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[Intervention Review]

Interventions to improve psychosocial well-being in female BRCA-mutation carriers following risk-reducing surgery

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ABSTRACT

Background

Women who carry a pathogenic mutation in either a BRCA1 DNA repair associated or BRCA2 DNA repair associated (BRCA1 or BRCA2) gene have a high lifetime risk of developing breast and tubo-ovarian cancer. To manage this risk women may choose to undergo risk-reducing surgery to remove breast tissue, ovaries, and fallopian tubes. Surgery should increase survival, but can impact women's lives adversely at the psychological and psychosexual levels. Interventions to facilitate psychological adjustment and improve quality of life post risk-reducing surgery are needed.

Objectives

To examine psychosocial interventions in female BRCA carriers who have undergone risk-reducing surgery and to evaluate the effectiveness of such interventions on psychological adjustment and quality of life.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE and Embase via Ovid, CINAHL, PsycINFO, Web of Science up to April 2019 and Scopus up to January 2018. We also handsearched abstracts of scientific meetings and other relevant publications.

Selection criteria

We included randomised controlled trials (RCT), non-randomised studies (NRS), prospective and retrospective cohort studies and interventional studies using baseline and postintervention analyses in female BRCA carriers who have undergone risk-reducing surgery.

Data collection and analysis

Two review authors independently assessed eligibility studies for inclusion in the review. We used standard methodological procedures expected by Cochrane.

Main results

We screened 4956 records from the searches, selecting 34 unique studies for full-text scrutiny, of which two met the inclusion criteria: one RCT and one NRS. The included studies assessed 113 female BRCA carriers who had risk-reducing surgery, but there was attrition, and outcome data were not available for all participants at final study assessments. We assessed the RCT as at a high risk of bias whilst the NRS

did not have a control group. Our GRADE assessment of the studies was very low-certainty due to the paucity of data and methodological shortcomings of the studies. The primary outcome of quality of life was only measured in the RCT and that was specific to the menopause. Both studies reported on psychological distress and sexual function. Neither study measured body image, perhaps because this is most often associated with risk-reducing mastectomy rather than oophorectomy.

The RCT (66 participants recruited with 48 followed to 12 months) assessed the short- and long-term effects of an eight-week mindfulness-based stress reduction (MBSR) training programme on quality of life, sexual functioning, and sexual distress in female BRCA carriers ($n = 34$) in a specialised family cancer clinic in the Netherlands compared to female BRCA carriers ($n = 32$) who received usual care. Measurements on the Menopause-Specific Quality of Life Questionnaire (MENQOL) showed some improvement at 3 and 12 months compared to the usual care group. At 3 months the mean MENQOL scores were 3.5 (95% confidence interval (CI) 3.0 to 3.9) and 3.8 (95% CI 3.3 to 4.2) for the MBSR and usual care groups respectively, whilst at 12 months the corresponding values were 3.6 (95% CI 3.1 to 4.0) and 3.9 (95% CI 3.5 to 4.4) (1 study; 48 participants followed up at 12 months). However, these results should be interpreted with caution due to the very low-certainty of the evidence, where a lower score is better. Other outcome measures on the Female Sexual Function Index and the Female Sexual Distress Scale showed no significant differences between the two groups. Our GRADE assessment of the evidence was very low-certainty due to the lack of blinding of participants and personnel, attrition bias and self-selection (as only one-third of eligible women chose to participate in the study) and serious imprecision due to the small sample size and wide 95% CI.

The NRS comprised 37 female BRCA carriers selected from three Boston-area hospitals who had undergone a novel sexual health intervention following risk-reducing salpingo-oophorectomy (RRSO) without a history of tubo-ovarian cancer. The intervention consisted of targeted sexual-health education, body awareness and relaxation training, and mindfulness-based cognitive therapy strategies, followed by two sessions of tailored telephone counselling. This was a single-arm study without a control group. Our GRADE assessment of the evidence was very low-certainty, and as there was no comparison group in the included study, we could not estimate a relative effect. The study reported change in psychosexual adjustment from baseline to postintervention (median 2.3 months) using measures of Female Sexual Function Index ($n = 34$), which yielded change with a mean of 3.91, standard deviation (SD) 9.12, $P = 0.018$ (1 study, 34 participants; very low-certainty evidence). The Brief Symptom Inventory, Global Severity Index yielded a mean change of 3.92, SD 5.94, $P < 0.001$. The Sexual Self-Efficacy Scale yielded change with a mean of 12.14, SD 20.56, $P < 0.001$. The Sexual Knowledge Scale reported mean change of 1.08, SD 1.50, $P < 0.001$ ($n = 36$). Participant satisfaction was measured by questionnaire, and 100% participants reported that they enjoyed taking part in the psychoeducation group and felt "certain" or "very certain" that they had learned new skills to help them cope with the sexual side effects of RRSO.

Authors' conclusions

The effect of psychosocial interventions on quality of life and emotional well-being in female BRCA carriers who undergo risk-reducing surgery is uncertain given the very low methodological quality in the two studies included in the review. The absence of such interventions highlights the need for partnership between researchers and clinicians in this specific area to take forward the patient-reported outcomes and develop interventions to address the psychosocial issues related to risk-reducing surgery in female BRCA carriers, particularly in this new era of genomics, where testing may become more mainstream and many more women are identified as gene carriers.

PLAIN LANGUAGE SUMMARY

Interventions to improve psychosocial well-being in women with a BRCA mutation following risk-reducing surgery

Background

Women who test positive for a fault (mutation) on one of the BRCA genes (BRCA1 DNA repair associated or BRCA2 DNA repair associated (BRCA1 or BRCA2)) are more at risk of developing breast and tubo-ovarian cancer (cancer of the fallopian tubes or ovaries). A significant number of female BRCA carriers will choose to have surgery to remove their breast tissue and fallopian tubes and ovaries in order to reduce their risk of developing breast cancer and tubo-ovarian cancer. This type of surgery can be life-changing, and women may experience negative physical and emotional changes as a result. These changes can affect the function and appearance of their bodies, which in turn can have a negative psychological effect on women and their relationships.

Review question

The aim of this review was to learn if interventions can help with the social and psychological effects of physical and emotional changes in women who have had risk-reducing surgery.

Main findings

We found two studies that examined a psychosocial intervention for women who had undergone removal of their fallopian tubes and ovaries to reduce their risk of tubo-ovarian cancer.

One randomised controlled trial (a study in which participants are assigned to one of two or more treatment groups using a random method) assessed a mindfulness-based stress reduction training programme for menopausal symptoms after risk-reducing surgery. Whilst there was improvement in the menopause-specific quality of life scores in the short and the long term for women with menopausal symptoms, the intervention was not associated with improvement in sexual functioning or distress.

Women who participated in a non-randomised study all received the study intervention and scored themselves on certain items related to psychosexual functioning and psychological adjustment before and after the intervention (targeted sexual-health education, body awareness and relaxation training, and mindfulness-based cognitive therapy strategies). They also received a group psychoeducation session and telephone counselling. The outcomes were based on the differences between the before and after scores. All women recruited to the study were at risk of tubo-ovarian cancer based on having a harmful or faulty BRCA gene, but there was no personal history of tubo-ovarian cancer in the group studied.

No studies reported on social and psychological interventions following risk-reducing surgery to have breast tissue removed in BRCA carriers.

Quality of the evidence

The certainty (quality) of the evidence ranged from moderate to very low, with only one randomised controlled trial and one non-randomised study that had no comparator included in the review. Both studies involved small numbers of women.

Conclusions

The limited, moderate- to very low-certainty evidence meant that we were unable to draw any conclusions regarding psychosocial interventions following risk-reducing surgery in female BRCA carriers on improvement in quality of life and psychological (emotional) adjustment. Further research is required to determine how best to support women who choose to have risk-reducing surgery.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Mindfulness-based stress reduction training versus usual care for female BRCA carriers post-risk-reducing surgery

Mindfulness-based stress reduction training versus usual care for female BRCA carriers post-risk-reducing surgery

Patient or population: female BRCA carriers post-risk-reducing surgery
Setting: a specialised family cancer clinic in Groningen, the Netherlands
Intervention: mindfulness-based stress reduction training
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with usual care	Risk with mindfulness-based stress reduction training			
Menopause-specific quality of life (quality of life) assessed with: MENQOL follow-up: mean 12 months	The mean menopause-specific quality of life was 3.9.	MD - 0.3 lower (- 0.94 lower to 0.34 higher)	-	48 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}
Sexual function (sexual function) assessed with: Female Sexual Function Index follow-up: mean 12 months	The mean sexual function was 16.3.	MD 0.5 higher (- 4.14 lower to 5.14 higher)	-	48 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}
Sexual distress (sexual distress) assessed with: Female Sexual Distress Scale follow-up: mean 12 months	The mean sexual distress was 12.4.	MD 5.2 higher (- 1.67 lower to 12.07 higher)	-	48 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}
Vasomotor symptoms (vasomotor) assessed with: MENQOL follow-up: mean 12 months	The mean vasomotor symptoms was 4.3.	MD - 0.7 lower (-1.55 lower to 0.15 higher)	-	48 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}
Psychosocial (psychosocial) assessed with: MENQOL follow-up: mean 12 months	The mean psychosocial was 3.8.	MD - 0.1 lower (- 0.91 lower to 0.71 higher)	-	48 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}
Physical symptoms (physical) assessed with: MENQOL follow-up: mean 12 months	The mean physical symptoms was 3.8.	MD - 0.6 lower (- 1.23 lower to 0.04 higher)	-	48 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}

Sexual symptoms (sexual) assessed with: MENQOL follow-up: mean 12 months	The mean sexual symptoms was 3.7.	MD 0.3 higher (- 0.8 lower to 1.4 higher)	-	48 (1 RCT)	⊕○○○ VERY LOW ^{1 2}
Body image (body image)	Study population		Not estimable	(0 studies)	Not assessed
	0 per 1000	0 per 1000 (0 to 0)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **MENQOL:** Menopause-Specific Quality of Life questionnaire; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low-certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Serious imprecision due to small sample size and wide 95% CI. Downgraded one level.

²Very serious risk of bias due to lack of blinding of participants and personnel, attrition bias, and self-selection bias (as only one-third of eligible women chose to participate in the study). Downgraded two levels.

Summary of findings 2. Psychosocial intervention to improve sexual health versus no intervention for adult women, 18 years of age or older, who tested positive for a pathogenic mutation in BRCA1 or BRCA2 and who had had risk-reducing surgery

Psychosocial intervention to improve sexual health versus no intervention for adult women, 18 years of age or older, who tested positive for a pathogenic mutation in BRCA1 or BRCA2 and who had had risk-reducing surgery

Patient or population: adult women, 18 years of age or older, who tested positive for a pathogenic mutation in BRCA1 or BRCA2 and who had had risk-reducing surgery

Setting: outpatient clinics in Boston, USA

Intervention: psychosocial intervention to improve sexual health

Comparison: no intervention

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
Quality of life	Not assessed by this study	0	Not estimable

Sexual function assessed with: rating scales, psychoeducational group session, telephone counselling follow-up: mean 2 months	Women showed significant improvement in sexual function (M = 3.91). Magnitude of change between baseline and postintervention varied, with moderate to moderately large effect sizes observed on the desire (M = 0.44) and arousal (M = 0.98) subscales of the FSFI. FSFI total score, satisfaction (M = 0.53), and pain (M = 0.93) subscales showed small to moderate effect sizes. Improvements in lubrication (M = 0.58) and orgasm (M = 0.73) scales were observed but were not statistically significant.	34 (1 observational study)	⊕○○○ VERY LOW ¹²
Body image	Not assessed by this study	0	Not estimable
Sexual self-efficacy scale assessed with: rating scale follow-up: mean 2 months	Women rated their perceived certainty or confidence to address sexual side effects of RRSO. Moderate to moderately large change effect was shown on this scale between baseline and postintervention (M = 12.14) (P < 0.001).	37 (1 observational study)	⊕○○○ VERY LOW ¹²
Sexual knowledge assessed with: measured on a true/false 10-item scale follow-up: mean 2 months	Women's perceived knowledge about sexual side effects of RRSO was significantly improved from baseline to postintervention (M = 1.08) (P < 0.001).	36 (1 observational study)	⊕○○○ VERY LOW ¹²
Participant satisfaction assessed with: questionnaire follow-up: mean 2 months	100% of women reported that they enjoyed participating in the psychoeducation group session and felt "certain" or "very certain" that they had learned new skills to help them cope with the sexual side effects of RRSO.	37 (1 observational study)	⊕○○○ VERY LOW ¹²

FSFI: Female Sexual Function Index; **RRSO:** risk-reducing salpingo-oophorectomy

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low-certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹No control group. Downgraded two levels.

²Self-selection to study. Downgraded one level.

BACKGROUND

The familial breast cancer genes BRCA1 DNA repair associated and BRCA2 DNA repair associated (BRCA1 and BRCA2) have garnered attention since individuals of public interest have revealed their personal decisions to undergo risk-reducing surgery for breast or tubo-ovarian cancer, or both, because of a family history of these cancers and a positive gene status (Evans 2015). Raising the public profile of inherited breast and tubo-ovarian cancer has resulted in substantial increases in referrals to cancer genetics services throughout the UK (Evans 2015; Foster 2007; Rosenberg 2016; Watson 2004). This exposure, alongside factors that have increased availability of genetic testing such as Next Generation Sequencing (NGS) and updated National Institute for Health and Care Excellence (NICE) guidelines on genetic testing in families with hereditary breast and ovarian cancer (HBOC) (NICE 2013), has influenced the perception and uptake of genetic testing. In addition, the 100,000 Genome Project has started to deliver results in 2019 from sequencing the genomes of 85,000 individuals with rare disease or cancers and has the potential to identify many more BRCA mutations. This is currently the largest national sequencing project of its kind in the world (Genomics England 2019). Prior to genetic testing for BRCA genes, which remains the most powerful tool for determining which individuals within a family are at risk (Euhus 2015), genetic counselling is offered where trained genetic counsellors can facilitate testing in a number of ways including discussion of family history, possible test outcomes, implications of the genetic test result, and risk management options (Stan 2013). Current NICE guidance sets out the classification, care and management of familial breast cancer and related risks in people with a family history of breast cancer and defines those whose risk warrants a specialist genetic consultation (NICE 2013).

Description of the condition

Hereditary breast and ovarian cancer is a syndrome that increases the risk of developing breast and tubo-ovarian cancer. It is estimated that up to 10% of invasive breast cancers are inherited, most of which are associated with the BRCA1 and BRCA2 genes (King 2003). Up to 17% of women diagnosed with tubo-ovarian cancers have an inherited pathogenic BRCA mutation (McAlpine 2012). NHS England has reported that a BRCA gene mutation accounts for 1020 of the 6800 cases of tubo-ovarian cancer diagnosed annually in the UK (NHS England 2015). Women who carry a pathogenic BRCA mutation are considered to have a significantly increased cumulative lifetime risk of developing breast cancer (40% to 85%) and risk of tubo-ovarian cancer (11% to 65%) (Antoniou 2003; den Heijer 2012; Ford 1998; King 2003), compared to women in the general population, where risk for breast and tubo-ovarian cancer is 12% and 1.3% respectively (Chen 2007). Whilst it is acknowledged that published estimates vary depending on study design, analyses, and populations studied (Hartmann 2016), multiple other factors such as age of diagnosis of cancer in the index family member, type of cancer, family history of cancer, and lifestyle factors contribute to this variation in risk (Mavaddat 2013). The Epidemiological Study of BRCA1 and BRCA2 mutation carriers (EMBRACE), one of the largest prospective studies, collaborating with 28 centres across the UK and Ireland, discriminated between the two BRCA genes. The estimated cumulative lifetime risks, up to 70 years of age, for women with a BRCA1 mutation are 60% risk of breast cancer, 59% for tubo-ovarian cancer, and 83% for a contralateral breast cancer; for women with a BRCA2 mutation risks were estimated as

55% for breast cancer, 16.5% for ovarian cancer, and 62% for contralateral breast cancer (Mavaddat 2013).

Following confirmation of a pathogenic BRCA mutation, women are faced with difficult choices of how best to manage their risk of developing breast or tubo-ovarian cancer. Options to consider are: enhanced surveillance with magnetic resonance imaging (MRI), mammogram, and CA125 blood test, and a transvaginal ultrasound scan of the ovaries and fallopian tubes; risk-reducing surgery to remove their breast tissue and/or ovaries and fallopian tubes; chemoprevention; and lifestyle interventions. A recent Cochrane Review protocol highlights the need for international guidelines in BRCA testing in women with tubo-ovarian cancer and other cancers to facilitate consistent screening practices (Eleje 2016). The UK Familial Ovarian Cancer Screening Study (UK FOCSS) recently published data on screening in women who are at high risk for tubo-ovarian cancer. It concluded that screening should not be viewed as an alternative to surgery, but it does seem to offer a better chance of avoiding a diagnosis of advanced incompletely resectable tubo-ovarian cancer in the interim (Rosenthal 2017). Serous tubal intraepithelial carcinoma (STIC) is considered to be a precursor lesion of high-grade serous ovarian cancer (HGSOC), and studies in germline BRCA carriers who have undergone bilateral salpingo-oophorectomy (BSO) as a risk-reducing procedure have reported that STIC lesions were present within the fallopian tube in 0.6% to 7% of cases (Crum 2013). A systematic review of the association of STIC and HGSOC (Chen 2017), whilst reporting on the variability and the significant methodological inconsistencies resulting in a wide range of reported incidence of concurrent STIC and HGSOC, did identify findings that strengthen the hypothesis that HGSOC originates from the fallopian tube. Based on growing evidence for this hypothesis, the use of prophylactic salpingectomy (without oophorectomy) is increasing, but there have yet to be formal studies to demonstrate the effectiveness and safety of such an approach (Chay 2016), whilst Ayres 2017 challenged the recommendation of this technique and urged caution using this technique alone for high-risk patients. Recently, the PROTECTOR study has been set up in the UK to offer a two-stage process for risk-reducing salpingo-oophorectomy (RRSO). The study aims to assess the impact on women of the new two-step option to prevent ovarian cancer and will assess women's views and the impact of this approach to prevent ovarian cancer on sexual function, hormone levels, quality of life, and overall satisfaction.

Given the high risks of breast and tubo-ovarian cancer associated with the BRCA genes, many women choose to undergo risk-reducing mastectomy or RRSO, or both, in order to maximise survival (Jeffers 2014). It has been reported that 18% to 40% of women with a BRCA gene mutation will opt for risk-reducing mastectomy (Euhus 2015), with the higher percentage reported in the UK (Euhus 2015; Gopie 2013). Approximately 60% of women between the ages of 35 and 70 years who are BRCA carriers will elect to undergo RRSO (Finch 2013). Prospective studies report a 93% reduction in breast cancer risk for women who undergo risk-reducing mastectomy (De Felice 2015). Similarly, RRSO may reduce the risk of tubo-ovarian cancer by 85% to 90% and breast cancer risk by 40% to 70% in women who are BRCA carriers (ACOG 2009). Whilst such surgical interventions have demonstrated increased overall survival for this population, surgery is life-changing and can impact women adversely at the psychological, psychosexual, and emotional levels (Hartmann 2016; Stan 2013). In general, women regard risk-reducing surgery as a positive experience and have a sense of relief

at the substantial cancer risk reduction and improvement in survival (Metcalfe 2004). However, studies have shown that despite this positive experience, women are faced with unexpected physical changes that affect the function and appearance of their bodies. These changes can have a negative impact on sexuality and relationships (Gahm 2013; Gopie 2013; Hallowell 2012). The focus of this Cochrane Review is the effectiveness of interventions on psychosocial outcomes, and survival will not be part of the scope.

Description of the intervention

Prior to genetic testing, women at risk of cancer are provided with genetic counselling by trained genetic counsellors or consultant geneticists, as directed by NICE guidance 164 (NICE 2013). As an activity, genetic counselling is "the process of helping people understand and adapt to the medical, psychological and familial implications of the genetic contributions to disease. The process includes interpretation, risk assessment, education and counselling" (Resta 2006). Genetic counselling is not synonymous with therapeutic counselling. The role of the genetic counsellor, according to Skirton 2010, is specifically as follows.

- To identify the needs of the individual or family and use an empathic client-centred approach in the provision of genetic counselling.
- To collect, select, interpret, and analyse information (including family and medical history, pedigree, laboratory results, and literature) relevant to the delivery of genetic counselling for individuals or families.
- To help people understand and adapt to the medical, psychological, social, and familial implications of genetic contributions to disease.
- To assess the chance of occurrence or recurrence.
- To provide education about inheritance, testing, management, prevention, resources, and research to relevant individuals or families.
- To promote informed choices and psychological adaption to the condition or risk of the condition.
- To apply expert knowledge to facilitate the individual or family to access the appropriate healthcare resources, including a medical diagnosis and resources for management of the condition.

Women with a diagnosis of cancer may experience a different pathway due to the recent 'mainstreaming' of cancer genetics in some areas in the UK and beyond (genetic testing outside of clinical genetics services). Women who have a diagnosis of cancer may access genetic testing at the time of diagnosis, with the pre-test counselling provided by oncologists or surgeons. If a mutation is identified, these women can be referred to genetic services for further information and genetic counselling. Individuals who test positive for a BRCA mutation are not routinely followed up by the genetics service after their result disclosure consultation, but are referred on for screening and risk-reducing consultations with surgeons.

The extent of need for psychosocial support in women who are BRCA carriers and who have undergone risk-reducing surgery has not been wholly quantified. However, retrospective and prospective studies have highlighted women's concerns and experiences (Brandberg 2008; den Heijer 2012; Gahm 2010; McGaughey 2006; Metcalfe 2004; van Oostrom 2003), with significant numbers of women reporting some adverse experience. Studies have report-

ed on long-term follow-up of BRCA carriers who had risk-reducing surgery (Bai 2019; Hall 2019). Studies have found that approximately one-third of women felt less feminine, with reported changes in sexual attractiveness (55%), feeling less physically attractive (53%), and self-consciousness about appearance (53%) (Hopwood 2000). Other concerns were related to surgical complications for which women received further psychiatric intervention (Hopwood 2000). Women without a diagnosis of cancer who underwent risk-reducing mastectomy felt embarrassed about their naked body (21%), were not satisfied with the appearance of reconstructed breasts (29%), but reported significant reduction in cancer-specific distress (Gopie 2013). Women who are BRCA gene carriers and have undergone oophorectomy have been shown to experience worsening menopausal symptoms and a decline in sexual functioning, particularly those women who had surgery before their natural menopause (Hall 2019).

This Cochrane Review focused on psychological, psychosexual, and psychoeducational interventions provided to support female BRCA carriers after risk-reducing surgery, and the effectiveness of such interventions on quality of life and the psychological consequences of risk-reducing surgical intervention. Whilst there is no universal definition of quality of life, it is used to describe general health status (Aaronson 1998; Barofsky 2012). Interventions for this review adhered to a previous Cochrane Review's definition of a psychosocial intervention as non-pharmacological, involving an interpersonal relationship between an individual or group of individuals, and one or more trained (usually professional) helpers (Galway 2012).

How the intervention might work

Genetic testing and the resulting medical decisions around risk reduction lead to a unique set of emotional, physical, and sexual issues for women who are BRCA carriers (Matloff 2009). Risk-reducing salpingo-oophorectomy results in surgically induced menopause, which is related to significantly compromised sexual function (Bober 2015; Finch 2011; Robson 2003), for which there is little effective treatment. Studies have shown that psychosocial interventions have improved women's sexual difficulties (Bober 2015). Improvements in overall sexual functioning, including desire, arousal, satisfaction, and pain, have been demonstrated using interventions that integrate elements of cognitive behavioural therapy with sexual-health education and mindfulness meditation (Bober 2015). Similarly, mindfulness-based interventions in people with breast cancer have shown improvements in quality of life and stress reduction (Lengacher 2009).

Why it is important to do this review

Whilst the literature recognises that risk-reducing procedures have a significant impact at a psychosocial level and can affect quality of life, both at an individual level and that of the family (Brotto 2012; Finch 2013; Gopie 2013; Hallowell 2012; Jeffers 2014; Stan 2013), psychosocial interventions in this population have yet to be systematically reviewed. Previous systematic reviews and meta-analyses have assessed the efficacy of psychological interventions in people attending sessions for sexual dysfunction (Frühau 2013). There has been an informative literature review on the influence of medical choices on quality of life in unaffected BRCA carriers (Harmsen 2015b). Given the developments in genetic testing and the increase in availability and uptake of testing, coupled with improved surgical techniques such as breast reconstruction, more

women are choosing to undergo prophylactic bilateral mastectomy: a 12% annual increase over the last decade has been reported in the USA (Euhus 2015). Long-term follow-up studies on the impact of risk-reducing mastectomy have shown that women had ongoing difficulties with body image up to two to nine years after surgery (den Heijer 2012; Unukovich 2012). Studies have shown that sexual side effects are the most commonly cited areas of concern post-RRSO for women who are BRCA gene carriers, yet 60% of the most common symptoms women experienced postsurgery had not been discussed before surgery (Campfield Bonadies 2011). There are numerous studies measuring self-report psychological and quality of life outcomes following risk-reducing surgery (Alamouti 2015; Altschuler 2008; Fang 2009; Hall 2019; Isern 2008; Lodder 2002; Modaffari 2019), but there is a need to use these research findings to develop interventions for use in clinical practice in order to improve the psychosocial well-being in this population. Women need to be provided with information and supportive interventions to ensure they have the best psychological outcomes following their decision to undergo risk-reducing surgery. It is noted that the pre-test counselling and decision aids may impact the need for post-test counselling and interventions, but this is not within the scope of this review. This review identified the psychosocial care and management of and its impact on this cohort of women post-risk-reducing surgery.

OBJECTIVES

To examine psychosocial interventions in female BRCA carriers who have undergone risk-reducing surgery, and to evaluate the effectiveness of such interventions on psychological adjustment and quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)
- Non-randomised studies (NRS), prospective and retrospective cohort studies
- Interventional studies

Types of participants

Women, 18 years or older, who tested positive for a pathogenic mutation in BRCA1 or BRCA2, or both. We included women who had had risk-reducing mastectomy or RRSO, or both. We included women with or without a diagnosis of breast or tubo-ovarian cancer.

Types of interventions

We sought to include the following:

- psychological interventions such as cognitive behavioural therapy, behavioural therapy, mindfulness-based stress reduction (MBSR);
- psychoeducational, to include information about RRSO-related sexual problems including vaginal health, relaxation training, and body awareness;
- psychosexual interventions such as sexual-health education and rehabilitation training after risk-reducing surgery; or
- all of the above.

We compared these interventions at baseline and at various time points postintervention.

Types of outcome measures

Primary outcomes

- Quality of life: improved quality of life assessed at specified time points during or postintervention, measured using a scale that has been validated through reporting of norms in a peer-reviewed publication such as the 36-Item Short Form Health Survey (SF-36), Ware 1998, or the cancer generic EORTC QLQ-C30 questionnaire (Fayers 2002). Menopause-Specific Quality of Life Intervention (MENQOL-Intervention) and a modified version (Hilditch 1996; Lewis 2005).
- Psychological distress: such as anxiety, depression or cancer worry measured using a scale that has been validated through reporting of norms in a peer-reviewed publication, such as Impact of Event Scale (Horowitz 1979), the Beck Depression Inventory (Beck 1974), or the General Health Questionnaire (Goldberg 1979).

Secondary outcomes

- Sexual functioning measured using a scale that has been validated through reporting of norms in a peer-reviewed publication, such as the Brief Symptom Inventory (Derogatis 1983), the Female Sexual Function Index (Rosen 2000), or the Female Sexual Distress Scale (Derogatis 2002).
- Body image measured using the Body Image Scale (Hopwood 2001).
- Psychosocial issues to include cognitive, emotional, and spiritual.

We included studies with different outcomes than those mentioned above provided that they measured the same construct.

We presented a 'Summary of findings' table for each study and reported the following outcomes listed in order of priority (see Data synthesis).

- Menopause-specific quality of life
- Psychological distress
- Sexual function
- Sexual distress
- Body image
- Sexual self-efficacy
- Sexual knowledge
- Participant satisfaction

Search methods for identification of studies

There were no language restrictions for our searches. We searched for papers in all languages and translated to English as necessary.

Electronic searches

In order to identify studies for inclusion in the review, we developed detailed search strategies for each of the following electronic databases (search date 24th April 2019).

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 4) in the Cochrane Library (Appendix 1).
- MEDLINE via Ovid (1995 to April week 2 2019) (Appendix 2).

- Embase via Ovid (1995 to 2019 week 16) ([Appendix 3](#)).
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) via Ebsco (1995 to 24 April 2019) ([Appendix 4](#)).
- PsycINFO via Ovid (1995 to 24 April 2019) ([Appendix 5](#)).
- Web of Science via Web of Knowledge.com (1995 to 24 April 2019) ([Appendix 6](#)).
- Scopus via SciVerse @ Elsevier (1995 to 18 January 2018) (we used the same key terms and free text as for the other strategies).

Searching other resources

Unpublished and grey literature

- National Cancer Institute (www.cancer.gov/about-cancer/treatment/clinical-trials) (searched 25 April 2019)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) (searched 25 April 2019).
- ISRCTN registry (www.isrctn.com/) (searched 25 April 2019).
- EThOS (ethos.bl.uk/Home.do) (searched 25 April 2019).

Handsearching

In order to identify any unpublished studies, we handsearched the reference lists of included studies and previous systematic reviews. We searched conference abstracts from the following sources from 2010 to date.

- Association of Genetic Nurse Counsellors
- Irish Society of Human Genetics
- Cancer Genetics Spring Meeting
- European Society of Human Genetics

- International Psycho Oncology Society
- American Psycho Oncology Society
- Gynecologic Oncology (Annual Meeting of the Society of Gynecologic Oncology)
- Annual Meeting of the European Society of Medical Oncology
- American Society of Clinical Oncology

Data collection and analysis

Selection of studies

We imported all study titles identified by the searches into Covidence and removed duplicates ([Covidence](#)). Two review authors (LJ and JR) independently screened the keywords, titles, and abstracts of electronic citations, excluding studies that clearly did not meet the inclusion criteria. Any disagreements were resolved by discussion amongst all review authors. Following screening, we obtained the full-text copies of potentially relevant references. Two review authors (LJ and JR) independently assessed the eligibility of the retrieved citations for inclusion. In case of differences of opinion, we planned to seek out the opinions of the other review authors (DF, PM, and MD), but this was not necessary. We planned that if additional information was needed to ascertain eligibility, we would contact the study authors, but this was not necessary. We identified and excluded duplicate reports and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We documented studies excluded after full-text assessment, providing the reasons for their exclusion in the 'Characteristics of excluded studies' table. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.

Figure 1. (Continued)

Data extraction and management

Two review authors (LJ and JR) independently extracted data from the original report using a data extraction template developed in Covidence and taking guidance from the Cochrane Effective Practice and Care Group (Cochrane EPOC 2013) (Appendix 7). The template was then developed by the main review author (LJ) for the included studies. Any disagreements would have been resolved by consensus between the two review authors or amongst all review authors (LJ, JR, DF, PM, and MD), but this was not necessary.

We used the adapted data extraction template for this review and, where possible, extracted the following information from the included studies.

- Author, year of publication, and journal citation (including language).
- Country of origin.
- Aim and inclusion criteria.
- Study design, methodology.
- Study population:
 - * the number of participants eligible;
 - * participant characteristics;
 - * age;
 - * affected or healthy at risk;
 - * type of cancer;
 - * type of risk-reducing surgery;
 - * BRCA1 or BRCA2 mutation.
- Intervention details:
 - * who delivered it;
 - * duration and number of sessions;
 - * mode of delivery;
 - * content of intervention;
 - * name of validated instruments.
- Outcomes:
 - * definition of outcome;
 - * time when outcome measured, e.g. one month, six months postsurgery;
 - * unit of measurement.
- Results:
 - * the number of participants evaluated at follow-up;
 - * reasons for loss to follow-up;
 - * how study handled missing responses if stated and the actual results;
 - * quality of life and secondary outcome measures final values and standard deviation (SD) of outcome;
 - * recorded number of participants assessed at each endpoint in the treatment arm and at follow-up to estimate the mean difference (MD) between treatment arm and its standard error.

We planned that had we found more than one publication of the same study, we would use the most recent publication for data extraction and collate multiple reports of the same study as the unit of interest in the review. This was not applicable for this version of the review but may be relevant in a future update.

Assessment of risk of bias in included studies

Two review authors (LJ and JR) independently assessed the risk of bias for each included study and reported this information in the 'Risk of bias' table as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and for non-randomised studies using the ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions) tool (Sterne 2016), as shown in Table 1 and Table 2 (see [Risk of bias in included studies](#)).

Measures of treatment effect

We presented mean differences (MDs) for outcome measures on the studies included in the review. We calculated effect sizes on the basis of means, SDs to indicate the size of the change over time in the intervention group for each outcome measure in the study reviewed. In each case a 95% confidence interval (CI) was generated around the MD score for each outcome measure. This was based on the standard error (SE) calculated using the number of women in the treatment arm for each outcome at the endpoints (Table 3; and Table 4).

It is unlikely that most psychosocial studies will use the same measurement scale to assess quality of life and emotional well-being and related constructs, and in such case in any future update of this review where additional studies are included, we will use the standardised mean difference (SMD). We will calculate effect sizes on the basis of means, SDs, and sample sizes for each study condition. We will also analyse the SE by number of women in the treatment arm and number of women at endpoints.

Unit of analysis issues

Had there been more than one study with a longitudinal design with repeated observations on participants, we would have defined several outcomes based on different periods of follow-up and conducted separate analyses, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). This was unnecessary as there was only one study with repeated observations, and the mean score for all of these observations is presented in Table 3.

Dealing with missing data

We did not impute missing data for any of the outcomes.

Assessment of heterogeneity

As there was insufficient high-quality data in only two included studies, we did not perform a meta-analysis or any assessment of heterogeneity.

Assessment of reporting biases

We did not assess for potential reporting bias as only two studies were included in the review.

Data synthesis

As only one RCT and one NRS were included in the review, there were no appropriate data to pool.

'Summary of findings' and GRADE assessment

Where possible, we have presented the overall certainty of the evidence for each outcome (see [Types of outcome measures](#)) according to the GRADE approach, which takes into account issues not

only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We created a 'Summary of findings' table (Summary of findings 2) based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), employing GRADEpro GDT (GRADEpro GDT 2015). We used the GRADE checklist and GRADE Working Group definitions for certainty of evidence (Meader 2014).

- High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

As only two studies were included in the review, subgroup analysis was not possible. If appropriate we will carry out subgroup analysis in future updates of the review.

Sensitivity analysis

As only two studies were included in the review, there was no need to conduct sensitivity analysis. If appropriate we will carry out sensitivity analysis in future updates of the review.

RESULTS

Description of studies

Results of the search

The search identified 9197 references, of which 4241 were duplicate references and were excluded. We screened 4956 references and excluded 4920 as irrelevant; these included editorials, commentaries, letters, and meetings abstracts. We retrieved the full-text articles for 36 references (two of which related to the same studies, leaving a total of 34 unique studies). Two review authors (LJ, JR) independently assessed these articles and excluded 34 references as they did not meet the inclusion criteria. We included two studies in the review (Bober 2015; van Driel 2019a).

Included studies

Setting

van Driel 2019a was an RCT that recruited participants from a highly specialised family cancer clinic of the university medical centre Groningen in the Netherlands.

In Bober 2015, a prospective cohort study, participants were selected from three Boston-area hospitals through clinics for women at high risk for tubo-ovarian and breast cancer, from gynaecological surgeons and patient databases at these institutions. Women were also recruited via community newsletters from Facing Our Risk of Cancer Empowered (FORCE), a national advocacy group for BRCA1 and BRCA2 women.

Inclusion criteria

van Driel 2019a included women who had undergone RRSO before the age of 52 years and reported at least two moderate-to-severe menopausal symptoms in the preceding two weeks.

Bober 2015 included English-speaking women under the age of 50 years who had undergone RRSO for tubo-ovarian cancer risk reduction one year prior to enrolment; endorsed at least one distressing symptom of sexual dysfunction on the Sexual Problem Subscale of the Sexual Function Questionnaire; and who was a BRCA1 or BRCA2 carrier.

Exclusion criteria

van Driel 2019a excluded women undergoing cancer treatment at the time of inclusion, women receiving psychiatric care, and women who had insufficient understanding of the Dutch language to allow them to complete the questionnaires.

Bober 2015 excluded women with a history of tubo-ovarian cancer, pelvic radiation, or chemotherapy within the previous year. Women with other cancers were not excluded unless active treatment had ended less than a year prior to enrolment.

Study design and methodology

van Driel 2019a was an RCT where women were randomised to an eight-week mindfulness-based stress reduction (MBSR) training programme or usual care.

Bober 2015 was a single-arm trial design without a control group. Assessments were completed at baseline and two months postintervention. This was a feasibility study so, by definition, the authors did not set out to assess effectiveness of the intervention in a rigorous manner.

Study population

van Driel 2019a included 66 participants: MBSR (n = 34) and usual care (n = 32). Women were BRCA carriers with a mean age of 47.7 years (MBSR 47.0 years, usual care 48.5 years). Of the total cohort, 17 women had a history of breast cancer, 9 in the intervention group and 8 in the control group; 31 had undergone risk-reducing mastectomy, 19 in the intervention group and 12 in the control group; and 19 were using hormone replacement therapy, 11 in the intervention group and 8 in the control group.

Bober 2015 included an evaluable sample of 37 women. Participants were all BRCA carriers with a mean age of 44.42 years (n = 35). Mean years since RRSO was 3.84 (n = 36). Of the total cohort, 14 women had a history of breast cancer, and 15 were on medication for depression, anxiety, pain, or hot flashes.

Intervention details

Mindfulness-based stress reduction

In van Driel 2019a the intervention consisted of an eight-week MBSR training programme. This comprised weekly sessions of 2.5 hours each, a silent retreat evening lasting 4 hours, and a commitment to performing mindfulness-based exercises at home for 30 to 45 minutes 6 days a week using instructions provided on an MP3 player.

The usual care group consisted of information provided by a specialist nurse during the intake visit. This covered lifestyle advice for

hot flashes, night sweats, vaginal dryness, sexual functioning, cardiovascular health, and bone health.

An information booklet summarising the usual care information was given to both groups, and approximately 12 weeks postrandomisation all participants were offered a repeat appointment with the nurse to address any issues.

All participants completed questionnaires at baseline and 3, 6, and 12 months postrandomisation.

Validated instruments

Menopause-specific Quality of Life questionnaire (MENQOL) (Hilditch 1996), Female Sexual Function Index (FSFI) (Rosen 2000), Female Sexual Distress Scale (FSDS) (Derogatis 2002), Generalised Anxiety Disorder 7 (GAD-7) (Spitzer 2006), Patient Health Questionnaire 2 (PHQ-2) (Kroenke 2003).

Outcome

Mindfulness-based stress reduction improved menopause-specific quality of life over both the short and long term in women with at least two moderate-to-severe menopausal symptoms after RRSO. Mindfulness-based stress reduction did not improve sexual functioning or sexual distress.

Psychoeducational session

In Bober 2015 the intervention comprised a single, half-day psychoeducational group session, take-home educational materials, and two follow-up tailored telephone counselling calls. Patient-reported assessments of sexual health and psychological functioning were completed in-person immediately prior to the psychoeducational session (baseline) and by mail two months following the session.

The intervention was facilitated by the lead investigator, a clinical psychologist, and an expert in sexual rehabilitation after cancer treatment.

The 3.5-hour group session was structured around three modules, as follows.

- Module 1: focused on psychoeducation about RRSO-related sexual problems, including improving vaginal health.
- Module 2: focused on relaxation training and body awareness.
- Module 3: was guided by principles of mindfulness-based cognitive therapy, such as addressing negative assumptions related to sexual self-esteem.

In the final portion of the group session (Module 3), women created an individual action plan. Women completed a 'Next Steps' worksheet, which identified the problems they wanted to address and at least two actionable steps that they could take based on what they had learned. It was explained that the worksheet would be reviewed during the upcoming phone call.

Take-home educational materials

Materials included instructions for mindfulness-based body scan and muscle relaxation exercises. Information about vaginal dila-

tors, personal products, and resources for sexual-health websites and books.

Telephone counselling

Tailored individual telephone counselling was provided to each woman on two occasions. The first telephone session two to four weeks post-educational session dealt with remaining questions from the psychoeducational group, and action plans were reviewed and modified if needed to help women move their personalised goals forward. The second telephone counselling session was a 'booster' to help women review and consolidate their progress and plan for maintenance moving ahead.

Validated instruments

Female Sexual Function Index (FSFI) (Rosen 2000), Brief Symptom Inventory-18 (Derogatis 1983), Sexual Self-Efficacy Scale (Desrochers 2009), Sexual Knowledge Scale (Robinson 1999), participant satisfaction (Bober 2015).

Outcome

Women showed significant improvement on both sexual function and psychological distress from baseline to postintervention measured at two months.

Excluded studies

We excluded 31 studies for the following reasons.

- Twenty studies were excluded as there was no intervention, and only patient-reported outcome measures in response to questionnaires or data from medical records were used (Alamouti 2015; Altschuler 2008; Geiger 2007; Hooker 2014; Isern 2008; Julian-Reynier 2010; Kash 2000; Kim 2013; King 2009; Koslow 2013; Kotsopoulos 2017; Laarhoven 2011; Lorenz 2014; McCarthy 2017; Mutter 2015; Shigehiro 2016; Spear 2008; Tercyak 2007; Tollin 2013; Westin 2011).
- Two studies were excluded as they were concerned with decision analysis in relation to risk management (Culver 2011; Meijers-Heijboer 2000).
- Two studies were excluded as the focus was on timing of risk-reducing surgery (Harmsen 2015b; Landsbergen 2010).
- Four studies were excluded as participants were not BRCA carriers or had not had risk-reducing surgery (Ackermann 2006; Fang 2006; Fang 2009; Lodder 2002).
- Two studies used an intervention of supportive expressive group therapy or enhanced counselling, but not all women had risk-reducing surgery or were BRCA carriers (Esplen 2004; Miller 2005).
- One study was a duplicate of an included study (van Driel 2019a).

Risk of bias in included studies

We evaluated risk of bias using the Cochrane 'Risk of bias' tool (Table 1) (Higgins 2011a). Results of the individual studies (one RCT and one NRS) are presented in Characteristics of included studies and Figure 2. We applied the ROBINS-1 tool to evaluate risk of bias of the NRS (Table 2).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Effects of interventions

See: [Summary of findings for the main comparison Mindfulness-based stress reduction training versus usual care for female BRCA carriers post-risk-reducing surgery](#); [Summary of findings 2 Psychosocial intervention to improve sexual health versus no intervention for adult women, 18 years of age or older, who tested positive for a pathogenic mutation in BRCA1 or BRCA2 and who had had risk-reducing surgery](#)

As two heterogeneous studies were included no meta-analysis was possible. The RCT reporting MBSR was effective at improving quality of life in the short and long term for women with menopausal symptoms after RRSO as compared to usual care ([van Driel 2019a](#)); however, it was not associated with an improvement in sexual functioning or distress. The data in the [Summary of findings for the main comparison](#) reports the difference between groups at the 12 month point. At 3 (T1) and 12 (T3) months, there were improvements in the MENQOL for the MBSR group compared with the usual care group (both $P = 0.04$). At 3 months, mean MENQOL scores were 3.5 (95% confidence interval (CI) 3.0 to 3.9) and 3.8 (95% CI 3.3 to 4.2) for the MBSR and usual care groups, respectively; at 12 months, the corresponding values were 3.6 (95% CI 3.1 to 4.0) and 3.9 (95% CI 3.5 to 4.4). No significant differences were found between the MBSR and usual care groups for the other scores. At randomisation (T0), 63% (41/65) of women reported 5 or more complaints with a bothersome score of 6 or higher (scale ranged from 1 to 8). Differences in improvements were found for the MENQOL total score (T1: 0.56, $P = 0.04$; T3: 0.56, $P = 0.04$) and for the vasomotor (T1: 0.93, $P = 0.04$; T3: 0.98, $P = 0.02$) and physical (T1: 0.65, $P = 0.01$; T3: 0.69, $P = 0.03$) subscales in the MBSR group compared with the usual care group at 3 and 12 months after the start of the intervention. At six months, there was an improvement in the MBSR group compared with the usual care group ($P = 0.31$), but there was little difference in the psychosocial and sexual subscales of the MENQOL between the MBSR and usual care group at any assessment point. A clinically relevant improvement (≥ 1 improvement in MENQOL total score) was also seen in 28.6% of the MBSR group compared with 16.7%

of the usual care group at T1. Regarding the secondary outcomes, 94% (61/65) of women reported clinically relevant sexual dysfunction, and 65% (42/65) reported clinically relevant sexual distress at randomisation (T0); however, there was little difference observed between the MBSR and usual care group for the FSDS and FSFI total scores or subscales at any assessment points ([Summary of findings for the main comparison](#)).

The NRS reported change in psychosexual adjustment from baseline to postintervention (median 2.3 months) using measures of FSFI ($n = 34$), which yielded change with a mean of 3.91, SD 9.12, $t = 2.50$, $P = 0.018$, and Cohen's $d = 0.43$ ([Bober 2015](#)). The Brief Symptom Inventory, Global Severity Index yielded a mean change of 3.92, SD 5.94, $t = 4.01$, $P < 0.001$, and Cohen's $d = 0.66$. The Sexual Self-Efficacy Scale yielded change with a mean of 12.14, SD 20.56, $t = 3.59$, $P < 0.001$, and Cohen's $d = 0.59$. The Sexual Knowledge Scale ($n = 36$) reported mean change of 1.08, SD 1.50, $t = 4.33$, $P < 0.001$, Cohen's $d = 0.72$. There was no comparison group. Women in the study showed significant improvement in overall sexual function, reduced psychological distress, and perceived sexual self-efficacy and increased knowledge about sexual side effects. Moderate-to-moderately-large change effects were reported on some of the subscales such as desire, arousal, and anxiety. There were small to moderate change effect sizes for the FSFI total score and on the subscales of satisfaction and pain as well as on the somatisation subscale. The subscales for lubrication and orgasm showed small improvement effects. We assessed the overall certainty of the evidence as very low for all outcomes ([Summary of findings 2](#)).

The participant satisfaction questionnaire showed that all 37 participants reported having enjoyed participating in the psychoeducation group, and 100% reported that they were "certain" or "very certain" that they had learned new skills to help them cope with the side effects of having their ovaries removed, whilst 98% felt more empowered to address sexual problems and 95% reported that they were satisfied with the content of the group session.

Body image and spiritual outcomes were not addressed by either of the studies.

The authors of this study draw attention to the essence of mindfulness-based cognitive therapy theory to help explain the differences in the size effects of the subscales for the FSFI. This therapy is focused on changing the function of the psychological event rather than changing the event itself, so for this cohort of women who had undergone RRSO, although they would be unable to change the physical impact of surgically induced menopause such as diminished intensity of orgasm and loss of lubrication resulting in discomfort, they were given the skills to learn to adapt to and positively cope with other aspects of their sexual experience. See [Table 4](#) for the change from baseline to postintervention.

DISCUSSION

Summary of main results

We found limited evidence from two included studies reporting on different outcomes ([Bober 2015](#); [van Driel 2019a](#)). The RCT showed that MBSR improved menopause-specific quality of life over both the short and long term in women with at least two moderate-to-severe menopausal symptoms after RRSO, but the intervention did not improve sexual functioning ([van Driel 2019a](#)). The improvement in the total MENQOL score was mainly the result of improvements in the subscales of vasomotor (i.e. burden caused by hot flushes, night sweats, and sweating in general) and physical symptoms (i.e. burden caused by stamina reduction, aches, and urination frequency). The average difference on a seven-point scale in the vasomotor subscale and the physical subscale was 0.93 and 0.65 points, respectively. Clinicians and patients could therefore expect a modest-to-moderate reduction of perceived burden (i.e. bother) by vasomotor and physical symptoms of approximately 13% and 9%, respectively.

The NRS showed improvement in sexual adjustment from baseline to postintervention in women with a deleterious BRCA mutation who had RRSO but no history of ovarian cancer ([Bober 2015](#)). Almost 38% of the cohort had a history of breast cancer, but the focus of the study was psychosexual adjustment following RRSO. The limited evidence from this study also suggests that a psychosexual intervention following RRSO can improve psychological distress. The results must be interpreted with caution as they come from one small feasibility study with a very small number of participants ($n = 37$).

Differences in study populations may explain some of the variations. Another difference was that the MBSR protocol used in the RCT was a general protocol, whereas the intervention in the NRS specifically targeted sexual difficulties. The two studies had heterogeneous populations, with some women having a diagnosis of breast cancer and some not, but the diagnosis of genetic predisposition to cancer entails psychological and physical sequelae that persist lifelong ([Modaffari 2019](#)), and this review focused on interventions for BRCA carriers with or without a cancer diagnosis.

Overall completeness and applicability of evidence

We found no studies of psychosocial interventions in female BRCA mutation carriers who had risk-reducing mastectomy. We found only one study that measured menopause-specific quality of life after RRSO.

Quality of the evidence

We assessed the certainty (quality) of the evidence as very low across studies. The decrease in certainty was the difference between an RCT and the NRS both starting at opposite ends of the GRADE ranking spectrum. Given that there were only two included studies, each with different methods, the potentially large impact if the average effect of one study differs in direction from the other, as was the case in this review, must be acknowledged. See [Summary of findings 2](#).

Potential biases in the review process

The search for this review was extensive and generated a number of studies, of which most were irrelevant. Searching for BRCA genes encompasses science, surgery, and cancer, and it is possible that the search was more weighted to particular outcomes. Our review was focused on a very specific group of women on which studies can be difficult to carry out as numbers are relatively small.

Agreements and disagreements with other studies or reviews

Previous studies and reviews are divided on the benefit that psychosocial interventions can offer to women with breast or gynaecological cancer, or both. These previous studies and reviews were not included in our review, as they did not meet our review criteria. Most were not specific to women with a deleterious BRCA mutation but more generally to sporadic breast cancer or gynaecological cancers.

A Cochrane Review reported on interventions for psychosexual dysfunction in women treated for gynaecological malignancy and found five RCTs of a medical or psychological intervention ([Flynn 2009](#)). The psychological interventions included access to a clinical nurse specialist, psychoeducational group therapy, and couple-coping intervention. The authors concluded that all three of these studies were of poor methodological quality.

The authors of [Brotto 2012](#) evaluated a mindfulness-based cognitive behavioural intervention for sexual dysfunction in women who had a diagnosis of endometrial or cervical cancer. The study had a wait-list control, and results showed that the treatment led to significant improvements in all of their validated measures.

A systematic review and meta-analysis by [van Driel 2019b](#) reviewed the evidence on the effectiveness of psychological interventions in reducing symptoms associated with menopause in women who had either a natural or treatment-induced menopause. They identified 12 RCTs, and found that psychological interventions reduced hot flush bother in the short and medium term and menopausal symptoms in the short term. They also found a lack of studies reporting on the influence of psychological interventions on sexual functioning.

Significantly, [Bober 2018](#) extended the previous work included in this review and carried out a similar psychosexual intervention on women who had received treatment for tubo-ovarian cancer. Results showed significant improvements in overall sexual functioning and psychological distress that were maintained at six months follow-up.

Applying group-based cognitive-behavioural stress management, [Stagl 2015](#) reported on an 11-year follow-up of an RCT for women

with breast cancer. Their results showed that women who had received cognitive-behavioural stress management in the few weeks following their surgery reported better quality of life and depressive symptoms as well as better physical and emotional well-being than those women in the control group.

Many studies have reported on quality of life in breast and tubal-ovarian cancer and BRCA carriers, but none following a psychosocial intervention. A systematic review by [Razdan 2016](#) reported on quality of life among patients after bilateral prophylactic mastectomy and included 22 studies, but all used patient-reported outcomes which showed that following bilateral prophylactic mastectomy, women reported high psychosocial well-being and positive body image. The authors concluded that the methodological quality of the studies evaluated was less than ideal.

An integrative review of the literature on body image after bilateral prophylactic mastectomy in BRCA carriers highlighted the retrospective design of most of the 13 included studies ([McGaughey 2006](#)). Only two studies evaluated body image before and after bilateral prophylactic mastectomy using questionnaires or qualitative interviews, but none offered an intervention. A bibliographic review of the literature from 1974 to 2007 provided an informative and historical review of health-related quality of life in breast cancer patients ([Montazeri 2008](#)). There were no specific references to BRCA patients, as much of the data were pre-BRCA testing, but the author notes that the research in this area has made a considerable contribution to improving breast cancer care, with the caveat that the exact benefit of the studies was hard to define.

AUTHORS' CONCLUSIONS

Implications for practice

The purpose of this review was to identify psychosocial interventions available to women with a deleterious BRCA mutation who had undergone risk-reducing surgery, given that a clear need for such interventions has been identified in the literature. The lack of evidence for psychosocial interventions identified by this review raises the question of why research findings are not being translated into or further developed for use in clinical practice in the form of interventions for this group of women. The absence of such interventions highlights the need for partnership working between researchers and clinicians in this specific area. Next-generation sequencing, along with targeted cancer treatments, increasing knowledge around the biology of cancers, and the results of the 100K Genome Project, will open up genetic testing to many more women. As long as surgical interventions remain the dominant risk-reducing option and management of women with a deleterious BRCA gene, health professionals will have a responsibility to ensure there is provision to holistically manage the outcomes of such surgery. The authors of one study included in this review argue that

if healthcare providers felt that they had resources to offer patients for treatment-related sexual dysfunction, they would be more encouraged to address these issues with them prior to surgery, which could also encourage high-risk women to choose to undergo risk-reducing surgery.

Best practice is that women receive pre-test counselling prior to genetic testing. Whilst this is generally the case, and genetic counselling is offered by trained and registered genetic counsellors or geneticists, the shift to mainstreaming of genetics will see counselling being provided by surgeons and oncologists who will have had some basic level of online training in providing genetic counselling. It remains to be seen how this variance in skill level of counselling will impact patients who are making life-changing decisions based on their genetic status.

Implications for research

Whilst there are numerous studies measuring self-report psychological and quality of life outcomes following risk-reducing surgery, the next step is to take these findings forward and develop interventions to improve the psychosocial well-being of this population. As our knowledge of cancer genomics and targeted treatments develop, it is imperative that psychosocial issues are managed alongside the scientific and molecular outcomes for patients undergoing genetic testing and making life-changing decisions.

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REFERENCES

References to studies included in this review

Bober 2015 {published data only}

Bober S, Recklitis C, Bakan J, Garber J, Patenaude A. Addressing sexual dysfunction after risk-reducing salpingo-oophorectomy: effects of a brief, psychosexual intervention. *Journal of Sexual Medicine* 2015;**12**(1):189-197.

van Driel 2019a {published data only}

van Driel CMG, de Bock GH, Schroevers MJ, Mourits MJ. Mindfulness-based stress reduction for menopausal symptoms after risk-reducing salpingo-oophorectomy (PURSUE study): a randomised controlled trial. *BJOG* 2019;**126**:402-11.

References to studies excluded from this review

Ackermann 2006 {published data only}

Ackermann S, Lux MP, Fasching PA, Strissl P, Renner SP, Poehls U, et al. Acceptance for preventive genetic testing and prophylactic surgery in women with a family history of breast and gynaecological cancers. *European Journal of Cancer Prevention* 2006;**15**(6):474-9.

Alamouti 2015 {published data only}

Alamouti R, Hachach-Haram N, Farhadi J. Multidisciplinary management of risk-reducing mastectomy and immediate reconstruction: treatment algorithm and patient satisfaction. *European Journal of Plastic Surgery* 2015;**38**(5):385-90.

Altschuler 2008 {published data only}

Altschuler A, Nekhlyudov L, Rolnick SJ, Greene SM, Elmore JG, West CN, et al. Positive, negative, and disparate - women's differing long-term psychosocial experiences of bilateral or contralateral prophylactic mastectomy. *Breast Journal* 2008;**14**(1):25-32.

Culver 2011 {published data only}

Culver JO, MacDonald DJ, Thornton AA, Sand SR, Grant M, Bowen DJ, et al. Development and evaluation of a decision aid for BRCA carriers with breast cancer. *Journal of Genetic Counseling* 2011;**20**(3):294-307.

Esplen 2004 {published data only}

Esplen MJ, Hunter J, Leszcz M, Warner E, Narod S, Metcalfe K, et al. A multicenter study of supportive-expressive group therapy for women with BRCA1/BRCA2 mutations. *Cancer* 2004;**101**(10):2327-40.

Fang 2006 {published data only}

Fang CY, Daly MB, Miller SM, Zerr T, Malick J, Engstrom P. Coping with ovarian cancer risk: the moderating effects of perceived control on coping and adjustment. *British Journal of Health Psychology* 2006;**11**(4):561-80.

Fang 2009 {published data only}

Fang CY, Cherry C, Devarajan K, Li T, Malick J, Daly MB. A prospective study of quality of life among women undergoing risk-reducing salpingo-oophorectomy versus gynecologic

screening for ovarian cancer. *Gynecological Oncology* 2009;**112**(3):594-600.

Geiger 2007 {published data only}

Geiger AM, Nekhlyudov L, Herrinton LJ, Rolnick SJ, Greene SM, West CN, et al. Quality of life after bilateral prophylactic mastectomy. *Annals of Surgical Oncology* 2007;**14**(2):686-94.

Harmsen 2015a {published data only}

Harmsen MG, Arts-de Jong M, Hoogerbrugge N, Maas AH, Prins JB, Bulten J, et al. Early salpingectomy (Tubectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers (TUBA study): a prospective non-randomised multicentre study. *BMC Cancer* 2015;**19**(15):593.

Hooker 2014 {published data only}

Hooker GW, King L, VanHusen L, Graves K, Peshkin BN, Isaacs C, et al. Long-term satisfaction and quality of life following risk reducing surgery in BRCA1/2 mutation carriers. *Hereditary Cancer Clinical Practice* 2014;**12**(1):1186-97. [DOI: [10.1186/1897-4287-12-9](https://doi.org/10.1186/1897-4287-12-9)]

Isern 2008 {published data only}

Isern AE, Tengrup I, Loman N, Olsson H, Ringberg A. Aesthetic outcome, patient satisfaction, and health-related quality of life in women at high risk undergoing prophylactic mastectomy and immediate breast reconstruction. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2008;**61**(10):1177-87.

Julian-Reynier 2010 {published data only}

Julian-Reynier C, Bouhnik AD, Mouret-Fourme E, Gauthier-Villars M, Berthet P, Lasset C, et al. Time to prophylactic surgery in BRCA1/2 carriers depends on psychological and other characteristics. *Genetics in Medicine* 2010;**12**(12):801-7.

Kash 2000 {published data only}

Kash KM, Ortega-Verdejo K, Dabney MK, Holland JC, Miller DG, Osborne MP. Psychosocial aspects of cancer genetics: women at high risk for breast and ovarian cancer. *Seminars in Surgical Oncology* 2000;**18**(4):333-8.

Kim 2013 {published data only}

Kim D, Kang E, Hwang E, Sun Y, Hwang Y, Yom CK, et al. Factors affecting the decision to undergo risk-reducing salpingo-oophorectomy among women with BRCA gene mutation. *Familial Cancer* 2013;**12**(4):621-8.

King 2009 {published data only}

King HM. Risk reduction decision making in women with BRCA1/2 gene mutations. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2009;**70**(2B):1347.

Koslow 2013 {published data only}

Koslow S, Pharmer LA, Scott AM, Stempel M, Morrow M, Pusic AL, et al. Long-term patient-reported satisfaction after contralateral prophylactic mastectomy and implant reconstruction. *Annals of Surgical Oncology* 2013;**20**(11):3422-9.

Kotsopoulos 2017 {published data only}

Kotsopoulos J, Sun P, Narod S. Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers response. *Journal of the National Cancer Institute* 2017;**109**(1):177. [DOI: [10.1093/jnci/djw177](https://doi.org/10.1093/jnci/djw177)]

Laarhoven 2011 {published data only}

Laarhoven HWM, Prins JB, Schlooz MS, Besselink RM, Bogemann L, Koolwijk MPA, et al. Patient empowerment by group medical consultations in the follow-up of breast cancer survivors and surveillance of women with a BRCA mutation. *Cancer Research* 2011;**71**:24 Suppl 3. [DOI: [10.1158/0008-5472.SABCS11-0T3-02-03](https://doi.org/10.1158/0008-5472.SABCS11-0T3-02-03)]

Landsbergen 2010 {published data only}

Landsbergen KM, Brunner HG, Manders P, Hoogerbrugge N, Prins JB. Educational-support groups for BRCA mutation carriers satisfy need for information but do not affect emotional distress. *Genetic Counseling: Medical, Psychological, and Ethical Aspects* 2010;**21**(4):423-37.

Lodder 2002 {published data only}

Lodder LN, Frets PG, Trijsburg RW, Meijers-Heijboer EJ, Klijn JG, Seynaeve C, et al. One year follow-up of women opting for presymptomatic testing for BRCA1 and BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). *Breast Cancer Research and Treatment* 2002;**73**(2):97-112.

Lorenz 2014 {published data only}

Lorenz T, McGregor B, Swisher E. Relationship satisfaction predicts sexual activity following risk-reducing salpingo-oophorectomy. *Journal of Psychosomatic Obstetrics & Gynaecology* 2014;**35**(2):62-8.

McCarthy 2017 {published data only}

McCarthy CM, Hamill JB, Kim HM, Qi J, Wilkins E, Pusic AL. Impact of bilateral prophylactic mastectomy and immediate reconstruction on health-related quality of life in women at high risk for breast carcinoma: results of the Mastectomy Reconstruction Outcomes Consortium Study. *Annals of Surgical Oncology* 2017;**24**(9):2502-8.

Meijers-Heijboer 2000 {published data only}

Meijers-Heijboer EJ, Verhoog LC, Brekelmans CTM, Seynaeve C, Tilanus-Linthorst MMA, Wagner A, et al. Genetic testing and prophylactic surgery in familial clusters of BRCA1 or BRCA2 mutation. *Gynakologe* 2000;**33**(10):768-9.

Miller 2005 {published data only}

Miller SM, Roussi P, Daly MB, Buzaglo JS, Sherman K, Godwin AK, et al. Enhanced counseling for women undergoing BRCA1/2 testing: impact on subsequent decision making about risk reduction behaviors. *Health Education & Behaviour* 2005;**32**(5):654-67.

Mutter 2015 {published data only}

Mutter RW, Frost MH, Hoskin TL, Johnson JL, Hartmann LC, Boughey JC. Breast cancer after prophylactic mastectomy (bilateral or contralateral prophylactic mastectomy), a clinical

entity: presentation, management, and outcomes. *Breast Cancer Research & Treatment* 2015;**153**(1):183-90.

Shigehiro 2016 {published data only}

Shigehiro M, Kita M, Takeuchi S, Ashihara Y, Arai M, Okamura H. Study on the psychosocial aspects of risk reducing salpingo-oophorectomy (RRSO) in BRCA1/2 mutation carriers in Japan: a preliminary report. *Japanese Journal of Clinical Oncology* 2016;**46**(3):254-9.

Spear 2008 {published data only}

Spear SL, Schwarz KA, Venturi ML, Barbosa T, Al-Attar A. Prophylactic mastectomy and reconstruction: clinical outcomes and patient satisfaction. *Plastic & Reconstruction Surgery* 2008;**122**(1):1-9.

Tercyak 2007 {published data only}

Tercyak KP, Peshkin BN, Brogan BM, DeMarco T, Pennanen MF, Willey SC, et al. Quality of life after contralateral prophylactic mastectomy in newly diagnosed high-risk breast cancer patients who underwent BRCA1/2 gene testing. *Journal of Clinical Oncology* 2007;**25**(3):285-91.

Tollin 2013 {published data only}

Tollin S. Prophylactic, risk-reducing surgery in unaffected BRCA positive women: quality of life, sexual functioning and satisfaction with decision. *Oncology Nursing Forum* 11 2013;**40**(6,S):E447.

Westin 2011 {published data only}

Westin SN, Sun CC, Lu KH, Schmeler KM, Soliman PT, Lacour RA, et al. Satisfaction with ovarian carcinoma risk-reduction strategies among women at high risk for breast and ovarian carcinoma. *Cancer* 2011;**117**(12):2659-67.

Additional references
Aaronson 1998

Aaronson NK. Assessing the quality of life of patients with cancer: east meets west. *European Journal of Cancer* 1998;**34**(6):767-9.

ACOG 2009

American College of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins-Gynecology, ACOG Committee on Genetics, Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstetrics and Gynecology* 2009;**113**(4):957-66.

Antoniou 2003

Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *American Journal of Human Genetics* 2003;**72**(5):117-30.

Ayres 2017

Ayres C, Ratnayake G, McNally O, Quinn M. Challenging salpingectomy as a risk-reducing measure for ovarian cancer: histopathological analysis of the tubo-ovarian interface in

women undergoing risk-reducing salpingo-oophorectomy. *International Journal of Gynecological Cancer* 2017;**27**(4):703-7.

Bai 2019

Bai L, Arver B, Johansson H, Sandelin K, Wickman M, Brandberg Y. Body image problems in women with and without breast cancer 6-20 years after bilateral risk-reducing surgery - a prospective follow-up study. *Breast* 2019;**44**:120-7.

Barofsky 2012

Barofsky I. Can quality or quality-of-life be defined?. *Quality of Life Research* 2012;**21**(4):625-31.

Beck 1974

Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. *Modern Problems of Pharmacopsychiatry* 1974;**7**(0):151-69.

Bober 2018

Bober SL, Recklitis CJ, Michaud AL, Wright AA. Improvement in sexual function after ovarian cancer: effects of sexual therapy and rehabilitation after treatment for ovarian cancer. *Cancer* 2018;**124**(1):176-82.

Brandberg 2008

Brandberg Y, Sandelin K, Erikson S, Jurell G, Liljegren A, Lindblom A, et al. Psychological reactions, quality of life, and body image after bilateral prophylactic mastectomy in women at high risk for breast cancer: a prospective 1-year follow-up study. *Journal of Clinical Oncology* 2008;**26**(24):3943-9.

Brotto 2012

Brotto LA, Erskine Y, Carey M, Ehlen T, Finlayson S, Heywood M, et al. A brief mindfulness-based cognitive behavioral intervention improves sexual functioning versus wait-list control in women treated for gynecologic cancer. *Gynecologic Oncology* 2012;**125**(2):320-5.

Campfield Bonadies 2011

Campfield Bonadies D, Moyer A, Matloff ET. What I wish I'd known before surgery: BRCA carriers' perspectives after bilateral salpingo-oophorectomy. *Familial Cancer* 2011;**10**(1):79-85.

Chay 2016

Chay WY, McCluggage WG, Lee CH, Köbel M, Irving J, Millar J, et al. Outcomes of incidental fallopian tube high-grade serous carcinoma and serous tubal intraepithelial carcinoma in women at low risk of hereditary breast and ovarian cancer. *International Journal of Gynecological Cancer* 2016;**26**(3):431-6.

Chen 2007

Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *Journal of Clinical Oncology* 2007;**25**(11):1329-33.

Chen 2017

Chen F, Gaitskell K, Garcia MJ, Albukhari A, Tsaltas J, Ahmed AA. Serous tubal intraepithelial carcinomas associated with high-grade serous ovarian carcinomas: a systematic review. *BJOG* 2017;**124**(6):872-8.

Cochrane EPOC 2013

Effective Practice, Organisation of Care (EPOC). Data collection form. EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services; 2013. epoc.cochrane.org/epoc-specific-resources-review-authors (accessed 9 June 2017).

Crum 2013

Crum CP, Herfs M, Ning G, Bijron JG, Howitt BE, Jimenez CA, et al. Through the glass darkly: intraepithelial neoplasia, top-down differentiation, and the road to ovarian cancer. *Journal of Pathology* 2013;**231**(4):402-12.

De Felice 2015

De Felice F, Marchetti C, Musella A, Palaia I, Perniola G, Musio D, et al. Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. *Annals of Surgical Oncology* 2015;**22**(9):2876-80.

Deeks 2001

Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001;**323**(7305):157-62.

den Heijer 2012

den Heijer M, Seynaeve C, Timman R, Duivenvoorden HJ, Vanheusden K, Tilanus-Linthorst M, et al. Body image and psychological distress after prophylactic mastectomy and breast reconstruction in genetically predisposed women: a prospective long-term follow-up study. *European Journal of Cancer* 2012;**48**(9):1263-8.

Derogatis 1983

Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychological Medicine* 1983;**13**(3):595-605.

Derogatis 2002

Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *Journal of Sex and Marital Therapy* 2002;**28**(4):317-30.

Desrochers 2009

Desrochers G, Bergeron S, Khalifé S, Dupuis MJ, Jodoin M. Fear avoidance and self-efficacy in relation to pain and sexual impairment in women with provoked vestibulodynia. *Clinical Journal of Pain* 2009;**25**(6):520-7.

Egger 1997

Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997;**315**(7121):1533-7.

Eleje 2016

Eleje GU, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, Okonkwo OO. Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. *Cochrane Database of Systematic Reviews* 2016, Issue 12. [DOI: [10.1002/14651858.CD012464](https://doi.org/10.1002/14651858.CD012464)]

Euhus 2015

Euhus DM. Risk-reducing mastectomy for BRCA gene mutation carriers. *Annals of Surgical Oncology* 2015;**22**(9):2807-9.

Evans 2015

Evans DG, Wisely J, Clancy T, Lalloo F, Wilson M, Johnson R, et al. Longer term effects of the Angelina Jolie effect: increased risk-reducing mastectomy rates in BRCA carriers and other high-risk women. *Breast Cancer Research* 2015;**17**:143.

Fayers 2002

Fayers P, Bottomley A, EORTC Quality of Life Group, Quality of Life Unit. Quality of life research within the EORTC - the EORTC QLQ-C30. *European Journal of Cancer* 2002;**38**(Suppl 4):S125-33.

Finch 2011

Finch A, Narod SA. Quality of life and health status after prophylactic salpingo-oophorectomy in women who carry a BRCA mutation: a review. *Maturitas* 2011;**70**(3):261-5.

Finch 2013

Finch A, Metcalfe KA, Chiang J, Elit L, McLaughlin J, Springate C, et al. The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. *Psycho-Oncology* 2013;**22**(1):212-9.

Flynn 2009

Flynn P, Kew F, Kisely SR. Interventions for psychosexual dysfunction in women treated for gynaecological malignancy. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: [10.1002/14651858.CD004708.pub2](https://doi.org/10.1002/14651858.CD004708.pub2)]

Ford 1998

Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *American Journal of Human Genetics* 1998;**62**(3):676-89.

Foster 2007

Foster C, Watson M, Eeles R, Eccles D, Ashley S, Davidson R, et al. Predictive genetic testing for BRCA1/2 in a UK clinical cohort: three-year follow-up. *British Journal of Cancer* 2007;**96**(5):718-24.

Frühauf 2013

Frühauf S, Gerger H, Schmidt HM, Munder T, Barth J. Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis. *Archives of Sexual Behavior* 2013;**42**(6):915-33.

Gahm 2010

Gahm J, Wickman M, Brandberg Y. Bilateral prophylactic mastectomy in women with inherited risk of breast cancer - prevalence of pain and discomfort, impact on sexuality, quality of life and feelings of regret two years after surgery. *Breast* 2010;**19**(6):462-9.

Gahm 2013

Gahm J, Hansson P, Brandberg Y, Wickman M. Breast sensibility after bilateral risk-reducing mastectomy and immediate

breast reconstruction: a prospective study. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2013;**66**(11):1521-7.

Galway 2012

Galway K, Black A, Cantwell M, Cardwell C, Mills M, Donnelly M. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: [10.1002/14651858.CD007064.pub2](https://doi.org/10.1002/14651858.CD007064.pub2)]

Genomics England 2019

Genomics England. www.genomicsengland.co.uk (accessed 9 May 2019).

Goldberg 1979

Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychological Medicine* 1979;**9**(1):139-45.

Gopie 2013

Gopie JP, Mureau MA, Seynaeve C, Ter Kuile MM, Menke-Pluymers MB, Timman R, et al. Body image issues after bilateral prophylactic mastectomy with breast reconstruction in healthy women at risk for hereditary breast cancer. *Familial Cancer* 2013;**12**(3):479-87.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 5 June 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Hall 2019

Hall E, Finch A, Jacobson M, Rosen B, Metcalfe K, Sun P, et al. Effects of bilateral salpingo-oophorectomy on menopausal symptoms and sexual functioning among women with a BRCA1 or BRCA2 mutation. *Gynecologic Oncology* 2019;**152**:145-50.

Hallowell 2012

Hallowell N, Baylock B, Heiniger L, Butow PN, Patel D, Meiser B, et al. Looking different, feeling different: women's reactions to risk-reducing breast and ovarian surgery. *Familial Cancer* 2012;**11**(2):215-24.

Harmsen 2015b

Harmsen MG, Hermens RP, Prins JB, Hoogerbrugge N, de Hullu JA. How medical choices influence quality of life of women carrying a BRCA mutation. *Critical Reviews in Oncology/Hematology* 2015;**96**(3):555-68.

Hartmann 2016

Hartmann LC, Lindor NM. Risk-reducing surgery in hereditary breast and ovarian cancer. *New England Journal of Medicine* 2016;**374**(24):2404.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011a

Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated

March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JPT, Altman DG, Sterne JAC, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hilditch 1996

Hilditch JR, Lewis J, Peter A, van Maris B, Ross A, Franssen E, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas* 1996;**24**:107-21.

Hopwood 2000

Hopwood P, Lee A, Shenton A, Baidam A, Brain A, Lalloo F, et al. Clinical follow-up after bilateral risk reducing ('prophylactic') mastectomy: mental health and body image outcomes. *Psycho-Oncology* 2000;**9**(6):462-72.

Hopwood 2001

Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. *European Journal of Cancer* 2001;**37**(2):189-97.

Horowitz 1979

Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. *Psychosomatic Medicine* 1979;**41**(3):209-18.

Jeffers 2014

Jeffers L, Morrison PJ, McCaughan E, Fitzsimons D. Maximising survival: the main concern of women with hereditary breast and ovarian cancer who undergo genetic testing for BRCA1/2. *European Journal of Oncology Nursing* 2014;**18**(4):411-8.

King 2003

King MC, Marks JH, Mandell JB, New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003;**302**(5645):643-6.

Kroenke 2003

Kroenke K, Spitzer RL, Williams JBW. The patient health questionnaire-2. *Medical Care* 2003;**41**:1284-92.

Langendam 2013

Langendam MW, Akl EA, Dahm P, Glasziou P, Guyatt G, Schünemann HJ. Assessing and presenting summaries of evidence in Cochrane Reviews. *Systematic Reviews* 2013;**23**(2):81.

Lengacher 2009

Lengacher CA, Johnson-Mallard V, Post-White J, Moscoso MS, Jacobsen PB, Klein TW, et al. Randomized controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer. *Psycho-Oncology* 2009;**18**(12):1261-72.

Lewis 2005

Lewis JE, Hilditch JR, Wong CJ. Further psychometric property development of the Menopause-Specific Quality of Life questionnaire and development of a modified version, MENQOL-Intervention questionnaire. *Maturitas* 2005;**50**(3):209-21.

Matloff 2009

Matloff ET, Barnett RE, Bober SL. Unraveling the next chapter: sexual development, body image, and sexual functioning in female BRCA carriers. *Cancer Journal* 2009;**15**(1):15-8.

Mavaddat 2013

Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al. EMBRACE. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *Journal of the National Cancer Institute* 2013;**105**(11):812-22.

McAlpine 2012

McAlpine JN, Porter H, Köbel M, Nelson BH, Prentice LM, Kalloger SE, et al. BRCA1 and BRCA2 mutations correlate with TP53 abnormalities and presence of immune cell infiltrates in ovarian high-grade serous carcinoma. *Modern Pathology* 2012;**25**(5):740-50.

McGaughey 2006

McGaughey A. Body image after bilateral prophylactic mastectomy: an integrative literature review. *Journal of Midwifery & Women's Health* 2006;**51**(6):e45-9. [DOI: [10.1016/j.jmwh.2006.07.002](https://doi.org/10.1016/j.jmwh.2006.07.002)]

Meader 2014

Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Systematic Reviews* 2014;**3**:82.

Metcalfe 2004

Metcalfe KA, Esplen MJ, Goel V, Narod SA. Psychosocial functioning in women who have undergone bilateral prophylactic mastectomy. *Psycho-Oncology* 2004;**13**(1):14-25.

Modaffari 2019

Modaffari P, Ponzone P, Ferrari A, Cipullo I, Liberale V, D'Alonzo M, et al. Concerns and expectations of risk-reducing surgery in women with hereditary breast and ovarian cancer syndrome. *Journal of Clinical Medicine* 2019;**8**(3):313. [DOI: [10.3390/jcm8030313](https://doi.org/10.3390/jcm8030313)]

Montazeri 2008

Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. *Journal of Experimental & Clinical Cancer Research* 2008;**27**:32. [DOI: [10.1186/1756-9966-27-32](https://doi.org/10.1186/1756-9966-27-32)]

NHS England 2015

NHS England. Clinical Commissioning Policy: Genetic testing for BRCA1 and BRCA2 mutations. www.england.nhs.uk/commissioning?s=BRCA (accessed 16 September 2017).

NICE 2013

National Institute for Health and Care Excellence. Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. Clinical guideline. www.nice.org.uk/guidance/cg164 (accessed prior to 18 September 2019).

Razdan 2016

Razdan SN, Patel V, Jewell S, McCarthy CM. Quality of life among patients after bilateral prophylactic mastectomy: a systematic review of patient-reported outcomes. *Quality of Life Research* 2016;**25**(6):1409-21.

Resta 2006

Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE, Strecker MN, et al. A new definition of genetic counseling: National Society of Genetic Counselor's Task Force report. *Journal of Genetic Counseling* 2006;**15**(2):77-83.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Robinson 1999

Robinson JW, Faris PD, Scott CB. Psychoeducational group increases vaginal dilation for younger women and reduces sexual fears for women of all ages with gynecological carcinoma treated with radiotherapy. *International Journal of Radiation Oncology & Biological Physics* 1999;**44**(3):497-506.

Robson 2003

Robson M, Hensley M, Barakat R, Brown C, Chi D, Poyner E, et al. Quality of life in women at risk for ovarian cancer who have undergone risk-reducing oophorectomy. *Gynecologic Oncology* 2003;**89**(2):281-7.

Rosen 2000

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *Journal of Sex & Marital Therapy* 2000;**26**(2):191-208.

Rosenberg 2016

Rosenberg SM, Ruddy KJ, Tamimi RM, Gelber S, Schapira L, Come S, et al. BRCA1 and BRCA2 mutation testing in young women with breast cancer. *JAMA Oncology* 2016;**2**(6):730-6.

Rosenthal 2017

Rosenthal AN, Fraser LS, Philpott S, Manchanda R, Burnell M, Badman P, et al. Evidence of stage shift in women diagnosed with ovarian cancer during Phase II of the United Kingdom Familial Ovarian Cancer Screening Study. *Journal of Clinical Oncology* 2017;**35**(13):1411-20.

Skirton 2010

Skirton H, Patch C, Voelckel MA. Using a community of practice to develop standards of practice and education for

genetic counsellors in Europe. *Journal of Community Genetics* 2010;**1**(4):169-73.

Spitzer 2006

Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalised anxiety disorder. *Archives of Internal Medicine* 2006;**166**:1092.

Stagl 2015

Stagl JM, Lechner SC, Carver CS, Bouchard LC, Gudenkauf LM, Jutagir DR, et al. A randomized controlled trial of cognitive-behavioral stress management in breast cancer: survival and recurrence at 11-year follow-up. *Breast Cancer Research & Treatment* 2015;**154**(2):319-28.

Stan 2013

Stan DL, Shuster LT, Wick MJ, Swanson CL, Pruthi S, Bakkum-Gamez JN. Challenging and complex decisions in the management of the BRCA mutation carrier. *Journal of Women's Health* 2013;**22**(10):825-34.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Unukovych 2012

Unukovych D, Sandelin K, Wickman M, Arver B, Johansson H, Brandberg Y, et al. Breast reconstruction in patients with personal and family history of breast cancer undergoing contralateral prophylactic mastectomy, a 10-year experience. *Acta Oncologica* 2012;**51**(7):934-41.

van Driel 2019b

van Driel CM, Stuursma A, Schroevers MJ, Mourits MJ, de Bock GH. Mindfulness, cognitive behavioural and behaviour-based therapy for natural and treatment-induced menopausal symptoms: a systematic review and meta-analysis. *BJOG* 2019;**126**:330-9.

van Oostrom 2003

van Oostrom I, Meijers-Heijboer H, Lodder LN, Duivenvoorden HJ, van Gool AR, Seynaeve C, et al. Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. *Journal of Clinical Oncology* 2003;**21**(20):3867-74.

Ware 1998

Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *Journal of Clinical Epidemiology* 1998;**51**(11):903-12.

Watson 2004

Watson M, Foster C, Eeles R, Eccles D, Ashley S, Davidson R, et al. Psychosocial impact of breast/ovarian (BRCA1/2) cancer-predictive genetic testing in a UK multi-centre clinical cohort. *British Journal of Cancer* 2004;**91**(10):1787-94.

References to other published versions of this review

Jeffers 2017

Jeffers L, Reid J, Fitzsimons D, Morrison PJ, Dempster M.
Interventions to improve psychosocial well-being in female

BRCA-mutation carriers following risk-reducing surgery.
Cochrane Database of Systematic Reviews 2017, Issue 12. [DOI:
[10.1002/14651858.CD012894](https://doi.org/10.1002/14651858.CD012894)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bober 2015

Methods	Prospective cohort study
Participants	BRCA1, BRCA2 mutation carriers. 37 participants enrolled. All had risk-reducing bilateral salpingo-oophorectomy. Have at least 1 distressing symptom of sexual dysfunction
Interventions	Psychosexual intervention integrating elements of cognitive behavioural therapy with sexual health education
Outcomes	Sexual function: desire, arousal, lubrication, orgasm, satisfaction, pain Psychological distress: somatisation, depression, anxiety Sexual self-efficacy Sexual knowledge
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Table 2

van Driel 2019a

Methods	Randomised controlled trial
Participants	66 female BRCA carriers who had undergone risk-reducing salpingo-oophorectomy before the age of 52 years and reported at least 2 moderate-to-severe menopausal symptoms in the 2 weeks prior to enrolment
Interventions	Mindfulness-based stress reduction training over an 8-week period vs usual care
Outcomes	Menopause-specific quality of life, sexual function, and sexual distress
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation performed by independent trial co-ordination centre via a web application using a computerised random number generator

van Driel 2019a (Continued)

Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very serious risk of bias due to lack of blinding of participants and personnel, attrition bias, and self-selection bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Due to the nature of the intervention assessors would be aware of the group
Incomplete outcome data (attrition bias) All outcomes	High risk	High loss to follow-up (outcomes only available for 48 of 66 enrolled participants)
Selective reporting (reporting bias)	Low risk	Study reported numbers of participants at each time point
Other bias	High risk	Self-selection bias as only one-third of eligible women chose to participate in the study

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ackermann 2006	Wrong population, not BRCA carriers and had not undergone risk-reducing surgery. Indication of study was the acceptance for genetic testing of untested women with a positive family history and their attitude toward prophylactic surgery.
Alamouti 2015	Questionnaire and PROMs Women completed a validated Breast-Q questionnaire detailing their experience in a number of domains including body image and perception, sexuality, and cosmetic outcome after their surgery. They also attended an individual interview for further analysis of patient experience and expectations, but there was no psychosocial intervention.
Altschuler 2008	Questionnaire and PROMs The study explored the nuances of women's satisfaction with risk-reducing mastectomy using a qualitative, open-ended format as part of a mailed survey.
Culver 2011	Wrong intervention The study indicator was decision-making needs and the use of a decision aid as an adjunct to genetic counselling. Phase 1 used focus group.
Espen 2004	Wrong indicator, and most women had not had risk-reducing surgery prior to intervention of 12 sessions of supportive-expressive group therapy that lasted 6 months. Before and after measures of psychosocial functioning, knowledge, and surveillance/surgery activities were completed. During the intervention and postintervention some participants underwent risk-reducing surgery.
Fang 2006	No intervention. Assessments of problem-focused coping, perceived control and distress were collected upon entry into the programme and again at 3-month follow-up. Behavioural adherence

Study	Reason for exclusion
	to screening during the 12-month period following programme entry was obtained from clinic records.
Fang 2009	Wrong study population, as not all were BRCA carriers or undergoing surgery and PROMs. The primary objective of the study was to prospectively assess quality of life among women at increased risk for tubo-ovarian cancer who were undergoing RRSO or serial screening. Participants were considering RRSO due to: 1) a family history of tubo-ovarian cancer, 2) a family history suggestive of a hereditary breast/ovarian pattern, and/or 3) the presence of a known disease-related gene mutation in the family.
Geiger 2007	Questionnaire and PROMs Retrospective data collected through a mailed survey
Harmsen 2015a	Wrong intervention - timing of surgical intervention. The indicator was the time participants chose to undergo standard RRSO (at age 35 to 40 (BRCA1) or 40 to 45 (BRCA2)) or an alternative strategy (risk-reducing surgery upon completion of childbearing and RRSO at age 40 to 45 (BRCA1) or 45 to 50 (BRCA2)).
Hooker 2014	Questionnaire and PROMs Data collected through a mailed survey.
Isern 2008	Surgical indication Indicator was the clinical evaluation of aesthetic results and complications. Patient satisfaction and quality of life were evaluated with 1 study-specific and 2 standardised health-related questionnaires administered at time of clinical follow-up.
Julian-Reynier 2010	Wrong indication - timing to risk-reducing surgery The aim of this prospective study was to investigate the psychosocial and medical factors that determine timing of prophylactic surgery in women carriers of a deleterious BRCA1 or BRCA2 mutation.
Kash 2000	Not all women had risk-reducing surgery. PROMs Women completed a questionnaire about genetic testing, psychological distress, and health beliefs.
Kim 2013	Wrong indication. No intervention The objective of this study was to identify factors that affect the decision to undergo RRSO in BRCA1 or BRCA2 mutations carriers in South Korea. Medical records were reviewed to collect data.
King 2009	Wrong population, as not all had undergone risk-reducing surgery. PROMs "137 unaffected, positive BRCA1/2 gene mutation carriers (42 who opted for prophylactic mastectomy, 95 who did not) served as participants. All women completed an on-line battery that assessed the following theory-based decision making variables: advantages and disadvantages of prophylactic mastectomy (normative decision theory), physician recommendation (shared decision making theory), cancer worry (affect theory), and information-seeking coping style."
Koslow 2013	Wrong intervention. PROMs, not all women underwent risk-reducing surgery Indicator was whether satisfaction and health-related quality of life differ between women who do and who do not undergo CPM in the setting of implant reconstruction using the BREAST-Q, a validated patient-reported outcome instrument.

Study	Reason for exclusion
Kotsopoulos 2017	Wrong indication, PROMs Whether or not bilateral oophorectomy reduces breast cancer risk among women with a BRCA1 or BRCA2 mutation. Data collected from questionnaires or by phone by a genetic counsellor or research assistant.
Laarhoven 2011	Not all women had risk-reducing surgery. Design for randomised controlled trial In order to fulfil the needs for psychosocial support and information, the study introduced group medical consultations. Primary outcome measures were empowerment and psychological distress (SCL 90). Secondary outcome measures were fear of cancer, information needs before the consultation and the received information, self-examination of the breasts, patient satisfaction, quality of life, and cost-effectiveness. Data were collected via self-reported questionnaires 1 week before the visit and at 1-week and 3-month follow-up.
Landsbergen 2010	Not all women had undergone risk-reducing surgery. Wrong indication - decision making Female BRCA mutation carriers were approached by a social worker after genetic test disclosure and offered participation in educational-support groups to meet their needs regarding BRCA-related information in order to support decision-making processes regarding cancer surveillance or prophylactic surgery.
Lodder 2002	PROMs 26 women were identified as BRCA1/BRCA2 mutation carriers and 37 as non-mutation carriers. Not all the mutation carriers had risk-reducing surgery. Study also included partners.
Lorenz 2014	Wrong population - not BRCA carriers A secondary analysis of quality of life measures collected in 85 women at high risk for tubo-ovarian cancer. Participants completed validated measures of mental, physical, and relationship health.
McCarthy 2017	Wrong indication - timing for risk-reducing mastectomy and reconstruction and PROMs. Patient-reported outcome data were prospectively collected as part of the Mastectomy Reconstruction Outcomes Consortium Study, and data on a subgroup of 204 high-risk women who elected to have risk-reducing mastectomy and immediate reconstruction were evaluated.
Meijers-Heijboer 2000	Decision-making behaviour
Miller 2005	Wrong indication. Not all women will had risk-reducing surgery The indicator was genetic counselling or enhanced genetic counselling to help participants anticipate their reactions to possible test outcomes and plan for postresult consequences.
Mutter 2015	Wrong indication, medical outcomes. PROMs Medical records were reviewed, and study-specific questionnaires were sent to all women.
Shigehiro 2016	Wrong study design. Qualitative interviews and PROMs Worry about cancer, emotional state, and cancer-specific distress level were evaluated using a 4-point Likert scale, the Profile of Mood States-Short Form, and the Impact of Event Scale-Revised, respectively, before and 1 year after the surgery. In addition, participants were interviewed regarding their expectations for the risk-reducing surgery, the effects of the surgery, and recovery from surgery, before surgery and at 1, 6, and 12 months after surgery.
Spear 2008	Wrong indication, wrong intervention

Study	Reason for exclusion
	Timing, type of mastectomy and reconstruction, complications, and cancer occurrence/recurrence were examined. Participants reported their level of satisfaction and willingness to undergo the procedure again.
Tercyak 2007	Wrong indication, wrong population - only 15% BRCA carriers Compared outcomes of patients who opted for immediate CPM versus those who did not. Study group particularly interested in the impact of CPM during the immediate postdiagnostic period (1 month after testing) and after the completion of adjuvant treatment (12 months after testing).
Tollin 2013	Wrong intervention As this was a web-based study, participants were able to complete all research instruments online.
Westin 2011	Not all study participants were BRCA carriers. PROMs Questionnaire package to ascertain demographic and clinical information as well as quality of life and beliefs regarding issues pertinent to women at high risk for developing breast and ovarian cancer. These questionnaires provided women with a variety of statements to describe their perceptions about screening, chemoprevention strategies, and risk-reducing surgery using Likert-based scales.

CPM: contralateral prophylactic mastectomy

PROMs: patient-reported outcome measures

RRSO: risk-reducing salpingo-oophorectomy

ADDITIONAL TABLES

Table 1. Interpretation of domain levels and overall risk of bias judgement in ROBINS-I (Continued)

Judgement	Within each domain	Across domains	Criterion
Low risk of bias	The study is comparable to a well-performed randomised trial with regard to this domain.	The study is comparable to a well-performed randomised trial.	The study is judged to be at low risk of bias for all domains.
Moderate risk of bias	The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-performed randomised trial.	The study provides sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.	The study is judged to be at low or moderate risk of bias for all domains.
Serious risk of bias	The study has some important problems in this domain.	The study has some important problems.	The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.
Critical risk of bias	The study is too problematic in this domain to provide any useful	The study is too problematic to provide any useful evidence and	The study is judged to be at critical risk

Table 1. Interpretation of domain levels and overall risk of bias judgement in ROBINS-I *(Continued)*

	evidence on the effects of intervention.	should not be used in any synthesis.	of bias in at least one domain.
No information	No information on which to base a judgement about risk of bias for this domain	No information on which to base a judgement about risk of bias	There is no clear indication that the study is at serious or critical risk of bias, and there is a lack of informa- tion in one or more key domains of bias (<i>a judgement is required for this</i>).

Table 2. ROBINS- I ROB in NRS

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Bober 2015	Moderate	No information	Low	No information	Low	Serious	Low
Support for judgement	<p>"to meet study eligibility, women needed to be <50, English speaking, have undergone RRSO for ovarian cancer risk reduction prior to enrolment, and endorse at least one distressing symptom of sexual dysfunction on the Sexual Problem Subscale of the Sexual Function Questionnaire.</p> <p>Exclusion criteria included history of ovarian cancer, pelvic radiation, or chemotherapy within the previous year. Women</p> <p>with a history of other cancers were not excluded unless active treatment had ended less than 1 year prior."</p>	There is no matching of a control group.	"trial was designed to improve subject satisfaction with sexual function, increase knowledge about sexual function after RRSO, increase self-efficacy to manage sexual side effects, and decrease psychological distress."	There is no comparator group.	"Forty-three women enrolled in the study and attended one of the scheduled groups (56% of eligible women screened). Six women did not return the postintervention assessment, despite reminders, yielding an evaluable sample of 37 women (86% completion rate)."	"The 3.5 hour group session was structured around 3 modules facilitated by the lead investigator... At approximately 2 and 4 weeks after the psychoeducational session, tailored, individual telephone counselling was provided to each participant by the lead investigator of the study"	"Differences in baseline and postintervention scores of the FSFI, BSI-18, sexual self-efficacy scale, and sexual knowledge scale were examined using the paired samples <i>t</i> -test. Analyses were repeated with the nonparametric Wilcoxon signed rank test. Results from nonparametric analyses were consistent with <i>t</i> -tests and therefore not included in this report... For outcome measures in which changes were

statistically significant, percentage change from baseline to postintervention was examined by calculating Cohen's *d* as a measure of effect size."

Table 2. ROBINS- I ROB in NRS *(Continued)*

BSI-18: Brief Symptom Inventory-18
FSFI: Female Sexual Function Index
RRSO: risk-reducing salpingo-oophorectomy

Table 3. Mindfulness-based stress reduction versus usual care

	T0	T1	T2	T3
MENQOL total score				
Usual care	3.8 (3.4 to 4.3)	3.8 (3.3 to 4.3)	3.7 (3.2 to 4.1)	3.9 (3.5 to 4.4)
MBSR	4.1 (3.7 to 4.5)	3.5 (3.0 to 3.9)	3.7 (3.2 to 4.1)	3.6 (3.1 to 4.0)
P	-	0.04	0.31	0.04
Vasomotor sub scale				
Usual care	4.2 (3.6 to 4.8)	4.1 (3.5 to 4.8)	4.2 (3.5 to 4.8)	4.3 (3.7 to 4.9)
MBSR	4.5 (4.0 to 5.1)	3.5 (2.9 to 4.1)	3.8 (3.1 to 4.4)	3.6 (3.0 to 4.2)
P	-	0.04	0.09	0.02
Psychosocial sub scale				
Usual care	3.7 (3.2 to 4.2)	3.6 (3.0 to 4.1)	3.6 (3.0 to 4.2)	3.8 (3.3 to 4.4)
MBSR	3.8 (3.3 to 4.3)	3.4 (2.8 to 3.9)	3.6 (3.0 to 4.2)	3.7 (3.1 to 4.3)
P	-	0.31	0.95	0.50
Physical sub scale				
Usual care	3.5 (3.1 to 3.9)	3.6 (3.2 to 4.0)	3.5 (3.0 to 3.9)	3.8 (3.3 to 4.2)
MBSR	3.5 (3.2 to 3.9)	3.0 (2.6 to 3.4)	3.3 (2.9 to 3.7)	3.2 (2.7 to 3.6)
P	-	0.01	0.32	0.03
Sexual sub scale				
Usual care	4.0 (3.1 to 4.8)	3.9 (3.0 to 4.7)	3.5 (2.7 to 4.3)	3.7 (2.9 to 4.4)
MBSR	4.4 (3.6 to 5.2)	4.1 (3.3 to 4.9)	4.2 (3.4 to 5.0)	4.0 (3.2 to 4.8)
P	-	0.66	0.39	0.77

MBSR: mindfulness-based stress reduction

MENQOL: Menopause-Specific Quality of Life questionnaire

Table 4. Change in psychosexual adjustment from baseline to postintervention

(n = 37)	Baseline		Postintervention		Change		95% CI
	M	SD	M	SD	M	SD	
Measure							
FSFI total (n = 34)	15.63	10.23	19.54	9.47	3.91	9.12	0.84 to 6.98
Desire	1.98	1.14	2.42	1.09	0.44	0.83	0.17 to 0.71
Arousal	2.69	1.98	3.68	1.84	0.98	1.86	0.38 to 1.58
Lubrication (n = 36)	2.38	2.09	2.97	2.05	0.58	2.03	-0.08 to 1.24
Orgasm	2.86	2.39	3.59	2.23	0.73	2.32	-0.02 to 1.48
Satisfaction	2.70	1.73	3.23	1.67	0.53	1.40	0.08 to 0.98
Pain	2.35	2.36	3.28	2.45	0.93	2.28	0.20 to 1.66
BSI-18 GSI	50.89	7.99	46.97	7.52	3.92	5.94	2.01 to 5.83
Somatisation	50.89	8.22	48.14	8.20	2.76	7.35	0.39 to 5.13
Depression	49.76	8.48	47.54	7.31	2.22	7.72	0.27 to 4.71
Anxiety	51.16	7.85	47.41	6.36	3.76	5.89	1.86 to 5.66
Sexual self-efficacy scale	63.54	24.98	75.68	18.38	12.14	20.56	5.52 to 18.76
Sexual knowledge scale	7.97	1.63	9.06	1.17	1.08	1.50	0.6 to 1.56
Change scores are expressed in absolute value.							

BSI-18: Brief Symptom Inventory-18
 CI: confidence interval
 FSFI: Female Sexual Function Index
 GSI: Global Severity Index
 SD: standard deviation

APPENDICES

Appendix 1. CENTRAL search strategy

- #1. MeSH descriptor: [Genes, BRCA1] this term only
- #2. MeSH descriptor: [BRCA1 Protein] this term only
- #3. MeSH descriptor: [Genes, BRCA2] this term only
- #4. MeSH descriptor: [BRCA2 Protein] this term only
- #5. BRCA* or brca*
- #6. (BRCA* or brca*) near/5 (carrier* or tumor* or tumour* or gene* or suppress* or protein* or mutat* or alter* or damage* or inherit* or heredit*)
- #7. #1 or #2 or #3 or #4 or #5 or #6
- #8. MeSH descriptor: [Prophylactic Surgical Procedures] this term only
- #9. MeSH descriptor: [Mastectomy] explode all trees
- #10. MeSH descriptor: [Ovariectomy] this term only
- #11. Any MeSH descriptor with qualifier(s): [Surgery - SU]
- #12. (risk reduc* or prophylactic) near/5 (surg* or mastectom* or RRM or ovar* or RRBSO or BSO or bilateral salpingo-oophorectom* or oophorectomy* or interven*)
- #13. #8 or #9 or #10 or #11 or #12
- #14. #7 and #13

Appendix 2. MEDLINE search strategy

1. Genes, BRCA1/
2. BRCA1 Protein/
3. Genes, BRCA2/
4. BRCA2 Protein/
5. (BRCA* or brca* or hereditary breast-ovarian cancer syndrome or hereditary breast ovarian cancer syndrome or HBOC).mp.
6. ((BRCA* or brca*) adj5 (carrier* or tumor* or tumour* or gene* or suppress* or protein* or mutat* or alter* or damage* or inherit* or heredit*)).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Prophylactic Surgical Procedures/
9. exp Mastectomy/
10. Ovariectomy/
11. surgery.fs.
12. ((risk reduc* or prophyla*) adj5 (surg* or procedur* or tech* or mastectom* or RRM or ovar* or RRBSO or BSO or bilateral salpin-go-oophorectom* or oophorectomy* or interven*)).mp.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13
15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomized.ab.
18. placebo.ab.
19. drug therapy.fs.
20. randomly.ab.
21. trial.ti.
22. groups.ab.
23. exp cohort studies/
24. exp case-control studies/
25. (cohort* or prospective* or retrospective* or (case* and (control* or series)))mp.
26. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. (animals not (humans and animals)).sh.
28. 26 not 27
29. 14 and 28

Key

[mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Appendix 3. Embase search strategy

1. tumor suppressor gene/
2. BRCA1 protein/

3. BRCA2 protein/
4. (BRCA* or brca*).mp.
5. ((BRCA* or brca*) adj5 (carrier* or tumor* or tumour* or gene* or suppress* or protein* or mutat* or alter* or damage* or inherit* or heredit*)).mp.
6. 1 or 2 or 3 or 4 or 5
7. prophylactic surgical procedure/
8. exp mastectomy/
9. ovariectomy/
10. surgery.fs.
11. ((risk reduc* or prophylactic) adj5 (surg* or mastectom* or RRM or ovar* or RRBSO or BSO or bilateral salpingo-oophorectom* or oophorectomy* or interven*)).mp.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12
14. exp controlled clinical trial/
15. randomized.ab.
16. randomly.ab.
17. trial.ab.
18. groups.ab.
19. exp cohort analysis/
20. cohort*.mp.
21. exp retrospective study/
22. exp prospective study/
23. (case* and series).mp.
24. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 13 and 24

Key

[mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Appendix 4. CINAHL search strategy

S25 S9 AND S23 Limiters - Published Date: 19950101-20180131; Publication Type: Clinical Trial, Meta Analysis, Meta Synthesis, Randomized Controlled Trial, Research, Systematic Review

S24 S9 AND S23

S23 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22

S22 "interven"

S21 (MH "Surgery, Operative")

S20 "ovariectomy"

S19 (MH "Oophorectomy") OR "oophorectomy"

S18 "bilateral salpingo-oophorectom"

S17 "BSO"

S16 "RRBSO"

S15 "OVAR"

S14 "RRM"

S13 "mastectom"

S12 (MH "Mastectomy") OR (MH "Prophylactic Mastectomy")

S11 "risk reducing surg"

S10 "prophylactic surgical procedures"

S9 S1 OR S2 OR S4 OR S5 OR S7 OR S8

S8 "BRCA"

S7 "brca"

S6 "(BRCA* or brca*) N5 (carrier* or tumor* or tumour* or gene* or supress* or protein* or mutat* or alter* or damage* or inherit* or heredit*)"

S5 "BRCA* OR brca"

S4 "brca2"

S3 "brca protein"

S2 "brca1"

S1 (MH "Genes, BRCA")

Appendix 5. PsycINFO search strategy

```

1 PROPHYLACTIC SURGICAL PROCEDURES.mp.[mp = title,abstract,heading word, table of contents, key concepts,original title,tests & mea-
sures]
2 exp MASTECTOMY/
3 exp OVARIECTOMY/
4 exp SURGERY/
5 risk reduc* surg*.mp.[mp = title,abstract, heading word, table of contents, key concepts,original title,tests & measures]
6 mastectom*.mp. [mp = title,abstract, heading word, table of contents, key concepts,original title,tests & measures]
7 RRM.mp. [mp = title,abstract, heading word, table of contents, key concepts,original title,tests & measures]
8 OVAR*.mp. [mp = title,abstract, heading word, table of contents, key concepts,original title,tests & measures]
9 RRBSO.mp. [mp = title,abstract, heading word, table of contents, key concepts,original title,tests & measures]
10 BSO.mp. [mp = title,abstract, heading word, table of contents, key concepts,original title,tests & measures]
11 bilateral salpingo-oophorectom*.mp. [mp = title,abstract, heading word, table of contents, key concepts,original title,tests & measures]
12 oophorectomy*.mp. [mp = title,abstract, heading word, table of contents, key concepts,original title,tests & measures]
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 brca.mp.
15 brca1.mp.
16 brca*.mp.
17 brca2.mp.
18 14 or 15 or 16 or 17
19 13 and 18
20 limit 19 to yr = "195-Current"
1 from 20 keep 1-254

```

Appendix 6. Web of Science

3 #2 AND #1

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years

#2 **TOPIC:** (prophylactic surgical procedures) OR **TOPIC:** (mastectom*) OR **TOPIC:** (ovariectomy) OR **TOPIC:** (surgery)
OR **TOPIC:** (RRM) OR **TOPIC:** (RRBSO) OR **TOPIC:** (BSO) OR **TOPIC:** (BILATERAL SALPINGO-OOPHORECTOM*) OR **TOPIC:**
(oophorectomy*)

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years

#1 **TOPIC:** (brca*)

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years

Appendix 7. Data extraction form

Review title or ID

- Study ID (surname of first author and year first full report of study was published e.g. Smith 2001).
- Report IDs of other reports of this study (e.g. duplicate publications, follow-up studies).
- Notes.

General information

- Date form completed (dd/mm/yyyy).
- Name/ID of person extracting data.
- Report title (title of paper/ abstract/ report that data are extracted from).
- Report ID (if there are multiple reports of this study).
- Country of origin.
- Publication type (e.g. full report, abstract, letter).
- Study funding source (including role of funders).
- Possible conflicts of interest (for study authors).
- Notes.

Eligibility

Study characteristics

- Review inclusion criteria (insert inclusion criteria for each characteristic as defined in the protocol): Yes/No/Unclear.
- Location in text (page and paragraph/figure/table).
- Type of study.

- Randomised trial /non-randomised trial.
- Other design (specify).
- Participants.
- Types of intervention.
- Types of outcome measures.
- Decision.
- Reason for exclusion.
- Notes.

Do not proceed if study excluded from review**Population and setting**

- Description.
- Include comparative information for each group (i.e. intervention and controls) if available.
- Location in text (page and paragraph/figure/table).
- Population description (from which study participants are drawn).
- Setting (including location and social context).
- Inclusion criteria.
- Exclusion criteria.
- Method(s) of recruitment of participants.
- Notes.

Methods

- Descriptions as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Study aim.
- Design (e.g. parallel, crossover, non-RCT).
- Start date.
- End date.
- Duration of participation (from recruitment to last follow-up).
- Notes.

'Risk of bias' assessment

See Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). Additional domains may be required for non-randomised studies.

Domain

- Risk of bias: low/high/unclear:
 - * support for judgement;
 - * location in text (page and paragraph/figure/table);
 - * random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias):
 - * outcome group: all/(if required);
 - * outcome group.
- Blinding of outcome assessment (detection bias):
 - * outcome group: all/(if required);
 - * outcome group.
- Incomplete outcome data (attrition bias).
- Selective outcome reporting? (reporting bias).
- Other bias.
- Notes.

Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Total number randomised (or total population at start of study for NRCTs).
- Clusters (if applicable, number, type, number people per cluster).
- Baseline imbalances.
- Withdrawals and exclusions (if not provided below by outcome).
- Age.
- Sex.
- Race/ethnicity.
- Subgroups measured.
- Cancer (Y/N).
- Type of cancer.
- Risk-reducing mastectomy.
- RRSO.
- BRCA1 or BRCA2.
- Subgroups reported.
- Notes.

Intervention groups

(Copy and paste table for each intervention and comparison group)

- Intervention Group 1.
- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Group name.
- Number randomised to group (specify whether number of people or clusters).
- Description (include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention).
- Duration of treatment period.
- Timing (e.g. frequency, duration of each episode).
- Delivery (e.g. mechanism, medium, intensity, fidelity).
- Providers (e.g. number, profession, training, ethnicity etc. if relevant).
- Co-interventions.
- Notes.

Outcomes

(Copy and paste table for each outcome)

- Outcome 1.
- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Outcome name.
- Time points measured (specify whether from start or end of intervention).
- Time points reported.
- Outcome definition (with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious).
- Person measuring/reporting.
- Unit of measurement (if relevant).
- Scales: upper and lower limits (indicate whether high or low score is good).
- Is outcome/tool validated?
Yes/No/Unclear.
- Imputation of missing data (e.g. assumptions made for ITT analysis).

- Notes.

Results

(Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required)

For randomised or non-randomised trial: dichotomous outcome

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Comparison.
- Outcome.
- Subgroup.
- Time point (specify whether from start or end of intervention).
- Note whether: post-intervention or change from baseline.
- Adjusted.
- Unadjusted.
- Intervention.
- Comparison.
- Number of events.
- Number of participants.
- Number of events.
- Number of participants.

Baseline data

- Intervention.
- Comparison
- Number of events.
- Number participants.
- Number of events.
- Number of participants.
- Number of missing participants and reasons.
- Number of participants moved from other group and reasons.
- Any other results reported.
- Unit of analysis (e.g. by individuals, health professional, practice, hospital, community).
- Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation).
- Notes.

For randomised or non-randomised trial : continuous outcome

- Description as stated in report/paper:
 - * location in text (page and paragraph/figure/table);
 - * comparison;
 - * outcome;
 - * subgroup;
 - * time point (specify whether from start or end of intervention);
 - * post-intervention or change from baseline;
 - * results;
 - ☐ note whether: post-intervention or change from baseline;
 - ☐ and whether adjusted or unadjusted;
 - ☐ intervention;
 - ☐ comparison;
 - ☐ mean;
 - ☐ SD (or other variance);
 - ☐ number of participants;
 - ☐ mean;
 - ☐ SD (or other variance);
 - ☐ number of participants.

Baseline data

- Intervention.
- Comparison.
- Mean.
- SD (or other variance).
- Number of participants.
- Mean.
- SD (or other variance).
- Number of participants.
- Number of missing participants and reasons.
- Number of participants moved from other group and reasons.
- Any other results reported.
- Unit of analysis (e.g. by individuals, health professional, practice, hospital, community).
- Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation).
- Notes.

For randomised or non-randomised trial: other outcome

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Comparison.
- Outcome.
- Subgroup.
- Time point (specify whether from start or end of intervention).
- Type of outcome.

- Results:
 - * intervention result;
 - * SD (or other variance);
 - * control result;
 - * SD (or other variance);
 - * overall results;
 - * SE (or other variance);
 - * number of participants;
 - * intervention;
 - * control;
 - * number of missing participants and reasons;
 - * number of participants moved from other group and reasons;
 - * any other results reported;
 - * unit of analysis (e.g. by individuals, health professional, practice, hospital, community);
 - * statistical methods used and appropriateness of these methods;
- Notes:

For controlled before-after study

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Comparison.
- Outcome.
- Subgroup.
- Timepoint (specify whether from start or end of intervention).
- Post-intervention or change from baseline.
- Results:
 - * intervention result;
 - * SD (or other variance);
 - * control result;
 - * SD (or other variance);
 - * overall results;
 - * SE (or other variance);
 - * No. participants;
 - * intervention;
 - * control;
 - * number of missing participants and reasons;
 - * number of participants moved from other group and reasons;
 - * any other results reported;
 - * unit of analysis (individuals, cluster/ groups or body parts);
 - * statistical methods used and appropriateness of these methods.
- Notes.

For interrupted time series or repeated measures study

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Comparison.
- Outcome.
- Subgroup.
- Length of time points measured (e.g. days, months).
- Total period measured.
- Number of participants measured.
- Number of missing participants and reasons.
- Number of time points measured.

- Pre-intervention.
- Post-intervention.
- Mean value (with variance measure).
- Difference in means (post- and pre-intervention).
- Percent relative change.
- Result reported by authors (with variance measure).
- Unit of analysis (individuals or cluster/groups).
- Statistical methods used and appropriateness of these methods.
- Notes.

Applicability

- Does the study directly address the review question? (any issues of partial or indirect applicability):
Yes/No/Unclear.
- Notes.

Other information

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Key conclusions of study authors.
- References to other relevant studies.
- Correspondence required for further study information (what and from whom).
- Further study information requested (from whom, what and when).
- Correspondence received (from whom, what and when).
- Notes

CONTRIBUTIONS OF AUTHORS

All authors read and approved the final review draft.

Lisa Jeffers: conceptualising the topic for the review, drafting the manuscript

Joanne Reid: reviewing and editing the manuscript

Donna Fitzsimons: reviewing and editing the manuscript

Patrick J Morrison: reviewing and editing the manuscript

Martin Dempster: reviewing and editing the manuscript

DECLARATIONS OF INTEREST

Lisa Jeffers: I have already acknowledged the Cochrane Fellowship in my protocol.

Joanne Reid: none known

Donna Fitzsimons: none known

Patrick J Morrison: none known

Martin Dempster: none known

SOURCES OF SUPPORT**Internal sources**

- No internal sources of support, Other.

External sources

- Health and Social Care R&D Division of the Public Health Agency (Northern Ireland), UK.

Funded Lisa Jeffers to undertake this review as part of its Cochrane Fellowship Ireland scheme

DIFFERENCES BETWEEN PROTOCOL AND REVIEW**Assessment of heterogeneity**

If in a future update additional studies are identified, we expect some heterogeneity due to clinical and methodological diversity. We will therefore assess heterogeneity between studies by visual inspection of forest plots; by estimation of the percentage heterogeneity

between trials that cannot be ascribed to sampling error (I^2 statistic) (Higgins 2003); by a formal statistical test of the significance of the heterogeneity (Chi² test) (Deeks 2001); and, if possible, by subgroup analyses. If there is no evidence of heterogeneity, we will use a fixed-effect model, which assumes a common underlying effect behind every trial. If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for this. If we suspect marked heterogeneity, we will not combine estimates. All potential causes of such heterogeneity will be explored through subgroup and sensitivity analysis. We will use a random-effects model if meta-analysis is appropriate; we will assume each trial to be measuring a different, true effect. Whilst it is acknowledged that a random-effects model is more susceptible to publication bias, we will incorporate methods to formally test publication bias into the analysis as outlined below.

Assessment of reporting biases

In a future update, if appropriate (i.e. if the review includes more than 10 randomised controlled trials (RCTs)), we will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias. Additionally, we will explore possible sources of asymmetry in funnel plot, such as selective outcome reporting, poor methodological quality leading to spuriously inflated effects in smaller studies, true heterogeneity, artefactual and chance as outlined by Egger 1997. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, we will perform further meta-analysis using a fixed-effect model. If the review includes fewer than 10 RCTs, then we will use a qualitative assessment of reporting biases, whereby the authors will review and summarise the evidence from the RCTs.

Data synthesis

If in a future update we include both RCTs and non-randomised studies, and if sufficient, clinically similar studies are available, we will pool their results in meta-analyses using Review Manager 5 (RevMan 2014). We will use adjusted summary statistics if available; otherwise we will use unadjusted results. Where more than one adjusted effect is reported in a paper, we will use the estimate that is identified as the primary adjusted effect by the study authors.

We will use random-effects employing inverse-variance weighting for any meta-analysis.

For continuous outcomes, we will pool the mean differences between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale; otherwise we will pool the standardised mean difference. For any dichotomous outcomes, we will calculate the risk ratio for each study and then pool these. The final discussion will include a narrative synthesis of the findings of each study design.

Subgroup analysis and investigation of heterogeneity

We will not perform post hoc subgroup analysis. Where appropriate, we will undertake subgroup analysis, potentially grouping the trials by the following.

- Type of treatment regimen (psychological, psychoeducational, psychosexual intervention)
- Duration of treatment (short term less than one month, longer term more than three months)
- Cancer diagnosis (affected women) or no cancer (healthy at-risk women)
- Type of risk-reducing surgery (mastectomy or risk-reducing salpingo-oophorectomy)

Sensitivity analysis

In a future update, where possible, we will perform the following sensitivity analyses.

- Exclusion of studies that are at high risk of bias
- Using unadjusted results

If possible, we will conduct the analyses on an intention-to-treat basis. If this is not possible, we will use available-case analysis. The sensitivity analysis will consider how the results would have differed for assumed means or event rates for missing data.