively little room for improvement in these areas.

Our trial had several limitations. First, we compared the Internet-based CBT to a waiting-list control group only. We also considered including a comparison group undergoing face-to-face CBT and/or a less active intervention (e.g., an attention placebo control group). However, we felt that it was important to first establish the efficacy of the Internet-based CBT program, with a subsequent step being a comparative-effectiveness study, and we considered it inappropriate to ask women with a DSM-IV diagnosis to commit time and energy to an attention placebo control group.

Second, only 62% of the women in the intervention group successfully completed the CBT. However, our results are based on intention-to-treat analyses, with 82% of the intervention group completing the post-treatment questionnaire; a follow-up rate that is quite high for this type of intervention trial[71]. We would also note that the therapy compliance rate is similar to that reported in previous trials of Internet-based therapy[33,34,72] and face-to-face sex therapy[22].

Third, there was differential loss-to-follow-up, with fewer patient cases available for the T2 assessment for the intervention group than the control group. However, we adjusted for non-ignorable drop-out patterns to account for this difference and also conducted LOCF and tipping point analyses as more conservative approaches to investigating the impact

of missing data on study outcomes. We suspect that the high study completion rate in the control group (96.5%) may reflect the fact that these women were afforded the opportunity to participate in the CBT after completing their trial participation (60% actually did so). This may have provided an additional incentive to complete the assessments.

Finally, it was not possible (because of insufficient budget) to allow the sexologists to perform an exit interview to establish at follow-up if the participants still met criteria for a DSM-IV diagnosis of a sexual dysfunction. In lieu of this, we calculated the RCI as an alternative indicator of clinically meaningful change. The results indicated that compared with the control group, a significantly greater percentage of women in the intervention group evidenced a clinically meaningful improvement in sexual functioning.

Our study also had a number of important strengths. We employed a randomized trial design, the sample size was large, and women were recruited via both academic and community hospitals.

Our findings indicate that Internet-based CBT has a salutary effect on sexual functioning, body image and sex-related menopausal symptoms of BCSs with a DSM-IV diagnosis of a sexual dysfunction. A next step would be to investigate which elements of the CBT contribute most to the efficacy of the intervention and if comparable outcomes can be achieved with a less intensive or briefer Internet-based intervention.

APPENDIX

Description of the methods used to deal with the differential loss-to-follow-up between the intervention and control group

Introduction

The rate of missing T2 questionnaires was significantly different between the intervention and control group (see the Results section of the manuscript), with less cases in the intervention group completing T2 than in the control group. The differential loss-to-follow-up could potentially bias the results, as women in the intervention group who did not complete all assessments were often those who have stopped the Internet-based cognitive behavioral therapy (CBT) prematurely or who did not start the CBT (Appendix Table A2). Consequently, it is possible that the sexual functioning of the unobserved group might have been worse than that of the observed group. This, in turn, might affect the positive conclusions of our primary analyses regarding the effect of the Internet-based CBT on the sexual functioning of breast cancer survivors with a DSM-IV diagnosis of sexual dysfunction. We used three approaches to evaluate the possible effects of the missing data on the study results: (1) including a pattern mixture model in the mixed-effect models; (2) reanalyzing the data using Last Observation Carried Forward for the missing assessments; and (3) tipping point analysis. The methods are described below.

Pattern mixture model

As a first method, we used a pattern mixture model[62] (PMM) in our primary intention-to-treat (ITT) analyses. By including the pattern of missingness in the mixed-effect model, one adjusts for non-ignorable drop-out. The possible patterns for our study are listed in Appendix Table A3.

In the ITT-analyses, we combined the patterns OMO and OOM (both including one missing assessment), as groups were small. The pattern OOO was used as the reference group, as it was the largest group. The patterns of missingness were included in the mixed-effect model by adding the variable 'patternmiss' as an interaction with both group and time. The SPSS syntax for the dependent variable Female Sexual Function Index (FSFI) total score is as follows:

```
MIXED FSFItotal BY group time chemotherapy patternmiss
 /CRITERIA=CIN(95) MXITER(100) MXSTEP(10) SCORING(1) SINGULAR(0.000000000001)
 HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0.000001, ABSO-
 LUTE)
```

/FIXED=group time chemotherapy patternmiss group*time group*chemotherapy time*chemotherapy group*patternmiss time*patternmiss | SSTYPE(3)
/METHOD=REML
/PRINT=CORB COVB SOLUTION TESTCOV
/RANDOM=INTERCEPT | SUBJECT(ID) COVTYPE(ID)
/REPEATED=time | SUBJECT(ID) COVTYPE (AR1)
/EMMEANS=TABLES(group)
/EMMEANS=TABLES(time)
/EMMEANS=TABLES(group*time) .

Where group: 1 = intervention; 2 = control group
time: 0 = T2; 1 = T1; 2 = T0
chemotherapy: 0 = no; 1 = yes
patternmiss: 1 = OMM; 2 = OMO/OOM; 3 = OOO.
Note: SPSS uses the category with the highest value as the reference category.

If the interaction between patternmiss and time or group was significant, this indicated that having missing data predicted change in the dependent variable. However, by including the patterns of missingness in the model, one adjusts for the contribution of the missing data pattern to the outcome of the model.

The results of the mixed-effect models adjusting for non-ignorable drop-out were similar to the results of the models without this adjustment: the significance levels were equal, and the effect sizes of the models including the PMM were slightly larger (ranging from .01 to .07; Appendix Table A4).

We reanalyzed the data using Last Observation Carried Forward and performed tipping point analysis for all statistically significant primary outcome measures (i.e., the outcome measures with both a significant overall model and significant contrast(s)), except for the SAQ discomfort subscale. This scale can only be completed by women who had vaginal penetration in the past month. In case of no vaginal penetration, this scale has a missing score. As a consequence, it was not possible to impute this scale for women who had a missing assessment because, when using imputation, one assumes that a woman had vaginal penetration, while in fact this is unknown.

Last Observation Carried Forward

In Last Observation Carried Forward (LOCF)[65], the participant's last available assessment is substituted for each of her missing assessments. There is some concern about the use of this approach in patient groups where one expects significant deterioration in functioning after loss-to-follow-up from a study, e.g., in a situation where the treatment under investigation is associated with significant toxicity or in cases where functioning is expected

to worsen over time (e.g., in Parkinson's disease). In these cases, LOCF would create an overly optimistic picture of the functioning of patients in the treatment arm for whom follow-up assessments are missing. In our study, women in the intervention group who did not complete all assessments had either stopped the Internet-based CBT prematurely or never started it to begin with (Appendix Table A2). We believe that the use of LOCF for this group is justifiable, as one would not expect the sexual functioning of these women to deteriorate after drop-out, particularly considering the reasons for attrition from the Internet-based CBT (see the Results section of our manuscript), which are only partially related to the intervention itself. One might even argue that LOCF is a quite conservative approach for the current study, since it assumes that sexual functioning did not improve (further) in *any* of the women lost-to-follow-up.

Appendix Table A5 lists the results from the mixed-effect models using the LOCF-imputed data. Most of the outcomes that were statistically significant in the primary ITT-analyses, remained so in the analyses based on the LOCF-data. The effect sizes were smaller, with decreases ranging from .03 to .15 points. The FSFI lubrication subscale was no longer significant (overall model *p* value ITT = .013; overall model *p* value LOCF = .051), which was also reflected in the FSFI total score (as the FSFI total score is a summated score of six subscales, including the lubrication subscale) (overall model *p* value ITT = .031; overall model *p* value LOCF = .106). The overall model of the PAIR social subscale (which had a significant overall model in the ITT analyses, but no significant contrasts), was no longer significant in the LOCF analysis (overall model *p* value ITT = .044; overall model *p* value LOCF = .096).

Because it would be of added value to investigate how the primary analysis would maintain if the drop-out patients in the intervention group had worse results than non-drop-out patients, we performed tipping point analyses for all significant primary outcomes.

Tipping point

Since one cannot entirely rule out the possibility that (some) patients' sexual functioning worsened after being lost-to-follow-up, we also carried out a tipping point analysis[66]. Tipping point is defined as the point at which differences in the mean scores between the observed and the missing cases would be of sufficient magnitude to negate the positive results based on the observed cases only. In a tipping point analysis, missing values are imputed with the mean value of the observed cases in the intervention group, subtracted by a shift parameter δ, so that the resulting *p* value for the treatment comparison is equal to a prespecified significance level (in our case, $p = .05$). A series of analyses are performed with a range of increasing δ so that one can assess at which point the study conclusions change from favorable to unfavorable for the intervention under study, i.e., from statistically significant to non-significant. This δ is called the tipping point.

After the tipping point is established, a judgment has to be made as to whether it is clinically plausible. Norman and colleagues[67] have argued that, for patient-reported outcome measures, a half standard deviation difference is typically clinically meaningful. Thus, in order to draw conclusions about the observed tipping point, we compared it to the pooled standard deviation of the intervention and control groups at T0. We established *a priori* that a tipping point larger than half of the pooled standard deviation would be considered clinically implausible (as has been proposed by Ratitch et al.[73]), and thus would support the robustness of our original, primary results (i.e., that the Internet-based CBT is efficacious).

We imputed the missing values of women in the intervention group at a specific assessment (point T1 or T2) with the mean of the observed intervention group plus or minus δ. Adding or subtracting δ was dependent on the scoring of the questionnaire. For example, for the FSFI total score, where a higher score indicates better sexual functioning, we subtracted δ, so that the missing outcomes of the unobserved group were imputed with a score that reflected a decreased level of sexual functioning. We estimated a starting value of δ based on the range of the scale and the change in intervention group from T0 to T2.

As the reason for missing observations in the control group was typically disease recurrence or metastases (see the CONSORT diagram in the manuscript), we did not expect that loss-to-follow-up of women in the control group reflected a change in sexual functioning. Therefore, we decided to impute the missing values of women in the control group with the mean of the observed control group at the specific assessment point (i.e., T1 or T2).

We established the tipping point for all primary outcomes that were significant in the original analyses (i.e., the outcomes that had both a significant overall model and significant specific contrast(s)): FSFI total scale, FSFI desire subscale, FSFI arousal subscale, FSFI lubrication subscale, SAQ pleasure subscale, and FSDS-R. Appendix Table A6 displays the tipping point for each outcome measure and compares it to the pooled standard deviation of the intervention and control groups at T0.

The tipping points for FSFI total, FSFI desire, FSFI arousal, FSFI lubrication, SAQ pleasure, and FSDS-R exceeded the established threshold of half a standard deviation.

Discussion

The models that were adjusted for non-ignorable drop-out yielded slightly better results compared to the unadjusted models (i.e., effect sizes increased with .01 to .07 points). In the analyses based on LOCF-data, the FSFI total score was no longer significant (p = .106 versus p = .031 in the primary analysis). However, as the FSFI total score is a summated score of six FSFI subscales, the change in significance of the FSFI total score can be explained by the fact that the FSFI lubrication subscale was no longer statistically significant. Additionally, the scores on the FSFI subscales orgasm, satisfaction and pain (that were non-significant in the primary analyses) decreased even further when using the LOCF-data,

thus influencing the FSFI total score negatively. The fact that the LOCF-method is quite conservative, and yet most of the scales (FSFI desire, FSFI arousal, SAQ pleasure, FSDS-R, FACT-ES, and QLQ-BR23 body image subscale) remained significant, and effect sizes decreased relatively little, provides support for the conclusions based on the primary analyses that the Internet-based CBT had a positive effect on sexual functioning, body image, and menopausal symptoms.

The results of the tipping point analysis support the robustness of the original, primary study results. That is, the differences between the means of the non-missing intervention group and missing intervention group needed to alter the study conclusions from favorable for the Internet-based CBT to unfavorable, are largely implausible, as all tipping points exceeded the established threshold of half a standard deviation.

Taken together, the results of the PMM, LOCF and tipping point analysis support the robustness of the conclusions drawn from the primary analyses that the Internet-based CBT has a significant, salutary effect on sexual functioning of breast cancer survivors with a DSM-IV diagnosis of sexual dysfunction.

Table A1. Study outcome measures and corresponding questionnaires

Variable	Questionnaire	Details
Primary outcomes		
Sexual functioning	FSFI[44,45]	• Assesses sexual functioning • 19 items; 5- and 6-point Likert scales • Subscales: desire; arousal; lubrication; orgasm; satisfaction; pain • Total score*: 2-36 / Subscale scores*: desire 1.2-6; arousal 0-6; lubrication 0-6; orgasm 0-6; satisfaction 0.8-6; pain 0-6; higher score indicates better sexual functioning • Time frame: past 4 weeks
	FSDS-R[49,50]	• Assesses distress related to sexual dysfunction • 13 items; 5-point Likert scale (0 'never' to 4 'always') • Total score: 0-52; higher score indicates higher level of sexual distress • Time frame: past 30 days
	SAQ[47,48]	• Assesses sexual functioning • 10 items; 4-point Likert scales • Subscales: pleasure; discomfort; habit • Subscale scores: pleasure 0-18; discomfort 0-6; habit 0-3; higher score indicates higher levels of pleasure; lower score indicates lower levels of discomfort; habit is a single item (0 'less sexual activity than usual' to 3 'much more sexual activity than usual') • Time frame: past month
Intimacy	PAIR Inventory[51]	• 36 items; 5-point Likert scale (0 'strongly disagree' to 4 'strongly agree') • Subscales: emotional intimacy; social intimacy; sexual intimacy; intellectual intimacy; recreational intimacy; conventionality • Subscale score*: 0-96; higher score indicates higher levels of intimacy • Time frame: 'how the relationship is now'
Secondary outcomes		
Body image	EORTC QLQ-BR23 body image subscale[52]	• 4 items; 4-point Likert scale (1 'not at all' to 4 'very much') • Score: 0-100; higher score indicates higher level of functioning • Time frame: past week
Menopausal symptoms	FACT-ES[54]	• 18 items; 5-point Likert scale (0 'not at all' to 4 'very much') • Score range: 0-72; higher score indicates fewer menopausal symptoms • Time frame: past 7 days
Marital functioning	MMQ[53]	• 20 items; 9-point Likert scale (range 0-8) • Scales: marital adjustment (M); sexual adjustment (S); general life adjustment (GL) • Scale scores*: S + GL: 0-40; M: 0-80; higher score indicates greater dissatisfaction in the specific domain • Time frame: past 2 weeks
Psychological distress	HADS[55,56]	• 14 items; 4-point Likert scale (range 0-3) • Subscales: depression (HADS-D); anxiety (HADS-A) • Total score: 0-42 / Subscale scores: 0-21; higher score indicates more psychological distress • Time frame: past week

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Table A1. (*continued*)

Variable	Questionnaire	Details
Health-related quality of life	SF-36[57,58]	• 36 items; dichotomous and 3- to 6-point Likert scales • Subscales: physical functioning; role limitations due to physical health problems; bodily pain; social functioning; general mental health; role limitations due to emotional problems; vitality; general health perceptions • Subscale score*: 0-100; higher score indicates higher levels of functioning/well-being • Time frame: past week

*The score is calculated based on weighted items.
EORTC QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire of the European Organisation of Research and Treatment of Cancer; FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; MMQ = Maudsley Marital Questionnaire; PAIR Inventory = Personal Assessment of Intimacy in Relationships Inventory; SAQ = Sexual Activity Questionnaire; SF-36 = 36-Item Short Form Health Survey.

Table A2. Missing data patterns for groups that successfully completed the CBT, stopped CBT prematurely, or never started CBT

Missing data pattern	CBT successfully completed	CBT stopped prematurely	CBT never started
OMM	0 (0.0)	2 (33.3)	5 (19.2)
OMO/OOM	0 (0.0)	2 (33.3)	8 (30.8)
OOO	52 (100.0)	2 (33.3)	13 (50.0)

Note. Data are shown as No. (%).
Abbreviations: CBT = cognitive behavioral therapy; OMM = observed at T0 (baseline assessment), missing at T1 (mid-treatment assessment), missing at T2 (post-treatment assessment); OMO = observed at T0, missing at T1, observed at T2; OOM = observed at T0, observed at T1, missing at T2; OOO = observed at all assessments.

Table A3. Possible missing data patterns and their occurrence in the intervention and control groups

Missing data pattern	T0	T1	T2	Intervention group	Control group
OMM	Observed	Missing	Missing	7 (8.3)	2 (2.4)
OMO	Observed	Missing	Observed	2 (2.4)	2 (2.4)
OOM	Observed	Observed	Missing	8 (9.5)	1 (1.2)
OOO	Observed	Observed	Observed	67 (79.8)	80 (94.1)

Note. Data for intervention and control groups are shown as No. (%).
Abbreviations: OMM = observed at T0, missing at T1, missing at T2; OMO = observed at T0, missing at T1, observed at T2; OOM = observed at T0, observed at T1, missing at T2; OOO = observed at all measurements; T0= baseline assessment; T1= mid-treatment assessment; T2= post-treatment assessment.

Table A4. Mean values at baseline, mid-treatment and post-treatment, and between-group differences for the mixed-effect models of the primary and secondary outcome measures for the models without adjustment for non-ignorable drop-out

	T0*			T1*		
Outcome measure	**No. of patients**	**Mean**	**SD**	**No. of patients**	**Mean**	**SD**
PRIMARY OUTCOMES						
Overall sexual functioning						
FSFI total, $p = .043$¤						
Intervention	83†	13.76	6.92	72†	17.16	9.20
Control§	80†	13.27	7.75	73†	15.46	8.29
Sexual desire						
FSFI desire, $p < .001$¤						
Intervention	84	2.03	0.84	74	2.63	1.08
Control§	85	1.96	0.90	80	2.05	0.83
Sexual arousal						
FSFI arousal, $p = .015$¤						
Intervention	84	2.19	1.47	75	2.85	1.76
Control§	85	2.05	1.43	81	2.32	1.68
Vaginal lubrication						
FSFI lubrication, $p = .016$¤						
Intervention	84	2.20	1.69	75	2.88	1.98
Control§	85	2.26	2.01	81	2.54	1.96
Orgasmic function						
FSFI orgasm, $p = .138$¤						
Intervention	84	2.46	1.91	75	3.11	2.10
Control§	85	2.33	1.97	81	2.70	2.00
Sexual satisfaction						
FSFI satisfaction, $p = .300$¤						
Intervention	83†	2.94	1.26	74†	3.71	1.56
Control§	80†	2.54	1.26	75†	3.15	1.42
Sexual pain						
FSFI pain, $p = .506$¤						
Intervention	84	1.86	2.05	74	2.11	2.18
Control§	85	1.84	2.23	80	2.14	2.28
Sexual pleasure						
SAQ pleasure, $p = .002$¤						
Intervention	83	4.50	3.06	74	6.82	4.21
Control§	85	4.21	2.86	79	5.65	3.68
Discomfort during sex						
SAQ discomfort, $p = .004$¤						
Intervention	63‡	3.67	1.86	55‡	2.87	1.61
Control§	52‡	3.27	2.05	52‡	2.79	1.98

	T2*			Between-group difference T0-T1				Between-group difference T0-T2			
	No. of patients	Mean	SD	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	68†	19.15	9.53	1.51	1.27	.235	.15	3.61	1.43	.013	.40
	75†	14.90	8.61								
	69	2.82	1.02	0.51	0.14	<.001	.46	0.66	0.15	<.001	.72
	81	2.08	1.00								
	69	3.09	1.80	0.44	0.25	.076	.21	0.82	0.28	.004	.46
	82	2.10	1.66								
	69	3.27	2.06	0.45	0.31	.146	.18	0.92	0.32	.004	.45
	82	2.37	2.02								
	69	3.48	2.14	0.34	0.33	.304	.13	0.69	0.34	.047	.31
	82	2.62	2.06								
	68†	3.91	1.58	0.24	0.23	.288	.13	0.38	0.25	.130	.24
	76†	3.12	1.43								
	69	2.58	2.39	0.09	0.30	.772	.04	0.37	0.34	.269	.17
	82	2.08	2.19								
	69	7.43	4.35	1.19	0.60	.049	.24	2.26	0.63	<.001	.58
	81	4.86	3.52								
	52‡	2.62	1.57	-0.75	0.28	.009	.42	-0.95	0.30	.002	.61
	52‡	2.88	1.91								

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Table A4. (*continued*)

Outcome measure	T0*			T1*		
	No. of patients	Mean	SD	No. of patients	Mean	SD
Intercourse frequency						
SAQ habit, *p* = .043¤						
Intervention	84	0.55	0.90	74	0.89	1.07
Control§	84	0.45	0.77	80	0.45	0.67
Sexual distress						
FSDS-R, *p* = .002¤						
Intervention	84	25.80	9.28	74	22.62	9.95
Control§	85	23.98	7.96	81	22.00	9.33
Emotional intimacy						
PAIR emotional intimacy, *p* = .981¤						
Intervention	82†	75.61	17.21	74†	75.89	16.10
Control§	78†	69.18	22.92	74†	70.05	22.61
Social intimacy						
PAIR social intimacy, *p* = .046¤						
Intervention	82†	61.95	18.62	74†	64.11	18.88
Control§	78†	63.75	18.83	74†	64.38	18.80
Sexual intimacy						
PAIR sexual intimacy, *p* = .493¤						
Intervention	82†	67.95	17.44	74†	69.19	17.22
Control§	78†	63.64	18.80	74†	64.54	19.57
Intellectual intimacy						
PAIR intellectual intimacy, *p* = .589¤						
Intervention	82†	69.80	15.13	74†	70.73	13.48
Control§	78†	67.03	17.53	74†	66.81	19.97
Recreational intimacy						
PAIR recreational intimacy, *p* = .085¤						
Intervention	82†	75.22	12.78	73†	75.59	15.25
Control§	78†	77.28	17.54	74†	74.70	18.39
Conventionality						
PAIR conventionality, *p* = .160¤						
Intervention	82†	64.85	16.90	74†	66.78	18.96
Control§	78†	60.92	20.78	74†	58.86	20.48
SECONDARY OUTCOMES						
Menopausal symptoms						
FACT-ES, *p* = .006¤						
Intervention	84	50.26	8.46	75	53.09	9.27
Control§	85	52.94	8.20	81	52.45	7.99
Body image						
QLQ-BR23 body image, *p* = .012¤						
Intervention	84	68.65	25.76	75	72.67	25.98
Control§	85	65.78	26.60	81	70.99	24.97

	T2*			Between-group difference T0-T1				Between-group difference T0-T2			
	No. of patients	Mean	SD	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	69 82	1.13 0.60	1.00 0.81	0.37	0.17	.027	.26	0.42	0.19	.028	.21
	69 82	17.86 20.89	9.53 9.55	-1.72	1.23	.162	.17	-4.75	1.37	.001	.55
	67† 76†	77.19 70.84	16.40 20.89	-0.35	2.17	.870	.02	-0.48	2.60	.854	.03
	67† 76†	65.76 63.39	18.69 18.84	1.89	1.85	.308	.14	4.35	1.74	.014	.42
	67† 76†	71.70 65.47	16.74 19.02	1.60	2.21	.469	.10	2.44	2.09	.244	.19
	67† 76†	77.97 72.32	17.13 22.15	1.00	2.24	.654	.06	2.60	2.54	.308	.16
	67† 76†	76.00 74.63	13.73 19.49	3.59	1.82	.049	.25	3.77	1.97	.058	.32
	67† 76†	67.37 61.26	20.02 22.01	4.29	2.25	.057	.24	2.83	2.44	.248	.19
	69 82	53.55 54.04	9.05 7.61	3.25	1.00	.001	.39	1.96	1.14	.089	.27
	69 82	81.64 72.36	22.44 25.01	0.39	2.64	.882	.02	7.86	3.01	.010	.41

(Continued on next page)

Table A4. (*continued*)

Outcome measure	T0*			T1*		
	No. of patients	Mean	SD	No. of patients	Mean	SD
Marital functioning - Marital satisfaction						
MMQ marital, $p = .598$¤						
Intervention	82†	11.84	7.77	74†	11.54	7.95
Control§	78†	14.06	10.33	74†	14.73	11.13
Marital sexual satisfaction						
MMQ sexual, $p = .050$¤						
Intervention	82†	22.06	6.83	74†	18.89	9.09
Control§	78†	22.73	7.74	74†	21.33	8.51
Marital functioning - General Life satisfaction						
MMQ general life, $p = .562$¤						
Intervention	82†	8.93	4.63	74†	9.43	5.06
Control§	78†	9.32	4.92	74†	9.05	4.84
Depression						
HADS depression, $p = .948$¤						
Intervention	84	4.54	3.04	75	4.64	3.19
Control§	84	3.92	3.22	81	4.20	3.34
Anxiety						
HADS anxiety, $p = .670$¤						
Intervention	84	6.15	3.41	75	6.49	3.45
Control§	84	6.01	4.31	81	6.02	4.14
Psychological distress						
HADS total, $p = .891$¤						
Intervention	84	10.69	5.62	75	11.13	6.01
Control§	84	9.93	6.90	81	10.22	6.68
Physical functioning						
SF-36 physical functioning, $p = .987$¤						
Intervention	84	79.40	18.36	75	78.09	21.04
Control§	85	82.10	14.16	81	81.23	17.62
Role limitations due to physical problems						
SF-36 role physical, $p = .954$¤						
Intervention	83	68.98	35.48	75	68.67	38.58
Control§	85	62.94	40.75	81	66.36	41.68
Bodily pain						
SF-36 bodily pain, $p = .856$¤						
Intervention	84	71.31	22.54	75	70.09	24.61
Control§	85	71.78	20.39	81	70.02	20.81
General health perceptions						
SF-36 general health, $p = .629$¤						
Intervention	84	65.24	20.55	75	64.13	20.37
Control§	85	67.52	22.29	81	64.17	23.37

	T2*		Between-group difference T0-T1				Between-group difference T0-T2			
	No. of patients	Mean	SD	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	68†	12.03	9.75	-0.98	1.09	.369	.11	-1.17	1.30	.370	.14
	76†	15.14	11.79								
	68†	16.60	9.16	-2.31	1.17	.049	.25	-2.97	1.29	.023	.38
	76†	20.66	8.64								
	67†	8.22	4.70	0.65	0.63	.307	.13	0.14	0.65	.833	.04
	76†	8.53	4.65								
	69	4.55	3.81	-0.12	0.37	.747	.04	-0.12	0.48	.809	.04
	82	4.09	3.49								
	69	6.02	3.46	0.24	0.40	.555	.07	-0.09	0.50	.856	.03
	82	5.85	3.91								
	69	10.57	6.61	0.12	0.64	.852	.02	-0.19	0.87	.832	.02
	82	9.93	6.74								
	69	79.64	19.35	0.29	1.84	.875	.02	0.07	1.80	.971	.01
	82	82.87	16.65								
	69	73.91	37.48	-1.84	5.97	.759	.04	-1.17	6.95	.866	.03
	82	70.12	40.72								
	69	72.30	21.71	1.58	2.99	.598	.07	1.36	3.21	.673	.07
	82	72.18	21.84								
	69	63.01	22.18	1.66	2.19	.450	.09	-0.26	2.42	.914	.02
	82	65.96	23.01								

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Table A4. (*continued*)

Outcome measure	T0*			T1*		
	No. of patients	Mean	SD	No. of patients	Mean	SD
Vitality						
SF-36 vitality, $p = .490$¤						
Intervention	84	59.35	16.09	75	58.73	19.63
Control§	85	59.24	19.22	81	60.43	18.48
Social functioning						
SF-36 social functioning, $p = .767$¤						
Intervention	84	79.61	19.09	75	76.50	22.60
Control§	85	81.18	20.74	81	80.40	18.95
Role limitations due to emotional problems						
SF-36 role emotional, $p = .307$¤						
Intervention	83	86.35	29.47	75	81.78	33.91
Control§	85	75.69	36.87	81	76.95	36.38
General mental health						
SF-36 mental health, $p = .547$¤						
Intervention	84	75.24	14.49	75	72.96	16.21
Control§	85	75.29	16.92	81	73.48	15.73

Note. Bold font indicates significant overall interaction effect between group and time. Reported are the raw means and standard deviations. Models were adjusted for chemotherapy treatment.

Abbreviations: FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; MMQ = Maudsley Marital Questionnaire; PAIR = Personal Assessment of Intimacy in Relationships Inventory; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire of the European Organisation of Research and Treatment of Cancer; SAQ = Sexual Activity Questionnaire; SD = standard deviation; SE = standard error; SF36 = 36-Item Short Form Health Survey.

*T0 = baseline; T1 = mid-treatment; T2 = post-treatment.

[i]Effect size was calculated based on the t-test statistic: (2*t)/(√degrees of freedom); (0.2 small, 0.5 moderate, 0.8 large).

†Scale was completed by less than total number of participants as only partnered participants could complete it.

‡Scale was completed by less than total number of participants as only participants who had had vaginal penetration could provide an answer.

¤p value of the overall interaction effect between group and time.

§Control group is reference group.

	T2*			Between-group difference T0-T1				Between-group difference T0-T2			
	No. of patients	Mean	SD	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	69	61.74	20.97	-2.80	2.53	.269	.13	-0.72	2.96	.808	.04
	82	61.10	19.95								
	69	79.71	23.59	-2.16	3.35	.519	.08	-0.14	3.63	.969	.01
	82	80.79	20.05								
	69	81.16	34.53	-8.09	6.17	.191	.16	-9.59	6.92	.167	.21
	82	77.64	37.06								
	69	74.14	16.72	-0.39	2.23	.861	.02	-2.60	2.59	.318	.15
	82	76.24	16.47								

Table A5. Mean values at baseline, mid-treatment and post-treatment, and between-group differences for the mixed-effect models of the primary and secondary outcome measures based on the Last Observation Carried Forward data

	T0*			T1*		
Outcome measure	**No. of patients**	**Mean**	**SD**	**No. of patients**	**Mean**	**SD**
PRIMARY OUTCOMES						
Overall sexual functioning						
FSFI total, $p = .106$¤						
Intervention	83†	13.76	6.92	81†	16.98	8.96
Control§	80	13.27	7.75	77†	15.40	8.28
Sexual desire						
FSFI desire, $p < .001$¤						
Intervention	84	2.03	0.84	83	2.57	1.09
Control§	85	1.96	0.90	84	2.09	0.90
Sexual arousal						
FSFI arousal, $p = .034$¤						
Intervention	84	2.19	1.47	84	2.83	1.71
Control§	85	2.05	1.43	85	2.32	1.68
Vaginal lubrication						
FSFI lubrication, $p = .051$¤						
Intervention	84	2.20	1.69	84	2.83	1.94
Control§	85	2.26	2.01	85	2.56	1.97
Orgasmic function						
FSFI orgasm, $p = .303$¤						
Intervention	84	2.46	1.91	84	3.08	2.06
Control§	85	2.33	1.97	85	2.72	2.01
Sexual satisfaction						
FSFI satisfaction, $p = .472$¤						
Intervention	83†	2.94	1.26	83†	3.65	1.53
Control§	80†	2.54	1.26	79†	3.08	1.44
Sexual pain						
FSFI pain, $p = .615$¤						
Intervention	84	1.86	2.05	83	2.13	2.16
Control§	85	1.84	2.23	84	2.10	2.28
Sexual pleasure						
SAQ pleasure, $p = .008$¤						
Intervention	83	4.50	3.06	83	6.68	4.09
Control§	85	4.21	2.86	83	5.51	3.66
Intercourse frequency						
SAQ habit, $p = .039$¤						
Intervention	84	0.55	0.90	83	0.88	1.09
Control§	84	0.45	0.77	84	0.44	0.66

	T2*			Between-group difference T0-T1				Between-group difference T0-T2			
	No. of patients	Mean	SD	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	83†	17.83	9.65	1.27	1.17	.276	.13	2.85	1.34	.035	.33
	78†	14.65	8.70								
	84	2.67	1.06	0.45	0.13	.001	.41	0.56	0.14	<.001	.64
	84	2.06	0.99								
	84	2.92	1.82	0.39	0.23	.093	.19	0.69	0.27	.010	.40
	85	2.08	1.68								
	84	2.99	2.07	0.38	0.29	.184	.16	0.73	0.30	.015	.37
	85	2.36	2.06								
	84	3.23	2.16	0.28	0.30	.349	.11	0.50	0.32	.125	.23
	85	2.60	2.09								
	83†	3.70	1.61	0.22	0.21	.306	.12	0.26	0.23	.260	.18
	79†	3.05	1.45								
	84	2.34	2.36	0.07	0.27	.792	.03	0.29	0.31	.353	.14
	85	2.01	2.19								
	84	6.82	4.41	1.10	0.56	.049	.23	1.86	0.60	.002	.49
	84	4.74	3.54								
	84	1.08	1.02	0.37	0.15	.018	.27	0.39	0.18	.031	.20
	85	0.58	0.81								

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Table A5. (*continued*)

Outcome measure	T0*			T1*		
	No. of patients	Mean	SD	No. of patients	Mean	SD
Sexual distress						
FSDS-R, *p* = .017¤						
Intervention	84	25.80	9.28	83	22.56	9.69
Control§	85	23.98	7.96	85	21.98	9.23
Emotional intimacy						
PAIR emotional intimacy, *p* = .960¤						
Intervention	82†	75.61	17.21	82†	76.34	15.67
Control§	78†	69.18	22.92	78†	70.36	22.23
Social intimacy						
PAIR social intimacy, *p* = .096¤						
Intervention	82†	61.95	18.62	82†	63.61	18.47
Control§	78†	63.74	18.83	78†	64.62	18.97
Sexual intimacy						
PAIR sexual intimacy, *p* = .595¤						
Intervention	82†	67.95	17.44	82†	69.90	16.93
Control§	78†	63.64	18.80	78†	64.26	19.36
Intellectual intimacy						
PAIR intellectual intimacy, *p* = .856¤						
Intervention	82†	69.80	15.13	82†	70.51	13.45
Control§	78†	67.03	17.53	78†	67.33	19.71
Recreational intimacy						
PAIR recreational intimacy, *p* = .078¤						
Intervention	82†	75.22	12.78	81†	76.22	14.91
Control§	78†	77.28	17.54	78†	74.87	18.21
Conventionality						
PAIR conventionality, *p* = .194¤						
Intervention	82†	64.85	16.90	82†	66.07	18.69
Control§	78†	60.92	20.78	78†	58.97	20.49
SECONDARY OUTCOMES						
Menopausal symptoms						
FACT-ES, *p* = .010¤						
Intervention	84	50.26	8.46	84	52.90	8.99
Control§	85	52.94	8.20	85	52.80	7.99
Body image						
QLQ-BR23 body image, *p* =.033¤						
Intervention	84	68.65	25.76	84	73.51	25.22
Control§	85	65.78	26.60	85	70.59	25.18
Marital functioning - Marital satisfaction						
MMQ marital, *p* = .594¤						
Intervention	82†	11.84	7.77	82†	11.51	7.79
Control§	78†	14.06	10.33	78†	14.48	10.99

	T2*			Between-group difference T0-T1				Between-group difference T0-T2			
	No. of patients	Mean	SD	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	84	19.23	9.45	-1.44	1.14	.209	.14	-3.70	1.30	.005	.44
	85	21.09	9.50								
	81†	76.89	16.11	-0.35	2.02	.861	.02	-0.69	2.41	.777	.04
	79†	71.04	20.70								
	81†	65.01	18.29	1.54	1.70	.366	.11	3.70	1.71	.032	.34
	79†	63.47	18.96								
	81†	70.96	17.29	1.73	2.04	.395	.11	1.76	1.96	.369	.14
	79†	65.37	19.05								
	81†	76.49	17.00	0.52	2.10	.806	.03	1.31	2.38	.581	.08
	79†	72.41	21.80								
	81	76.49	13.48	3.51	1.67	.037	.25	3.55	1.87	.06	.30
	79	74.63	19.30								
	81†	67.09	19.70	3.77	2.09	.072	.22	2.57	2.27	.259	.18
	79†	61.11	21.82								
	84	53.08	8.85	2.83	0.93	.002	.35	1.62	1.06	.129	.23
	85	54.25	7.59								
	84	79.56	23.15	0.51	2.45	.835	.02	6.37	2.81	.025	.34
	85	70.78	26.12								
	82†	11.97	9.57	-0.91	1.01	.369	.11	-1.12	1.21	.355	.14
	79†	15.11	11.57								

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Table A5. (*continued*)

Outcome measure	T0*			T1*		
	No. of patients	Mean	SD	No. of patients	Mean	SD
Marital sexual satisfaction						
MMQ sexual, p = .084¤						
Intervention	82†	22.06	6.83	82†	19.22	8.86
Control§	78†	22.73	7.74	78†	21.80	8.71
Marital functioning - General Life satisfaction						
MMQ general life, p = .582¤						
Intervention	82†	8.93	4.63	82†	9.30	4.93
Control§	78†	9.32	4.92	78†	8.97	4.86
Depression						
HADS depression, p = .947¤						
Intervention	84	4.54	3.04	84	4.58	3.07
Control§	84	3.92	3.22	85	4.04	3.35
Anxiety						
HADS anxiety, p= .713¤						
Intervention	84	6.15	3.41	84	6.29	3.40
Control§	84	6.01	4.31	85	5.88	4.12
Psychological distress						
HADS total, p = .925¤						
Intervention	84	10.69	5.62	84	10.87	5.82
Control§	84	9.93	6.90	85	9.92	6.69
Physical functioning						
SF-36 physical functioning, p = .958¤						
Intervention	84	79.40	18.36	84	78.59	20.55
Control§	85	82.10	14.16	85	81.18	17.37
Role limitations due to physical problems						
SF-36 role physical, p = .983¤						
Intervention	83	68.98	35.48	84	69.05	37.15
Control§	85	62.94	40.75	85	65.59	42.25
Bodily pain						
SF-36 bodily pain, p = .781¤						
Intervention	84	71.31	22.54	84	70.52	23.95
Control§	85	71.78	20.39	85	69.60	21.24
General health perceptions						
SF-36 general health, p = .698¤						
Intervention	84	65.24	20.55	84	63.98	20.89
Control§	85	67.52	22.29	85	64.93	23.28
Vitality						
SF-36 vitality, p = .498¤						
Intervention	84	59.35	16.09	84	59.35	19.07
Control§	85	59.24	19.22	85	61.18	18.49

	T2*			Between-group difference T0-T1				Between-group difference T0-T2			
	No. of patients	Mean	SD	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	82†	17.99	9.31	-2.21	1.08	.043	.24	-2.35	1.22	.056	.31
	79†	21.13	8.84								
	81†	8.54	4.64	0.60	0.58	.306	.13	0.25	0.63	.69	.06
	79†	8.77	4.85								
	84	4.49	3.62	-0.11	0.34	.745	.04	-0.08	0.44	.863	.03
	85	3.99	3.47								
	84	5.93	3.29	0.22	0.37	.552	.07	-0.03	0.47	.945	.01
	85	5.76	3.89								
	84	10.42	6.24	0.11	0.60	.857	.02	-0.11	0.80	.891	.01
	85	9.75	6.70								
	84	79.88	18.77	0.44	1.69	.795	.03	0.01	1.67	.993	.00
	85	82.53	16.70								
	84	73.81	35.97	-0.79	5.55	.887	.02	-1.15	6.45	.859	.03
	85	68.82	41.53								
	84	72.89	20.89	1.90	2.77	.494	.08	1.49	2.96	.616	.08
	85	71.89	22.04								
	84	63.36	22.09	1.46	2.01	.468	.08	0.10	2.26	.965	.01
	85	65.51	23.83								
	84	61.31	20.14	-2.72	2.34	.245	.13	-1.45	2.78	.602	.08
	85	61.59	19.90								

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Table A5. (*continued*)

Outcome measure	T0*			T1*		
	No. of patients	Mean	SD	No. of patients	Mean	SD
Social functioning						
SF-36 social functioning, p = .749¤						
Intervention	84	79.61	19.09	84	77.98	22.26
Control§	85	81.18	20.74	85	81.32	18.96
Role limitations due to emotional problems						
SF-36 role emotional, p = .187¤						
Intervention	83	86.35	29.47	84	80.95	34.04
Control§	85	75.69	36.87	85	77.65	35.78
General mental health						
SF-36 mental health, p = .441¤						
Intervention	84	75.24	14.49	84	73.86	16.15
Control§	85	75.29	16.92	85	74.35	15.91

Note. Bold font indicates significant overall interaction effect between group and time. Reported are the raw means and standard deviations. Models were adjusted for chemotherapy treatment.

Abbreviations: FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; MMQ = Maudsley Marital Questionnaire; PAIR = Personal Assessment of Intimacy in Relationships Inventory; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire of the European Organisation of Research and Treatment of Cancer; SD = standard deviation; SE = standard error; SF36 = 36-Item Short Form Health Survey.

*T0 = baseline; T1 = mid-treatment; T2 = post-treatment.

[i]Effect size was calculated based on the t-test statistic: (2*t)/(√degrees of freedom); (0.2 small, 0.5 moderate, 0.8 large).

†Scale was completed by less than total number of participants as only partnered participants could provide an answer.

‡Scale was completed by less than total number of participants as only participants who had had vaginal penetration could provide an answer.

¤p value of the overall interaction effect between group and time.

§Control group is reference group.

	T2*			Between-group difference T0-T1				Between-group difference T0-T2			
	No. of patients	Mean	SD	Mean Change	SE	*p*	Effect size[i]	Mean Change	SE	*p*	Effect size[i]
	84	79.91	22.29	-2.14	3.12	.493	.08	-0.33	3.38	.921	.01
	85	81.18	19.92								
	84	78.57	36.09	-8.69	5.70	.128	.18	-11.12	6.49	.088	.25
	85	77.25	36.81								
	84	74.24	16.92	-0.41	2.06	.842	.02	-2.78	2.44	.257	.17
	85	76.66	16.35								

Table A6. Results of the tipping point analyses for the primary significant outcomes

Outcome measure	Tipping point	*p* of overall model*	Contrast T0-T1		Contrast T0-T2		Pooled SD T0‡	Tipping point/ pooled SD T0
			p†	ES†	*p*†	ES†		
FSFI total	-4.10	.049	.409	.10	.018	.36	7.37	0.56
FSFI desire	-1.97	.049	.035	.25	.030	.33	0.87	2.26
FSFI arousal	-1.06	.049	.186	.15	.014	.38	1.45	0.73
FSFI lubrication	-1.34	.049	.304	.12	.015	.37	1.86	0.72
SAQ pleasure	-4.55	.048	.376	.10	.016	.38	2.96	1.54
FSDS-R	+11.30	.049	.887	.02	.032	.33	8.64	1.31

Abbreviations: ES = effect size; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; SAQ = Sexual Activity Questionnaire; SD = standard deviation; T0 = baseline assessment; T1 = mid-treatment assessment; T2 = post-treatment assessment.

**p* value of the overall interaction effect of group and time; when a larger δ was used, the overall interaction effect changed from statistically significant to non-significant.

†p values and effect sizes for the models that defined the tipping point.

‡The pooled standard deviation of the intervention and control group at T0 was used.

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5

Internet-based cognitive behavioral therapy realizes long-term improvement in the sexual functioning and body image of breast cancer survivors

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ABSTRACT

The study aim was to evaluate the long-term efficacy of Internet-based cognitive behavioral therapy (CBT) for sexual dysfunctions in 84 breast cancer survivors. The positive effects of the intervention on overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication, discomfort during sex, sexual distress and body image observed immediate post-treatment were maintained at three- and nine-month follow-ups. Although sexual pleasure decreased during follow-up, it did not return to baseline levels. Our findings provide evidence that Internet-based CBT has a sustained, positive effect on sexual functioning and body image of breast cancer survivors with a sexual dysfunction.

INTRODUCTION

Sexual problems are common among women who have been treated for breast cancer (BC)[1-3], with prevalence rates of 45% to 77%[1,3]. The standard treatment for female sexual dysfunction is cognitive behavioral therapy (CBT)[4], which is traditionally delivered in a face-to-face setting. More recently, Internet-based sex therapy for both men and women has been shown to be effective[5-7]. First trials have demonstrated the efficacy of Internet-based CBT[5] and an online mindfulness-based CBT[6] for female sexual dysfunction in the general population. Schover et al.[8] demonstrated the feasibility of a 12-week Internet-based self-help intervention for sexual problems specifically in BC and gynecological cancer survivors. We previously reported on the short-term (i.e., immediate post-intervention) results of a randomized controlled trial (RCT) of the efficacy of an Internet-based CBT in improving the sexual functioning of BC survivors[9]. Women who underwent the intervention reported significantly greater improvement in overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication, sexual pleasure, discomfort during sex, sexual distress and body image from baseline to immediate post-CBT assessment, as compared to women in a waiting-list control group. No significant group differences from baseline to immediate post-CBT were observed for orgasmic function, sexual satisfaction, sexual pain, intercourse frequency, relationship intimacy, menopausal symptoms, marital functioning, psychological distress, or health-related quality of life.

In the current article, we report the results of the longer-term evaluation of the intervention effects as assessed at three and nine months post-CBT. Our interest was in determining if the positive treatment effects observed in the short-term were sustained over time, and whether there were additional longer-term benefits of treatment that emerged only during the longer follow-up period.

METHODS

Participants

From September 2013 to May 2015, we recruited women with a history of BC and a diagnosis of sexual dysfunction from 10 hospitals in the Netherlands. Inclusion criteria were: age 18 to 65 years; a diagnosis of histologically confirmed BC six months to five years prior to study entry; completion of BC treatment (with the exception of maintenance endocrine therapy and immunotherapy); disease-free at time of study entry; sufficient command of the Dutch language; and a sexual dysfunction diagnosed by a psychologist/sexologist during a diagnostic interview using the criteria of the Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision (DSM-IV)[10]). Single as well as partnered women could participate. Sexual orientation was irrelevant for eligibility.

Exclusion criteria were as follows: no Internet access; serious psychiatric comorbidity (e.g., depressive disorder, alcohol dependency), as these problems often need to be treated first before addressing a sexual dysfunction[11]; treatment for another type of cancer (with the exception of cervix carcinoma in situ and basal cell carcinoma); presence of severe relationship problems; concurrent therapy to alleviate problems with sexuality/intimacy; concurrent CBT for other psychological problems; and participation in another trial investigating problems with sexuality/intimacy. The institutional review boards of all recruiting hospitals approved the trial.

Procedure

We identified potentially eligible patients (i.e., those who met criteria in terms of age, BC diagnosis, time since diagnosis and current disease status) via hospital databases and/or the Netherlands Cancer Registry. Patients received a letter describing the study and were asked to return a postcard indicating if they were potentially interested in participating in the study. Interested women were interviewed by phone by a member of the study staff to confirm basic eligibility for the trial. Subsequently women were interviewed by phone by a psychologist/sexologist to determine if they met DSM-IV criteria for one or more diagnoses of sexual dysfunction. Women who were eligible for and interested in trial participation were sent a baseline questionnaire and an informed consent form. Consenting women were randomly assigned to either a waiting-list control group or a group undergoing the Internet-based CBT.

Internet-based CBT

Extensive information on the content of the Internet-based CBT is provided elsewhere[9]. Briefly, the CBT was composed of 4-5 modules (selected out of a total of 10 modules by the psychologist/sexologist) that best suited the sexual problems of each individual participant. Each module included information texts on a range of topics, including the nature of sexual problems, the biopsychosocial model, the sexual response curve, the interplay between sexuality and intimacy, and communication with the partner. Accompanying homework exercises included sensate focus exercises, task concentration training, exposure exercises for sexual pain, and cognitive restructuring. This resulted in a therapy of approximately 20 therapist-guided weekly sessions to be completed within 24 weeks. The contact between the therapist and participant took place via email, with the addition of two telephone contacts, one at mid-CBT and one at completion of the CBT.

Timing of assessments

Study questionnaires were completed at baseline (T0), mid-CBT (T1), post-CBT (T2), and at three- (T3) and nine-month (T4) follow-ups. The results of the RCT pertaining to the effects of the Internet-based CBT from T0 to T2 have been reported in detail previously[9].

The T3 and T4 assessments were completed by the intervention group only, as women in the waiting-list control group were offered the opportunity to undergo the Internet-based CBT immediately after completion of the T2 assessment and thus did not complete the follow-up assessments.

Study measures

Sociodemographic and basic clinical information was obtained during screening and via the baseline questionnaire. We assessed the primary outcomes, sexual functioning and relationship intimacy, at all five assessment points. Sexual functioning was measured with the Female Sexual Function Index (FSFI[12,13]), the Sexual Activity Questionnaire (SAQ[14,15]), and the Female Sexual Distress Scale-Revised (FSDS-R[16,17]). Relationship intimacy was measured with the Personal Assessment of Intimacy in Relationships Inventory (PAIR[18]).

At T0 through T3, we assessed the following secondary outcomes: body image (subscale of the European Organisation for Research and Treatment of Cancer breast cancer module; QLQ-BR23[19]), menopausal symptoms (Functional Assessment of Cancer Treatment-Endocrine Symptoms; FACT-ES[20]), marital functioning (Maudsley Marital Questionnaire; MMQ[21]), psychological distress (Hospital Anxiety and Depression Scale; HADS[22,23]), and health-related quality of life (36-item Short Form Health Survey; SF-36[24,25]). A more detailed description of all outcome measures is provided elsewhere[9].

Statistical analysis

We calculated questionnaire scores according to published scoring algorithms. Missing values were replaced by the average score of the completed items in the same scale for each individual, provided that ≥ 50% of the items in that scale had been completed.

To evaluate the intra-individual difference in the trajectory of change over time for both the primary and secondary outcomes, we used a growth curve modelling approach based on restricted maximum likelihood estimation with random intercept and slope. We checked for the presence of a linear effect of time from T0 to T3 or T4. Subsequently, we added a quadratic effect of time to the model to determine if an initial improvement or deterioration in the outcome was followed by a deceleration of this change over time. The choice between the model including only a linear effect of time and the model including both a linear and quadratic effect of time was based on model fit statistics: the Bayesian information criterion (BIC)[26] and Akaike information criterion (AIC)[27].

If, for a primary outcome, the model including a quadratic effect of time had the best fit and was statistically significant, we fitted a piecewise linear growth model to the data[28]. Piecewise linear growth models can be used when specific transition points can be specified, such as the end of treatment. They model nonlinearity by including two interrelated linear slopes reflecting the growth trajectory before and after this transition point[29]. In our analyses the transition point was the end of CBT, with an active treatment phase

before (P1: pre-, mid- and immediate post-treatment) and the follow-up phase after this transition point (P2: immediate post-treatment, 3 months and 9 months follow-up)[28]. We tested if changes during the active treatment and follow-up period were significantly different from zero. Evidence of a sustained effect of the Internet-based CBT over time was considered present if, after a statistically significant improvement in the outcome during P1, the time coefficient for P2 was non-significant. The change during the active treatment phase and follow-up period was accompanied by effect sizes (ES), and was based on the *t*-test statistic: $(2*t)/(\sqrt{df})$. An ES of .20 was considered small, .50 moderate and clinically significant, and .80 large[30].

As the secondary outcomes were not assessed at T4 (see the Discussion section), we decided not to use a piecewise growth model on these outcomes, as too few measurement points were available. Instead we evaluated the presence of a linear and quadratic effect of time and subsequently calculated effect sizes based on the mean scores and pooled standard deviation (see Tables 1 and 2). The *p* value for statistical significance was set at .05. All analyses were conducted on an intention-to-treat basis.

RESULTS

Recruitment and participant flow in the trial is reported in detail elsewhere[9]. Specific to the current analysis, 169 women were randomly assigned into the trial, with 84 assigned to the intervention group. All 84 women completed the T0 questionnaire, 75 (89.3%) completed the T1 assessment, 69 (82.1%) the T2 assessment, 64 (76.2%) the T3 assessment, and 65 (77.4%) the T4 assessment.

The mean age of the intervention group was 51.6 years (standard deviation (SD) = 7.7), most had completed post-high school education (76.2%), were employed (77.4%) and the large majority had a partner (97.6%). The majority was postmenopausal (84.5%) and sexually active at baseline (73.8%). The mean time since BC diagnosis was 38.1 months (SD = 17.0). The majority had undergone breast conserving treatment (58.3%), followed by a mastectomy with reconstruction (22.6%) and a mastectomy only (19.0%). The majority had undergone chemotherapy (77.4%), endocrine therapy (84.5%), and radiotherapy (86.9%). Twenty percent of the women had undergone immunotherapy.

The majority of women (57.1%) was diagnosed with two sexual dysfunctions according to DSM-IV criteria (versus 32.1% with one dysfunction, and 10.7% with three dysfunctions), the most prevalent of which was hypoactive sexual desire disorder (82.1%), followed by sexual arousal disorder (42.9%), dyspareunia (32.1%), orgasmic disorder (9.5%), sexual aversion disorder (6.0%), sexual dysfunction not otherwise specified (4.8%) and vaginismus (1.2%). The majority of women (67.9%) first experienced sexual problems during the BC treatment (versus 11.9% before and 20.2% after BC treatment).

At both T3 and T4, 7.7% of women reported using antidepressants. At T3 and T4, 4.6% and 9.4% reported using sedatives, and 9.2% and 6.3% reported using sleep medications, respectively. Only one woman reported having had contact with a psychologist for her sexual dysfunction after completion of the CBT program.

The CBT was completed successfully (according to the judgment of the therapist) by 61.9% of the women, 31.0% ended the CBT prematurely, and 7.1% never started the CBT. The most common reasons for ending the CBT prematurely were personal circumstances (15.2%), time constraints (12.1%), the intensity of the CBT (9.1%), relationship problems (9.1%) or dislike of the online approach (9.1%). The reasons for women not starting the CBT (after agreeing to do so) were time constraints (two women), perceived therapy burden (one woman), lack of motivation (one woman), and physical problems interfering with the use of a computer (one woman). Two women did not provide a reason.

Primary outcomes

For each primary outcome, the model including both a linear and a quadratic effect of time showed the best fit based on the AIC and BIC. We fitted the piecewise growth model for the outcomes that had a statistically significant quadratic effect of time (see Table 2). Maintenance of the treatment effect during the 9 months follow-up (P2) was observed for overall sexual functioning (FSFI total score: p_{P2} = .238), sexual desire (FSFI desire subscale: p_{P2} = .246), sexual arousal (FSFI arousal subscale: p_{P2} = .302), vaginal lubrication (FSFI lubrication subscale: p_{P2} = .069), orgasmic function (FSFI orgasm subscale: p_{P2} = .105), sexual satisfaction (FSFI satisfaction subscale: p_{P2} = .455), discomfort during intercourse (SAQ discomfort subscale: p_{P2} = .264) and sexual distress (FSDS-R: p_{P2} = .977). Tables 1 and 2 display the mean scores and effect sizes.

We observed a statistically significant decrease during P2 for sexual pleasure (SAQ pleasure subscale: p_{P2} = .044), intercourse frequency (SAQ habit subscale: p_{P2} = .028) and intellectual intimacy (PAIR intellectual subscale: p_{P2} = .003). We would note that, although there was a decrease in sexual pleasure and intercourse frequency during the follow-up period, the follow-up scores did not return to baseline levels (see mean scores and effect sizes in Tables 1 and 2). Intellectual intimacy scores did return to the baseline level. Although we found both a linear and quadratic effect of time for sexual intimacy (PAIR sexual subscale, see Table 2), no significant changes were detected within P2.

Table 1. Mean scores and standard deviations for the primary and secondary outcome measures

	T0†			T1†			T2†			T3†			T4†		
Outcome measure	**No. of patients**	**Mean**	**SD**	**No. of patients**	**Mean**	**SD**	**No. of patients**	**Mean**	**SD**	**No. of patients**	**Mean**	**SD**	**No. of patients**	**Mean**	**SD**
PRIMARY OUTCOMES															
Overall sexual functioning															
FSFI total															
Intervention	83‡	13.76	6.92	72‡	17.16	9.20	68‡	19.15	9.53	64‡	18.33	10.57	61‡	18.62	10.31
Sexual desire															
FSFI desire															
Intervention	84	2.03	0.84	74	2.63	1.08	69	2.82	1.02	64	2.67	1.15	65	2.78	1.23
Sexual arousal															
FSFI arousal															
Intervention	84	2.19	1.47	75	2.85	1.76	69	3.09	1.80	64	2.98	2.00	65	2.96	2.09
Vaginal lubrication															
FSFI lubrication															
Intervention	84	2.20	1.69	75	2.88	1.98	69	3.27	2.06	64	3.07	2.24	65	2.87	2.23
Orgasmic function															
FSFI orgasm															
Intervention	84	2.46	1.91	75	3.11	2.10	69	3.48	2.14	64	3.28	2.31	65	3.06	2.30
Sexual satisfaction															
FSFI satisfaction															
Intervention	83‡	2.94	1.26	74‡	3.71	1.56	68‡	3.91	1.58	64‡	3.77	1.63	61‡	3.94	1.54
Sexual pain															
FSFI pain															
Intervention	84	1.86	2.05	74	2.11	2.18	69	2.58	2.39	64	2.57	2.55	65	2.50	2.47
Sexual pleasure															
SAQ pleasure															
Intervention	83	4.50	3.06	74	6.82	4.21	69	7.43	4.35	63	6.90	4.55	63	6.81	4.23

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Table 1. (*continued*)

Outcome measure	T0†			T1†			T2†			T3†			T4†		
	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD
Discomfort during sex															
SAQ discomfort															
Intervention	63¶	3.67	1.86	55¶	2.87	1.61	52¶	2.62	1.57	47¶	2.31	1.77	48¶	2.77	2.04
Intercourse frequency															
SAQ habit															
Intervention	84	0.55	0.90	74	0.89	1.07	69	1.13	1.00	64	0.89	0.93	64	0.83	0.72
Sexual distress															
FSDS-R															
Intervention	84	25.80	9.28	74	22.62	9.95	69	17.86	9.53	64	17.52	11.00	64	17.69	9.73
Emotional intimacy															
PAIR emotional intimacy															
Intervention	82‡	75.61	17.21	74‡	75.89	16.10	67‡	77.19	16.40	62‡	78.00	14.84	63‡	78.86	14.70
Social intimacy															
PAIR social intimacy															
Intervention	82‡	61.95	18.62	74‡	64.11	18.88	67‡	65.76	18.69	62‡	66.39	17.15	63‡	66.92	18.36
Sexual intimacy															
PAIR sexual intimacy															
Intervention	82‡	67.95	17.44	74‡	69.19	17.22	67‡	71.70	16.74	62‡	70.84	16.87	63‡	69.71	18.28
Intellectual intimacy															
PAIR intellectual intimacy															
Intervention	82‡	69.80	15.13	74‡	70.73	13.48	67‡	77.97	17.13	62‡	71.10	16.46	63‡	71.17	14.53
Recreational intimacy															
PAIR recreational intimacy															
Intervention	82‡	75.22	12.78	73‡	75.59	15.25	67‡	76.00	13.73	62‡	76.97	14.53	63‡	77.90	14.83

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Table 1. (*continued*)

Outcome measure	T0†			T1†			T2†			T3†			T4†		
	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD
Conventionality															
PAIR conventionality															
Intervention	82‡	64.85	16.90	74‡	66.78	18.96	67‡	67.37	20.02	62‡	68.77	18.25	63‡	68.13	18.32
SECONDARY OUTCOMES															
Menopausal symptoms															
FACT-ES															
Intervention	84	50.26	8.46	75	53.09	9.27	69	53.55	9.05	64	54.68	9.06		n.a.	
Body image															
QLQ-BR23 body image															
Intervention	84	68.65	25.76	75	72.67	25.98	69	81.64	22.44	64	83.72	19.44		n.a.	
Marital functioning - Marital satisfaction															
MMQ marital															
Intervention	82‡	11.84	7.77	74‡	11.54	7.95	68‡	12.03	9.75	62‡	10.44	7.95		n.a.	
Marital sexual satisfaction															
MMQ sexual															
Intervention	82‡	22.06	6.83	74‡	18.89	9.09	68‡	16.60	9.16	62‡	16.52	9.03		n.a.	
Marital functioning - General Life satisfaction															
MMQ general life															
Intervention	82‡	8.93	4.63	74‡	9.43	5.06	67‡	8.22	4.70	62‡	8.15	4.91		n.a.	
Depression															
HADS depression															
Intervention	84	4.54	3.04	75	4.64	3.19	69	4.55	3.81	64	4.19	3.45		n.a.	

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Table 1. (*continued*)

Outcome measure	T0†			T1†			T2†			T3†			T4†		
	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD
Anxiety															
HADS anxiety															
Intervention	84	6.15	3.41	75	6.49	3.45	69	6.02	3.46	64	5.94	3.91		n.a.	
Psychological distress															
HADS total															
Intervention	84	10.69	5.62	75	11.13	6.01	69	10.57	6.61	64	10.13	6.67		n.a.	
Physical functioning															
SF-36 physical functioning															
Intervention	84	79.40	18.36	75	78.09	21.04	69	79.64	19.35	64	80.77	19.82		n.a.	
Role limitations due to physical problems															
SF-36 role physical															
Intervention	83	68.98	35.48	75	68.67	38.58	69	73.91	37.48	64	76.95	35.72		n.a.	
Bodily pain															
SF-36 bodily pain															
Intervention	84	71.31	22.54	75	70.09	24.61	69	72.30	21.71	64	72.80	21.39		n.a.	
General health perceptions															
SF-36 general health															
Intervention	84	65.24	20.55	75	64.13	20.37	69	63.01	22.18	64	69.05	19.28		n.a.	
Vitality															
SF-36 vitality															
Intervention	84	59.35	16.09	75	58.73	19.63	69	61.74	20.97	64	64.84	20.53		n.a.	
Social functioning															
SF-36 social functioning															
Intervention	84	79.61	19.09	75	76.50	22.60	69	79.71	23.59	64	83.20	22.07		n.a.	

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Table 1. (*continued*)

Outcome measure	T0†			T1†			T2†			T3†			T4†		
	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD	No. of patients	Mean	SD
Role limitations due to emotional problems															
SF-36 role emotional															
Intervention	83	86.35	29.47	75	81.78	33.91	69	81.16	34.53	64	86.98	32.32		n.a.	
General mental health															
SF-36 mental health															
Intervention	84	75.24	14.49	75	72.96	16.21	69	74.14	16.72	64	76.69	16.23		n.a.	

Abbreviations: FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; MMQ = Maudsley Marital Questionnaire; PAIR = Personal Assessment of Intimacy in Relationships Inventory; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire module of the European Organisation for Research and Treatment of Cancer; SAQ = Sexual Activity Questionnaire; SD = standard deviation; SF36 = 36-Item Short Form Health Survey.

†T0 = baseline; T1 = mid-treatment; T2 = post-treatment; T3= 3 months follow-up, T4= 9 months follow-up.

‡Scale was completed by less than total number of participants as only partnered participants could complete it.

¶Scale was completed by less than total number of participants as only participants who had had vaginal penetration could provide an answer.

Table 2. Statistically significant linear and quadratic effects of time for the primary and secondary outcomes

		Linear and Quadratic growth model				P1†				P2†			
Outcome measure		**Coefficient**	**SE**	***p***	**ES‡**	**Coefficient**	**SE**	***p***	**ES‡**	**Coefficient**	**SE**	***p***	**ES‡**
PRIMARY OUTCOMES													
Overall sexual functioning													
FSFI total	Linear	**3.70**	**0.77**	**<.001**		**2.33**	**0.61**	**<.001**	**0.45**	-0.77	0.65	.238	-0.14
	Quadratic	**-0.75**	**0.18**	**<.001**									
Sexual desire													
FSFI desire	Linear	**0.54**	**0.09**	**<.001**		**0.36**	**0.07**	**<.001**	**0.57**	-0.09	0.07	.246	-0.13
	Quadratic	**-0.10**	**0.02**	**<.001**									
Sexual arousal													
FSFI arousal	Linear	**0.66**	**0.16**	**<.001**		**0.41**	**0.12**	**.001**	**0.39**	-0.13	0.13	.302	-0.12
	Quadratic	**-0.13**	**0.04**	**.001**									
Vaginal lubrication													
FSFI lubrication	Linear	**0.79**	**0.17**	**<.001**		**0.48**	**0.13**	**<.001**	**0.42**	-0.26	0.14	.069	-0.21
	Quadratic	**-0.17**	**0.04**	**<.001**									
Orgasmic function													
FSFI orgasm	Linear	**0.77**	**0.20**	**<.001**		**0.47**	**0.15**	**.001**	**0.35**	-0.25	0.15	.105	-0.18
	Quadratic	**-0.16**	**0.05**	**.001**									
Sexual satisfaction													
FSFI satisfaction	Linear	**0.66**	**0.14**	**<.001**		**0.43**	**0.10**	**<.001**	**0.47**	-0.08	0.11	.455	-0.08
	Quadratic	**-0.12**	**0.03**	**<.001**									
Sexual pain													
FSFI pain	Linear	**0.42**	**0.20**	**.034**	**0.27**								
	Quadratic	-0.07	0.05	.118									
Sexual pleasure													
SAQ pleasure	Linear	**2.24**	**0.38**	**<.001**		**1.36**	**0.28**	**<.001**	**0.56**	**-0.59**	**0.29**	**.044**	**-0.23**
	Quadratic	**-0.47**	**0.09**	**<.001**									

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Table 2. (*continued*)

		Linear and Quadratic growth model				P1†				P2†			
Outcome measure		**Coefficient**	**SE**	***p***	**ES‡**	**Coefficient**	**SE**	***p***	**ES‡**	**Coefficient**	**SE**	***p***	**ES‡**
Discomfort during intercourse													
SAQ discomfort	Linear	**-1.07**	**0.16**	**<.001**		**-0.59**	**0.14**	**<.001**	**-0.57**	0.17	0.15	.264	0.15
	Quadratic	**0.21**	**0.04**	**<.001**									
Intercourse frequency													
SAQ habit	Linear	**0.44**	**0.11**	**<.001**		**0.28**	**0.07**	**<.001**	**0.43**	**-0.17**	**0.07**	**.028**	**-0.24**
	Quadratic	**-0.10**	**0.03**	**<.001**									
Sexual distress													
FSDS-R	Linear	**-5.39**	**0.75**	**<.001**		**-3.90**	**0.66**	**<.001**	**-0.72**	-0.02	0.70	.977	0.00
	Quadratic	**0.85**	**0.17**	**<.001**									
Social intimacy													
PAIR social	Linear	**2.24**	**1.03**	**.031**	**0.28**								
	Quadratic	-0.32	0.25	.200									
Sexual intimacy													
PAIR sexual	Linear	**2.90**	**1.33**	**.031**		1.61	1.18	.172	0.16	-1.30	1.25	.299	-0.12
	Quadratic	**-0.66**	**0.32**	**.040**									
Intellectual intimacy													
PAIR intellectual	Linear	**4.66**	**1.37**	**.001**		**3.34**	**1.07**	**.002**	**0.36**	**-3.33**	**1.13**	**.003**	**-0.34**
	Quadratic	**-1.14**	**0.33**	**.001**									
SECONDARY OUTCOMES													
Menopausal symptoms													
FACT-ES	Linear	**2.65**	**0.82**	**.001**	**0.48**								
	Quadratic	-0.43	0.26	.097									
Body image													
QLQ-BR23 body image	Linear	**7.52**	**2.49**	**.003**	**0.46**								
	Quadratic	-0.81	0.80	.318									

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Table 2. (*continued*)

		Linear and Quadratic growth model				P1†				P2†			
Outcome measure		**Coefficient**	**SE**	***p***	**ES‡**	**Coefficient**	**SE**	***p***	**ES‡**	**Coefficient**	**SE**	***p***	**ES‡**
Marital sexual satisfaction													
MMQ sexual	Linear	**-3.98**	**1.00**	**<.001**					**-0.69**				0.01
	Quadratic	**0.77**	**0.33**	**.019**									
General health perceptions													
SF-36 general health	Linear	**-4.15**	**2.09**	**.048**					-0.10				**0.29**
	Quadratic	**1.71**	**0.68**	**.013**									

Note. Bold font indicates a significant effect of time and time coefficients for P1 or P2 that are significantly different from zero.
Abbreviations: ES= effect size; FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; MMQ = Maudsley Marital Questionnaire; PAIR = Personal Assessment of Intimacy in Relationships Inventory; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire module of the European Organisation for Research and Treatment of Cancer; SAQ = Sexual Activity Questionnaire; SE = standard error; SF36 = 36-Item Short Form Health Survey.
†P1= active treatment phase; P2= follow-up phase.
‡The effect size for all primary outcomes and for the secondary outcomes with only a significant linear effect of time was calculated based on the *t* test statistic: (2*t)/(√*df*). For the secondary outcomes with a significant quadratic effect of time the effect size was based on the mean scores and pooled SD: ($mean_{T2}$-$mean_{T0}$)/pooled $SD_{T0\text{-}T2}$ or ($mean_{T3}$-$mean_{T2}$)/pooled $SD_{T2\text{-}T3}$; small 0.2; moderate 0.5, large 0.8.

We observed a statistically significant linear effect of time, but not a quadratic effect, for sexual pain (FSFI pain subscale: $p_{linearT0\text{-}T4}$ = .034) and social intimacy (PAIR social subscale: $p_{linearT0\text{-}T4}$ = .031). This indicates that there was a continuous decrease in sexual pain and an increase in social intimacy from T0 to T4. There were no statistically significant changes over time observed for the PAIR subscales emotional intimacy, recreational intimacy, or conventionality.

Secondary outcomes

The secondary outcomes were assessed from T0 to T3. For each outcome, the model including both a linear and quadratic effect of time showed the best fit based on the AIC and BIC. We observed a statistically significant linear effect of time, but not a quadratic effect, for menopausal symptoms (FACT-ES: $p_{linearT0\text{-}T3}$ = .001) and body image (QLQ-BR23 body image subscale: $p_{linearT0\text{-}T3}$ = .003). This indicates that there was a continuous improvement in both outcomes from T0 to T3 (see Tables 1 and 2).

We observed a significant linear and quadratic effect of time for marital sexual satisfaction (MMQ sexual subscale: $p_{quadraticT0\text{-}T3}$ = .019) and general health (SF-36 general health subscale: $p_{quadraticT0\text{-}T3}$ = .013). The mean scores and effect sizes (see Tables 1 and 2) show that the improvement in marital sexual satisfaction was maintained during P2. Women's general health improved during P2.

There were no statistically significant changes over time in marital satisfaction or marital general life satisfaction (MMQ marital and general life subscales), psychological distress (HADS total, depression and anxiety scales) or the other health-related quality of life domains (SF-36 subscales).

DISCUSSION

These results indicate that the positive effects of Internet-based CBT on overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication, discomfort during sex, sexual distress and body image of BC survivors with a DSM-IV diagnosis of sexual dysfunction observed at the end of CBT[9] were maintained during the three- and nine- month follow-up periods. The linear effect from baseline to three-month follow-up for body image indicates that this outcome improved even further after the completion of the CBT. Sexual pleasure was the only domain that, after an improvement during the Internet-based CBT, decreased significantly in the follow-up period. It did not, however, return to baseline levels. This SAQ subscale includes items covering a wide variety of topics, such as enjoying sex, desiring to have sex, feeling satisfied after sex and the frequency of intercourse. It may be that, after completion of the CBT, the loss of therapist encouragement to engage in sex may have resulted in some loss of effect in these areas. This was also reflected in the modest,

although not statistically significant decrease in the other sexual function measures. The fact that we observed a quadratic effect of time for sexual intimacy, but no significant changes within either P1 or P2 may be due to the fact that the changes in scores for this variable from T0 to T4, although significant, were relatively small and were no longer significant when analyzing the two time periods separately.

In the current analysis, we observed maintenance of the treatment effect in orgasmic function, sexual satisfaction, sexual pain, menopausal symptoms, sexual relationship satisfaction and social intimacy. We would note that, based on our original between-group analysis of the short-term effects of the CBT program[9], improvements from the baseline to T2 assessment in these outcomes were also observed in the waiting-list control group or were only marginally significantly better in the CBT group. This was also the case for intercourse frequency and intellectual intimacy. Nevertheless, the current results demonstrate that, except for a slight decrease in intercourse frequency (although not to baseline levels) and a decrease in intellectual intimacy, these outcomes remained stable in the period after completion of the Internet-based CBT.

Women reported an improvement in general health perceptions three months post-CBT. It might be that after completing the Internet-based CBT women started reflecting on the changes that they had experienced in their sexual functioning, and consequently evaluated their general health more positively.

Relationship intimacy, marital functioning, psychological distress, and health-related quality of life did not change significantly during CBT[9] or, as shown in the current analysis, after completion of the CBT. This probably reflects the fact that there was relatively little room for improvement in these areas, as women who had serious relationship problems or psychological comorbidity were excluded from study participation.

Both the pre- and post-CBT FSFI scores of our study sample were lower (indicating a lower level of sexual functioning) than those reported by women from the general population treated with Internet-based CBT for sexual problems[5]. In large part, this may reflect the fact that the women in our study had a sexual dysfunction according to DSM-IV criteria, whereas those in the trial of Jones and McCabe[5] were selected on the basis of self-reported sexual problems only. It could also be that BC survivors who seek sex therapy have more severe sexual problems than women from the general population[13] who seek professional help.

The current study had several limitations that should be noted. First, we could not compare the longer term sexual functioning of the intervention group with that of the waiting-list control group. As noted earlier, women in the control group were offered the opportunity to undergo the Internet-based CBT after completion of the T2 questionnaire. This was done because both we and the institutional review board did not consider it to be ethically acceptable to withhold therapy from the women in the control group, all of whom had a sexual dysfunction according to DSM-IV criteria, for an extended period of time. However, as the control group had only minor changes on the outcome measures in the

23 weeks between baseline and the T2 assessment[9], we think that a sudden improvement in the follow-up period would have been unlikely.

Second, in order to reduce respondent burden and increase response rates, we did not assess the secondary outcomes at the nine-month post-CBT point. This necessitated use of different statistical methods for the analysis of the primary and secondary outcomes.

Third, there was some loss to follow-up during the course of our study (10.7%, 17.9%, 23.8% and 22.6% at T1 through T4, respectively). This is not uncommon in such intervention trials[31]. We dealt with the issue of missing data by using appropriate mixed-effects models[32].

Our study also had a number of strengths, including the availability of several post-intervention follow-up assessments, the use of a range of relevant, validated outcomes measures, and the inclusion of women from both academic and community hospitals.

Our results indicate that the positive effects of Internet-based CBT on most sexual functioning domains, sexual distress and body image of BC survivors with a sexual dysfunction according to DSM-IV criteria are maintained well beyond the immediate post-CBT period. The availability of clinically effective, Internet-based sex therapy for breast cancer survivors will hopefully increase the likelihood that women who otherwise might not seek professional help for their sexual problems due to practical or social reasons (e.g., reluctance to discuss sexual issues in face-to-face settings) will do so.

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6

Internet-based cognitive behavioral therapy for DSM-IV sexual dysfunctions in breast cancer survivors: predictors of treatment response

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ABSTRACT

Objectives

We evaluated factors predictive of the effect of Internet-based cognitive behavioral therapy (CBT) in breast cancer survivors with a sexual dysfunction.

Methods

Fifty-five women completed questionnaires assessing sexual functioning and distress at baseline and post-CBT.

Results

Higher therapy compliance and better partner baseline sexual functioning predicted better post-CBT sexual functioning. Higher therapy compliance and higher partner relationship satisfaction predicted lower sexual distress. Therapy compliance, in turn, was predicted by active partner involvement in therapy and a stronger therapeutic relationship.

Conclusions

To increase the effect of Internet-based CBT, we recommend partner involvement in therapy and establishing a strong therapeutic relationship.

INTRODUCTION

As many as 45% to 77% of breast cancer (BC) survivors experience some degree of sexual problems after completion of their BC treatment[1,2]. Sexual problems can be treated effectively with cognitive behavioral therapy (CBT)[3]. Traditionally, CBT is delivered in a face-to-face setting, but more recently Internet-based sex therapy has been demonstrated to be effective[4-10]. It has been suggested that the relatively anonymous setting of Internet-based therapy may facilitate the reporting of sensitive information[11]; a feature that can be particularly relevant when treating sexual problems. Several studies have demonstrated the feasibility and efficacy of online sex therapy for female sexual problems both in the general[7,8] and in the BC population[9,10].

In a randomized controlled trial (RCT)[10], we evaluated the efficacy of Internet-based CBT in improving the sexual functioning of BC survivors with a Diagnostic and Statistical Manual of Mental Disorders (fourth edition (DSM-IV)[12]) diagnosis of sexual dysfunction. At posttreatment, women who underwent the Internet-based CBT reported significantly greater improvement in sexual functioning and body image, and a greater decrease in sexual distress compared with a waiting-list control group.

It is useful to be able to predict who can benefit most from sex therapy. An early study of face-to-face sex therapy showed that, in couples from the general population, a positive treatment response was associated with better pre-treatment general and sexual relationships, a higher pre-treatment motivation for therapy, and greater engagement in homework assignments[13]. In couples entering face-to-face sex therapy because of the female partners' low sexual desire, better treatment outcome was associated with older age and a shorter duration of the sexual problem[14]. Stephenson, Rellini and Meston[15] found that women with higher pre-treatment relationship satisfaction showed larger improvements in sexual satisfaction and distress in response to CBT. In contrast, Ter Kuile et al.[16] were unable to identify any significant predictors of treatment success in a study of women with lifelong vaginismus. To our knowledge, the only study evaluating predictors of successful Internet-based sex therapy was performed in men suffering from erectile dysfunction and premature ejaculation[17]. In that study, the participant's baseline levels of sexual functioning, sexual problems of the partner and quality of the therapeutic relationship were the most important predictors of positive post-treatment sexual functioning.

A number of BC-specific factors should be considered when evaluating predictors of the outcome of sex therapy in BC survivors, such as treatment-related factors (e.g., surgery type, chemotherapy, endocrine therapy, radiotherapy, immunotherapy, time since diagnosis). As BC survivors often report body image issues following treatment[18,19] and as women who experience body image problems more often report sexual problems[20], this variable is also important to consider when evaluating predictors of treatment response in the BC population.

In summary, although Internet-based sex therapy is effective in alleviating female sexual problems, information on predictors of treatment success is limited, particularly among BC survivors. The present study, carried out as part of a larger RCT of the efficacy of an Internet-based CBT program in improving the sexual functioning of BC survivors[10], aimed to: (a) describe the experience of women with the Internet-based CBT; and (b) identify predictors of positive treatment outcome.

METHODS

A detailed description of the design of the trial has been reported elsewhere[10,21]. Here, we provide only a description of the participants, procedures, measures and analysis plan of the current study.

Participants

We recruited BC survivors from 10 hospitals in the Netherlands. Inclusion criteria were: age 18 to 65 years; a diagnosis of histologically confirmed BC 6 months to 5 years prior to study entry; completion of BC treatment (with the exception of maintenance endocrine therapy and immunotherapy); disease-free at time of study entry; sufficient command of the Dutch language; and a DSM-IV-based diagnosis of sexual dysfunction as established by a psychologist/sexologist during a diagnostic interview. Single as well as partnered women, and both homosexual and heterosexual women could participate.

Exclusion criteria were: no Internet access; serious psychiatric comorbidity (e.g., depressive disorder, alcohol dependency, as determined on the basis of the Mini International Neuropsychiatric Interview[22]); treatment for another type of cancer (with the exception of cervix carcinoma in situ and basal cell carcinoma); presence of severe relationship problems (based on the therapist's judgment and a score > 35 on the marital satisfaction subscale of the Maudsley Marital Questionnaire[23]); concurrent therapy to alleviate problems with sexuality/intimacy; concurrent CBT for other psychological problems; and participation in another trial investigating problems with sexuality/intimacy. The institutional review boards of all recruiting hospitals approved the trial.

Procedure

We identified potentially eligible patients (i.e., those who met criteria in terms of age, BC diagnosis, time since diagnosis and current disease status) via hospital databases and/or the Netherlands Cancer Registry. Patients received a letter describing the study and were asked to return a postcard indicating if they were potentially interested in participating in the study. Interested women were interviewed by telephone by a member of the study staff to confirm basic eligibility for the trial. Subsequently women were interviewed by

telephone by a psychologist/sexologist to determine if they met DSM-IV criteria for one or more diagnoses of sexual dysfunction. Women who were eligible for and interested in trial participation were sent a baseline questionnaire and an informed consent form. Consenting women were randomly assigned to either a waiting-list control group or a group undergoing the Internet-based CBT. In total, 169 women were included in the RCT, of whom 84 women were randomized to the CBT group. The partners of the women were also requested to complete a baseline questionnaire.

Internet-based CBT

Detailed information on the content of the Internet-based CBT is provided elsewhere[10]. Briefly, the CBT consisted of four to five modules (selected out of a total of 10 modules by the psychologist/sexologist) that best suited the sexual problems of each participant. Each module contained several interventions, each of which comprised the following elements: an introduction, psycho-education, homework assignments, reports to the therapist and receiving feedback from the therapist. This resulted in a program of approximately 20 therapist-guided weekly sessions, that had to be completed within 24 weeks. The therapist supervising the CBT was the same therapist who performed the initial intake interview (with a few exceptions due to, for example, illness or vacations). The contact between the therapist and participant took place via email and was asynchronous. Telephone evaluations were held mid- and post-CBT. Women were encouraged by their therapist to involve their partner in the treatment, either by engaging them in homework exercises or by logging into the treatment program and writing their own reports to the therapist. However, participation of the partner was not mandatory.

Timing of assessments

All women completed the baseline questionnaire. Participants were sent additional questionnaires at mid-CBT and post-CBT. The latter was accompanied by an evaluation form. A reminder was sent to participants who did not complete the questionnaire within one week, followed by a second reminder by telephone if necessary. Only the post-CBT questionnaire was used in the current analysis. All women, including those who dropped out from the therapy, were requested to complete all study questionnaires.

Measures

Patient-reported outcome measures

Sociodemographic and basic clinical information was obtained during screening and via the baseline questionnaire. Sexual functioning was assessed with the Female Sexual Function Index (FSFI)[24,25], and sexual distress with the Female Sexual Distress Scale-Revised (FSDS-R)[26,27]. Additional variables assessed at baseline included: body image (subscale of

the European Organisation for Research and Treatment of Cancer Breast Cancer module; QLQ-BR23)[28], relationship satisfaction (marital satisfaction subscale of the Maudsley Marital Questionnaire; MMQ)[23] and psychological distress (Hospital Anxiety and Depression Scale; HADS)[29-31]. Partners completed the MMQ marital satisfaction subscale and the International Index of Erectile Function (IIEF; male partners)[32,33] or the FSFI (female partners). A detailed description of the outcome measures is provided in Table 1. We calculated questionnaire scores according to published scoring algorithms. Missing values were replaced by the average score of the completed items in the same scale for each individual, provided that at least 50% of the items in that scale had been completed.

Evaluation of the therapy program

In the post-CBT evaluation questionnaire, we asked a series of questions concerning the participant's satisfaction with several aspects of the Internet-based CBT (Table 2). The woman and her therapist also completed questions concerning therapy-related issues at post-treatment: 'To what extent did you experience a connection with [the sexologist/the client]?'; 'To what extent has the treatment been effective in reducing [your/the client's] sexual problems?'; and 'To what extent has the treatment improved [your/the client's] ability to cope with your/her sexual problems?'. The response options ranged from 1 (very satisfied, very much, and always, respectively) to 5 (very unsatisfied, not at all, and never, respectively).

Therapy compliance

To measure therapy compliance, we used an item that was completed by the therapist post-CBT: 'How many of the total number of therapy sessions that you considered to be optimal for this client did she actually complete?'. Responses were on a 5-point scale, ranging from 1 (the client completed very few of the sessions that I deemed necessary (< 25%)) to 5 (the client completed all of the sessions that I deemed necessary (100%)). Because of small numbers, the groups of 100% and > 75% were combined, resulting in a 4-point scale (< 25%; 25-50%; 50-75%; > 75%).

Table 1. Patient-reported outcome measures

Variable	Questionnaire	Details
Sexual functioning	FSFI[24,25]	• Assesses sexual functioning
		• 19 items; 5- and 6-point Likert scales
		• Subscales: desire; arousal; lubrication; orgasm; satisfaction; pain
		• Total score[a]: 2-36 / Subscale scores[a]: desire 1.2-6; arousal 0-6; lubrication 0-6; orgasm 0-6; satisfaction 0.8-6; pain 0-6; higher score indicates better sexual functioning
		• Time frame: past 4 weeks
		• Cronbach's α Dutch validation sample: total score .97; desire .90; arousal .96; lubrication .97; orgasm .95; satisfaction .87; pain .98.
		• Cronbach's α study sample: total score .94-.97; desire .78; arousal .92; lubrication .94; orgasm .95; satisfaction .72; pain .97.
	FSDS-R[26,27]	• Assesses distress related to sexual dysfunction
		• 13 items; 5-point Likert scale (0 'never' to 4 'always')
		• Total score: 0-52; higher score indicates higher level of sexual distress
		• Time frame: past 30 days
		• Cronbach's α Dutch validation sample: .97.
		• Cronbach's α study sample: .92-.93.
Body image	QLQ-BR23 Body Image subscale[28]	• 4 items; 4-point Likert scale (1 'not at all' to 4 'very much')
		• Score: 0-100; higher score indicates higher level of functioning
		• Time frame: past week
		• Cronbach's α Dutch validation sample: .83-.86.
		• Cronbach's α study sample: .88.
Marital functioning	MMQ[23]	• 20 items; 9-point Likert scale (range 0-8)
		• Scales: marital adjustment (M); sexual adjustment (S); general life adjustment (GL)
		• Scale scores[a]: S + GL: 0-40; M: 0-80; higher score indicates greater dissatisfaction in the specific domain
		• Time frame: past 2 weeks
		• Cronbach's α Dutch validation sample: marital .87-.88; sexual .64-.82; general life .60-.68.
		• Cronbach's α study sample: marital, women and partners .85.
Psychological distress	HADS[29,30,31]	• 14 items; 4-point Likert scale (range 0-3)
		• Subscales: depression (HADS-D); anxiety (HADS-A)
		• Total score: 0-42 / Subscale scores: 0-21; higher score indicates more psychological distress
		• Time frame: past week
		• Cronbach's α Dutch validation sample: anxiety .84; depression .79; total score .88.
		• Cronbach's α study sample: total score .82.

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Table 1. (*continued*)

Variable	Questionnaire	Details
Sexual functioning (male partners)	IIEF[32,33 b]	• 15 items; 5-/6-point Likert scale (0-5 or 1-5) • Subscales: erectile function (EF); orgasmic function (OF); sexual desire (SD); intercourse satisfaction (IS); overall satisfaction (OS) • Total score: 5-75 / Subscale scores: EF 1-30; OF 0-10; SD 2-10; IS 0-15; OS 2-10; higher score indicates a higher level of functioning in specific domain • Time frame: past 4 weeks • Cronbach's α study sample: total score .95.

Note. FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; MMQ = Maudsley Marital Questionnaire; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire module of the European Organisation for Research and Treatment of Cancer.

[a]The score is calculated based on weighted items.

[b]Dutch version of the questionnaire has not been validated.

Table 2. Process-evaluation of the Internet-based CBT

Item	Total (n = 72)[a], n (%)	Successful completion of CBT (n = 52), n (%)	Premature end of CBT (n = 20), n (%)	*p**	ES
How satisfied are you with the Internet-based therapy in general?					
very satisfied	14 (19.4)	14 (26.9)	0 (0.0)	<.001	0.41
satisfied	38 (52.8)	29 (55.8)	9 (10.2)		
neutral	13 (18.1)	7 (13.5)	6 (31.6)		
unsatisfied	6 (8.3)	2 (3.8)	4 (21.1)		
very unsatisfied	0 (0.0)	0 (0.0)	0 (0.0)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		
How satisfied are you about the information given by the therapist about the content and method of the Internet-based therapy?					
very satisfied	25 (34.7)	22 (42.3)	3 (15.0)	0.011	0.30
satisfied	38 (52.8)	26 (50.0)	12 (60.0)		
neutral	7 (9.7)	3 (5.8)	4 (20.0)		
unsatisfied	2 (2.8)	1 (1.9)	1 (5.0)		
very unsatisfied	0 (0.0)	0 (0.0)	0 (0.0)		
missing	0 (0.0)	0 (0.0)	0 (0.0)		
How satisfied are you about the modules that were selected for your therapy?					
very satisfied	9 (12.7)	9 (17.3)	0 (0.0)	<.001	0.45
satisfied	39 (54.9)	32 (61.5)	7 (36.8)		
neutral	16 (22.5)	10 (19.2)	6 (31.6)		
unsatisfied	7 (9.9)	1 (1.9)	6 (31.6)		
very unsatisfied	0 (0.0)	0 (0.0)	0 (0.0)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		
How satisfied are you with the amount of information that was provided in the CBT program?					
very satisfied	16 (22.2)	16 (30.8)	0 (0.0)	0.001	0.40
satisfied	34 (47.2)	25 (48.1)	9 (47.4)		
neutral	14 (19.4)	9 (17.3)	5 (26.3)		
unsatisfied	6 (8.3)	1 (1.9)	5 (26.3)		
very unsatisfied	1 (1.4)	1 (1.9)	0 (0.0)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		
How satisfied are you with the clarity of the information that was provided in the CBT program?					
very satisfied	18 (25.0)	16 (30.8)	2 (10.5)	0.014	0.29
satisfied	37 (51.4)	28 (53.8)	9 (47.24)		
neutral	11 (15.3)	5 (9.6)	6 (31.6)		
unsatisfied	4 (5.6)	3 (5.8)	1 (5.3)		
very unsatisfied	1 (1.4)	0 (0.0)	1 (5.3)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		

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Table 2. (*continued*)

Item	Total (n = 72)[a], n (%)	Successful completion of CBT (n = 52), n (%)	Premature end of CBT (n = 20), n (%)	*p**	ES
How satisfied are you with the content of the modules?					
very satisfied	11 (15.3)	11 (21.2)	0 (0.0)	0.001	0.39
satisfied	35 (48.6)	28 (53.8)	7 (36.8)		
neutral	18 (25.0)	10 (19.2)	8 (42.1)		
unsatisfied	7 (9.7)	3 (5.8)	4 (21.2)		
very unsatisfied	0 (0.0)	0 (0.0)	0 (0.0)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		
How satisfied are you with the clarity of the homework exercises?					
very satisfied	9 (12.5)	9 (17.3)	0 (0.0)	0.015	0.29
satisfied	35 (48.6)	27 (51.9)	8 (42.1)		
neutral	20 (27.8)	12 (23.1)	8 (42.1)		
unsatisfied	6 (8.3)	4 (7.7)	2 (10.5)		
very unsatisfied	1 (1.4)	0 (0.0)	1 (5.3)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		
How satisfied are you with the usability of the Internet program?					
very satisfied	13 (18.1)	12 (23.1)	1 (5.0)	0.269	0.13
satisfied	25 (34.7)	16 (30.8)	9 (45.0)		
neutral	17 (23.6)	13 (25.0)	4 (20.0)		
unsatisfied	12 (16.7)	8 (15.4)	4 (20.0)		
very unsatisfied	5 (6.9)	3 (5.8)	2 (10.0)		
missing	0 (0.0)	0 (0.0)	0 (0.0)		
How satisfied are you about the reachability of the sexologist?					
very satisfied	33 (45.8)	29 (55.8)	4 (21.1)	0.003	0.35
satisfied	32 (44.4)	21 (40.4)	11 (57.9)		
neutral	6 (8.3)	2 (3.8)	4 (21.1)		
unsatisfied	0 (0.0)	0 (0.0)	0 (0.0)		
very unsatisfied	0 (0.0)	0 (0.0)	1 (5.0)		
How satisfied are you about the reaction time of the sexologist?					
very satisfied	37 (51.4)	32 (61.5)	5 (26.3)	0.011	0.30
satisfied	29 (40.3)	17 (32.7)	12 (63.2)		
neutral	5 (6.9)	3 (5.8)	2 (10.5)		
unsatisfied	0 (0.0)	0 (0.0)	0 (0.0)		
very unsatisfied	0 (0.0)	0 (0.0)	0 (0.0)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		

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Table 2. (*continued*)

Item	Total (n = 72)[a], n (%)	Successful completion of CBT (n = 52), n (%)	Premature end of CBT (n = 20), n (%)	*p**	ES
How satisfied are you about the number of contact moments with the sexologist?					
very satisfied	28 (38.9)	24 (46.2)	4 (21.1)	0.035	0.25
satisfied	34 (47.2)	23 (44.2)	11 (57.9)		
neutral	7 (9.7)	5 (9.6)	2 (10.5)		
unsatisfied	1 (1.4)	0 (0.0)	1 (5.3)		
very unsatisfied	1 (1.4)	0 (0.0)	1 (5.3)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		
To what extent did you experience a connection with the sexologist?					
very much	31 (43.1)	27 (51.9)	4 (20.0)	0.001	0.41
quite	24 (33.3)	19 (36.5)	5 (25.0)		
somewhat	13 (18.1)	5 (9.6)	8 (40.0)		
barely	2 (2.8)	0 (0.0)	2 (10.0)		
not at all	2 (2.8)	1 (1.9)	1 (5.0)		
How satisfied are you about your commitment to the therapy?					
very satisfied	7 (9.7)	6 (11.5)	1 (5.0)	<.001	0.49
satisfied	31 (43.1)	30 (57.7)	1 (5.0)		
neutral	16 (22.2)	9 (17.3)	7 (35.0)		
unsatisfied	14 (19.4)	5 (9.6)	9 (45.0)		
very unsatisfied	4 (5.6)	2 (3.8)	2 (10.0)		
To what extent has the treatment been effective in reducing your symptoms?					
very much	18 (25.0)	18 (34.6)	0 (0.0)	<.001	0.47
quite	20 (27.8)	17 (32.7)	3 (15.0)		
somewhat	16 (22.2)	8 (15.4)	8 (40.0)		
barely	12 (16.7)	7 (13.5)	5 (25.0)		
not at all	6 (8.3)	2 (3.8)	4 (20.0)		
To what extent has the treatment been effective in improving your ability to cope with your problems?					
very much	18 (25.0)	18 (34.6)	0 (0.0)	<.001	0.49
quite	28 (38.9)	22 (42.3)	6 (30.0)		
somewhat	14 (19.4)	8 (15.4)	6 (30.0)		
barely	6 (8.3)	2 (3.8)	4 (20.0)		
not at all	6 (8.3)	2 (3.8)	4 (20.0)		
How often did you complete the homework assignments?					
always	10 (14.1)	8 (15.4)	2 (10.5)	<.001	0.42
almost always	40 (56.3)	35 (67.3)	5 (26.3)		
sometimes	10 (14.1)	7 (13.5)	3 (15.8)		
almost never	8 (11.3)	2 (3.8)	6 (31.6)		
never	3 (4.2)	1 (0.0)	3 (15.8)		
missing	1 (1.4)	0 (0.0)	1 (5.0)		

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Table 2. (*continued*)

Item	Total (n = 72)[a], n (%)	Successful completion of CBT (n = 52), n (%)	Premature end of CBT (n = 20), n (%)	*p***	OR
Would you recommend this therapy to another person?					
yes	52 (72.2)	45 (86.5)	7 (38.9)	<.001	10.10
no	18 (25.0)	7 (13.5)	11 (61.1)		
missing	2 (2.8)	0 (0.0)	2 (10.0)		

Note. CBT = cognitive behavioral therapy; ES = effect size; OR = odds ratio.

[a]The process-evaluation was based on 72 women who underwent the CBT and who completed the evaluation questionnaire.

**p* value of the Mann-Whitney U test of differences between the 52 and 20 women.

***p* value of the Pearson chi-square test of differences between the 52 and 20 women.

Statistical analysis

The potential predictors of therapy outcome were divided into four categories: patient-related, BC treatment-related, partner-related and therapy-related predictors (Table 3). The variables were selected on the basis of existing literature regarding predictors of successful sex therapy[13-15,17].

We used descriptive statistics to characterize the study sample and to evaluate the participants' satisfaction with the Internet-based CBT. Mann-Whitney U-tests were used to compare the therapy satisfaction of women who successfully completed the CBT with those who discontinued the CBT prematurely. The correlation between the participant's and the therapist's judgment regarding therapy-related issues was evaluated with Spearman's rank-order correlation and the difference in scores with the Wilcoxon Signed-Ranks test. Correlation coefficients of .10-.29 were considered as small, .30-.49 as moderate, and ≥ .50 as large[34].

Because of the large number of potential predictors and the relatively small sample size, we first performed univariable linear regression analyses for each potential predictor with either the post-CBT FSFI total score or FSDS-R score as the dependent variable[35]. The independent variables that predicted the outcome measure in the univariable analysis at the $p < .10$ level were subsequently included in a multivariable linear regression analysis, with the baseline FSFI or FSDS-R score included as a covariate. As the available evidence from the literature on predictors of Internet-based sex therapy is limited, we did not prioritize predictors, but rather entered all potential predictors simultaneously into the regression model (i.e., in one block). Subsequently, the variables that did not contribute to the model at $p < .05$ were eliminated from the model, one at a time. The fit of the smaller model was compared to that of the larger model using Akaike Information Criterion (AIC)[36]. For the multivariable linear regression analyses, a $p < .05$ was considered statistically significant for both the total model and the predictors. The R^2 statistic was used to evaluate the goodness of fit of the individual model[37]. We performed the predictor analyses on the data of women who completed the baseline and post-CBT assessment and who had a male partner.

Table 3. Variables used in univariable regression and their associations with the outcome measures

		Post-CBT FSFI score			Post-CBT FSDS-R score			Therapy compliance		
Predictor	**Description**	**n**	**R^2**	***p***	**n**	**R^2**	***p***	**n**	**R^2**	***p***
Patient-related										
Age woman	Years (range: 30-66)	55	0.034	0.180	55	0.004	0.650	64	0.013	0.377
Menopausal status	Pre-/postmenopausal	55	0.128	0.007*	55	0.021	0.295	64	0.002	0.717
No. of DSM-IV diagnoses of sexual dysfunction	1 diagnosis/≥ 2 diagnoses	55	0.012	0.425	55	0.039	0.148	64	0.001	0.852
Sexually active at baseline	yes/no	55	0.206	0.001*	55	0.014	0.397	64	0.003	0.682
Baseline sexual functioning	FSFI total score at baseline	55	0.277	<.001*	55	0.225	<.001*	64	0.016	0.314
Baseline sexual distress	FSDS score at baseline	55	0.003	0.703	55	0.260	<.001*	64	0.001	0.797
Baseline relationship satisfaction	MMQ marital satisfaction subscale at baseline - woman	55	0.065	0.06*	55	0.088	0.028*	64	0.000	0.905
Baseline body image	QLQ-BR23 body image subscale score at baseline	55	0.005	0.617	55	0.014	0.386	64	0.001	0.784
Baseline psychological distress	HADS score at baseline	55	0.117	0.01*	55	0.202	0.001*	64	0.000	0.996
BC treatment-related										
Type of surgery	BCT/mastectomy alone/mastectomy with reconstruction	55	0.014	0.687	55	0.021	0.577	64	0.002	0.933
	BCT vs. mastectomy alone			1.000			1.000			1.000
	BCT vs. mastectomy with reconstruction			1.000			1.000			1.000
	Mastectomy alone vs. mastectomy with reconstruction			1.000			1.000			1.000
Chemotherapy	yes/no	55	0.003	0.679	55	0.002	0.761	64	0.004	0.607
Current endocrine therapy	yes/no	55	0.004	0.657	55	0.001	0.869	64	0.052	0.07*
Radiotherapy	yes/no	55	0.001	0.788	55	0.019	0.322	64	0.004	0.636
Immunotherapy	yes/no	55	0.003	0.701	55	0.044	0.124	64	0.007	0.522
Time since BC diagnosis	Months	55	0.019	0.309	55	0.000	0.972	64	0.000	0.934

(Continued on next page)

Table 3. (*continued*)

Predictor	Description	Post-CBT FSFI score			Post-CBT FSDS-R score			Therapy compliance		
		n	R^2	*p*	n	R^2	*p*	n	R^2	*p*
Partner-related										
Baseline sexual functioning	IIEF total score at baseline	55	0.354	<.001*	55	0.106	0.016*	64	0.045	0.092*
Baseline relationship satisfaction	MMQ marital satisfaction subscale at baseline - partner	55	0.120	0.01*	55	0.222	<.001*	64	0.022	0.246
Therapy-related[a]										
Involvement of partner in homework assignments	never/almost never/sometimes/(almost) always	53	0.001	0.853	53	0.025	0.257			[b]
Partner wrote own reports to therapist	yes/no	54	0.000	0.984	54	0.010	0.464	62	0.123	0.005*
Frequency of homework completion	(almost) never/sometimes/(almost) always	55	0.059	0.205	55	0.067	0.166			[b]
	(almost) never vs. sometimes			1.000			1.000			
	(almost) never vs. (almost) always			0.353			0.482			
	sometimes vs. (almost) always			0.670			0.334			
Quality of the therapeutic relationship	very or quite/somewhat or barely or not at all	55	0.115	0.011*	55	0.106	0.015*	64	0.197	<.001*
Therapy compliance	> 75%/50-75%/25-50%/< 25%	55	0.100	0.019*	55	0.096	0.021*	n.a.	n.a.	n.a.

Note. BC = breast cancer; BCT = breast conserving treatment; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; MMQ = Maudsley Marital Questionnaire; QLQ-BR23 = Breast Cancer-specific Quality of Life Questionnaire module of the European Organisation for Research and Treatment of Cancer.

*Univariable regression is significant at the < .10 level (2-tailed).

[a]The therapy-related variables are based on items answered by the therapist.

[b]We did not include this variable in the analysis regarding therapy compliance as the answer of the therapist concerning this item is dependent on therapy compliance.

As the baseline FSFI and FSDS-R scores were included in the final multivariable predictor models (see the Results section), we performed an exploratory analysis to evaluate if the baseline scores were actual predictors of therapy success or merely predictors of sexual functioning or distress over time (e.g., a lower score at baseline predicts a lower post-CBT score). We used linear regression analysis including an interaction between the baseline FSFI or FSDS-R score and group (intervention versus control), with post-CBT FSFI or FSDS-R score as the dependent variable. A significant interaction would indicate that the baseline score was a predictor of therapy success. If the interaction was non-significant, we deleted the interaction from the analysis to evaluate the independent effects of the baseline score and group on the outcome. Finally, again based on results of the final predictor models, we performed another exploratory analysis in which we evaluated factors predictive of therapy compliance. For this we used the same approach as for detecting predictors of therapy success.

RESULTS

From September 2013 to April 2015, 84 women were randomized to the intervention group. Seventy-eight women actually started the Internet-based CBT. Of these 78 women, 76 women had a partner, of whom 66 agreed to complete study questionnaires (64 men and 2 women). Sixty-seven percent of the 78 women completed the CBT successfully. Seventy-two women completed the evaluation questionnaire.

The mean age of these 72 women was 51.6 years (standard deviation (SD) = 7.9). Most women had completed a vocational (36.1%) or academic (41.7%) education and had a partner (98.6%). The majority of women was postmenopausal (81.9%) and sexually active at baseline (77.8%). The mean time since BC diagnosis was 37.6 months (SD = 17.0). The majority had undergone breast conserving treatment (55.6%), chemotherapy (76.4%), endocrine therapy (81.9%), and radiotherapy (84.7%). Fewer women had undergone immunotherapy (18.1%). Most women (73.6%) were diagnosed with two DSM-IV sexual dysfunctions. The most prevalent sexual dysfunction was hypoactive sexual desire disorder (HSDD; 81.9%), followed by sexual arousal disorder (44.4%), dyspareunia (34.7%), orgasmic disorder (11.1%), sexual aversion disorder (6.9%), sexual dysfunction not otherwise specified (5.6%) and vaginismus (1.4%). The majority of the 66 partners had completed a post-high school education (68.2%), and the mean age was 53.4 years (SD = 8.5).

Patient evaluation of the Internet-based CBT

The majority of the women (72%) was satisfied or very satisfied with the therapy in general. Fifty-two percent indicated that the intervention had been quite or very much effective in reducing their sexual problems, and almost two-thirds indicated that it had improved their ability to cope with their sexual problems. Overall, the women who successfully completed

the CBT (as indicated by the therapist) reported higher satisfaction with their treatment than those who ended the CBT prematurely (Table 2).

The women's and their therapists' ratings of the degree to which the CBT reduced the sexual problems were relatively strongly correlated (r = .59, p < .001), as was their perception of the extent to which the CBT had improved the women's ability to cope with her sexual problems (r = .64, p < .001). Although their judgment about the quality of the therapeutic relationship was also relatively strongly correlated (r = .50, p < .001), the women's ratings were significantly higher than those of the therapists (ES = .34, p = .016). Although three-quarters of both the women and the therapists indicated that they felt (very) strongly connected with the therapist/client, a larger percentage of women experienced a very strong connection (43.1% of the women vs. 11.1% of the therapists; data not shown in tabular form).

Predictors of successful treatment outcome

Fifty-five women completed both the baseline and post-CBT assessment and had a male partner who had completed the baseline questionnaire, and thus could be included in the initial predictor analyses. There were no significant differences between the 55 women included in the predictor analyses and the 23 women who were excluded in terms of sociodemographic, clinical or baseline characteristics.

Higher post-CBT female sexual functioning was predicted by higher baseline female sexual functioning (FSFI total score; β = .273, p = .041), higher therapy compliance (β = .220, p = .043) and higher baseline sexual functioning of the partner (IIEF total score; β = .390, p = .005); fitted model R^2 = .445 (Table 4). In the subsequent exploratory analysis that included both the intervention and control group, no statistically significant interaction was observed between baseline female sexual functioning and group on post-CBT sexual functioning. We therefore excluded the interaction, resulting in an analysis that demonstrated that higher baseline female sexual functioning (β = .462, p < .001) and undergoing the CBT (β = .214, p = .004) independently predicted higher post-CBT sexual functioning; fitted model R^2 = .266.

Lower post-CBT sexual distress was predicted by lower baseline sexual distress (FSDS-R score; β = .367, p = .001), higher baseline female sexual functioning (FSFI total score; β = -.256, p = .020), higher baseline relationship satisfaction of the partner (MMQ marital subscale; β = .275, p = .011) and higher therapy compliance (β = -.269, p = .009); fitted model R^2 = .522 (Table 4). The exploratory analysis (including the intervention and control group) showed no statistically significant interaction between baseline female sexual functioning or sexual distress and group on post-CBT sexual distress. A subsequent analysis excluding the interactions indicated that lower baseline sexual distress (β = .513, p < .001), higher baseline female sexual functioning (β = -.175, p = .014) and undergoing the CBT (β

= -.220, p = .001) independently contributed to the prediction of lower post-CBT sexual distress, fitted model R^2 = .395.

Table 4. Final models for the linear regressions testing the predictors of post-CBT FSFI total score and FSDS-R score

Outcome predictors	n[a]	B	SE B	β	*p*	R^2
Outcome: post-CBT FSFI total score	55[b]					
Constant		1.059	3.475		.762	0.445
Baseline FSFI total score		.375	.179	.273	.041	
Therapy compliance		2.032	.979	.220	.043	
Baseline IIEF total score		.186	.063	.390	.005	
Outcome: post-CBT FSDS-R score	55[b]					
Constant		16.360	4.412		.001	0.522
Baseline FSDS-R score		.350	.101	.367	.001	
Baseline FSFI total score		-.322	.134	-.256	.020	
Baseline MMQ marital satisfaction score partner		.274	.104	.275	.011	
Therapy compliance		-2.278	.841	-.269	.009	
Outcome: therapy compliance	62					
Constant		1.437	.266		<.001	0.310
Active involvement of partner in therapy		.697	.253	.300	.008	
Therapeutic relationship		1.123	.281	.435	<.001	

Note. CBT = cognitive behavioral therapy; FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; IIEF = International Index of Erectile Function; SE = standard error.
[a]Because the male partner's sexual functioning was one of the significant predictors (at the univariable level) of successful therapy outcome, we excluded the participants without partner-reported data and with a female partner, which resulted in 64 women that were eligible for analysis.
[b]As a result of missing T2-assessments, the analyses were based on 55 women.

Predictors of treatment compliance

As therapy compliance was a predictor of both post-CBT sexual functioning and distress, we evaluated which factors were associated with higher therapy compliance (Table 3). This analysis included 62 women (i.e., the women whose male partner completed the baseline questionnaire, minus two women for whom data were missing on the partner's involvement in therapy). Higher therapy compliance was predicted by the active involvement of the partner in therapy (β = .300, p = .008) and a stronger therapeutic relationship (β = .435, p < .001); fitted model R^2 = .310 (Table 4).

DISCUSSION

We previously demonstrated that Internet-based CBT improves the sexual functioning and reduces the sexual distress of BC survivors with a DSM-IV sexual dysfunction[10]. In the current article, we evaluated which factors were predictive of a successful outcome of the Internet-based CBT. Better post-CBT sexual functioning was predicted by better baseline female sexual functioning, better baseline sexual functioning of the partner and higher therapy compliance. Predictors of lower post-CBT sexual distress included lower baseline sexual distress, better baseline female sexual functioning, higher baseline relationship satisfaction of the partner and higher therapy compliance. However, no significant interaction was found between baseline sexual functioning and group when we included the control group in the analysis, indicating that the baseline levels of sexual functioning and distress were not predictive of the effectiveness of the Internet-based CBT. The baseline levels were, however, predictive of the level of sexual functioning and distress over time (e.g., women with better baseline sexual functioning also had better post-CBT sexual functioning). These findings suggest that any BC survivor, regardless of her baseline level of sexual functioning or distress, may benefit from Internet-based CBT for sexual dysfunction. We did not identify any BC treatment-related factors that predicted post-CBT sexual functioning or distress, suggesting that women can profit from the intervention irrespective of their specific BC treatment.

An improvement in both post-CBT sexual functioning and distress was predicted by higher therapy compliance. Higher therapy compliance, in turn, was predicted by the active involvement of the partner in therapy (i.e., the partner wrote his/her own reports to the therapist) and a better therapeutic relationship. This suggests that, although these two latter factors are not associated directly with therapy success, they do influence the success of the therapy indirectly via their relationship with compliance. The finding regarding the association between a better therapeutic relationship and higher therapy compliance is consistent with research demonstrating that therapist-guidance can improve the adherence to and outcome of Internet-based CBT[38,39] and that guided self-management programs tend to be more effective than unguided programs[40,41]. More research into the importance of therapeutic alliance and factors that improve the therapeutic alliance in Internet-based interventions is needed, such as therapist-client contact frequency and time spent by the therapist per patient, the mode of communication during treatment (e.g., email, additional telephone contacts), and if the client-program alliance has an effect on client-therapist alliance and therapy success[39,42].

Better baseline sexual functioning of the partner and higher relationship satisfaction of the partner predicted better post-CBT female sexual functioning and lower sexual distress, respectively. It may be that partners with higher relationship satisfaction are more willing to discuss their sexual problems jointly during therapy and this may, in turn, reduce the

woman's sexual distress. The fact that the level of the partner's sexual functioning affects the progress made by the woman during therapy underscores the importance of including the partner in sexual counseling after BC.

Women who ended the CBT prematurely reported less satisfaction with the therapy than those who successfully completed the CBT. This is not surprising, as the most common reasons for ending the CBT prematurely included not only non-therapy-related factors such as personal circumstances (15.2%) and relationship problems (9.1%), but also factors that have an influence on the experience of the CBT, such as time constraints (12.1%), the intensity of the CBT (9.1%) and a preference for face-to-face therapy (9.1%). Overall, the majority of women indicated that they were satisfied with the CBT. The fact that both the women and therapists were positive about the quality of the therapeutic relationship is important, because it shows that, even when therapy is provided via the Internet, a strong therapeutic bond can be established.

Our study had several limitations that should be noted. First, some of our analyses were restricted to women whose partner also completed study questionnaires. As such, these findings cannot be generalized to women without a partner. Second, 10 partners did not consent to complete questionnaires and were thus missing from the analyses. Third, because of the relatively small sample size, it was not possible to analyze the predictive power of each specific DSM-IV diagnosis of sexual dysfunction on therapy success. Future trials should evaluate if the therapy is more or less effective among women with specific DSM-IV diagnoses. Fourth, women with serious psychiatric comorbidity and severe relationship problems were excluded from study participation, which might limit the generalizability of our results. Fifth, our CBT program consisted of 10 modules, each including a diverse range of cognitive behavioral interventions. Therefore, it was not possible to evaluate which CBT-components contribute most to the therapy success. Finally, we had no information on log-data available, such as number of emails, time spent online, and number of logins. Although this information can provide objective insight into the mechanisms that contribute to the effect of interventions, it also assumes a dose-response relationship, and it does not reflect if the program fits well with the needs of the user or how the program is used (e.g., spending more time online does not necessarily reflect optimal or efficient use of the program)[43]. Nevertheless future studies should evaluate how the use of different components of such programs, or a combination of components, contribute to their efficacy[43,44].

The study also had several noteworthy strengths. A wide range of sociodemographic, clinical and therapy-related variables were available as potential predictors of therapy success. We also were able to include data obtained directly from the women's partners. Consistent with the DSM-IV[12] definition of sexual dysfunction, we included measures of both sexual functioning and distress, and thus we were able to investigate predictors for both of these important indicators of therapy success.

To our knowledge, this is the first study describing predictors of a successful outcome of Internet-based CBT for sexual dysfunctions in BC survivors. The predictors that we identified were similar to those found in the general population[13,15,17]. Our findings suggest that all BC survivors, regardless of their specific BC treatment or their baseline level of sexual functioning and distress, may benefit from Internet-based therapy. We recommend that, to enhance compliance with and effectiveness of the CBT program, particular attention be paid to the therapeutic relationship and to the involvement of the partner in the therapy.

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7

Sexual functioning and relationship satisfaction of partners of breast cancer survivors who receive Internet-based sex therapy

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ABSTRACT

As part of a larger, randomized controlled trial, we evaluated longitudinally the sexual functioning and relationship satisfaction of 69 partners of breast cancer (BC) survivors who received Internet-based cognitive behavioral therapy (CBT) for sexual dysfunction. The findings suggest that Internet-based CBT positively affects the partners' immediate post-CBT and longer-term overall sexual satisfaction, sexual intimacy and sexual relationship satisfaction. No sustained changes in other areas of sexual functioning were observed. Our CBT program was focused primarily on the sexual health of the BC survivors. We recommend that future programs include more psychoeducational and behavioral elements targeted at the partners.

INTRODUCTION

Sexual problems are a frequent, long-term consequence of the diagnosis and treatment of breast cancer (BC)[1,2]. Between 45-77% of BC survivors report sexual problems after treatment[3,4]. Frequently occurring problems include decreased sexual desire, decreased sexual arousal or lubrication, dyspareunia, and vaginal dryness[5,6]. As the sexuality of partners is interrelated[7,8], it is not surprising that about 75% of partners of BC survivors indicate that the BC and its treatment negatively impact their sexuality and sexual relationship[9]. Changes reported by partners of cancer survivors include a reduction of sexual activity and a lack of fulfillment in relation to sex[9]. Given the dyadic nature of the sexual relationship, it has been recommended to involve the partner when offering psychosexual counseling to women who have had BC[5,10].

Research has demonstrated the efficacy of different psychosexual interventions in improving the sexual functioning of BC survivors, including studies in which the partner was involved in therapy[11-17]. However, no studies have evaluated the self-reported sexual functioning of partners in response to sex therapy specifically targeting sexual dysfunction after BC. In a randomized controlled trial (RCT), we evaluated the efficacy of Internet-based cognitive behavioral therapy (CBT) in improving the sexual functioning of BC survivors with a sexual dysfunction[12,13]. The intervention had a positive, clinically relevant effect on women's sexual functioning, sexual distress and body image immediately post-CBT[12] as well as at nine-months follow-up[13]. The Internet-based CBT program included psychoeducation on a range of topics concerning general as well as BC-specific sexuality issues, homework exercises and reports to and feedback from the therapist. Women were encouraged by their therapist to involve their partner in the therapy and/or homework exercises. To our knowledge, no studies have collected data directly from the partner during and after CBT for sexual dysfunction in BC survivors. In this article, we report on the evaluation of changes that occurred during and up to nine months after Internet-based CBT in sexual functioning, relationship intimacy and relationship satisfaction among partners of BC survivors with a sexual dysfunction who underwent the Internet-based CBT program.

METHODS

Participants

This longitudinal, within-subject study is part of a larger RCT of the efficacy of Internet-based CBT for sexual dysfunctions in BC survivors. A detailed description of the RCT is provided elsewhere[12]. Here we only report the information pertinent to the current analyses.

Women with a history of BC and their partners (if present) were recruited from 10 hospitals in the Netherlands. Women were included based on the following criteria: age

18 to 65 years; a diagnosis of histologically confirmed BC six months to five years prior to study entry; completion of BC treatment (with the exception of maintenance endocrine therapy and immunotherapy); disease-free at time of study entry; sufficient command of the Dutch language; and a sexual dysfunction according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV[18]), as established by a psychologist/sexologist during a diagnostic interview. Single as well as partnered women, and both heterosexual and homosexual women could participate.

Exclusion criteria were as follows: no Internet access; serious psychiatric comorbidity (e.g., depressive disorder, alcohol dependency); treatment for another type of cancer; presence of severe, general relationship problems; concurrent therapy to alleviate problems with sexuality/intimacy; concurrent CBT for other psychological problems; and participation in another trial investigating problems with sexuality/intimacy. The institutional review boards of all recruiting hospitals approved the trial.

Procedure

We identified potentially eligible women via hospital databases and the Netherlands Cancer Registry. Patients received a letter describing the study. Interested women were screened for eligibility for the trial by a member of the study staff and subsequently by a psychologist/sexologist. Eligible women were requested to complete a baseline questionnaire, and consenting women were randomly assigned to either a waiting-list control group or a group that received the Internet-based CBT. We asked women in the intervention group if their partners were willing to complete the study questionnaires. If so, the partner was sent an informed consent form and baseline questionnaire.

Internet-based CBT

Extensive information on the content of the Internet-based CBT is provided elsewhere[12]. Briefly, the CBT was composed of 4 to 5 modules (selected out of a total of 10 modules by the psychologist/sexologist) that best suited the sexual problems of each individual woman. During the intake interview, the therapist discussed the desired goals of treatment with the patient and proposed a treatment plan. The treatment plan was flexible, and the choice of modules could be adjusted during therapy according to the woman's (and partner's) needs. Each module included information texts on a range of topics, including the nature of sexual problems, the biopsychosocial model, the sexual response curve, the interplay between sexuality and intimacy, and communication with the partner. Accompanying homework exercises included sensate focus exercises, task concentration training, exposure exercises for sexual pain, and exercises promoting cognitive restructuring. Partner involvement was integrated throughout the CBT program, including both a specific module focusing on the partner, as well as in the sensate focus exercises, the couple's discussions of the woman's sexual response curve, in evaluating changes in the couple's sex life after BC, and as part

of the communication exercises about sexuality and sexual preferences. This resulted in a therapy of approximately 20 therapist-guided weekly sessions to be completed within 24 weeks. The contact between the therapist and client took place via email. Involvement of the partner in the therapy and homework exercises was recommended, but not required. It was possible for partners to be actively involved in the therapy by logging into the program.

Study measures

Partners completed study questionnaires at baseline (T0), mid-CBT (T1), post-CBT (T2), and at three- (T3) and nine-month (T4) follow-ups. Sociodemographic information was obtained via the baseline questionnaire. We assessed the primary outcomes - sexual functioning and relationship intimacy - at all assessment points. Male partners' sexual functioning was measured with the International Index of Erectile Function (IIEF[19]) and female partners' sexual functioning with the Female Sexual Function Index (FSFI[20,21]). Relationship intimacy was assessed with the Personal Assessment of Intimacy in Relationships Inventory (PAIR[22]). The secondary outcome, marital functioning, was assessed from T0 to T3 (Maudsley Marital Questionnaire; MMQ[23]).

Statistical analysis

We calculated questionnaire scores according to published scoring algorithms. Missing values were replaced by the average score of the completed items in the same scale for each individual, provided that ≥ 50% of the items in that scale had been completed.

To evaluate the intra-individual difference in the trajectory of change over time for both the primary and secondary outcomes, we used a growth curve modelling approach based on restricted maximum likelihood estimation with random intercept and slope. We checked for the presence of a linear effect of time from T0 to T3 or T4. Subsequently, we added a quadratic effect of time to the model to determine if an initial improvement or deterioration in the outcome was followed by a discontinuation or deceleration of this effect. The choice between the model including only a linear effect of time and the model including both a linear and quadratic effect of time was based on model fit statistics: the Bayesian information criterion (BIC)[24] and Akaike information criterion (AIC)[25].

If, for a primary outcome, the model including a quadratic effect of time had the best fit and the quadratic effect of time was statistically significant, we fitted a piecewise linear growth model to the data to determine if the discontinuation or deceleration of the effect was statistically significant[26]. Piecewise linear growth models can be used when specific transition points can be specified, such as the end of treatment. They model nonlinearity by including two interrelated linear slopes reflecting the growth trajectory before and after this transition point[27]. In our analyses the transition point was the end of CBT, with an active treatment phase before (P1: pre-, mid- and immediate posttreatment) and the

follow-up phase after this transition point (P2: immediate posttreatment, three-month, and nine-month follow-ups)[26]. We tested if changes during the active treatment and follow-up period were significantly different from zero. Evidence of a sustained effect of the CBT over time was considered present if, after a statistically significant improvement in the outcome during P1, the time coefficient for P2 was non-significant. The change during the active treatment phase and follow-up period was accompanied by effect sizes (ES) based on the *t*-test statistic: $(2*t)/(\sqrt{df})$. An ES of .20 was considered small, .50 moderate and clinically significant, and .80 large[28].

As the secondary outcomes were not assessed at T4, we decided not to use a piecewise growth model on these outcomes, as too few measurement points were available. Instead we evaluated the presence of a linear and quadratic effect of time and subsequently calculated ES based on the difference in mean scores (i.e., T0 to T2, and T2 to T3) and pooled standard deviation. The *p* value for statistical significance was set at .05.

First, we performed the analyses on an intention-to-treat basis. However, as the rate of missing follow-up questionnaires appeared to be related to the degree of the women's compliance to the Internet-based CBT (see Results section), this suggested that the data were not missing at random. As a second step, we therefore adjusted for non-ignorable drop-out in the analyses[29]. This allowed evaluation of the contribution of missing data patterns to the outcome by adding the missing data pattern and its interaction with time to the model. As some patterns included too few cases, we combined patterns, resulting in two groups: a group with a maximum of two missing assessments from T2 to T4, and a group with three or more missing assessments from T1 to T4. Last, in response to the outcomes of the analyses adjusted for non-ignorable drop-out, we performed per-protocol analyses, including only the partners of those women who successfully completed the Internet-based CBT.

As an exploratory analysis, we investigated whether male partners who ever logged into the Internet-based CBT program to report to the therapist about their experiences with the homework exercises (yes versus no) reported a larger improvement in overall sexual functioning during the CBT or a more sustained improvement during follow-up than partners who did not log into the program. We added this variable to the model that included the linear and quadratic effect of time.

The analyses regarding the partners' sexual functioning were based on the data of male partners, as only two female partners completed study questionnaires. The data of the female partners were included in the analyses of the PAIR Inventory and MMQ.

RESULTS

Recruitment and participant flow of the RCT are reported in detail elsewhere[12]. Specific to the current analysis, 169 women were randomly assigned into the trial, 84 of whom were assigned to the intervention group. Sixty-nine partners agreed to complete questionnaires and completed the T0 assessment, 62 (89.9%) completed the T1 assessment, 55 (79.7%) the T2 assessment, 53 (76.8%) the T3 assessment, and 52 (75.4%) the T4 assessment.

The mean age of the partners was 53.6 years (standard deviation (SD) = 8.5), 97.1% were male, and 68.1% had completed post-high school education. Sixty-eight percent of the partners were part of a couple that completed the CBT successfully, 27.5% ended the CBT prematurely, and 4.3% never started the CBT. Fifty-four percent of the partners logged into the CBT program themselves to report on their experiences with the homework exercises (7.2% missing data).

The mean time since BC diagnosis was 37.0 months (SD = 17.3). Most couples (92.8%) had been in a relationship for more than five years. The majority of the women had undergone breast conserving treatment (58.0%), 20.3% a mastectomy only, and 21.7% a mastectomy with reconstruction. The majority of women had undergone chemotherapy (76.8%), endocrine therapy (85.5%) and radiotherapy (85.5%). Nineteen percent of the women had undergone immunotherapy.

Among the women, hypoactive sexual desire disorder was the most prevalent sexual dysfunction (85.5%), followed by sexual arousal disorder (42.0%), dyspareunia (33.3%), orgasmic disorder (11.6%), sexual aversion disorder (7.2%), sexual dysfunction not otherwise specified (4.3%) and vaginismus (1.4%).

Intention-to-treat analysis

Primary outcomes

For each primary outcome, the model including both a linear and a quadratic effect of time showed the best fit based on the AIC and BIC. We found a statistically significant linear and quadratic effect of time for overall sexual functioning, erectile functioning, orgasmic functioning, intercourse satisfaction, overall sexual satisfaction, and sexual relationship intimacy ($p < .05$), which indicated that these outcomes improved during the CBT, and that this improvement decelerated after completion of the CBT. To assess if the post-CBT deceleration was statistically significant, we fitted a piecewise growth model for these outcomes. See Table 1 for the results of the growth curve models and piecewise growth curve models.

A statistically significant improvement during the active treatment phase (P1) and maintenance of the treatment effect during the nine-month follow-up phase (P2) were observed for overall sexual satisfaction (IIEF overall satisfaction subscale: $p_{P1} < .001$, $p_{P2} = .098$) and

sexual relationship intimacy (PAIR sexual subscale: p_{P1} = .020, p_{P2} = .190). We observed a statistically significant improvement during P1, followed by a decrease during P2 for overall sexual functioning (IIEF total score: p_{P1} = .001, p_{P2} = .001), orgasmic functioning (IIEF orgasmic function subscale: p_{P1} = .015, p_{P2} = .046) and intercourse satisfaction (IIEF intercourse satisfaction subscale: p_{P1} = .001, p_{P2} = .001). We observed no change during P1 and a statistically significant decrease during P2 for erectile functioning (IIEF erectile function subscale: p_{P1} = .236, p_{P2} = .026). Tables 1 and 2 display the effect sizes and mean scores.

There were no statistically significant changes over time observed for the IIEF subscale sexual desire, and for the PAIR subscales emotional intimacy, social intimacy, intellectual intimacy, recreational intimacy or conventionality.

Secondary outcomes

The secondary outcomes were assessed from T0 to T3. For each outcome, the model including both a linear and quadratic effect of time showed the best fit based on the AIC and BIC. We observed a significant linear and quadratic effect of time for sexual relationship satisfaction (MMQ sexual subscale: $p_{quadraticT0\text{-}T3}$ = .012). The effect sizes and mean scores (see Tables 1 and 2) show that sexual relationship satisfaction improved during P1 and that this effect was maintained during P2. There were no statistically significant changes over time in the MMQ subscales marital satisfaction or marital general life satisfaction.

Intention-to-treat analysis adjusted for non-ignorable drop-out

Adjustment of the models for non-ignorable drop-out resulted in a better fit based on the AIC and BIC. For each primary and secondary outcome, the model including both a linear and a quadratic effect of time showed the best fit based on the AIC and BIC. No statistically significant effects of time were observed for the IIEF, PAIR and MMQ subscales in the context of a model including the adjustment for non-ignorable drop-out (data not shown in tabular form), indicating that the drop-out had an effect on the outcomes. Evaluation of the drop-out patterns suggested that the completion of assessments was related to therapy compliance, as 86% of the partners who completed all assessments were part of a couple that completed the CBT successfully. We therefore performed per-protocol analyses, including only the partners of BC survivors who completed the CBT successfully (n = 47).

Per-protocol analysis

For each primary and secondary outcome, the model including both a linear and a quadratic effect of time showed the best fit based on the AIC and BIC. We fitted the piecewise growth model for the primary outcomes that had a statistically significant quadratic effect of time (data not shown in tabular form).

Table 1. Linear and quadratic effects of time for the primary and secondary outcomes

		Linear and Quadratic growth model		P1†						P2†					
							95% CI						95% CI		
Outcome measure		**Coefficient**	***p***	**Coefficient**	**SE**	***p***	**Lower bound**	**Upper bound**	**ES‡**	**Coefficient**	**SE**	***p***	**Lower bound**	**Upper bound**	**ES‡**
PRIMARY OUTCOMES															
Overall sexual functioning															
IIEF total score	Linear	**6.09**	**<.001**	**3.60**	**1.06**	**.001**	**1.48**	**5.72**	**0.91**	**-4.13**	**1.13**	**.001**	**-6.40**	**-1.85**	**-1.01**
	Quadratic	**-1.59**	**<.001**												
Erectile function															
IIEF erectile function	Linear	**2.10**	**.019**	0.99	0.83	.236	-0.65	2.63	0.17	**-1.96**	**0.88**	**.026**	**-3.69**	**-0.23**	**-0.32**
	Quadratic	**-0.62**	**.004**												
Orgasmic functioning															
IIEF orgasmic function	Linear	**1.04**	**.015**	**0.70**	**0.28**	**.015**	**0.14**	**1.26**	**0.65**	**-0.56**	**0.27**	**.046**	**-1.11**	**-0.01**	**-0.57**
	Quadratic	**-0.24**	**.019**												
Sexual desire															
IIEF sexual desire	Linear	0.24	.205												
	Quadratic	-0.08	.056												
Intercourse satisfaction															
IIEF intercourse satisfaction	Linear	**1.76**	**<.001**	**1.02**	**0.30**	**.001**	**0.43**	**1.61**	**0.89**	**-1.10**	**0.30**	**.001**	**-1.70**	**-0.50**	**-1.01**
	Quadratic	**-0.45**	**<.001**												
Overall sexual satisfaction															
IIEF overall satisfaction	Linear	**0.88**	**<.001**	**0.57**	**0.15**	**<.001**	**0.28**	**0.87**	**1.02**	-0.22	0.13	.098	-0.48	0.04	-0.47
	Quadratic	**-0.18**	**<.001**												

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Table 1. (*continued*)

		Linear and Quadratic growth model		P1†						P2†					
							95% CI						95% CI		
Outcome measure		**Coefficient**	***p***	**Coefficient**	**SE**	***p***	**Lower bound**	**Upper bound**	**ES‡**	**Coefficient**	**SE**	***p***	**Lower bound**	**Upper bound**	**ES‡**
Emotional intimacy															
PAIR emotional	Linear	0.90	.612												
	Quadratic	-0.15	.690												
Social intimacy															
PAIR social	Linear	-0.45	.721												
	Quadratic	0.14	.652												
Sexual intimacy															
PAIR sexual	Linear	**4.89**	**.001**	**2.78**	**1.17**	**.020**	**0.45**	**5.11**	**0.60**	-1.29	0.97	.190	-3.25	0.66	-0.37
	Quadratic	**-1.04**	**.004**												
Intellectual intimacy															
PAIR intellectual	Linear	1.18	.320												
	Quadratic	-0.24	.388												
Recreational intimacy															
PAIR recreational	Linear	0.21	.855												
	Quadratic	0.11	.689												
Conventionality															
PAIR conventionality	Linear	0.65	.594												
	Quadratic	-0.13	.665												

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Table 1. (*continued*)

		Linear and Quadratic growth model		P1†						P2†					
							95% CI						95% CI		
Outcome measure		**Coefficient**	***p***	**Coefficient**	**SE**	***p***	**Lower bound**	**Upper bound**	**ES‡**	**Coefficient**	**SE**	***p***	**Lower bound**	**Upper bound**	**ES‡**
SECONDARY OUTCOMES															
Marital satisfaction															
MMQ marital	Linear	0.45	.613												
	Quadratic	-0.24	.394												
Sexual relationship satisfaction															
MMQ sexual	Linear	**-3.19**	**.002**						**-0.40**						0.07
	Quadratic	**0.80**	**.012**												
Marital general life satisfaction															
MMQ general life	Linear	0.07	.913												
	Quadratic	-0.09	.601												

Note. CI = confidence interval; ES = effect size; IIEF = International Index of Erectile Function; MMQ = Maudsley Marital Questionnaire; PAIR = Personal Assessment of Intimacy in Relationships Inventory; SD = standard deviation; SE = standard error. Bold font indicates a significant effect of time and time coefficients for P1 or P2 that are significantly different from zero.

†P1 = active treatment phase; P2 = follow-up phase.

‡The effect size for the primary outcomes was calculated based on the *t* test statistic: (2*t)/(√*df*). For the secondary outcomes, the effect size was based on the mean scores and pooled SD: ($mean_{T2}$-$mean_{T0}$)/pooled $SD_{T0\text{-}T2}$ or ($mean_{T3}$-$mean_{T2}$)/pooled $SD_{T2\text{-}T3}$; small 0.2; moderate 0.5, large 0.8.

Table 2. Mean scores and standard deviations for the primary and secondary outcome measures of the partners

	T0†			T1†			T2†			T3†			T4†		
Outcome measure	**No. of participants**	**Mean**	**SD**	**No. of participants**	**Mean**	**SD**	**No. of participants**	**Mean**	**SD**	**No. of participants**	**Mean**	**SD**	**No. of participants**	**Mean**	**SD**
PRIMARY OUTCOMES															
Overall sexual functioning															
IIEF total score	67	38.02	20.46	59	39.95	22.39	53	47.11	21.12	52	42.85	21.90	51	38.98	22.29
Erectile functioning															
IIEF erectile function	67	16.66	10.57	60	16.43	11.22	53	19.79	10.58	52	18.02	10.85	51	15.94	11.04
Orgasmic functioning															
IIEF orgasmic function	67	5.55	4.48	59	5.80	4.37	53	7.38	3.99	52	6.62	4.52	51	6.14	4.53
Sexual desire															
IIEF sexual desire	67	6.88	1.57	60	6.78	1.69	53	7.09	1.70	52	7.00	1.73	51	6.57	1.93
Intercourse satisfaction															
IIEF intercourse satisfaction	67	4.32	4.59	60	5.13	5.19	53	6.91	4.89	52	5.52	5.37	51	4.69	5.27
Overall sexual satisfaction															
IIEF overall satisfaction	67	4.61	2.19	59	5.42	2.49	53	5.94	2.59	52	5.69	2.54	51	5.65	2.44
Emotional intimacy															
PAIR emotional	69	75.07	16.37	62	76.58	18.09	55	76.87	17.88	53	78.30	17.42	52	77.92	15.14
Social intimacy															
PAIR social	69	61.80	18.27	62	60.58	19.63	55	63.45	19.40	53	64.00	17.94	52	63.58	18.20
Sexual intimacy															
PAIR sexual	69	56.00	18.89	62	60.32	18.96	55	62.18	20.64	53	62.42	20.98	52	60.27	19.13
Intellectual intimacy															
PAIR intellectual	69	67.01	15.50	62	68.77	15.73	55	68.44	16.38	53	70.42	16.10	52	68.42	16.31

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Table 2. (*continued*)

Outcome measure	T0†			T1†			T2†			T3†			T4†		
	No. of participants	Mean	SD	No. of participants	Mean	SD	No. of participants	Mean	SD	No. of participants	Mean	SD	No. of participants	Mean	SD
Recreational intimacy															
PAIR recreational	69	72.70	16.83	62	71.81	13.40	55	74.69	15.47	53	73.28	14.22	52	75.65	12.75
Conventionality															
PAIR conventionality	69	64.41	15.94	62	64.90	16.44	55	65.81	19.40	53	67.43	17.95	52	65.50	17.33
SECONDARY OUTCOMES															
Marital satisfaction															
MMQ marital	69	12.18	8.65	62	11.94	8.26	55	11.85	10.41	53	10.69	9.92		n.a.*	
Sexual relationship satisfaction															
MMQ sexual	69	20.15	9.74	62	18.34	10.59	55	16.02	11.16	53	16.83	11.78		n.a.*	
Marital general life satisfaction															
MMQ general life	69	8.51	5.38	62	8.42	5.38	55	7.84	5.92	53	7.49	4.60		n.a.*	

Note. CBT = cognitive behavioral therapy; IIEF = International Index of Erectile Function; MMQ = Maudsley Marital Questionnaire; PAIR = Personal Assessment of Intimacy in Relationships Inventory; SD = standard deviation.
†T0 = baseline; T1 = mid-treatment; T2 = post-treatment; T3 = 3 month follow-up, T4 = 9 month follow-up.
* n.a. = not applicable, secondary outcome measures were not assessed at T4.

The outcomes of the per-protocol analyses were similar to the intention-to-treat analyses, except for erectile functioning (improvement during P1 (p_{P1} = .028) and decrease during P2 (p_{P2} = .006)), orgasmic functioning (improvement during P1 (p_{P1} = .017) and maintenance during P2 (p_{P2} = .056)) and sexual desire (stable during P1 (p_{P1} = .180) and decrease during P2 (p_{P2} = .006)).

Partner's use of the online program and overall sexual functioning

The results of the growth curve model indicated that partners who logged into the program did not report a larger improvement during the CBT or a more sustained improvement during follow-up in overall sexual functioning than partners who did not log in. This was also reflected in the IIEF total scores of these two partner subgroups (data not shown in tabular form). In this analysis, the effects of time (linear and quadratic) on overall sexual functioning were similar to those observed in the intention-to-treat analysis.

DISCUSSION

The results of the intention-to-treat analyses indicate that the partners' overall sexual functioning, erectile functioning, orgasmic functioning, intercourse satisfaction, overall sexual satisfaction, sexual relationship intimacy, and sexual relationship satisfaction improved during the Internet-based CBT. However, only the improvement in the partners' overall sexual satisfaction, sexual relationship intimacy, and sexual relationship satisfaction were maintained during a three- to nine-month follow-up. No significant changes over time were observed for sexual desire or any of the other areas of relationship intimacy or relationship satisfaction. The per-protocol analyses resulted in similar conclusions regarding the long-term effects of the CBT. We would note that the sustained effect on orgasmic functioning detected in the per-protocol analysis was marginal, as the deterioration during follow-up was borderline non-significant (p_{P2} = .056). Partners who logged into the program themselves did not report a larger improvement or a more sustained effect during follow-up in sexual functioning than partners who did not log in.

As we had no control group, we cannot assert with certainty that the changes in sexual health observed in the partners are attributable to the CBT. However, as we have reported previously, the results of our RCT indicated that the Internet-based CBT significantly improved the BC survivors' sexual functioning[12,13]. Since the partners of the BC survivors were indirectly exposed to the intervention, it seems likely that the partners' improvements in sexual health are a result of the CBT program.

The intervention did, however, appear to have more sustained, long-term effects on the BC survivors as compared to their partners. The BC survivors reported sustained improvements in various sexual functioning domains[13], while the partners reported a long-term

improvement only in overall sexual satisfaction. This difference in effect is not entirely unexpected in that the Internet-based CBT specifically addressed the sexual functioning of the BC survivors. This may have resulted in both members of the couple acquiring skills that benefit the women's long-term sexual functioning, but not that of the partner.

The fact that some of the IIEF subscale-scores depend on having had intercourse might also explain the lack of long-term improvement in most areas of the partners' sexual functioning. The CBT may have encouraged couples to engage in intercourse, and with the end of therapy and the loss of therapeutic support, intercourse frequency may have decreased. This is supported by the finding that 57.8% of the partners reported having intercourse at baseline, as compared to 77.3% and 54.5% at immediate post-CBT and nine-month follow-up, respectively. The fact that the partners did report a sustained improvement in overall sexual satisfaction, a subscale that is not dependent on intercourse, further supports this interpretation of the results. We also suspect that, because the FSFI is less focused on intercourse than the IIEF is, we were able to detect sustained positive effects of the intervention on the BC survivors' sexual health, but not on that of their partners. The focus of the IIEF on intercourse reflects the enduring idea that heterosexual sexuality revolves primarily around vaginal penetration[30].

While the partners' sexual functioning improved during the Internet-based CBT, their IIEF scores at immediate post-CBT were lower than those of general population peers, although higher than those of men with erectile dysfunction (ED)[19]. The overall sexual satisfaction scores of the partners were, despite the sustained positive effect of the CBT on this outcome, still closer to those of an ED-population. These findings suggest that BC and its treatment affect not only the sexual functioning of BC survivors, but also that of their male partners.

Our study had several limitations that should be noted. First, we could not compare our partner sample to a control group. Both we and the institutional review board considered it to be ethically unacceptable to request partners of women in the control group – who did not receive the CBT at that time – to complete assessments, especially since the initial invitation for study participation was addressed to the BC survivors. We did, however, compare the sexual health of the partner sample with external control groups[19]. Second, in order to reduce respondent burden and increase response rates, we did not assess the secondary outcomes at the nine-month post-CBT point. This necessitated use of different statistical methods for the analysis of the secondary outcomes. Third, it might be that only highly motivated partners agreed to complete study questionnaires, which may have introduced bias. Fourth, we had only one variable available concerning the partner's use of the Internet-based intervention. We would recommend that future trials collect more detailed information about the partner's involvement in and adherence to such a program (e.g., frequency and duration of log-ins and number of messages sent). Finally, the loss to

follow-up during the course of the study was not at random. However, we adjusted for drop-out patterns in the analyses and performed additional per-protocol analyses.

Our study also had a number of strengths, including the collection of data derived directly from the partners of patients undergoing sex therapy, the availability of several postintervention follow-up assessments, and the assessment of both sexual functioning and relationship satisfaction.

Our results suggest that the positive effects of Internet-based CBT targeting the sexual functioning of BC survivors also positively affect the partner's overall sexual satisfaction and sexual relationship satisfaction. The results of this observational study should be confirmed in an RCT setting. Another subsequent step would be to investigate which elements of the CBT or combination of modules contribute most to the efficacy of the intervention in BC survivors as well as in their partners. We recommend expanding the content of Internet-based sex therapy for women who have been treated for BC to include more tailored information and interventions for the partners. Topics to be incorporated into future programs could include dealing with fear of harming the woman by initiating sex, finding time for intimacy with the pressures of life in general and life post-BC, the changing role from caregiver to (sexual) partner, coping as a couple with changes in erotic sensations, coping as a partner with the woman's vulvovaginal atrophy and sexual pain and arousal problems, and renegotiating intimacy and expanding the range of sexual activities. A future program could also include weekly, recurring communication exercises to further stimulate communication about sexuality. Such a partner-tailored program could provide partners with tools to not only facilitate improvement in their spouse's sexual functioning, but in their own sexual functioning as well.

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General discussion

8

In the previous chapters we reported on the outcomes of a randomized controlled trial (RCT) of Internet-based cognitive behavioral therapy (CBT) in breast cancer survivors with a sexual dysfunction according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV[1]). We described patient-related and clinical factors associated with the women's DSM-IV sexual dysfunctions and their sexual functioning and distress, and the association between the sexual functioning of breast cancer survivors and their partners. We reported on the short- and long-term efficacy of the Internet-based CBT program in improving the sexual functioning of the women as well as that of their partners. We not only evaluated changes in the women's sexual functioning, but also in their level of sexual distress, relationship intimacy, marital functioning, body image, menopausal symptoms, psychological distress and health-related quality of life (HRQL). We also investigated predictors of a successful outcome of the therapy in terms of the breast cancer survivors' sexual functioning and distress levels. This chapter discusses the study results, methodological considerations and implications for further research.

MAIN FINDINGS

Although many women experience sexual problems after the treatment of breast cancer (BC)[2,3], little is known about BC survivors with a diagnosis of sexual dysfunction according to the criteria of the DSM-IV[1]. The baseline data that were collected as part of our RCT provide insight into the sexual functioning of this specific group of women. The most prevalent sexual dysfunctions for which the women in our sample received a diagnosis were hypoactive sexual desire disorder (83%), sexual arousal disorder (40%) and dyspareunia (33%) (**Chapter 3**). Women who had been treated with endocrine therapy were more often diagnosed with hypoactive sexual desire disorder (HSDD), and women treated with immunotherapy more often with dyspareunia. In line with research in the general population[4], older age was associated with less sexual distress.

Not only the BC survivors' sexual functioning, but also that of their partners was affected, which was reflected in the large proportion (55%) of the male partners that reported moderate or severe erectile dysfunction (**Chapter 3**). This finding is consistent with findings of previous studies[5,6], and underscores that it is important for health care professionals to involve both partners in the discussion about sexuality after BC, and especially - if applicable - in subsequent sex therapy. The effect of the women's BC treatment on the partner was also reflected in the finding that partners of women who had undergone breast reconstruction reported better orgasmic and overall sexual functioning than partners of women who had received breast-conserving therapy. Although both the BC survivors and their partners reported low levels of sexual functioning, we identified few

correlations between the self-reported sexual functioning of the women and that of their partners.

The Internet-based CBT program improved women's overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication, sexual pleasure, and resulted in less discomfort during sex (i.e., vaginal dryness and penetration-related pain) and less sexual distress (**Chapter 4**). Women also reported an improved body image. No changes were observed at post-CBT for orgasmic functioning, sexual satisfaction, frequency of sexual activity, relationship intimacy, marital functioning, menopausal symptoms, psychological distress, or health-related quality of life. During the nine-month follow-up period, all improvements were maintained, except for sexual pleasure, which decreased – although not to baseline levels. Body image improved even further during follow-up (**Chapter 5**).

An evaluation of the predictors of therapy success indicated that better post-CBT sexual functioning was associated with better baseline female sexual functioning, better baseline sexual functioning of the partner and higher therapy compliance. Predictors of lower post-CBT sexual distress included lower baseline sexual distress, better baseline female sexual functioning, higher baseline relationship satisfaction of the partner and higher therapy compliance (**Chapter 6**). Therapy compliance, in turn, was predicted by the active involvement of the partner in therapy and a better therapeutic relationship. The baseline levels of sexual functioning and distress were, however, not predictive of the effectiveness of the Internet-based CBT; they were only predictive of the level of sexual functioning and distress over time (e.g., women with better baseline sexual functioning also had better post-CBT sexual functioning). The specific components of BC treatment were not predictive of post-intervention sexual functioning. The findings suggest that any BC survivor, regardless of her baseline level of sexual functioning or distress or her specific BC treatment, may benefit from Internet-based CBT for sexual dysfunction. We recommended that, to enhance compliance with and the effectiveness of the CBT program, particular attention be paid to the therapeutic relationship and to the involvement of the partner in therapy.

The Internet-based CBT program had a sustained, positive effect on the partners' overall sexual satisfaction, sexual intimacy and sexual relationship satisfaction (**Chapter 7**). Although the partners' overall sexual functioning, orgasmic functioning and intercourse satisfaction improved during the Internet-based CBT, these effects were not maintained after a nine-month follow-up period.

BC treatment and sexual functioning

To our knowledge, our study is the first to evaluate the association between specific BC treatment features and specific DSM-IV sexual dysfunctions (**Chapter 3**). The finding that endocrine therapy was associated with HSDD is consistent with previous research that has shown that endocrine therapy negatively affects sexual functioning[7,8], but also suggests that endocrine treatment is a specific risk factor for the development of HSDD. The

negative influence of endocrine treatment on the effect and production of estrogens and androgens might be an explanation for this association, as a decrease in sex steroid hormones is one of the factors in the multifactorial etiology of decreased sexual desire[9]. The underlying mechanism for the association between endocrine treatment and this specific DSM-IV sexual dysfunction warrants further research.

The association between immunotherapy and dyspareunia might be explained by the potential relationship between immunotherapy and menopausal symptoms, including vaginal dryness, which was reported in a previous study[10]. However, another study did not observe an increased likelihood of amenorrhea in patients receiving trastuzumab[11]. As both studies included a small number of patients treated with immunotherapy, more research into the relationship between immunotherapy and menopausal symptoms is required.

Association between BC survivors' and their partners' sexual functioning

We detected fewer correlations between the sexual functioning of BC survivors and their partners (**Chapter 3**) than reported by studies in a non-clinical sample[12] and in a prostate cancer sample[13], in which most areas of the couples' sexual functioning were found to be correlated, albeit only moderately so in the non-clinical sample (i.e., ranging from r = .08 to .46)[12]. This might be explained, at least in part, by differences between male and female sexual functioning, such as men reporting higher sexual desire than women[14], the gender differences in the degree of concordance between the perception of genital response and actual genital sexual arousal[15], and differences in orgasm frequency[16,17]. The correlations reported by Badr et al.[13] were stronger (r = .30-.80). It seems, however, that Badr et al.[13] did not exclude couples from the analysis that were sexually inactive. This may have influenced the findings, as both questionnaires used in the analysis assign a score of zero to the response option 'no sexual activity'. When sexually inactive couples are included in the correlation analysis and both partners select this option, this may increase the possibility of finding a (larger) correlation.

Partners of women who underwent breast reconstruction (BR) reported better orgasmic functioning and overall sexual functioning than partners of women who had undergone breast-conserving treatment (BCT) (**Chapter 3**). A possible explanation could be that a BR might result in a better body image than does BCT, with subsequent positive effects on the woman's as well as on her partner's sexual functioning. However, we did not observe a significant association between surgical procedure and women's body image. Another explanation might be that male partners experience a reconstructed breast as more sexually attractive than a conserved breast, resulting in higher levels of overall sexual functioning and orgasmic functioning.

Efficacy of the intervention

Breast cancer survivors

We observed improvements in multiple areas of BC survivors' sexual functioning after undergoing Internet-based CBT (**Chapter 4** and **5**). This was not unexpected, as the majority of women were diagnosed with two sexual dysfunctions (**Chapter 3** and **4**) and thus there was ample room for improvement in several areas of sexual functioning. This finding is in line with research demonstrating that many sexually dysfunctional women are diagnosed with multiple sexual dysfunctions[18]. Our findings regarding the efficacy of the Internet-based CBT are similar to those of a previous study of a 10-week Internet-based CBT program for sexual dysfunction in women in the general population[19]. In this latter study, sexually dysfunctional women reported improved sexual and relationship functioning immediately following CBT, as well as 3 months post-CBT. We would point out that the post-treatment level of sexual functioning of our study sample was lower than that of women in the trial of Jones and McCabe[19]. This might suggest that our intervention was less effective in improving sexual functioning. However, this difference might be explained, in part, by the fact that we included BC survivors who had a DSM-IV diagnosis of sexual dysfunction, while the recruitment of women to the trial of Jones and McCabe[19] was based on self-reported sexual problems. Another possible explanation is that, for their analyses of the effect of the CBT program, Jones and McCabe[19] included only the women who indicated that they were sexually active at baseline. In our opinion, this approach limits the generalizability of the results, as only the better functioning subgroup of the study sample is evaluated. The difference in the baseline and post-CBT FSFI scores between the two studies could also be indicative of the extent to which the sexual functioning of BC survivors is affected by BC diagnosis and treatment. This idea is supported by the fact that most baseline FSFI scores of our BC survivors were lower (indicating a lower level of sexual functioning) than those of a group of Dutch women with sexual problems who sought professional help[20]. Interestingly, the post-treatment sexual functioning of the women in the trial of Jones and McCabe[19] was still lower than that of healthy women[20], suggesting that it is challenging for women with sexual problems to achieve a level of sexual functioning that is equal to that of healthy women, even with the help of therapy. This is possibly even more so for BC survivors, given the effects of BC treatment on both the emotional and physical aspects of sexual functioning. This suggests that the aim of interventions targeting the sexual functioning of BC survivors should not necessarily be to return to the levels of sexual functioning experienced before the diagnosis of cancer, but rather to support women in adjusting to their altered body and sexuality after BC.

Although the Internet-based CBT realized long-term improvement in the sexual functioning of BC survivors, some loss of treatment gains (although not statistically significant) was observed in most areas during follow-up (**Chapter 5**). A similar loss of treatment gains

during follow-up was reported by Jones and McCabe[19]. It may be that, after completion of the CBT, the loss of therapist encouragement to engage in sex may result in some loss of effect. The recent developments in eHealth may offer possibilities for post-therapy support, for example, by integrating a smartphone application into the therapy program that provides continuing support, that can be used to reinforce the lessons learned in therapy, to provide additional homework exercises, and to strengthen the relapse prevention elements that are often part of such CBT programs.

In our trial, we did not observe any significant improvement over time in women's sexual satisfaction (**Chapter 4** and **5**). This is surprising in that the mean baseline scores of the FSFI satisfaction subscale indicated that there was ample room for improvement in this area. A possible explanation for the lack of improvement might be that the items in this subscale primarily assess a woman's satisfaction with her sexual relationship with her partner. Consequently, a woman's response to these questions might not only be a reflection of her own sexual satisfaction, but possibly also of her assumptions about the sexual satisfaction of her partner[21], something that women may feel uncertain about. Also, it is important to note that most women in our sample (87.6%) developed sexual problems during or after the BC treatment, reflecting a rather abrupt change in sexual health. While many women's sexual functioning improved as a result of therapy, it may not have returned to pre-BC levels (something that we were not able to measure). Yet, women may have rated their satisfaction with their sex lives in relation to their pre-BC situation, rather than to their situation just prior to entering CBT program.

We would note that, as a result of the correction for multiple testing (i.e., use of a more stringent *p* value, set at 0.01 rather than 0.05), a number of outcomes were labeled as being statistically non-significant, while in fact there appeared to be a trend toward improvement from baseline to immediate post-intervention. This was the case for orgasmic functioning, frequency of sexual activity, social intimacy, recreational intimacy and sexual relationship satisfaction (**Chapter 4**). The fact that orgasmic functioning improved to a lesser extent than sexual desire and arousal might be explained by the fact that, although sexual desire and arousal are a prerequisite to achieving an orgasm, an improvement in desire and/or arousal does not necessarily result in an equally large improvement in orgasmic functioning. The fact that, in general, many women experience problems in achieving an orgasm[22], most likely as a result of insufficient clitoral stimulation during sexual activity[23], might be an additional explanation for the smaller improvement observed in orgasmic functioning. Expanding our treatment program with specific communication exercises to coach women in verbalizing their sexual preferences to their partner, especially with regard to clitoral stimulation, may therefore have improved the women's orgasmic functioning to a greater extent.

The Internet-based CBT realized a long-term improvement in vaginal lubrication during sexual activity (**Chapter 4** and **5**). This finding is somewhat unexpected in that postmeno-

pausal women often experience vaginal dryness[24], and that BC treatment (particularly chemotherapy and endocrine therapy) induces menopause in premenopausal women, and can exacerbate menopausal symptoms, including vaginal dryness and atrophy, in women who were already post-menopausal[25]. Healthy postmenopausal women who experience vaginal dryness can use hormone replacement therapy (HRT)[26,27]. However, the use of HRT is contraindicated in BC survivors[28], as approximately 80% of breast cancers are estrogen/progesterone positive[29]. The fact that our study sample, despite the inability to use hormone supplementation, reported improved vaginal lubrication after Internet-based CBT is in line with previous research[30] demonstrating that, although postmenopausal women experience more vaginal dryness than premenopausal women in a non-aroused state, this difference is no longer present with sufficient erotic stimulation. Vaginal dryness and dyspareunia in postmenopausal women are therefore probably not the result of a physical inability to self-lubricate, but rather seem to reflect a problem with sexual arousal[30]. The fact that women in our study reported a sustained improvement in vaginal lubrication during sexual activity may indicate that the Internet-based CBT was successful in teaching women and their partners effective ways to achieve sexual stimulation.

Women in the CBT group reported a decrease in discomfort during sex (Sexual Activity Questionnaire (SAQ) discomfort scale), but no change in levels of pain during sex (FSFI pain subscale) (**Chapter 4**). Whereas the FSFI subscale assesses the frequency and degree of pain in the context of vaginal penetration, the SAQ subscale also includes the degree of vaginal dryness during sexual activity; an aspect of sexual functioning that improved as a result of the Internet-based CBT. This might explain these seemingly contradictory findings. Another explanation might be that, despite improvement in vaginal lubrication during sex, the degree of vaginal atrophy remained unchanged due to decreased estrogen levels, causing pain during vaginal penetration.

Partners

Although the partners of women in the intervention group reported a sustained improvement in overall sexual satisfaction, sexual intimacy and sexual relationship satisfaction, our intervention did not realize a sustained improvement in other areas of the partners' sexual functioning. As indicated previously in **Chapter 7**, this finding was not surprising, as the intervention focused mainly on the sexual functioning of the BC survivors. However, the fact that the scores on the International Index of Erectile Function (IIEF) of our partner sample were significantly lower than those of a healthy population[31] suggests that there was room from improvement in the partners' sexual functioning. It may therefore be important to not only encourage the partners to participate in therapy, but to consider it as an integral element of the therapy as is often the case in face-to-face sex therapy, in which the partner is present during the therapy sessions. More active involvement of the partner enables therapists to obtain a better picture of the partner's functioning and to use

partner-specific interventions, if necessary. Our CBT program did contain a module that specifically targeted the sexual functioning of male partners, including psycho-education and exercises. However, the content of this module was apparently not sufficient to realize sustained improvements. Future programs should therefore include more psycho-educational information and exercises targeted at male sexual dysfunctions.

Greater partner involvement could also facilitate the therapist in carrying out a more thorough evaluation of potential relationship patterns underlying the sexual problems, since couples with sexual problems often have more dysfunctional conflict-resolution styles than healthy couples; this can be either a cause or an effect of sexual problems[32]. Although an exclusion criterion of our study was the presence of severe relationship problems, this does not necessarily mean that there were no dysfunctional dyadic coping or communication styles that may have negatively affected the couple's sexual functioning.

METHODOLOGICAL CONSIDERATIONS

Our study had a number of methodological strengths, including the randomized controlled design, a large sample size, multicenter participation, the relatively long follow-up period of nine months, and the collection of data from partners of the BC survivors. However, the study also has some methodological limitations relating to the content and form of the CBT, the design of the study, the nature and quality of the assessments and to issues of cost-effectiveness.

Form and content of the CBT

Innovations in eHealth

Internet-based interventions have been demonstrated to be a feasible and effective treatment approach for a wide range of psychological disorders[33,34]. Since 2012, the year in which we conducted the pilot study that preceded our RCT, many innovations have taken place in the field of eHealth, with online programs becoming more interactive (e.g., through the use of animation, videos and feedback via smartphone applications or wearables). Conducting a clinical trial is a time-consuming activity. It is not uncommon for a trial to span a period of 7 years from applying for research funding to publishing the results[35]. Thus it is almost inevitable that new approaches and technologies emerge during the course of a clinical trial that would have been useful if available earlier on.

In the light of the current state of the art of eHealth, our intervention is in need of significant revision, as it consists primarily of written text supported by still images. A revised version of the program could include videos in which sexologists provide psycho-education and explain accompanying exercises, or psycho-educational animation videos about, for

example, genital anatomy and stimulation. Audio-guided sensate focus or relaxation exercises could be incorporated into the program, and availability and use could be enhanced by providing the exercises via a smartphone application. A smartphone application also enables the use of persuasive technology, which can be described as 'computerized software or information systems designed to reinforce, change or shape attitudes or behaviors or both without using coercion or deception'[36]. Fleming et al.[37] recommend the use of persuasive technology in Internet interventions, such as notifications via smartphone or email, continued feedback regarding a patient's therapy progress, use of a scheduling application for completion of next week's intervention with a reminder service, and messages throughout the program regarding the benefits of following the program on a regular basis[38]. Furthermore, Fleming et al.[37] propose the use of serious gaming in eHealth interventions for the purpose of education and improving therapy adherence. An example of the use of serious gaming in sex therapy can be found in a recently developed online psychosexual educational program[39] that uses "touchable" videos of virtual vulvas. The videos enable users of the program to familiarize themselves with the different techniques for clitoral stimulation that are explained in the program. In the development of the program, 1055 women were queried about location, pressure, shapes and style of genital touch[40], resulting in 12 commonly applied techniques that formed the basis for the episodes, each focusing on a different masturbation technique. In addition to providing the opportunity to practice the techniques, the feedback of the virtual women serves as an example for giving feedback to the partner during genital stimulation. The program also includes videos in which women describe their experiences with sexual pleasure and demonstrate the techniques used in masturbation. The efficacy of such serious gaming techniques and other innovations introduced by smartphone applications seem promising[37], and should be evaluated in an RCT setting.

A challenge for future trials is how to use continuous enhancement of an intervention during the course of the study[41] in order to keep up with technological improvements. Rapid development and testing of a new technology can be achieved by constant refining of the product based on the repeated feedback of end-users, in close collaboration between researchers, designers, software developers and end-users[37]. When the prototype has been sufficiently evaluated and improved, a larger RCT can be performed. Despite the lack of such an iterative process in our trial and the need for a revision, we would argue that our trial can be viewed as a "proof of principle" and provides a foundation for the future development of Internet-based psychosexual counseling programs for BC survivors and their partners.

Third wave CBTs

Another consideration in evaluating the content of the CBT program that we evaluated pertains to the emergence of 'third wave' CBTs, such as Mindfulness-based cognitive

therapy and Acceptance and Commitment Therapy (ACT)[42]. Our intervention was based primarily on the principles of second wave CBT, i.e., focusing on dysfunctional cognitions (e.g., thoughts, interpretations, attributions) and their influence on emotions and behavior. In this view, psychopathology is seen as a result of biased information processing, characterized by maladaptive beliefs and automatic thoughts, and therapy attempts to modify these cognitive processes[42]. In contrast, third wave CBTs do not attempt to change or replace the cognitions, but rather aim to teach the patient to become aware of distressing cognitions, to realize that they are 'just thoughts' and not necessarily an accurate representation of reality, and to prevent an automatic response of rumination[42]. There is thus a focus on the realization that the metacognitive processes are inaccurate - and therefore not the cognitions, but rather the metacognition or attitude towards these cognitions need to be changed[43]. In sex therapy, mindfulness-based exercises can increase the awareness of pleasurable sensations[44], increase genital-subjective sexual arousal concordance[45] and help patients to become less judgmental about the quality of the sensations or to not perceive them as below standard; an attitude-shift that might be particularly suitable for formerly sexually healthy BC patients who have to cope with an altered sexuality.

The effectiveness of Mindfulness-based (cognitive) therapy for female sexual dysfunctions has been demonstrated in the general population[46-48] and in gynaecological cancer survivors[49,50]. The effectiveness of ACT in the treatment of depression and anxiety has been established[51-55], but research into its effectiveness for sexual dysfunctions is still limited. First studies are being conducted, including a study evaluating the use of the theoretical framework of ACT to improve adherence to treatment for erectile dysfunction in prostate cancer survivors[56]. In BC survivors, studies evaluating ACT and Mindfulness-based therapy for sexual problems are limited, but results from other trials seem promising and encourage the inclusion of third-wave CBT in future sex therapies for the BC population.

Face-to-face and self-management interventions

For reasons described in **Chapter 4**, we compared our intervention group to a waiting-list control group only, and not to a group receiving face-to-face therapy. Research has shown that Internet-based CBT is as effective as face-to-face therapy for a range of psychological problems[57]. We expected that this would also be the case for online sex therapy, especially considering aspects of online therapy such as anonymity and accessibility, which may be particularly attractive in the treatment of sexual problems. Nevertheless, a comparison of Internet-based and face-to-face sex therapy for BC survivors with a DSM-IV sexual dysfunction, preferably including a cost-effectiveness analysis, could be useful.

It might also be valuable to develop and evaluate an Internet-based sex therapy program that is suitable for BC survivors experiencing less severe sexual problems. The intervention described in this thesis involved an intensive therapy program. Such a program may be appropriate for the treatment of DSM-based sexual dysfunctions, but less so for milder

sexual problems. The prevalence rates of sexual problems in BC survivors are between 45% and 77%[2,3]. However, only a small percentage of these women meets criteria for a DSM-diagnosis of sexual dysfunction and is in need of intensive therapy such as the one evaluated in our study. A 'light' version of our Internet-based therapy could be suitable for a larger group of women, and has the potential to be cost-effective. We therefore intend to develop and test, in an RCT context, a (guided) self-management version of our Internet-based CBT program targeting BC survivors experiencing milder sexual problems.

To date, the majority of self-management interventions have been developed for depression and anxiety and the available evidence indicates that they represent an effective treatment strategy[55,58,59]. First studies have demonstrated the feasibility of self-management interventions in improving the sexual functioning of cancer survivors[60,61]. In an unguided self-management program, participants complete a treatment protocol independently, without support of a therapist. Such a program consists primarily of psycho-educational information and instructions for exercises; minimal interventions that are effective in the management of sexual changes after cancer[62]. In guided self-management, a counselor is available, typically via email or telephone, to provide support in working through the treatment program. Although research has indicated that guided self-management programs tend to be more effective than unguided programs[63,64], we intend to test both in a future RCT, including a cost-effectiveness evaluation.

Potential contamination

Although only the women in the intervention group of our trial received the therapist-guided Internet-based CBT program, being invited to participate in a large RCT focusing on sexual functioning after treatment of BC and having an intake interview with a psychologist/sexologist may have influenced the sexual functioning of women in the control group. The 'permission for the sexual problems to exist' provided by the study invitation and intake interview, and the limited information that was given in the patient information brochure and the booklet '80 vragen over kanker en seksualiteit'[65], may have encouraged women in the control group to search for solutions for their sexual problems and/or to discuss their sexual changes with their partner. This may explain the slight improvement in sexual functioning and decrease of sexual distress from baseline to post-CBT in the control group. These 'minimal interventions' can be viewed as the first two steps of the PLISSIT model (i.e., Permission, Limited Information, Specific Suggestions, Intensive Therapy)[66]. The idea that these minimal interventions may have slightly improved the sexual functioning of the control group is consistent with previous research demonstrating that providing psycho-education can improve the sexual functioning of gynaecological patients[50] and cancer patients' awareness of sexuality, communication with the partner about sex, and management of sexual changes[62]. This idea further supports the need for the development of a 'light' version of our Internet-based CBT program.

Assessment of sexual functioning

A challenge in clinical trials evaluating the level of sexual functioning is how to handle sexual inactivity when assessing the level of sexual functioning. Several items of both the FSFI and IIEF include a response option 'did not attempt intercourse', which is assigned a score of zero. This shifts the scores towards the sexually dysfunctional end of the scale[67]. This approach is used by most patient-reported outcome measures assessing sexual functioning. In response to this problem, some researchers choose, when evaluating the efficacy of sex therapy, to exclude all participants from their analyses who indicate that they are not sexually active. This approach may, however, affect the generalizability of the results, as it leads to a selection of the better functioning participants. We therefore chose to include sexually inactive couples in our analyses of the efficacy of our CBT program. Moreover, as we only included women with a DSM-IV sexual dysfunction, it seems likely that couple's sexual inactivity was a reflection of this DSM-diagnosis and thus of low levels of sexual functioning.

Another disadvantage of the IIEF is that many of the items focus on sexual intercourse, i.e., penile penetration of the vagina. This reflects the traditional view of heterosexual sex as being synonymous with coitus; also known as the 'coital imperative'[68]. The coital imperative conveys the message that non-coital sexual activities are either meant to precede coitus, to be optional, or to be a substitute when coitus is not possible for some reason[68]. The IIEF also includes an item querying about the frequency of coitus, with higher scores reflecting higher frequency. This assumes that more frequent intercourse reflects higher intercourse satisfaction and better overall sexual functioning. We would argue that using frequency of sexual activity as an indication of the quality of sexual functioning is a flawed approach. There are data that indicate that more frequent sex is not necessarily reflective of, and certainly not synonymous with, increased relationship satisfaction and satisfaction with life[69] or happiness[70]. Rather, aspects such as sexual desire, arousal and pleasure are considered to be better indicators of the quality of sexual functioning. Similar issues are present with the FSFI, as many items assess the degree of lubrication and ease of vaginal penetration[71]. We would recommend that future questionnaires assessing sexual functioning should broaden their focus to include masturbation, oral and manual stimulation and sexual pleasure. Additionally, in questionnaires assessing female sexual functioning, clitoral stimulation should receive more attention, as only 25% of women experience orgasm through vaginal penetration alone[72].

Not only do these features of the questionnaires raise questions about their content validity, they may also affect the conclusions of clinical trials of sex therapy. As indicated in **Chapter 7**, the differential effects of the Internet-based CBT on the sexual functioning of BC survivors and their partners observed in our study (**Chapter 4**, **5** and **7**) may, in part, be explained by the focus of the IIEF on coital activity. This may have limited our ability to detect sustained positive effects of the CBT program on male sexual functioning;

something that was less of an issue in assessing the impact of the program on the BC survivors, as the FSFI places more emphasis on sexual activity, in general.

Assessments and follow-up

In our trial, we did not ask women in the control group to complete the 3- and 9-month follow-up assessments. Thus we were unable to compare the long-term changes in the intervention group with those of the (untreated) control group. We also did not assess the sexual functioning, relationship intimacy and marital functioning of the partners of women in the control group, resulting in an observational study of only the partners of the BC survivors who had been exposed to the CBT program. We believe that these limitations were inevitable, given both our and the institutional review board's position that it would be ethically inappropriate to withhold offering BC survivors who had initially been assigned to the waiting list control group the opportunity to follow the CBT program until the longer term follow-up had been completed. Similarly it was not considered appropriate to ask the partners of those randomly assigned to the control group to complete an extensive battery of questionnaires, given that they were neither invited to nor did they participate in the trial. Despite these design limitations, we believe that the long-term follow-up data on the intervention group and on their partners provide useful insights that complement the core of the clinical trial.

Drop-out and predictors of therapy success

Sixty-two percent of the intervention group completed the Internet-based CBT as planned (**Chapter 4**). This percentage is similar to completion rates observed in other trials of Internet-based interventions for psychological disorders, with an average drop-out rate of 31%[73]. We did not collect extensive data on the degree of adherence (e.g., number of completed interventions, log-in time, number of emails). Such data could have provided more insight into the factors that were predictive of therapy adherence. However, the optimal approach for measuring adherence in Internet-based therapies has not yet been established and further research is needed to understand the role of adherence on treatment outcomes[38].

In our trial, we were also unable to investigate which specific elements of the online CBT program were more or less effective (**Chapter 6**). The CBT program was evaluated as a "package deal". Future trials of eHealth interventions for sexual problems are needed to identify those features of the interventions that contribute most to therapy success, and those that are less salient.

The majority of the variables that we included as potential predictors of therapy success were similar to those used in the evaluation of face-to-face sex therapy, and our outcomes were consistent with the predictors of therapy success found in face-to-face treatments in the general population[74-76] (**Chapter 6**). Research into the predictors of therapy response

and adherence to eHealth interventions seems promising, as log-data of eHealth programs can offer objective insight into the mechanisms that contribute to the effect of the intervention. So far, research has mainly focused on log-data such as number of completed modules, time spent and number of log-ins[77-79]. Although this information is valuable, it assumes a dose-response relationship, and it does not reflect if the program fits well with the needs of the user or how the program is used (e.g., spending more time online does not necessarily reflect optimal or efficient use of the program)[80]. Future trials should evaluate how the use of different components of the treatment program or technology, or combinations of components, contribute to the efficacy of the treatment program[80-82].

Cost-effectiveness

The type of extensive sex therapy evaluated in our trial is not currently reimbursed by Dutch health insurance. As of 2014, psychosexual counseling is only reimbursed for patients with a DSM-diagnosis of paraphilia, gender identity disorder, hypersexuality, sexual dysfunction caused by another psychological disorder (e.g., depressive disorder), or if the psychosexual counseling is offered in the context of a hospital-based medical DBC (Dutch: Diagnose Behandel Combinatie) for treatment by a gynaecologist or urologist. The financial support of The Netherlands Cancer Institute enabled us to finance the costs of the therapy, so that we could successfully complete the trial. However, consequently, further implementation of the intervention in its current form is not financially feasible.

In 2017, our study was selected for a project of the Dutch Cancer Society in which the costs and benefits of several interventions targeting the quality of life of cancer patients was evaluated in the context of a Social Business Case. The Social Business Case is a structured cost-benefit assessment used to evaluate the economic and social usefulness of an intervention[83]. The financial profit for society is evaluated by comparing the costs of the intervention with the potential social benefits. These benefits are estimated and quantified based on research, literature, assumptions, and advice of an expert group. With regard to cost savings for health insurers, it was estimated that our Internet-based CBT program would reduce patient visits to the general practitioner, the mental health counselor working in general practice offices (Dutch: Praktijkondersteuner Huisarts - Geestelijke Gezondheidszorg (POH-GGZ)) and the gynecologist[84]. For patients, the Internet-based therapy resulted in a reduction in travel expenses and parking costs. A comparison of the total costs of the intervention with the total expected cost savings resulted in an expected financial profit of €0.14 per invested euro, and thus an expected loss of €0.86. It is important to note that this type of budget impact analysis expresses the benefits of an intervention in monetary terms, and does not take into account improvements in the patients' quality of life. We would argue that this approach is less applicable to psychosocial interventions, as the benefits of these interventions are less well expressed in financial terms. It is also questionable as to whether it is reasonable to expect that such psychosocial interventions

should be expected to yield monetary profit for the larger community. Nevertheless, we recognize that the cost of our Internet-based CBT intervention, with sustained guidance by sex therapists via email, was high – €2,000 per patient. To be viable economically, less expensive models of Internet-based sex therapy need to be developed and tested.

IMPLICATIONS FOR FUTURE RESEARCH

To date, many studies have evaluated and demonstrated the effectiveness of CBT for a range of psychological problems, but less is known about the working mechanisms of CBT, i.e., which components are essential for a treatment program to be effective. A challenge in answering this question is the fact that CBT is a technically eclectic treatment including many components that might effectuate change[85]. Although an evaluation of the effect of different treatment components provides insight into which features of a therapy are effective, it leaves the question of *how* these changes occur unanswered[86]. The expansion of the range of CBTs with 'third wave' therapies, each with its own content and mechanisms of change, present additional challenges for researchers. Additionally, further research into the predictors and moderators of the success of (eHealth) interventions is warranted, to be able to select patients who will benefit most from the intervention or to tailor the content of an intervention to the needs of the individual patient.

To our knowledge, our study is the first to collect data directly from the partner him/herself during the course of CBT targeting the sexual dysfunction of one member of the couple. More research is needed to determine the optimal involvement of the partner in sex therapy after cancer treatment and the prerequisites to effectuate a sustained effect in the partner's sexual functioning.

Lastly, given the very rapid advances in the development of eHealth interventions and related technology, future trials are needed that enable continuous enhancement of the intervention during the course of the study[41]. Constructive Technology Assessment (CTA) can be used to investigate this dynamic process, as it enables a continuous evaluation of relevant clinical, economic, patient-related and organizational aspects in the development of a new technology[87]. CTA attempts to influence technological design and implementation with the aim of improving the effectiveness of the technology in clinical practice, and uses traditional social sciences techniques, such as process analysis, scenario analysis and various forms of cost(-effectiveness) analyses[87]. These analyses evaluate and anticipate potential barriers that may be encountered in clinical adoption and therefore facilitate the uptake of dynamic types of interventions, such as Internet-based therapies.

CONCLUSIONS

The sexual functioning of BC survivors as well as that of their partners is affected by the disease and its treatment. Our Internet-based CBT program realized long-term improvement in the sexual functioning, sexual distress and body image of BC survivors. Although partners did not report sustained positive effects of the intervention on sexual functioning, they did benefit in terms of overall sexual satisfaction, feelings of sexual intimacy and sexual relationship satisfaction. The involvement of the partner in treatment improved the women's therapy compliance, which subsequently increased the women's post-CBT sexual functioning and decreased post-CBT sexual distress. The combination of these latter two findings advocates for the involvement of both partners in therapy. Future Internet-based interventions should involve the partner to a greater extent, by building in to such programs modules specifically targeting male sexual dysfunction.

To ensure that the intervention is available to patients, it is important that health care professionals discuss the potential impact of treatment on sexuality with BC survivors, and that they query women and their partners about sexual functioning during follow-up. This will enable the health care professionals to select the patients in need of professional help, and will give BC patients "permission" to discuss their sexual problems.

More information is needed on the cost-effectiveness of Internet-based sex therapy programs for sexual dysfunction after BC. Since methods such as a Social Business Case evaluate the treatment effects in financial terms only, this type of cost-benefit analysis is less suitable for the evaluation of psychosocial interventions, which primarily effectuate change in quality of life. As such, a cost-effectiveness analysis, which also focuses on gains in terms of quality of life, for instance by evaluating the Quality Adjusted Life Years (QALYs), may be more appropriate for Internet-based sex therapy.

A potentially cost-effective alternative to the intervention evaluated in this thesis could be a self-management version of the CBT program. Another benefit of such a 'light' version of our program is that it could be offered to the many BC survivors who experience milder sexual problems after BC treatment. The intervention described in this thesis can be viewed as a proof of principle for the efficacy of Internet-based CBT for sexual dysfunctions in BC survivors.

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Summary and Samenvatting (summary in Dutch)

9

SUMMARY

As a result of improved detection and treatment of breast cancer (BC), survival rates have improved, resulting in more attention for quality of life-related topics in BC survivors, including sexual functioning. Sexual problems are a frequent, long-term consequence of the diagnosis and treatment of BC. Frequently occurring sexual problems in BC survivors include decreased sexual desire, decreased sexual arousal and vaginal lubrication, dyspareunia, and vaginal dryness and atrophy. Although the prevalence of sexual problems among BC survivors is high, not all of these women experience sexual problems that meet criteria for a diagnosis of sexual dysfunction according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). Women with a DSM-IV dysfunction experience severe sexual problems that cause significant distress and that warrant professional help. The trial described in this thesis included BC survivors with a diagnosis of sexual dysfunction according the criteria of the DSM-IV.

Chapter 1 introduces Internet-based cognitive behavioral therapy (CBT) as a promising treatment option for DSM-IV-based sexual dysfunctions in BC survivors. Although traditional treatment methods such as face-to-face CBT are effective in alleviating sexual dysfunctions, there is a discrepancy between the reported need for sexual health care and the actual uptake of such care by BC survivors. Internet-based CBT could be an alternative, especially considering aspects of online therapy such as anonymity and accessibility, which may be particularly attractive in the treatment of sexual problems and which might lower the barrier for BC survivors to seek professional help for their sexual problems. Therefore, we evaluated the efficacy of an Internet-based CBT program to improve the sexual functioning of BC survivors with a DSM-IV sexual dysfunction.

In this thesis, we posed the following research questions:

1. Which patient-related and clinical factors are associated with BC survivors' sexual functioning and sexual distress, and with the sexual functioning of their partners?
2. What is the short-term efficacy of Internet-based CBT in improving the sexual functioning, sexual distress and other psychosocial outcomes in BC survivors with a DSM-IV sexual dysfunction?
3. What is the long-term effect of Internet-based CBT on the sexual functioning, sexual distress and other psychosocial outcomes in BC survivors with a DSM-IV sexual dysfunction?
4. What are the predictors of post-CBT sexual functioning and sexual distress of BC survivors with a DSM-IV sexual dysfunction who received Internet-based CBT?
5. What is the effect of Internet-based CBT on the sexual functioning and relationship satisfaction of partners of BC survivors with a DSM-IV sexual dysfunction?

Chapter 2 describes the design of the randomized controlled trial (RCT) in which we evaluated the efficacy of Internet-based cognitive behavioral therapy (CBT) program for sexual dysfunctions in BC survivors. Primary outcomes included sexual functioning and relationship intimacy, and secondary outcomes included body image, marital functioning, menopausal symptoms, psychological distress and health-related quality of life (HRQL). We compared the Internet-based CBT program to a waiting-list control group. Briefly, the CBT consisted of 4-5 modules (selected out of a total of 10 modules by the psychologist/sexologist) that best suited the sexual problems of each participant. Each module contained several interventions, each of which comprised the following elements: an introduction, psycho-education, homework assignments, reports to the therapist and receiving feedback from the therapist. This resulted in a program of approximately 20 therapist-guided weekly sessions that had to be completed within 24 weeks. The contact between the therapist and participant took place via email and was asynchronous. Women were encouraged by their therapist to involve their partner in the treatment. However, participation of the partner was not mandatory. Outcome measures were assessed at baseline (T0), mid-CBT (T1), immediate post-CBT (T2), and at equivalent times in the control group. Women in the intervention group completed additional questionnaires at three (T3) and nine months (T4) follow-up. Women in the waiting-list control group were offered the CBT program after completion of the T2 assessment.

Chapter 3 describes the baseline data that were collected as part of our RCT and provides insight into the sexual functioning of BC survivors with a DSM-IV sexual dysfunction and their partners. The most frequently diagnosed sexual dysfunctions in our sample of BC survivors were hypoactive sexual desire disorder (83%), sexual arousal disorder (40%) and dyspareunia (33%). Women who had been treated with endocrine therapy were more often diagnosed with hypoactive sexual desire disorder (HSDD), and women treated with immunotherapy more often with dyspareunia. In line with research in the general population, older age was associated with less sexual distress. Not only the BC survivors' sexual functioning, but also that of their partners was affected, as was evident from the large proportion (55%) of the male partners that reported moderate or severe erectile dysfunction. The effect of the women's BC treatment on the partner was also reflected in the finding that partners of women who had undergone breast reconstruction reported better orgasmic and overall sexual functioning than partners of women who had received breast-conserving therapy. Both the BC survivors and their partners reported low levels of sexual functioning. We identified few correlations between the self-reported sexual functioning of the women and that of their partners. This might be explained, at least in part, by differences between male and female sexual functioning, such as men reporting higher sexual desire than women, the gender differences in the degree of concordance between the perception of genital response and actual genital sexual arousal, and dif-

ferences in orgasm frequency. Nevertheless, the findings suggests that it is important for health care professionals to involve both partners in the discussion about sexuality after BC, and especially - if applicable - in subsequent sex therapy.

Chapter 4 presents the results pertaining to the short-term efficacy of the Internet-based CBT program in improving BC survivors' sexual functioning, relationship intimacy, body image, marital functioning and HRQL, and in decreasing their menopausal symptoms and psychological distress. Compared to women in the waiting-list control group, women who received the Internet-based CBT reported a greater improvement in overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication and sexual pleasure, and a greater decrease in discomfort/pain during sex and sexual distress than women in the control group. Women in the intervention group also reported a larger improvement in body image compared with the control group. A clinically significant change in sexual functioning was observed in 63% of women who received the intervention, versus in 32% of women in the waiting-list control group, indicating that the odds of a clinically significant improvement for the intervention group were 3.66 times greater than those of the waiting-list control group. No significant effects were observed for menopausal symptoms, orgasmic function, sexual satisfaction, frequency of sexual activity, relationship intimacy, marital functioning, psychological distress or HRQL. This study demonstrates that Internet-based CBT has a positive effect on the sexual functioning and body image of BC survivors with a sexual dysfunction.

Chapter 5 describes the long-term effects of the Internet-based CBT program on sexual functioning, relationship intimacy, body image, marital functioning, menopausal symptoms, psychological distress and HRQL of BC survivors with a DSM-IV sexual dysfunction. Eighty-four women of the intervention group of the study were included in the analysis. The positive effects of the treatment program on overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication, discomfort/pain during sex, sexual distress and body image observed at the end of CBT were maintained during a three- to nine-month follow-up period. Body image improved even further after the completion of the CBT. Sexual pleasure was the only domain that, after an improvement during the Internet-based CBT, decreased significantly during the follow-up period. It did not, however, return to baseline levels. The loss of therapist encouragement to engage in sexual activity after completion of the CBT may have resulted in some loss of effect in this area. This is supported by the fact that a modest, although not statistically significant, decrease was observed in the other sexual function measures. The results indicate that the positive effects of the Internet-based CBT on most sexual functioning domains, sexual distress and body image of BC survivors with a DSM-IV sexual dysfunction are maintained well beyond the immediate post-treatment period.

Chapter 6 describes which factors were predictive of a successful outcome of the Internet-based CBT, and presents the participant's evaluation of the therapy program. Better post-CBT sexual functioning was associated with better sexual functioning of women and their partners at baseline and higher therapy compliance. Lower post-CBT sexual distress was associated with lower baseline sexual distress, better baseline female sexual functioning, higher baseline relationship satisfaction of the partner, and higher therapy compliance. Therapy compliance, in turn, was predicted by the active involvement of the partner in therapy and a better therapeutic relationship. This suggests that, although these two latter factors are not associated directly with therapy success, they do influence the success of the therapy indirectly via their association with compliance. The baseline levels of sexual functioning and distress were predictive of the level of sexual functioning and distress over time (e.g., women with better baseline sexual functioning also had better post-CBT sexual functioning), but not of the effectiveness of the Internet-based CBT. The specific components of BC treatment were also not predictive of post-intervention sexual functioning. These findings suggest that any BC survivor, regardless of her baseline level of sexual functioning or distress or her specific BC treatment, may benefit from Internet-based CBT for sexual dysfunction. Overall, the majority of women indicated that they were satisfied with the CBT. The fact that both the women and therapists were positive about the quality of the therapeutic relationship is important, because it shows that, even when therapy is provided via the Internet, a strong therapeutic bond can be established. We recommend that, to enhance compliance with the CBT program as well as the effectiveness of the program, particular attention be paid to the therapeutic relationship and to the involvement of the partner in therapy.

Chapter 7 reports on the longitudinal evaluation of the effect of the Internet-based CBT program on the sexual functioning, relationship intimacy and relationship satisfaction of 69 partners of BC survivors. The results indicated that the partners' overall sexual functioning, erectile functioning, orgasmic functioning, intercourse satisfaction, overall sexual satisfaction, sexual relationship intimacy and sexual relationship satisfaction improved during the Internet-based CBT. However, only the improvement in the partners' overall sexual satisfaction, sexual relationship intimacy and sexual relationship satisfaction were maintained during a nine-month follow-up. No significant changes over time were observed for sexual desire or any of the other areas of relationship intimacy or relationship satisfaction. The intervention thus appeared to have more sustained, long-term effects on the BC survivors as compared to their partners. This difference in effect is not entirely unexpected in that the Internet-based CBT specifically addressed the sexual functioning of the BC survivors. This may have resulted in both members of the couple acquiring skills that benefit the women's long-term sexual functioning, but not that of the partner. Because not only the sexual functioning of BC survivors, but also that of their male partners is affected by BC

and its treatment, we recommend expanding the content of Internet-based sex therapy for post-BC sexual dysfunctions to include more tailored information and interventions for the partners, in order to provide them with tools to not only facilitate improvement in their spouse's sexual functioning, but that of themselves as well.

Chapter 8 discusses the main findings of this thesis, including the methodological limitations relating to the content and form of the CBT, the design of the study, the nature and quality of the assessments, and issues of cost-effectiveness. Our Internet-based CBT program realized long-term improvement in the sexual functioning, sexual distress and body image of BC survivors. Although partners did not report sustained positive effects of the intervention on their sexual functioning, they did benefit in terms of overall sexual satisfaction, feelings of sexual intimacy and sexual relationship satisfaction. Future Internet-based interventions should involve the partner to a greater extent, by including a range of modules specifically targeting male sexual dysfunction. More research is needed to determine the optimal involvement of the partner in sex therapy after cancer treatment and the prerequisites to effectuate a sustained effect in the partner's sexual functioning. Given the very rapid advances in the development of eHealth interventions and related technology, future trials should enable continuous enhancement of the intervention during the course of the study. Constructive Technology Assessment (CTA) can be used to investigate this dynamic process. Future trials should also evaluate how the use of different components of the treatment program or technology, or combinations of components, contribute to the efficacy of the treatment program. Additionally, further research into the predictors and moderators of the success of (eHealth) interventions is warranted, to be able to select patients who will benefit most from the intervention or to tailor the content to the needs of the individual patient. Lastly, more information is needed on the cost-effectiveness of Internet-based sex therapy programs for sexual dysfunction after BC. A potentially cost-effective alternative to the intervention evaluated in this thesis could be a self-management version of the CBT program. Another potential benefit of such a 'light' version of our program could be that it can be offered to the many BC survivors who experience milder sexual problems after BC treatment. We intend to develop and test, in an RCT context, a (guided) self-management version of our Internet-based CBT program. The intervention described in this thesis can be viewed as a proof of principle for the efficacy of Internet-based CBT for sexual dysfunctions in BC survivors.

SAMENVATTING (SUMMARY IN DUTCH)

Als gevolg van verbeterde opsporing en behandeling van borstkanker zijn de overlevingskansen voor vrouwen met borstkanker gestegen. Hierdoor is de aandacht voor de kwaliteit van leven na de behandeling van borstkanker, waaronder het seksueel functioneren, toegenomen. Seksuele problemen zijn een veelvoorkomend, langdurig gevolg van de diagnose en behandeling van borstkanker. Veelvoorkomende seksuele problemen bij ex-borstkankerpatiëntes zijn onder andere verminderd seksueel verlangen, verminderde seksuele opwinding en vaginale lubricatie, dyspareunie en vaginale atrofie en droogheid. Bij een deel van de ex-borstkankerpatiëntes is zelfs sprake van een diagnose 'seksuele disfunctie' volgens de criteria van The Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). Vrouwen met een DSM-IV seksuele disfunctie ervaren seksuele problemen die aanzienlijke lijdensdruk veroorzaken. In het geval van een DSM-IV seksuele disfunctie kan professionele hulp geïndiceerd zijn. De studie die wordt beschreven in dit proefschrift richtte zich op (ex-)borstkankerpatiëntes met een diagnose seksuele disfunctie volgens de criteria van de DSM-IV.

In **hoofdstuk 1** wordt via internet aangeboden cognitieve gedragstherapie (CGT) gepresenteerd als een veelbelovende behandeloptie voor DSM-IV seksuele disfuncties bij (ex-) borstkankerpatiëntes. Hoewel traditionele behandelmethoden zoals *face-to-face* CGT effectief zijn in het behandelen van seksuele disfuncties, is er een discrepantie tussen de gerapporteerde behoefte aan seksuologische gezondheidszorg en het daadwerkelijke gebruik van dergelijke zorg door (ex-)borstkankerpatiëntes. CGT via internet (internet-CGT) zou een alternatief kunnen zijn voor de meer traditionele, *face-to-face* behandelopties, onder andere vanwege de grotere toegankelijkheid en privacy die therapieprogramma's die via internet worden aangeboden kunnen bieden. Deze aspecten kunnen in het bijzonder aantrekkelijk zijn in de behandeling van problemen die gevoelig liggen, zoals seksuele disfuncties, en zouden de drempel voor (ex-)borstkankerpatiëntes kunnen verlagen om professionele hulp te zoeken. In deze studie evalueerden wij de effectiviteit van een internet-CGT-programma in het verbeteren van het seksueel functioneren van (ex-)borstkankerpatiëntes met een DSM-IV seksuele disfunctie en hun partners.

In het onderzoek waarover dit proefschrift gaat, stonden de volgende onderzoeksvragen centraal:

1. Welke patiënt-gerelateerde en klinische factoren zijn geassocieerd met het seksueel functioneren en de last die wordt ervaren als gevolg van de seksuele problemen (seksuele *distress*) van (ex-)borstkankerpatiëntes en met het seksueel functioneren van hun partners?

2. Wat zijn de korte- en de langetermijneffecten van CGT via internet op het seksueel functioneren, de seksuele *distress*, de intimiteit in de relatie en andere psychosociale aspecten van het functioneren van (ex-)borstkankerpatiëntes met een DSM-IV seksuele disfunctie?
3. Wat zijn de voorspellers van het post-CGT seksueel functioneren en de seksuele *distress* van deze groep vrouwen?
4. Wat is het effect van CGT via internet op het seksueel functioneren, de intimiteit in de relatie en de tevredenheid met de relatie van partners van deze vrouwen?

In **hoofdstuk 2** wordt de opzet van de gerandomiseerde gecontroleerde studie (randomized controlled trial; RCT) beschreven waarin we de effectiviteit van de internet-CGT voor seksuele disfuncties bij (ex-)borstkankerpatiëntes evalueerden. De primaire uitkomsten waren seksueel functioneren en intimiteit in de relatie. De secundaire uitkomsten waren lichaamsbeeld, tevredenheid met de relatie, menopauzale symptomen, psychische *distress* en gezondheidsgerelateerde kwaliteit van leven. De internet-CGT werd vergeleken met een wachtlijst-controlegroep; dit was een groep vrouwen die pas na afloop van de wachtperiode de CGT aangeboden kreeg. De CGT bestond uit 4 à 5 modules (geselecteerd uit een totaal van 10 modules door de psycholoog/seksuoloog) die het beste aansloten bij de seksuele problemen van de specifieke deelneemster. Elke module bevatte verschillende interventies, die elk de volgende elementen bevatten: een inleiding, psycho-educatie, huiswerkopdrachten, een rapportage aan de therapeut en feedback van de therapeut. Dit resulteerde in een programma van ongeveer 20 wekelijkse sessies die binnen 24 weken werden afgerond. De therapeut begeleidde en ondersteunde de deelneemsters tijdens het programma. Het contact tussen de therapeut en de deelneemster vond plaats via e-mail en was asynchroon (d.w.z. de therapeut en de deelneemster waren niet gelijktijdig online). Vrouwen werden aangemoedigd door de therapeut om hun partner te betrekken bij de behandeling. Partnerdeelname was echter niet verplicht. Vragenlijsten waarmee de onderzoeksuitkomsten werden gemeten werden ingevuld voor de start van de CGT (T0), halverwege de CGT (T1) en direct na het einde van de CGT (T2). De deelneemsters in de controlegroep vulden de vragenlijsten op vergelijkbare momenten tijdens de wachtlijstperiode in. Vrouwen in de interventiegroep vulden drie (T3) en negen maanden (T4) na het einde van de CGT follow-up vragenlijsten in. Vrouwen in de wachtlijst-controlegroep kregen het CGT-programma aangeboden na het invullen van de T2-vragenlijst.

In **hoofdstuk 3** worden de T0-gegevens beschreven die werden verzameld tijdens de RCT en dit hoofdstuk biedt inzicht in het seksueel functioneren van (ex-)borstkankerpatiëntes met een DSM-IV seksuele disfunctie en hun partners. De vaakst gediagnosticeerde seksuele disfuncties bij de vrouwen waren: seksuele stoornis met verminderd verlangen (83%), seksuele opwindingsstoornis (40%) en dyspareunie (33%). De meeste vrouwen

(64%) werden gediagnosticeerd met twee of meer seksuele disfuncties. Vrouwen behandeld met endocriene therapie werden vaker gediagnosticeerd met een seksuele stoornis met verminderd verlangen en vrouwen behandeld met immunotherapie kregen vaker een diagnose dyspareunie. Oudere leeftijd was geassocieerd met minder seksuele *distress*. Niet alleen het seksueel functioneren van de vrouwen, maar ook dat van hun partners was aangedaan, wat naar voren kwam in het grote deel (55%) van de mannelijke partners dat matige of ernstige erectieproblemen rapporteerde. Het effect van de borstkankerbehandeling op de partner kwam eveneens tot uiting in de bevinding dat partners van vrouwen die een borstreconstructie hadden ondergaan een beter orgastisch functioneren en algeheel seksueel functioneren rapporteerden dan partners van vrouwen die borstsparend waren behandeld. Zowel de vrouwen als hun partners rapporteerden lage niveaus van seksueel functioneren. Echter, er werden weinig significante correlaties waargenomen tussen het seksueel functioneren van de vrouwen en dat van hun partners. Dit kan, althans gedeeltelijk, worden verklaard door verschillen in mannelijk en vrouwelijk seksueel functioneren, zoals de rapportage van een hoger seksueel verlangen door mannen dan door vrouwen, de sekseverschillen in de mate van overeenstemming tussen de perceptie van genitale respons en de werkelijke genitale seksuele opwinding, en verschillen in de orgasmefrequentie. Desalniettemin suggereren de bevindingen dat het belangrijk is voor gezondheidsprofessionals om beide partners te betrekken in het bespreken van seksualiteit na borstkanker en in het bijzonder – indien van toepassing – in daarop volgende sekstherapie.

In **hoofdstuk 4** worden de resultaten met betrekking tot de kortetermijneffectiviteit van de internet-CGT gepresenteerd. Vergeleken met vrouwen in de controlegroep rapporteerden vrouwen die de internet-CGT ondergingen een grotere verbetering van T0 naar T2 in het algehele seksuele functioneren, het seksuele verlangen, de seksuele opwinding, de vaginale lubricatie en het seksueel genot, en een grotere afname van ongemak/pijn tijdens seks en seksuele *distress* dan vrouwen in de controlegroep. Voorts rapporteerden vrouwen in de interventiegroep een grotere verbetering in het lichaamsbeeld vergeleken met de controlegroep. Een klinisch significante verandering in het seksueel functioneren werd waargenomen bij 63% van de interventiegroep, versus bij 32% van de controlegroep. De kans op een klinisch significante verbetering was 3,66 keer groter voor de interventiegroep dan voor de controlegroep. Er werden geen significante veranderingen gevonden in menopauzale symptomen, orgasme, seksuele satisfactie, frequentie van seksuele activiteit, intimiteit in de relatie, relationeel functioneren, psychische *distress* of gezondheidsgerelateerde kwaliteit van leven. Deze studie toont aan dat internet-CGT een positief effect heeft op het seksueel functioneren en het lichaamsbeeld van (ex-)borstkankerpatiëntes met een seksuele disfunctie.

In **hoofdstuk 5** worden de langetermijneffecten van het internet-CGT-programma beschreven. In deze analyse werden de 84 vrouwen uit de interventiegroep van de studie opgenomen. De positieve effecten van het behandelingsprogramma op het algehele seksuele functioneren, het seksuele verlangen, de seksuele opwinding, de vaginale lubricatie, ongemak/pijn tijdens seks, de seksuele *distress* en het lichaamsbeeld, die werden waargenomen aan het einde van CGT, werden behouden gedurende een follow-up van drie tot negen maanden. Het lichaamsbeeld verbeterde nog verder na de afronding van de CGT. Seksueel genot was het enige domein dat, na een verbetering tijdens de internet-CGT, significant afnam tijdens de follow-up periode. Het bleef echter boven het T0-niveau. Het verlies van de ondersteuning door de therapeut om seksueel actief te zijn na afronding van de CGT kan hebben geleid tot enig verlies van effect op dit gebied. Dit wordt ondersteund door het feit dat eveneens een geringe, hoewel niet statistisch significante, afname werd waargenomen in de andere gebieden van het seksueel functioneren. De resultaten tonen aan dat de positieve effecten van CGT via internet op de meeste gebieden van het seksueel functioneren, de seksuele *distress* en het lichaamsbeeld behouden blijven in de periode na de behandeling.

In **hoofdstuk 6** worden voorspellende factoren voor een succesvolle uitkomst van de CGT via internet en de evaluatie van het therapieprogramma door de deelnemers beschreven. Een beter seksueel functioneren na de CGT was geassocieerd met een beter seksueel functioneren van vrouwen en hun partners bij T0, en met hogere therapietrouw. Lagere seksuele *distress* na de CGT was geassocieerd met een lager niveau van seksuele *distress* bij T0, een beter seksueel functioneren van de vrouw bij T0, een hogere tevredenheid van de partner met de relatie bij T0 en een hogere therapietrouw. Therapietrouw werd op zijn beurt voorspeld door de actieve betrokkenheid van de partner in de therapie en een betere therapeutische relatie. Dit suggereert dat, hoewel deze twee laatste factoren niet direct zijn geassocieerd met therapiesucces, zij indirect het succes van de therapie beïnvloeden via hun associatie met therapietrouw. De T0-niveaus van seksueel functioneren en seksuele *distress* waren voorspellend voor het niveau van seksueel functioneren en seksuele *distress* over de tijd (d.w.z. vrouwen met een beter seksueel functioneren bij T0 hadden ook een beter seksueel functioneren na de CGT), maar waren niet voorspellend voor de effectiviteit van de internet-CGT. De specifieke onderdelen van de borstkankerbehandeling waren eveneens niet voorspellend voor het seksueel functioneren na de interventie. Deze bevindingen suggereren dat elke (ex-)borstkankerpatiënte, ongeacht haar niveau van seksueel functioneren of seksuele *distress* bij T0 of haar specifieke borstkankerbehandeling, baat kan hebben bij CGT via internet voor seksuele disfuncties. De meerderheid van de vrouwen gaf aan over het algemeen tevreden te zijn met de CGT. Het feit dat zowel de vrouwen als de therapeuten positief waren over de kwaliteit van de therapeutische relatie is belangrijk, omdat het laat zien dat, zelfs wanneer therapie op afstand (d.w.z. via internet) wordt

aangeboden, een sterke therapeutische band kan worden opgebouwd. We raden aan om specifieke aandacht te besteden aan de therapeutische relatie en de partner actief te betrekken bij de therapie, om zo de naleving van het CGT-programma te verbeteren en de effectiviteit van de behandeling te vergroten.

In **hoofdstuk 7** wordt het effect van de internet-CGT op de 69 partners van (ex-)borstkankerpatiëntes uit de interventiegroep gerapporteerd. De resultaten toonden aan dat het algehele seksuele functioneren van de partners, de erectiele functie, de orgasmefunctie, de tevredenheid met geslachtsgemeenschap, de algehele seksuele satisfactie, de intimiteit in de seksuele relatie en de tevredenheid met de seksuele relatie verbeterden tijdens de CGT via internet. Alleen de verbeteringen in de algehele seksuele satisfactie, de intimiteit in de seksuele relatie en de tevredenheid met de seksuele relatie werden behouden tijdens een follow-up periode van negen maanden. Er werden geen significante veranderingen waargenomen in het seksuele verlangen of op andere gebieden van intimiteit in de relatie of tevredenheid met de relatie. De interventie leek dus meer blijvende, langetermijneffecten te hebben op het functioneren van (ex-)borstkankerpatiëntes dan op dat van de partners. Dit verschil in effect is niet geheel onverwacht, aangezien de internet-CGT zich specifiek richtte op het seksueel functioneren van de (ex-)borstkankerpatiëntes. Dit kan ertoe hebben geleid dat beide partners vaardigheden verwierven die een langdurig positief effect hadden op het seksuele functioneren van de vrouw, maar niet op dat van de partner. Omdat niet alleen het seksuele functioneren van de vrouwen, maar ook dat van hun mannelijke partners wordt beïnvloed door borstkanker en de behandeling, bevelen we aan om de inhoud van internettherapie voor seksuele disfuncties na borstkanker uit te breiden met meer op de partner toegespitste informatie en interventies. Zo kunnen partners leren om niet alleen het seksueel functioneren van hun vrouw te verbeteren, maar ook dat van zichzelf.

In **hoofdstuk 8** worden de belangrijkste bevindingen van het onderzoek waarover dit proefschrift gaat besproken, inclusief methodologische beperkingen met betrekking tot de inhoud en vorm van de CGT, de opzet van de studie, de aard en kwaliteit van de metingen, en kwesties met betrekking tot kosteneffectiviteit. Onze internet-CGT realiseerde een blijvende verbetering in het seksueel functioneren, de seksuele *distress* en het lichaamsbeeld van (ex-)borstkankerpatiëntes. Hoewel partners geen blijvende positieve effecten van de interventie op hun seksuele functioneren rapporteerden, vond wel een langdurige verbetering plaats in hun algehele seksuele tevredenheid, intimiteit in de seksuele relatie en tevredenheid met de seksuele relatie. Toekomstige interventies via internet zouden de partner in grotere mate moeten betrekken, door extra modules op te nemen die zich specifiek richten op mannelijk seksueel functioneren. Meer onderzoek is nodig om de optimale betrokkenheid van de partner in sekstherapie na kankerbehandeling te

bepalen en om vast te stellen wat de voorwaarden zijn om een blijvend effect op het seksueel functioneren van de partner te realiseren. Gezien de zeer snelle ontwikkelingen in e-health-interventies en de bijbehorende technologie, zouden toekomstige studies een werkwijze kunnen hanteren waarin de interventie in de loop van het onderzoek constant wordt verbeterd. Constructive Technology Assessment (CTA) kan worden gebruikt om dit dynamische proces te onderzoeken. Toekomstige studies zouden ook moeten evalueren hoe het gebruik van verschillende componenten van het behandelingsprogramma of de technologie, of combinaties van componenten, bijdragen aan de effectiviteit van het behandelingsprogramma. Daarnaast is verder onderzoek naar de voorspellers en moderatoren van het succes van (e-health-)interventies gewenst, om patiënten te kunnen selecteren die het meeste baat zullen hebben bij de interventie of om de inhoud van de interventie aan te kunnen passen aan de behoeften van de individuele patiënt. Ten slotte is meer informatie nodig met betrekking tot de kosteneffectiviteit van internetinterventies voor seksuele disfuncties na borstkanker. Een mogelijk kosteneffectief alternatief voor de interventie die in dit proefschrift is geëvalueerd, zou een zelfmanagementversie van het CGT-programma kunnen zijn. Een ander potentieel voordeel van een 'light'-versie van ons programma zou kunnen zijn dat het kan worden aangeboden aan de vele (ex-)borstkankerpatiëntes die na de borstkankerbehandeling mildere seksuele problemen ervaren. We zijn van plan om een (begeleide) zelfmanagementversie van ons internet-CGT-programma te ontwikkelen en te testen in een RCT. De interventie die in dit proefschrift wordt beschreven, kan worden gezien als een *proof of principle* voor de effectiviteit van CGT via internet voor seksuele disfuncties bij (ex-)borstkankerpatiëntes.

Appendices

Authors' contributions

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AUTHORS' CONTRIBUTIONS

Chapter 2

Hummel, S.B., van Lankveld, J.J.D.M., Oldenburg, H.S.A., Hahn, D.E.E., Broomans, E., & Aaronson, N.K. (2015). Internet-based cognitive behavioral therapy for sexual dysfunctions in women treated for breast cancer: design of a multicenter, randomized controlled trial. *BMC Cancer, 15*, 321.

Neil K. Aaronson was the principal investigator and Jacques J.D.M. van Lankveld, Hester S.A. Oldenburg and Daniela E.E. Hahn were the co-principal investigators of this study. Susanna B. Hummel was the PhD candidate on the study, and created the first draft of this manuscript based on the study protocol. Eva Broomans played a key role in the development of the online CBT program and was one of the primary sexologists of this study. All authors read and approved the final manuscript.

Chapter 3

Hummel, S.B., Hahn, D.E.E., van Lankveld, J.J.D.M., Oldenburg, H.S.A., Broomans, E., & Aaronson, N.K. (2017). Factors Associated With Specific Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Sexual Dysfunctions in Breast Cancer Survivors: A Study of Patients and Their Partners. *J Sex Med, 14*(10).

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Chapter 4

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All authors provided comments and approved the manuscript.

Chapter 5

Hummel, S.B., van Lankveld, J.J.D.M., Oldenburg, H.S.A., Hahn, D.E.E., Kieffer, J.M., Gerritsma, M.A., Kuenen, M.A., Bijker, N., Borgstein, P.J., Heuff, G., Lopes Cardozo, A.M.F., Plaisier, P.W., Rijna, H., van der Meij, S., van Dulken, E.J., Vrouenraets, B.C., Broomans, E., & Aaronson, N.K. (2018). Internet-Based Cognitive Behavioral Therapy Realizes Long-Term Improvement in the Sexual Functioning and Body Image of Breast Cancer Survivors. *J Sex Marital Ther*, 1-12.

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Chapter 7

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Susanna Blientje (Lisanne) Hummel was born in Amsterdam on June 10, 1987. In 2005, she completed secondary school at Het Keizer Karel College in Amstelveen. Subsequently, she studied Psychology at the University of Amsterdam (Honours Master Gezondheidszorgpsychologie, master track Clinical Psychology: 2011, cum laude). In 2012, she started her PhD project at the Division of Psychosocial Research and Epidemiology of The Netherlands Cancer Institute. The research was performed under the supervision of prof. dr. Neil K. Aaronson (The Netherlands Cancer Institute/University of Amsterdam) and prof. dr. Jacques J.D.M. van Lankveld (Open University of the Netherlands). Since September 2017 Lisanne has been working at the Department of Psychosomatic Gynaecology and Sexology of the Leiden University Medical Center as a postdoctoral researcher. Her focus is on a randomized controlled trial (RCT) evaluating the efficacy of a nurse-led sexual rehabilitation program for women treated with radiotherapy for gynaecological cancer, and on an RCT evaluating the efficacy of a cognitive behavioral therapy group program for women with dyspareunia. Lisanne is co-founder of and author for Bedmanieren.nl (www.bedmanieren.nl) and co-developer of the podcast series De herontdekking van haarzelf (www.deherontdekkingvanhaarzelf.nl).