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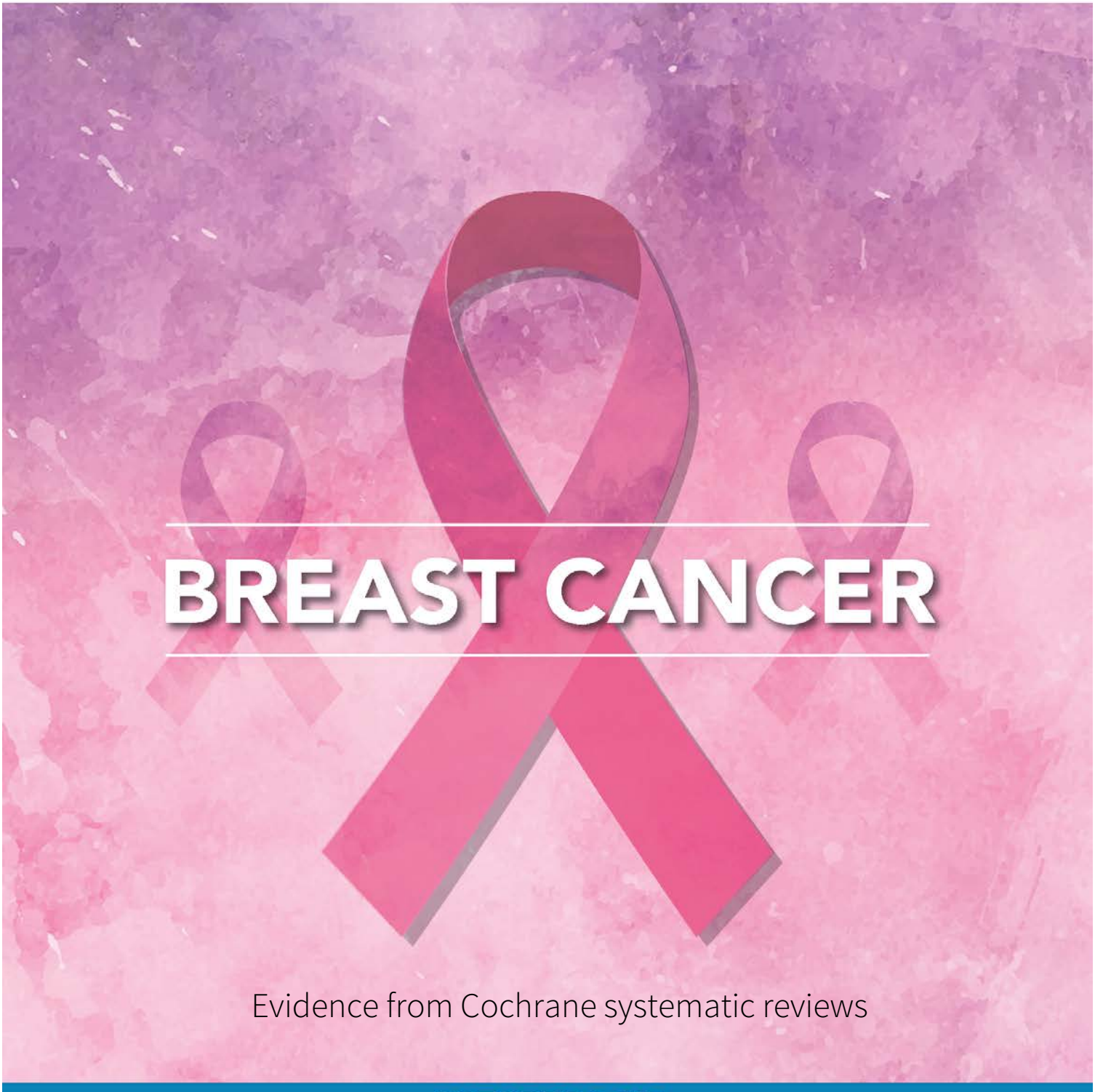

BREAST CANCER

Evidence from Cochrane systematic reviews

OCTOBER 2017

CONTENTS

INTRODUCTION

Breast cancer is the most common cancer in women worldwide. It is one of the most common causes of death from cancer in women. Almost 50% of breast cancer cases and 58% of deaths occur in less developed countries (GLOBOCAN 2008).

This booklet provides summaries of Cochrane systematic reviews for screening and prevention, treatment, and supportive and follow-up care for breast cancer.

What is a Cochrane systematic review?

A Cochrane systematic review asks a specific research question about a particular healthcare intervention in a clearly defined group of people with a health condition or problem; for example: What is the best way to administer chemotherapy and radiotherapy following surgery for early breast cancer? These reviews summarise the results of healthcare studies and provide the evidence on the effectiveness of the interventions. They are produced by Cochrane and published in an online database, the Cochrane Library (www.cochranelibrary.com).

Cochrane

Cochrane (www.cochrane.org) is a global independent network of researchers, professionals, patients, carers and people interested in health. Cochrane is a not-for-profit organisation with collaborators from more than 130 countries working together to produce credible, accessible health information that is free from commercial sponsorship and other conflicts of interest.

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Cochrane SA (www.southafrica.cochrange.org), based at the South African Medical Research Council in Cape Town, is a member of the Cochrane network. The vision of Cochrane SA is that healthcare decision making within Africa will be informed by high-quality, timely and relevant research evidence.

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The CCNet consists of people committed to the importance of consumer participation in informed healthcare decision-making processes. The Network promotes the use of evidence-based healthcare to guide well-informed decisions about health care. CCNet offers communication support and training on using evidence to enable consumers to sift through the facts and benefit from the Cochrane Collaboration's systematic reviews on evidence-based healthcare. To learn more about CCNet, visit their website at www.consumers.cochrane.org

Cochrane Breast Cancer Group

The Cochrane Breast Cancer Group provides up-to-date information about prevention, early diagnosis, treatments, follow-up care and supportive practices for women diagnosed with breast cancer. For more information visit their website www.breastcancer.cochrane.org.

Plain Language Summaries

This publication is a collection of plain language summaries (PLS) of Cochrane systematic reviews on breast cancer. A PLS is a summary of a systematic review written in simple language for non-medically trained users including policy makers and the public. A PLS aims to outline the relevance of the systematic review findings for healthcare implementation. In each case the details of the full comprehensive review are supplied for those who would like to access more detailed information.

SCREENING AND PREVENTION

Interventions for raising breast cancer awareness in women

Review question

We reviewed the evidence about the effect of different interventions for raising breast cancer awareness in women. We found two randomised controlled trials, the highest quality of research evidence.

Background

Breast cancer is the most commonly diagnosed cancer in women. Early detection, diagnosis and treatment of breast cancer are key to better outcomes. Since many women will discover a breast symptom themselves, it is important that they are breast cancer aware i.e. that they have the knowledge, skills and confidence to notice any breast changes and visit their doctor promptly.

Study characteristics

A search for trials investigating interventions on breast cancer awareness in women was run in January 2016. We found two trials with a total of 997 women.

The Promoting Early Presentation (PEP) study, funded by Breast Cancer UK, involved randomising 867 women to receive one of three interventions: (1) a written booklet and usual care, (2) a written booklet and usual care plus one-to-one discussion with a healthcare professional or (3) usual care only. Women were aged between 67 to 70 years and recruited into the study at breast cancer screening units in the UK.

The Zahedan University of Medical Sciences (ZUMS) study involved randomising 130 women into two groups that received either: (1) an educational programme using written and oral materials that focused on "breast cancer preventive behaviours" (e.g. having a healthy diet and positive beliefs towards breast self-examining behaviour) or (2) no intervention. Women were employed at ZUMS and aged between 35 and 39 years.

Key outcomes

Study outcomes were measured differently in the two studies. The PEP study assessed outcomes at one month, one year and two years after the intervention. The ZUMS study measured outcomes at one month after the intervention. Since the studies were very different in terms of the participants' age, interventions, outcomes and time points measured, the results are reported separately.

Knowledge of breast cancer symptoms

In PEP: women's knowledge of breast cancer symptoms seemed to somewhat improve after receiving either the written booklet or written booklet plus verbal interaction. These results improved when compared to usual care at two years post-intervention. In ZUMS: women's awareness of breast cancer symptoms increased one month after the educational programme.

Knowledge of age-related risk of breast cancer

In PEP: knowledge of age-related risk increased for women who had received a written booklet and interacted with a healthcare professional compared to usual care at two years post-intervention. For women who only received the booklet, there was less of a comparable increase in knowledge. In ZUMS: this study only measured if women perceived themselves to be at risk of getting breast cancer. This self-perception of risk did increase at one month following the intervention.

Self-reported breast checking

In PEP: women's reported monthly breast checking increased, but not significantly, at two years post-intervention compared to usual care. In ZUMS: women's reported "breast cancer preventive behaviours" increased one month after the intervention. Specifically, this refers to their positive beliefs towards breast self-examining behaviour.

Overall breast cancer awareness

In PEP: women's breast cancer awareness overall did not change after receiving a booklet alone compared to usual care at two years after the intervention. However, breast cancer awareness increased in women who had received a written booklet and interacted with a healthcare professional. This behaviour change was in comparison to usual care at two years post-intervention. In ZUMS: women's "breast cancer preventive behaviours" were reported to increase at one month. None of the studies reported on other parts of breast awareness, the intention to seek help, quality of life, adverse effects of the interventions, or breast cancer-related outcomes.

Quality of the evidence

The evidence was considered to be moderate quality in the PEP study and low quality in the ZUMS study. Neither study clearly defined 'breast cancer awareness'. The lack of high-quality studies limited our ability to draw conclusions. However, the PEP study results suggest that combining written information and a one-to-one discussion had a long-term effect on increasing women's breast cancer awareness. In the future, studies should use larger samples and follow the women for a longer time.

O'Mahony M, Comber H, Fitzgerald T, Corrigan MA, Fitzgerald E, Grunfeld EA, Flynn MG, Hegarty J. Interventions for raising breast cancer awareness in women. Cochrane Database of Systematic Reviews 2017, Issue *2*. Art. No.: CD011396. DOI: 10.1002/14651858.CD011396.pub2.

Screening for breast cancer with mammography

Screening with mammography uses X-ray imaging to find breast cancer before a lump can be felt. The goal is to treat cancer earlier, when a cure is more likely. The review includes seven trials that involved 600 000 women in the age range 39 to 74 years who were randomly assigned to receive screening mammograms or not. The studies which provided the most reliable information showed that screening did not reduce breast cancer mortality. Studies that were potentially more biased (less carefully done) found that screening reduced breast cancer mortality. However, screening will result in some women getting a cancer diagnosis even though their cancer would not have led to death or sickness. Currently, it is not possible to tell which women these are, and they are therefore likely to have breasts or lumps removed and to receive radiotherapy unnecessarily. If we assume that screening reduces breast cancer mortality by 15% after 13 years of follow-up and that overdiagnosis and overtreatment is at 30%, it means that for every 2000 women invited for screening throughout 10 years, one will avoid dying of breast cancer and 10 healthy women, who would not have been diagnosed if there had not been screening, will be treated unnecessarily. Furthermore, more than 200 women will experience important psychological distress including anxiety and uncertainty for years because of false positive findings.

Women invited to screening should be fully informed of both the benefits and harms. To help ensure that the requirements for informed choice for women contemplating whether or not to attend a screening programme can be met, we have written an evidence-based leaflet for lay people that is available in several languages on www.cochrane.dk. Because of substantial advances in treatment and greater breast cancer awareness since the trials were carried out, it is likely that the absolute effect of screening today is smaller than in the trials. Recent observational studies show more overdiagnosis than in the trials and very little or no reduction in the incidence of advanced cancers with screening.

Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD001877. DOI: 10.1002/14651858.CD001877.pub5.

Cancer genetic risk assessment for individuals at risk of familial breast cancer

The recognition of an inherited component to breast cancer has led to an increase in demand for information, reassurance, and genetic testing, which resulted in the creation of genetic clinics for familial cancer. Cancer genetic services can involve extended counselling, specialist screening and genetic testing for mutations. Risk assessment is the first step in the process of providing information and support to patients and their families about their risk of inheriting cancer. Information on evidence-based methods of delivering cancer genetic risk-assessment services is, however, sparse. For this review a systematic search, review, and assessment of the literature on the delivery of cancer genetic risk-assessment services for individuals concerned with familial breast cancer was undertaken.

This review included eight trials (10 papers) which covered the process of risk assessment for familial breast cancer. These focused on the psychosocial impact on patients, as well as other outcomes and aspects of service delivery, and provided data on 1973 participants. Due to the limited number of trials, this review found insufficient evidence to make any firm conclusions about the best way to deliver risk-assessment services for individuals concerned about a family history of breast cancer. All eight included studies did, however, demonstrate improvements in psychological well-being and a decrease in the levels of cancer worry as a result of the risk-assessment service. Although limited, the findings of this review suggest that cancer genetic risk-assessment services can help to reduce distress, improve the accuracy of the individual's perceived risk of breast cancer, and increase knowledge about breast cancer and genetics. Existing evidence suggests that such services do not cause patients any harm and, in the short-term, can have a positive effect by helping to ease distress and decrease cancer worry. From this review, it does not appear that the health professional delivering the risk assessment has a significant impact on these outcomes.

Hilgart JS, Coles B, Iredale R. Cancer genetic risk assessment for individuals at risk of familial breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003721.DOI: 10.1002/14651858.CD003721.pub3.

Levonorgestrel intrauterine system (LNG-IUS) for endometrial protection in women with breast cancer taking tamoxifen to prevent recurrence

Review question

Cochrane authors investigated whether the levonorgestrel-releasing intrauterine system (LNG-IUS) can reduce the risk of endometrial polyps, abnormal thickening of the lining of the uterus and endometrial cancer in women taking tamoxifen following breast cancer. The review also investigated whether use of the LNG-IUS influences the risk of abnormal vaginal bleeding or spotting, fibroids, breast cancer recurrence or death in women taking tamoxifen following breast cancer.

Background

Tamoxifen is commonly used by women to reduce the risk of breast cancer recurrence. Tamoxifen can also cause abnormal changes to the lining of the uterus (endometrium), including polyps and cancer. The LNG-IUS is a uterine device that releases the synthetic hormone levonorgestrel into the endometrium and causes marked endometrial suppression. As levonorgestrel is a progestin, and many breast cancers are progesterone-sensitive, it is important to study the safety of the LNG-IUS in breast cancer survivors.

Study characteristics

We included four randomised controlled trials involving 543 women. The studies took place in the United Kingdom, Turkey, Egypt and Hong Kong, and the primary outcome in all studies was abnormal changes in the lining of the uterus. Three studies reported on the outcome of fibroids. Three studies reported on abnormal vaginal bleeding or spotting. Two studies reported on the outcomes of breast cancer recurrence, and three studies reported on the outcomes of breast cancer-related death. The evidence is current to October 2015.

Key results

This review suggests that the LNG-IUS can reduce the risk of endometrial polyps and endometrial hyperplasia over a long-term follow-up period (24 to 60 months) in women taking tamoxifen following breast cancer. At 12 and 24 months of follow-up, more women in the LNG-IUS group experienced abnormal vaginal bleeding or spotting. However by 60 months of follow-up, no abnormal vaginal bleeding or spotting was reported in either group. There were insufficient data to show whether there is any effect on incidence of endometrial cancer (a cancer originating in glandular tissue), fibroids, breast cancer recurrence, or breast cancer-related death.

Quality of the evidence

The quality of the evidence was judged as moderate, due to limited sample sizes and low event rates for the outcome comparisons. Larger studies are necessary to assess the effects of the LNG-IUS on the incidence of endometrial cancer, and the impact of the LNGIUS on the risk of secondary breast cancer events.

Dominick S, Hickey M, Chin J, Su HI. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD007245. DOI: 10.1002/14651858.CD007245.pub3.

TREATMENT

Ductal carcinoma in situ

Post-operative tamoxifen for ductal carcinoma in situ

Ductal carcinoma in situ (DCIS) is a type of early breast cancer. It has no symptoms but is mostly detected by mammography screening. This type of 'pre' cancer is treated with surgery (e.g. mastectomy or lumpectomy), often in combination with radiotherapy. Some women are also given oral hormone tablets (tamoxifen), but it is unclear whether adding tamoxifen hormone treatment after surgery gives any added benefit. This review examined whether tamoxifen after local excision prevented any further episodes of cancer and whether women taking tamoxifen lived longer compared to those who did not take hormone therapy after local excision.

Our findings are based on two large studies with 3375 participants and should be applicable to most women having treatment for DCIS. Overall tamoxifen did reduce the number of future cancers or DCIS in either breast. However, women taking tamoxifen did not live longer than those who did not take it. A total of 15 women would have to take tamoxifen after treatment of DCIS for one woman to experience a benefit (i.e. no future cancers or DCIS in either breast after taking tamoxifen for five years). There are side effects of tamoxifen treatment such as blood clotting problems (stroke, deep vein thrombosis, pulmonary embolism) and endometrial cancer. However, no risk/benefit conclusions are possible because there was limited information about the side effects in this review. The effects of tamoxifen may have been 'diluted' by the effects of radiotherapy. This review cannot recommend which women might have more benefit from using tamoxifen in terms of age, menopausal status or type of DCIS (oestrogen receptor (ER)-positive versus ER-negative or human epidermal growth factor receptor 2 (HER2)-positive or HER2-negative DCIS).

Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ. Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD007847. DOI: 10.1002/14651858.CD007847.pub2.

Post-operative radiotherapy for ductal carcinoma in situ

Ductal carcinoma *in situ* (DCIS) is characterised by the development of cancerous cells in the milk ducts of the breast and is commonly diagnosed by mammography screening. Surgical removal of the breast offers a good prognosis, however many women and clinicians prefer breast conserving surgery (BCS), the removal of the DCIS plus a rim of normal breast tissue, as there is no guarantee that DCIS will progress to invasive cancer. This approach means that most of the normal breast is saved. The main risk of inadequately removing all the DCIS is either a recurrence of DCIS or the development of invasive breast cancer at a later time with the risk that this can progress to metastatic disease (cancer that has spread). Radiotherapy (RT) is treatment using ionising radiation. Giving RT after BCS is thought to reduce the risk of developing recurrent disease (either DCIS or invasive breast cancer).

This review aimed to assess both the benefit of adding RT to treatment and any potential long or short-term harm it may cause. Short-term harm includes skin rash and redness, or inflammation of lung tissue. Potential long-term side effects from RT include vascular disease (heart and major blood vessel disease), damage to the lungs, development of lung cancer, or osteoradionecrosis (bone damage resulting in bone death).

The review identified four large randomised controlled trials (3925 women) that compared treatment with breast conserving surgery alone and breast conserving surgery with the addition of RT. The addition of RT reduced the risk of a recurrence of either DCIS or invasive cancer in the treated breast by 51%.

Older trials of breast conserving surgery followed by RT for invasive breast cancer have shown long-term toxicity from the addition of RT. We found no evidence of increased toxicity from the use of RT although some trials did not report on the causes of non-breast cancer deaths (deaths which potentially could be related to side effects). The number of non-breast cancer deaths reported were similar in both radiotherapy and control groups. Changes in delivery of RT between older and more recent trials and a subsequent decrease in exposure of normal tissue may account for this finding. Longer follow up of trial participants is required before a definite conclusion can be drawn, however radiotherapy techniques are continuing to improve and future patients are likely to experience a further decrease in exposure of nearby normal tissues. Overall survival was high and similar between each group whether radiotherapy was used or not. There were no reports of short-term toxicity from use of radiotherapy, or quality of life data.

Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD000563. DOI: 10.1002/14651858.CD000563.pub7

Early and advanced breast cancer

Surgical removal of underarm lymph nodes in breast cancer

Review question

This review aimed to compare the benefits of surgical removal of underarm lymph nodes with the potential harms associated with this surgical procedure. The review also aimed to learn whether complete removal of all underarm nodes could be replaced by procedures that remove only a small number of lymph nodes.

Background

Surgical removal of underarm (axillary) lymph nodes is often part of the initial surgical treatment for patients with operable breast cancer. If cancer has spread to these lymph nodes, patients are advised to undergo additional treatments, such as chemotherapy or radiotherapy, to help treat their disease. If cancer has not spread to these lymph nodes, patients are spared extra treatments (with extra side effects). Surgical removal of lymph nodes can lead to short-term surgical complications (such as infection and wound healing problems) and long-term problems (such as shoulder stiffness, pain and arm swelling (lymphoedema)) when fluid accumulation causes restricted function and discomfort.

Modern strategies use a stepwise approach by first removing a small number of nodes and removing the others only if cancer is found at the first stage. This first stage can consist of 'random' axillary sampling, whereby the surgeon removes a small number of nodes (typically four) that can be felt. Alternatively, surgeons can use sentinel node techniques to identify those nodes most likely to contain cancer, leading to removal of as few nodes as possible. For patients with cancer in the sentinel nodes (or sample), complete removal of all underarm lymph nodes (axillary lymph node dissection) is usually recommended; however, radiotherapy to the axilla can also be given to obliterate any cancer cells in the lymph nodes. Some studies have explored alternative approaches such as no surgical treatment to the underarm nodes.

Study characteristics

The evidence is current to March 2015. The review identified 26 randomised controlled trials that compared axillary lymph node dissection (ALND) with alternative approaches involving less axillary surgery. Patients in these trials had operable primary breast cancer, and some trials included patients with palpably enlarged axillary lymph nodes. Ten trials including 3849 patients compared ALND with no axillary surgery. Six trials including 1559 patients compared ALND with axillary sampling. Seven trials including 9426 patients compared ALND with sentinel lymph node biopsy (SLNB). Four trials including 2585 patients compared ALND (with or without radiotherapy) with radiotherapy alone.

Key results

Moderate-quality evidence suggests that patients treated with approaches involving lesser axillary surgery (such as axillary sampling or SLNB) do not have a reduced chance of survival compared with those treated with ALND. Moderate-quality evidence indicates that overall survival is slightly reduced in patients who receive radiotherapy (but no axillary surgery) when compared with ALND. If survival is assumed to be 81% five years after surgery with ALND, then the evidence suggests it would be between 77% and 81% after treatment with radiotherapy alone.

Moderate-quality evidence suggests that patients who have no axillary lymph nodes removed at all are at increased risk of locoregional recurrence (regrowth of cancer, in the breast, mastectomy scar area or underarm glands). If it is assumed that 86% of patients receiving ALND are free of locoregional recurrence five years after surgery, evidence suggests that the corresponding figure for patients who have no lymph nodes removed at all would be between 66% and 76%. For patients treated with axillary sampling, low-quality evidence suggests that between 73% and 87% would be free of locoregional recurrence at five years.

Axillary recurrence rates were reported only in SLNB versus ALND trials, and researchers remain uncertain about the best treatment for this outcome because rates were very low (occurring in less than 1% of patients).

Low-quality evidence suggests that patients treated with ALND are at increased risk of lymphoedema compared with those treated with SLNB or no axillary surgery. On the basis of this evidence, we would expect that out of every 1000 patients receiving ALND, 132 would experience lymphoedema at one year after surgery, compared with between 22 and 115 of those receiving SLNB. Other long-term harms such as pain, impaired arm movement and numbness were also more likely with ALND than with SLNB.

Bromham N, Schmidt-Hansen M, Astin M, Hasler E, Reed MW. Axillary treatment for operable primary breast cancer. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD004561. DOI: 10.1002/14651858.CD004561.pub3.

Surgery versus primary endocrine therapy for elderly women with operable primary breast cancer

While younger women with early-stage, oestrogen-sensitive breast cancer are almost invariably treated with surgery plus endocrine therapy, (which deprives the cancer of the hormonal stimulus that induces its growth), women over the age of 70 years are frequently offered endocrine therapy alone. This is known as primary endocrine therapy.

Primary endocrine therapy using tamoxifen (a drug which blocks oestrogen receptors on the cancer cell, inhibiting its growth) was first suggested as a treatment for older women in the 1980s.

Tamoxifen was given without surgery, radiotherapy or chemotherapy on the basis that older women are more likely to have cancers with oestrogen receptors and will therefore respond well to treatment. In addition they were thought less suitable for major surgery because of other existing health issues. However, a tumour will often only respond to this treatment for between 18 and 24 months, and those women who relapse will have to consider additional hormone treatment or opt for surgery or radiotherapy at a greater age. The long-term data suggest that, at 12 years of follow-up, more elderly women treated by primary tamoxifen alone will suffer a progression of their cancer than those who have had surgery.

We undertook this review to assess the evidence for the clinical effectiveness of surgery (with or without endocrine therapy) compared with primary endocrine therapy in the treatment of operable breast cancer in women aged 70 years and over. Based on seven trials and an estimated 1081 deaths in 1571 women, the results of this review showed no benefit in respect to survival for either surgery or primary endocrine therapy. However, women who had surgery were less likely to relapse than women on primary endocrine therapy.

The authors conclude that surgery controls breast cancer better than tamoxifen alone in older women but does not extend survival. Both interventions were associated with adverse events. Tamoxifen-related adverse effects included hot flushes, skin rash, vaginal discharge, indigestion, breast pain, sleepiness, headache, vertigo, itching, hair loss, cystitis, acute thrombophlebitis, nausea, and indigestion.

Surgery-related adverse effects included tingling or numbness on the arm on the side of the surgery, and psychosocial problems. On this basis, primary endocrine therapy should only be offered to women with oestrogen receptor (ER)-positive tumours who are unfit for, or who refuse surgery. We need further trials to evaluate the clinical effectiveness of other agents such as aromatase inhibitors for use as primary endocrine therapy for an infirm older population with ER-positive tumours.

Morgan J, Wyld L, Collins KA, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD004272. DOI: 10.1002/14651858.CD004272.pub3.

Antibiotics to prevent surgical site infection after breast cancer surgery

Breast cancer accounts for one in 10 of all new cancer cases diagnosed and surgical removal of the breast is a common treatment approach. An infection of the surgical wound is often a complication of surgery and taking antibiotics just before the operation significantly reduces the chances of developing an infection. The review is not able to establish which antibiotic is most appropriate. No trials were found which considered the effect of antibiotics when the operation involved immediate breast reconstruction.

Jones DJ, Bunn F, Bell-Syer SV. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD005360. DOI: 10.1002/14651858.CD005360.pub4.

Fibrin glue instillation under skin flaps to prevent seroma-related morbidity following breast and axillary surgery

A higher incidence of postoperative seroma (fluid collection under skin) in people undergoing breast and axillary (under-arm) surgery for breast cancer is responsible for longer hospital stays, frequent repeat aspiration procedures, increased cost of breast disease, delays in the provision of adjunctive treatments and consequently potentially reduced overall all-cause survival. Fibrin glue (FG) instillation under skin flaps after surgery produces a 'fibrin clot', sealing leaky lymph vessels, which leads to reduced seroma formation and related comorbidities.

We systematically analysed the published trials comparing the usefulness of FG as a small-vessel sealing agent. Eighteen randomised controlled trials on 1252 people were retrieved following bibliographic searches on standard medical databases. There were significant clinical and methodological differences among the included trials. The use of FG following breast and axillary surgery did not reduce the incidence of postoperative seroma, mean volume of seroma, wound infections, postoperative complications and the length of hospital stays. FG reduced the total volume of drained seroma and the duration of persistent seroma requiring frequent aspirations.

This review showed no overall benefit of using FG. Although this conclusion is based on the combined analysis of 18 trials, the majority of these were of poor quality due to flaws in trial methods. Therefore, this conclusion should be taken cautiously and a major, multicentre, high-quality randomised controlled trial on people undergoing breast and axillary surgery for breast cancer is required to corroborate this conclusion.

Sajid MS, Hutson KH, Rapisarda IF, Bonomi R. Fibrin glue instillation under skin flaps to prevent seroma-related morbidity following breast and axillary surgery. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD009557. DOI: 10.1002/14651858.CD009557.pub2.

Different localization techniques during surgery of non-palpable breast lumps

Review question

We reviewed the evidence on new localization techniques against the gold standard (wire-guided) for the surgical removal of non-palpable breast lumps.

Background

Breast cancer screening has brought a shift towards earlier detection of non-palpable breast lumps (i.e. lumps that cannot be felt by palpation by a doctor). Surgical removal of non-palpable lumps can be challenging as it involves locating and removing the entire lump while removing the smallest amount of healthy tissue possible and maintaining optimal breast appearance. The commonly used technique in guiding the surgical removal of non-palpable breast lumps is wire-guided localization (WGL; inserting a wire to the centre of the lump). We wanted to examine whether WGL was better or worse than other newer alternatives.

Study characteristics

The evidence is current to 30 March 2015. Eleven trials met the inclusion criteria of this Cochrane review but we included only eight in our analyses. Six studies compared WGL to radio-guided occult lesion localization (ROLL; it uses a radioactive tracer injected into the lump) and two studies compared WGL to radioactive seed localization (RSL; it involves implanting an Iodine seed in the centre of the tumour). We included a total of 1273 participants with non-palpable breast lumps (627 participants (WGL), 443 participants (ROLL), 203 participants (RSL)). There was considerable variation in the participants' tumours in the studies. The included studies did not report any long-term outcomes.

Key results

People who had WGL and ROLL treatment gave similar results in being able to successfully localize and remove the lump as planned, and also similar postoperative complication rates. ROLL resulted in slightly fewer positive tumour margins (that is, the when the tumour is removed, some surrounding tissue is removed and cancer cells extend out into the margins) compared to WGL, and ROLL also had lower re-intervention rates (that is, less likely to require further surgery) over WGL, but neither differences were statistically significant.

WGL was superior to RSL in successfully locating the lump, but both techniques seemed equally effective in successfully removing the lump. Similarly, RSL provided fewer positive tumour margins compared to WGL (though not statistically significant). However only one study reported on re-intervention rates where the rates were comparable for RSL and WGL.

The studies either did not report or inconsistently reported information on the operation time, length of hospital stay, recurrence, breast appearance, and participant preference when using these different techniques.

Quality of the evidence

The overall quality of the evidence was good. There was no clear evidence to support one guided technique for surgically removing a non-palpable breast lesion over another. The results from this Cochrane review support the continuing use of WGL as a safe and tested technique. ROLL and RSL could be offered to participants as a comparable replacement for WGL. This Cochrane review highlights the need for more fully-powered trials (that is, trials large enough to detect intervention differences) to evaluate the best localization techniques.

Chan BKY, Wiseberg-Firtell JA, Jois RHS, Jensen K, Audisio RA. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD009206. DOI: 10.1002/14651858.CD009206.pub2.

Different types of implants for reconstructive breast surgery after mastectomy

Review question

We assessed the effects of different types of breast implants on short-term and long-term surgical complications, cosmetic outcomes, satisfaction with the surgical procedure and the quality of life in women undergoing breast reconstruction following a mastectomy (breast removal).

Background

An estimated 28%to 60%of women affected by breast cancer will undergo a mastectomy (i.e. surgical removal of the breast). Following a mastectomy, women can choose from many breast reconstruction options and achieve a natural feel with appropriate size and shape of the breast, according to individual needs. These reconstruction options are also available for the increasing number of women at high risk of developing hereditary breast cancer who undergo risk-reducing mastectomy. Options include implants that are silicone-filled (filled with an inert, man-made polymer in gel form), saline-filled (a silicone shell, filled with sterile salt water), anatomically shaped or round, textured or smooth, and of fixed-volume or variable-volume. We wanted to examine if different types of breast implants are associated with better or worse surgical outcomes and patient satisfaction.

Study characteristics

The evidence is current to July 2015. We conducted a review to compare short- and long-term surgical complications (such as scar tissue forming around the implant and squeezing it - referred to as 'capsular contracture', and 'implant rupture'), cosmetic outcomes, women's postoperative quality of life and satisfaction with different types of breast implants used in breast reconstruction. We found five randomised studies involving 202 women that provided data for five different comparisons: rough versus smooth surface, implant filler materials compared to each other (silicone versus saline, and hydrogel versus saline), anatomical versus round shape, and variable versus fixed-volume. Four studies included women who received a mastectomy for breast cancer and one study included women who had bilateral mastectomies for preventive purposes.

The authors of two studies reported that they did not have competing interests; the authors of three studies did not report this information. Three studies reported that their studies received financial support from research foundations; the other studies did not report any information regarding the source of their funding.

Key results

Only two studies reported differences between types of implants for some of the outcomes we considered.

One study on 65 women compared silicone-filled implants with saline-filled implants and showed that saline implants resulted in fewer cases of capsular contracture and a higher number of women who were satisfied with the reconstructed breast. However more women in the saline-filled implant group required further operations on the reconstructed breast than in the silicone-filled implant group.

Another study on 40 women compared variable-volume implants (inserted in a single surgical procedure) with fixed-volume implants (inserted in the second of two separate surgical procedures) and showed that there were significantly higher satisfaction levels and significantly lower reoperation rates with the fixed-volume

The remaining three studies reported on the following comparisons: rough versus smooth silicone-filled implants (20 women), PVPhydrogel versus saline-filled implants (41 women) and anatomically shaped versus round implants (36 women). These studies reported no differences between implant types for outcomes such as capsular contracture, other short-term complications or reoperation rates.

There were no studies that compared recent generation silicone implants with earlier versions or implants from different manufacturing companies.

Quality of the evidence

The evidence we found was limited: only a negligible, tiny fraction of women who undergo breast reconstruction have been studied in randomised controlled trials. The quality of evidence is very low, as the studies we identified suffered from major methodological limitations.

Despite the fact that several million women have had their breasts reconstructed over the last 20 years, the small number of studies and the low numbers of women included in these studies does not allow us to draw any definitive conclusions about the which is the best type of breast implant. This lack of evidence should be discussed when informing women about the risks and complications of different implant-based breast reconstruction options. There is a need for further studies, which include a larger number of women and compare different types of implants, to free women from decisions made on the basis of surgical opinion alone.

Rocco N, Rispoli C, Moja L, Amato B, Iannone L, Testa S, Spano A, Catanuto G, Accurso A, Nava MB. Different types of implants for reconstructive breast surgery. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD010895. DOI: 10.1002/14651858.CD010895.pub2.

Interventions for preventing lymphoedema (swelling of the arm) after breast cancer treatment

Review question

We reviewed the evidence about the effect of interventions on preventing lymphoedema in women after breast cancer surgery.

Background

About one in five people treated for breast cancer develop lymphoedema later on. We reviewed the available evidence to determine whether some methods, such as manual lymph drainage (amassage therapy), compression, exercise or only education could help prevent lymphoedema.

Study characteristics

The evidence is current to May 2013. Ten studies were included: four studies used manual lymph drainage with usual care, or combined with exercise or compression versus usual care or education alone (395 participants); three studies examined early versus late start of postoperative shoulder exercises (378 people); two studies used either progressive resistance exercise or restricted activity (358 people); and one study investigated a physiotherapy care plan versus no physiotherapy (65 people). The duration of patient follow-up ranged from two days to two years after the intervention.

Key results

No firm conclusion can be drawn about the effect of manual lymph drainage in addition to exercise and education on preventing the incidence of lymphoedema. This is because the two included studies found contradicting results. In addition, no firm conclusion can be drawn about manual lymph drainage in combination with other interventions, because only two studies were found that each tested different combinations. One of these studies found that manual lymph drainage combined with exercise lowered the risk of lymphoedema. The other study combined manual lymph drainage with compression, but this study was too small to draw conclusions.

Arm mobility (i.e. reaching upwards over the head) was better after manual lymph drainage than without it, but this improvement lasted only for the first few weeks after breast cancer surgery.

When assessing whether early or late shoulder exercises reduced the likelihood of developing lymphoedema, the studies did not provide a clear result. The likely incidence of lymphoedema ranged from 5% to 27% (early start) compared to 4% to 20% (for delayed start) during the first 6 to 12 months after surgery.

Starting shoulder exercises immediately after surgery may improve shoulder mobility in the first month, compared to starting after the first week but no firm conclusions can be drawn and mobility is comparable later on.

Progressive resistance training did not increase the risk of developing lymphoedema compared to restricted activity, on the basis that symptoms were monitored and treated immediately if they occurred.

For all investigated interventions, no firm conclusion can be drawn about their effectiveness in reducing pain or improving quality of life.

Quality of the evidence

The evidence was considered to be low quality, except for the evidence on resistance training, which was of moderate quality. This was because many studies had shortcomings in how they were conducted; there were only a small number of studies for each intervention; the results differed between comparable studies; and the groups studied were relatively small.

Stuiver MM, ten Tusscher MR, Agasi-Idenburg CS, Lucas C, Aaronson NK, Bossuyt PMM. Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD009765. DOI: 10.1002/14651858.CD009765.pub2.

Manual lymphatic drainage for lymphedema following breast cancer treatment

Background

More than one in five of breast cancer patients will develop breast cancer-related lymphedema (BCRL). BCRL is a swelling that can occur in the arm, breast, or chest wall as a result of breast cancer surgery and/or radiation therapy. BCRL can negatively impact comfort, function, and quality of life. Manual lymphatic drainage (MLD) is a hands-on therapy that is commonly used for BCRL and often as part of complex decongestive therapy (CDT). CDT consists of MLD, compression bandaging, lymph-reducing exercises (LREs), and skin care.

The review question

Is MLD safe and effective in treating BCRL?

Study characteristics

We found six trials published through May, 2013, totalling 208 participants.

Key results

When women were treated with a course of intensive compression bandaging, their swelling went down about 30% to 37%. When MLD was added to the intensive course of compression bandaging, their swelling went down another 7.11%. Thus, MLD may offer benefit when added to compression bandaging. Examining this finding more closely showed that this significant reduction benefit was observed in people with mild-to-moderate lymphedema when compared to participants with moderate-to-severe lymphedema. Thus, our findings suggest that individuals with mild-to-moderate BCRL are the ones who may benefit from adding MLD to an intensive course of treatment with compression bandaging. This finding, however, needs to be confirmed by further research. When women were given a standard elastic compression sleeve plus MLD and compared to women who received a standard compression sleeve plus a non MLD treatment, results were mixed (sometimes favoring MLD and sometimes favoring neither treatment.)

One-year follow-up suggests that once swelling had been reduced, participants were likely to keep their swelling down if they continued to use a custom-made sleeve.

MLD is safe and well tolerated.

Findings were contradictory for function (range of motion), with one trial showing benefit and the other not. Two trials measured quality of life, but neither trial presented results comparing the treatment group to the control, so findings are inconclusive.

No trial measured cost of care.

Quality of the evidence

Trials were small ranging from 24 to 45 participants. Most trials appeared to randomize participants adequately. However, in four trials the person measuring the swelling knew what treatment the participants were receiving, and this could have biased results.

Ezzo J, Manheimer E, McNeely ML, Howell DM, Weiss R, Johansson KI, Bao T, Bily L, Tuppo CM, Williams AF, Karadibak D. Manual lymphatic drainage for lymphedema following breast cancer treatment. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD003475. DOI: 10.1002/14651858.CD003475.pub2.

Sequencing of chemotherapy and radiotherapy for women following surgery for early breast cancer

Both chemotherapy and radiotherapy reduce the risk of breast cancer recurring and the risk of dying from breast cancer. Generally, these therapies are given after surgery but there is uncertainty about whether they should be given at the same time (concurrently) or one after the other (sequentially). If they are used sequentially, the radiotherapy or the chemotherapy could be used first and concerns have been expressed that the effectiveness of the therapy that is delayed might be reduced. However, it has also been suggested that using chemotherapy and radiotherapy at the same time may be more toxic than keeping them separate. This review examined the current evidence on the best way to administer chemotherapy and radiotherapy following breast-conserving surgery. We were able to include three randomised trials. Two of these, with 853 women, assessed radiotherapy and chemotherapy given at the same time versus chemotherapy given first followed by radiotherapy. The third trial randomised 244 women to radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy. The evidence produced by these three well-conducted trials suggests that recurrence of a woman's cancer and her chances of dying from breast cancer are similar regardless of the order of the treatments, provided that both radiotherapy and chemotherapy are commenced within seven months of the surgery. The trials provided limited information regarding adverse events, side effects or quality of life associated with the different sequences of treatment. The limited evidence available does suggest that the frequency and severity of side effects of chemotherapy and radiotherapy are similar regardless of which sequence is used. However, it should be noted that the women in these trials were treated, on average, in the early 2000s. As a result, the trials do not assess the modern types of radiotherapy, and new types of chemotherapy (such as taxanes) or other drugs (such as Herceptin). We will add relevant trials that include these more recent treatments to future updates of this review.

Hickey BE, Francis DP, Lehman M. Sequencing of chemotherapy and radiotherapy for early breast cancer. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD005212. DOI: 10.1002/14651858.CD005212.pub3.

Hypofractionated radiation therapy for breast conservation in early breast cancer

Review question

We asked if giving fewer radiation treatments (using a higher radiation dose at each visit) was as effective as the conventional 25 to 30 radiation treatments for women with early breast cancer who have breast conserving therapy (keep their breast).

Background

Breast cancer is the most common cancer diagnosed in women, with one in eight women in the United States and Australia, and one in nine women in the United Kingdom being diagnosed with the condition by age 85 years. Breast conserving therapy (removing the tumour but keeping an intact breast) has proven to be as effective as mastectomy (removing the breast tissue) in terms of survival for women with cancer confined to the breast (or the local lymph nodes, or both), as long as a five to six-week course of radiation therapy is delivered. This involves 25 to 30 visits to a radiation oncology department. Without radiation therapy after breast conserving surgery there is a significant risk of breast cancer returning in the breast (local recurrence). Furthermore, for every local recurrence avoided with radiation, one death is avoided at 15 years. Many women prefer breast conservation which has resulted in an increased demand for radiation services. Giving fewer daily radiation treatments (fractions) would be beneficial to women if this has the same effect on tumour control and survival, and cosmetic outcome. In order to reduce the number of treatments, the radiation dose delivered per fraction is increased. This may also reduce demand on radiation resources and be more convenient for women.

Study characteristics

Nine studies, involving 8228 women, were included in this review. Most of the women in the studies (91%) had tumours 3 cm or less in size, all had complete removal of the tumour on pathology and 68% had no evidence of cancer in their lymph nodes. Where the breast size was known, 83% had small or medium breasts.

Key results

The evidence is current up to May 2015. Local recurrence was not different for women having fewer treatments (four fewer local relapses per 1000 (where the true value may be anywhere between 16 fewer to 10 more local relapses per 1000)). Breast appearance was not different for women undergoing fewer treatments (31 fewer fair/poor breast appearance per 1000 (where the true value may be anywhere between 59 fewer to 3 more per 1000 with fair/poor breast appearance)).

Survival was not altered by having fewer treatments (13 fewer deaths per 1000 (where the true value could be between 31 fewer to 5 more deaths per 1000)) and there was no significant difference in late skin toxicity (4more episodes of toxicity per 1000; where the true value may be anywhere between 14 fewer to 36 more episodes of toxicity per 1000) or radiation toxicity. Acute skin toxicity is decreased with fewer treatments (326 fewer events per 1000 (where the true value may be anywhere between 264 fewer to 374 fewer acute skin toxicity events per 1000)). This review indicates that for women who fit these criteria, using fewer radiation treatments after tumour removal gives the same cancer control, with less skin reaction at the time and the likely the same side-effects in the long term.

Quality of the evidence

We found high quality evidence for the following outcomes: local recurrence-free survival, breast appearance, toxicity, overall survival and breast cancer-specific survival. We found moderate quality evidence for relapse-free survival, and no data for mastectomy rate (mastectomy may be required because of local recurrence or unacceptable treatment-related toxicity) or costs.

Hickey BE, James ML, Lehman M, Hider PN, Jeffery M, Francis DP, See AM. Fraction size in radiation therapy for breast conservation in early breast cancer. Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD003860. DOI: 10.1002/14651858.CD003860.pub4.

Partial breast irradiation for early breast cancer

What is the issue?

Women with early breast cancer who choose to keep their breast need to have radiotherapy (RT) as well as surgery to remove the cancer to make sure it does not regrow in the breast. RT is treatment with high energy x-rays. Having RT for breast cancer usually means 25 to 30 visits to the RT department, five times per week.

If breast cancer does regrow in the same breast (called local recurrence), it tends to come back in the area it was removed from. Women can also grow a new cancer (new 'elsewhere primary') in another part of the same breast. We are not sure if the RT given to stop cancer regrowth where the first cancer was does stop the growth of 'elsewhere primaries'.

Breast cancer is the most common cancer that women get. When women choose to keep their breast, it is important that they are happy with how it looks after treatment (cosmesis).

Why does it matter?

We always want to treat the smallest area we can with RT because this means fewer side effects. Treating only part of the breast could mean that RT might be able to be used again in another part of the same breast if needed. New ways of giving RT mean that treating part of the breast can be done with fewer treatments. This is likely to be easier for women and cost less money.

We asked if giving RT to part of the breast (called partial breast irradiation (PBI)) is as good as giving RT to the whole breast. It would need to control the cancer as well as giving RT to the whole breast does. It would also be important that the PBI gives about the same side effects and breast appearance as treating the whole breast.

We found seven studies, which involved 7586 women. Our evidence is current to May 2015. Local recurrence was rare, but more common with PBI (low-quality evidence) and the breast appearance (scored by doctors) was worse with PBI (low-quality evidence). Survival did not differ (high-quality evidence). Scarring in the breast was worse with PBI (moderate-quality evidence). The same number of women died of breast cancer with either treatment (moderate-quality evidence). The same number of women developed spread of breast cancer around their body with either treatment (moderate-quality evidence). There appeared to be the same number of women who eventually needed the breast removed (mastectomy) after both treatments. Mastectomy could happen because of cancer regrowth in the breast or bad side effects (low-quality evidence).

This means that at the moment, PBI does not give the same cancer control in the breast as treating the whole breast, but the difference was small. It may cause worse side effects. There are five big ongoing studies that will be important to answer this question. We hope to have a clearer answer in the next update of this review.

Hickey BE, Lehman M, Francis DP, See AM. Partial breast irradiation for early breast cancer. Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD007077. DOI: 10.1002/14651858.CD007077.pub3.

High-dose chemotherapy and bone marrow or stem cell transplantation for early poor prognosis breast cancer using a woman's own cells (autologous)

Background

Women with breast cancer who have multiple positive lymph nodes when first diagnosed are at high risk of recurrence. Conventional chemotherapy has limited success and is unsafe in high doses as it damages the bone marrow. One treatment considered promising was to give women very high doses of chemotherapy followed by transplantation of stem cells to regenerate their bone marrow. Cochrane review authors examined the evidence, which is current to October 2015.

Study characteristics

We included 14 randomised controlled trials (5600 women) which compared high-dose chemotherapy versus conventional chemotherapy in women with early breast cancer and with a high risk of recurrence. We defined these as women with breast cancer that has spread to multiple local lymph nodes without any evidence of spread beyond local lymph nodes. All studies reported their source of funding. Eight studies were funded by non-profit organisations, one by a public health insurance company, one by industry sources and four by a combination of non-profit organisations and industry sources. Four of the studies reported that authors had no potential conflict of interest, six reported that one or more of their authors had received some kind of support from pharmaceutical companies, and four did not mention whether any of their authors had any potential conflict of interest.

Key results

Using high-dose chemotherapy has little or no effect on increasing survival. Although rates of event-free survival were higher in the high-dose arm over three-year follow-up, this effect was not apparent at longer follow-up. Treatment-related deaths were much more common in the high-dose group. Side-effects were also more common and more severe in the high-dose group. We did not find an effect on the number of women developing second cancers.

Quality of the evidence

The evidence was of high quality.

Farquhar C, Marjoribanks J, Lethaby A, Azhar M. High-dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD003139. DOI: 10.1002/14651858.CD003139.pub3.

Prophylactic colony-stimulating factors to prevent infectious complications in patients with breast cancer undergoing chemotherapy

Patients with breast cancer receiving chemotherapy have an increased risk of infection mediated through a low number of protective white blood cells (neutropenia). Neutropenia is a common toxicity of many chemotherapy agents and is caused by the suppression of the bone marrow. The first sign of infection is usually a fever, which indicates a potentially life-threatening condition if it occurs during severe neutropenia (febrile neutropenia (FN)). FN requires hospital care including the administration of intravenous antibiotics and possible delays in the continuation of chemotherapy. Colony-stimulating factors (CSFs) are drugs administered during chemotherapy in order to prevent or reduce the incidence or duration of FN and neutropenia. This review included eight trials in which 2156 patients with breast cancer had randomly received CSFs or placebo or no treatment during chemotherapy. These trials were carried out between 1995 and 2008. Prophylactic treatment with CSFs significantly reduced the risk of developing FN by 73%. The estimated number of patients needed to be treated with CSFs in order to prevent one event of FN was 12. Although a significant decrease in mortality of all causes during chemotherapy and CSF therapy was noted, there was no reduction in infection-related mortality. There was no significant effect observed that planned chemotherapy schedules could be better maintained if CSFs were administered or that the number of patients with neutropenia decreased with CSFs. Notably, CSFs significantly reduced the need for hospital care yet frequently caused short-term adverse effects like bone pain and injection-site reactions. There were several limitations in this analysis: only a few trials could be included, the number of patients was low in many of these trials, and disease stages and chemotherapy treatments varied considerably. Moreover, the trial authors defined their outcomes differently, making comparisons across studies difficult. Information on the primary and secondary outcomes could not be obtained from all trials and the overall reporting quality was low. Many studies were dated and hence the administration of CSFs did not comply with current recommendations. Overall, CSFs have shown moderate evidence of benefit in the prevention of FN in patients with breast cancer receiving chemotherapy. The evidence that the administration of CSFs could reduce early mortality of all causes was weak and substantiates the need of further studies. There was no reduction in risk of infection-related mortality with CSF treatment.

Renner P, Milazzo S, Liu JP, Zwahlen M, Birkmann J, Horneber M. Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients. Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD007913. DOI: 10.1002/14651858.CD007913.pub2.

Efficacy and safety of trastuzumab in early breast cancer

Patients with early breast cancer may have HER2-positive or -negative tumours. HER2-positive cancers tend to be more aggressive. Knowing whether a cancer has high levels of the HER2 protein (about one in five breast cancers) influences the choice of treatment. Trastuzumab (brand name Herceptin) is a drug specifically available for these patients. The aim of the cancer treatment is to eliminate micrometastases at an early stage (i.e. adjuvant) so that more women survive without recurrence of the disease.

The review includes eight trials that involved 11,991 women with HER2-positive operable breast cancer who were assigned by chance to receive trastuzumab or not. Trastuzumab is always paired with a standard chemotherapy as starting treatment but it can also be continued alone or with hormone-blocking medications, such as an aromatase inhibitor or tamoxifen. Women were followed by clinicians for several years (three on average). The review found that trastuzumab significantly reduced recurrence and mortality. Some patients in treatment develop severe heart toxicity (i.e. congestive heart failure (CHF)). Breast cancer mortality is reduced by one-third but the risk of heart toxicity is five times more likely for women receiving trastuzumab than women receiving standard therapy alone. If 1000 women were given standard therapy alone (with no trastuzumab) then about 900 would survive and five would have experienced heart toxicities. If 1000 women were treated with standard chemotherapy and trastuzumab for one year, about 933 would survive (33 more women will have their lives prolonged), about 740 would be free of disease recurrence (95 more women will not experience the disease return), and 26 would have serious heart toxicity (21 more than the chemotherapy alone group) due to the drug. These heart toxicities are often reversible if the treatment is stopped straight away.

Longer treatment (one year) might involve a greater risk of severe heart toxicities than shorter treatment (six months or less), although these results are based on only two studies and few patients. In women at higher risk of recurrence and with no signs of a weak heart, trastuzumab offers far more benefits than risks. The balance of risks to benefits in patients at lower risk of recurrence (e.g. a small rather than a large tumour) must be carefully evaluated. The oncologist should share the decision with the patient concerning whether and how to start the treatment.

Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R. Trastuzumab containing regimens for early breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD006243. DOI: 10.1002/14651858.CD006243.pub2.

Fulvestrant in the treatment of postmenopausal women with advanced hormone-sensitive breast cancer

Review question

We reviewed the evidence concerning the effectiveness and safety of fulvestrant in prolonging time without further progression of cancer in women with advanced hormone-sensitive breast cancer. We found nine studies testing whether or not fulvestrant is superior to other treatment options.

Background

Seventy per cent of breast cancers are sensitive to hormones, and there are a variety of endocrine therapies that lower or block female hormones to treat these cancers. Fulvestrant is one such endocrine therapy that can be used to treat hormone-sensitive breast cancers by blocking oestrogen. It is administered by monthly injection for women with advanced disease. The definition of advanced disease is when the primary cancer in the breast has either spread to heavily involve the lymph nodes or grown to a considerably large size (stage III) or when the cancer has spread beyond the breast and the lymph nodes to other tissues or organs, or both (stage IV). The goal of treatment in these settings is to improve quality of life, reduce symptoms caused by the cancer, and extend length of life. It is noteworthy that the studies examined in this review predominantly used a lower dose of fulvestrant (250 mg) as compared to the now standard, more effective, and approved dose of 500 mg.

Study characteristics

The evidence is current to 7 July 2015. Our review identified nine clinical trials that compared the effectiveness and safety of fulvestrant against other standard treatments for advanced hormone-sensitive breast cancer and pooled the data from these trials to analyse all the data together. Three different endocrine therapies were analysed as comparator drugs against fulvestrant. Two of these drugs were the aromatase inhibitors anastrozole and exemestane, which lower oestrogen levels in postmenopausal women, and the third was tamoxifen, which works by blocking oestrogen. Four of the studies were in the first-line setting, meaning that fulvestrant was tested against these endocrine therapies as the initial treatment for advanced disease. Five of the studies tested fulvestrant in the second-line or more setting, meaning after the women had progressed on a prior initial treatment for advanced disease. Two studies examined fulvestrant in combination with anastrozole against anastrozole alone, and the other seven studies compared fulvestrant alone with other comparator drugs.

Key results

We found that fulvestrant was at least as effective as the other three standard endocrine therapies used in the treatment of advanced hormone-sensitive breast cancer and is possibly more effective at the new standard dose of 500 mg, rather than the lower dose of 250 mg, which was previously used and tested in all but one of the included studies. We also found that combining fulvestrant with an aromatase inhibitor did not improve effectiveness, and neither was effectiveness influenced by whether fulvestrant was used as the first treatment upon diagnosis of advanced disease or after another endocrine therapy. This was evident in the pooled data analysis for both survival time without progression of cancer and the rate of tumour shrinkage or stabilisation due to fulvestrant as compared with the other endocrine therapies. In addition, fulvestrant-treated women did not experience worse side effects than those receiving the comparator endocrine therapies, and quality of life was equivalent in both fulvestrant-treated women and women treated with the other endocrine therapies.

Fulvestrant can therefore be considered an effective and safe treatment for postmenopausal women with advanced hormone-sensitive breast cancer, when treatment with endocrine therapy is indicated.

Quality of the evidence

All studies were of high quality.

Lee CI, Goodwin A, Wilcken N. Fulvestrant for hormone-sensitive metastatic breast cancer. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD011093. DOI: 10.1002/14651858.CD011093.pub2.

Toremifene versus tamoxifen for advanced breast cancer

Breast cancer is the most common cancer in women. When it has spread beyond the breast, it is called advanced breast cancer. Treatments for advanced breast cancer include chemotherapy, endocrine therapy and possibly surgery and radiation therapy. Of endocrine therapy, tamoxifen (TAM) is the oldest and most-prescribed selective oestrogen-receptor modulator. However, several significant adverse effects have been described after long-term TAM treatment. Toremifene (TOR), which can also be used to treat advanced breast cancer, has a mechanism similar to that of TAM. The objective of this review was to compare TOR with TAM in terms of overall survival, response to treatment, time to progression, and adverse effects. Seven eligible studies were identified, all of which provided information on response to treatment (in 2061 patients), five on progression free survival (in 1436 patients) and four on overall survival (in 1374 patients). The trials were generally old (conducted between late 1980s and early 1990s) and were of modest quality.

Based on the data from these trials, 25.8% of the patients in the TOR group responded to the treatment, compared with 26.9% in the TAM group. The cancers of 50% of the patients in the TOR group had progressed after 6.1 months, compared with 5.8 months in the TAM group. Half of the patients in the TOR group survived longer than 27.8 months, compared with 27.6 months in the TAM group.

The risk for progression and death in the TOR group was not significantly different from that in the TAM group. The frequencies of most adverse events were also similar in the two groups, except that the number of headaches occurring in the TOR group was only about one-seventh of that in the TAM group. However, considering the results of other large trials, we cannot exclude the possibility that this is purely a play of chance. Due to the lack of data, no conclusions can be made as to the long-term adverse effects achieved with either treatment. The evidence from this review suggests that TOR and TAM are equally effective and the safety profile of the former is at least not worse than the latter in the first-line treatment of patients with advanced breast cancer. Thus, TOR may serve as a reasonable alternative to TAM when anti-oestrogens are applicable but TAM is not the preferred choice for some reason.

Mao C, Yang ZY, He BF, Liu S, Zhou JH, Luo RC, Chen Q, Tang JL. Toremifene versus tamoxifen for advanced breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD008926. DOI: 10.1002/14651858.CD008926.pub2.

Metastatic breast cancer

Platinum-containing regimens for metastatic breast cancer

What is the issue?

Metastatic breast cancer occurs when the cancer has spread to areas of the body beyond the breast and nearby lymph nodes. Although metastatic breast cancer is generally not curable, it is widely accepted that women with metastatic disease should receive some form of chemotherapy to help ease the severity of disease symptoms, while hopefully extending survival time. Chemotherapy containing platinum is known to be effective for treating a number of cancer types including lung, testicular, head and neck, bladder and ovarian cancers, but it also known to cause more adverse effects (such as nausea and vomiting, hair loss, anaemia, kidney damage and leukopenia (low white blood cells)) than other chemotherapy options. The two platinum agents most commonly used for treating metastatic breast cancer are carboplatin and cisplatin.

The original version of this review (2004) concluded that chemotherapy containing platinum did not increase survival time for women treated for metastatic breast cancer. Since then, however, researchers have discovered that there are a variety of subtypes of breast cancer which may respond differently to different types of chemotherapy. One of these subtypes — triple-negative breast cancer (TNBC) — makes up approximately 12 to 17% of breast cancers and is associated with shorter survival and higher likelihood that the cancer returns. Some researchers have speculated that chemotherapy containing platinum might be more effective in treating metastatic TNBC (mTNBC) than other chemotherapy options.

Why does it matter?

There are at least two reasons why it is important to update the evidence on this topic. First, it is important to assess whether our 2004 conclusions — based on 12 early studies — are representative of the 24 studies who have now published or provided results through to 2015. Second, it is important to assess whether chemotherapy containing platinum increases survival for women with mTNBC more than other chemotherapy options.

We asked…

whether chemotherapy treatments containing a platinum agent are more or less effective for treating women with metastatic breast cancer than chemotherapy treatments not containing a platinum agent. We also asked the same question, but with a focus on women with mTNBC.

We found…

24 studies involving 4418 women. The evidence is current to May 2015. Five of the 24 studies specifically assessed women with mTNBC while the other 19 studies assessed women with metastatic breast cancer in general (mainly women without mTNBC).

This review found that, compared to chemotherapy without platinum, chemotherapy with platinum did not increase survival time by any important degree for women with metastatic breast cancer in general (mainly women without mTNBC). The quality of the evidence for this was considered to be high, meaning that we are confident about the results. For women with mTNBC, however, this review found that chemotherapy containing platinum may increase survival time over chemotherapy without platinum, but the quality of the evidence for this is low at this point in time (largely due to the small number of studies that have assessed mTNBC). This review also found that chemotherapy including platinum reduced the number of breast cancer recurrences compared to chemotherapy that did not contain platinum in women with mTNBC, however these findings also currently come from low-quality evidence. There was no difference in the number of breast cancer recurrences for women receiving platinum or non-platinum chemotherapy for metastatic breast cancer in general. Chemotherapy with platinum was more likely to shrink tumours compared to chemotherapy without platinum, but this result needs to be considered cautiously.

Compared with women receiving chemotherapy without platinum, women receiving chemotherapy with platinum experienced higher rates of nausea/vomiting, anaemia, leukopenia and hair loss.

This means…

it is difficult to justify using chemotherapy containing platinum for the treatment of metastatic breast cancer that is not mTNBC, given that similarly effective but less toxic chemotherapy is commonly available. Chemotherapy containing platinum may provide a survival benefit to mTNBC participants of sufficient magnitude to justify its use, but the quality of the evidence for this is low at this point in time. Further studies are required before a more definitive conclusion can be made.

Egger SJ, Willson ML, Morgan J, Walker HS, Carrick S, Ghersi D, Wilcken N. Platinum-containing regimens for metastatic breast cancer. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD003374. DOI: 10.1002/14651858.CD003374.pub4.

Efficacy and safety of trastuzumab in metastatic breast cancer

Tumours characterised by the presence of the HER2 protein are found in about one in five women with metastatic breast cancer. These tend to be more aggressive and the prognosis and choice of treatment are affected. Trastuzumab (Herceptin®) is a targeted biological drug (a monoclonal antibody) that attaches to the HER2 protein, blocking the growth of malignant cells. We included seven trials with 1497 women who had HER2-positive metastatic breast cancer in this review. They were assigned by chance to receive trastuzumab with or without chemotherapy (taxane, anthracycline or capecitabine in four studies), hormonal therapy (aromatase inhibitors including letrozole or anastrozole in two studies) or targeted therapy (lapatinib in one study). Women treated with trastuzumab were followed up until disease progression in five studies and beyond disease progression in two studies. The length of trastuzumab administration varied between 8.7 and 30 months, and follow-up averaged two years after starting trastuzumab.

All studies found that trastuzumab extends time to disease progression, with gains varying between two and 11 months, and in five studies it extended time to death by between five and eight months. However, some patients develop severe heart toxicity (congestive heart failure) during treatment. While trastuzumab reduces breast cancer mortality by one-fifth, the risk of heart toxicity is between three and four times more likely. If 1000 women were given standard therapy alone (with no trastuzumab) about 300 would survive and 10 would have heart toxicities. With the addition of trastuzumab to this treatment, an additional 73 would have their lives prolonged, and an additional 25 would have severe heart toxicity. Omitting the anthracycline-trastuzumab arms (which would not be regarded as standard of care) 21 patients would have severe heart toxicity (11 more than the chemotherapy alone group). These heart toxicities are often reversible if the treatment is stopped once heart disease is discovered. Women with advanced disease might choose to accept this risk. On balance, this review shows that with trastuzumab the time to disease progression and survival benefits outweigh the risk of heart harm.

Trastuzumab does not increase the risk of haematological toxicities, such as neutropenic fever and anaemia; however, it seems to raise the risk of neutropenia. There were insufficient data on the impact of trastuzumab on quality of life, treatment-related deaths and brain metastases to reach a conclusion for these outcomes.

We rated the overall quality of the evidence as moderate, with the main weaknesses being the fact that all studies included were open label (not blinded), which may have affected the outcome assessments for time to disease progression and toxicities, and that two studies have not published their results for mortality.

Furthermore, the recruitment in three out of seven studies was stopped early and in three trials more than 50% of patients in the control groups were permitted to switch to the trastuzumab arms at disease progression, making it more difficult to understand the real net benefit of trastuzumab on mortality. The evidence to support the use of trastuzumab beyond disease progression is limited.

It is important to highlight that, although trastuzumab is used for women with HER2-positive early breast cancer, the women enrolled in these metastatic trials were not previously treated with trastuzumab. The effectiveness of trastuzumab for women relapsing after adjuvant trastuzumab is still an open issue, although it is likely that it is offered to the majority of them.

Balduzzi S, Mantarro S, Guarneri V, Tagliabue L, Pistotti V, Moja L, D'Amico R. Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD006242. DOI: 10.1002/14651858.CD006242.pub2.

Taxane-containing regimens for metastatic breast cancer

Review question

We reviewed the evidence about the effect of taxane-containing chemotherapy regimens in women with metastatic breast cancer. This is an update of a Cochrane review first published in 2003.

Background

Treatment for women with metastatic breast cancer (that is, cancer that has spread beyond the breast) usually involves chemotherapy to try to shrink or slow the growth of the cancer. Chemotherapy can involve a single drug or a combination of drugs. Paclitaxel and docetaxel are chemotherapy drugs known as taxanes. Taxanes can inhibit cancer cells from dividing and reproducing, and their adverse effects can include nausea, vomiting, and hair loss, as well as allergic reactions, which can be reduced by premedication. We wanted to examine whether or not taxane-containing chemotherapy improves survival and extends time to disease progression in women with metastatic breast cancer.

Study characteristics

The evidence is current to February 2013. We included 28 studies that randomised 6871 women. Women were assigned to receive either a taxane-containing chemotherapy regimen (single taxane or in combination with other chemotherapy drugs) or a non-taxane chemotherapy regimen. There were variations in the taxane-containing chemotherapy regimen and the non-taxane treatments. Approximately half of the studies used paclitaxel and the other half used docetaxel, and in the majority of cases, taxanes were administered every three weeks. Of the 28 studies, 20 studies included women who received taxanes as their first treatment after their diagnosis of metastatic breast cancer, and 21 studies involved women who had not been previously treated with anthracyclines in the metastatic setting. From those studies reporting median follow-up, this ranged from 9 months to 69 months.

Key results

This review showed that chemotherapy regimens including taxanes improved survival and decreased the progression of metastatic breast cancer. If the analyses were restricted to those studies where women received taxanes as their first treatment after their diagnosis of metastatic breast cancer, the survival benefit persisted. Taxanes also appeared to cause tumours to shrink more than chemotherapy regimens without taxanes. However, there were differences in side effects. The risk of experiencing neurotoxicity (tingling of hands and feet) with taxanes increased compared to non-taxane chemotherapy. Hair loss also seemed to be more likely with taxane than with non-taxane-containing regimens. However, less nausea/vomiting was observed with taxanes.

There was no difference in the rates of leukopaenia (low white blood cells) or treatment-related deaths between taxane and non-taxane chemotherapy. Of the studies that reported quality of life measures, there did not appear to be any differences (overall or on subscales) in quality of life between the two groups.

Quality of the evidence

We considered 19 out of the 28 studies to be at low risk of bias overall. However, some studies failed to report details on concealing drug treatments and methods of outcome assessment for those outcomes more likely to be at risk of bias (for example tumour response rate). The degree of variability seen across the included studies probably reflects the varying efficacy of the non-taxane chemotherapy regimens used in these studies and indicates that taxane-containing chemotherapies are more effective than some, but not all, nontaxane-containing regimens.

Ghersi D, Willson ML, Chan MMK, Simes J, Donoghue E, Wilcken N. Taxane-containing regimens for metastatic breast cancer. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD003366. DOI: 10.1002/14651858.CD003366.pub3.

Combination (several drugs at the same time) versus sequential chemotherapy (same drugs given one after the other) for metastatic breast cancer

Metastatic breast cancer is not currently a curable disease but one that can be very effectively treated with chemotherapy, endocrine therapy and targeted therapies. Average survival is about two years but some women live for many years longer. It is important to investigate the best way to give chemotherapy to treat metastatic breast cancer in order to optimise survival and quality of life and to minimise the side effects from treatment.

This review investigated whether giving a combination of drugs at the same time was more effective than giving the same drugs one at a time (sequential treatment).

A literature search conducted in October 2013 resulted in 12 randomised controlled studies with 2317 patients that could be included in the analysis. The patients had metastatic breast cancer and either they had not been treated or had received one or two treatments after their diagnosis of metastatic breast cancer. The primary outcomes were overall survival and progression-free survival (time from randomisation to the time of disease progression). Secondarily, we compared the degree the tumour shrunk in response to chemotherapy (overall response rate), toxicity and quality of life.

There was no difference in overall survival between the two groups but we found that when drugs were given one at a time there maybe more time before the tumours grew back again (longer progression-free survival). However, combination chemotherapy caused tumours to shrink more, although this did not result in longer survival than when using sequential chemotherapy. Rates of febrile neutropenia (infection) were higher in the combination arm but there was no difference in the rates of neutropenia (low white blood cells). There was no difference in quality of life between the two groups but there were only three trials that reported this information. Quality of life should be included as an outcome in future trials addressing this question. Overall, the studies did not consistently report the way patients were randomised and this may be a source of bias in the results.

Generally this review supports the recommendations by international guidelines to use sequential monotherapy unless there is rapid disease progression.

Dear RF, McGeechan K, Jenkins MC, Barratt A, Tattersall MHN, Wilcken N. Combination versus sequential single agent chemotherapy for metastatic breast cancer. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD008792. DOI: 10.1002/14651858.CD008792.pub2.

Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer

Breast cancer is the most common cancer in women. If the cancer has spread beyond the breast (metastatic disease), treatments include chemotherapy (anti-cancer drugs) and endocrine therapy (also known as hormonal treatment). Endocrine therapy is mainly given to women whose cancer is determined to be hormone-responsive, that is, where hormone receptors (oestrogen or progesterone receptors) are expressed in the tumour cells. The aim of this review was to see if starting treatment with chemotherapy or starting treatment with endocrine therapy provides more benefit in terms of survival, response to treatment, toxicity from treatment and quality of life. Ten eligible studies were identified, eight of which provided information on response to treatment (in 817 patients) and six on overall survival (in 692 patients). Trials were generally old (published between 1963 and 1995) and small in size (median of 70 women, range 50 to 226 women in each trial) and were of modest quality. The types of chemotherapy used were reasonably conventional by today's standards; the endocrine therapies varied considerably.

This review found that while initial treatment with chemotherapy rather than endocrine therapy may be associated with a higher response rate, the two initial treatments had a similar effect on overall survival. No single group of patients who might benefit from or be harmed by one treatment over the other were identified, although there was little information to address this question. Six of the seven fully published trials commented on increased toxicity associated with chemotherapy including nausea, vomiting and alopecia. Three of the seven trials mentioned aspects of quality of life but their findings provided differing results. Only one trial formally measured quality of life (QOL), concluding that QOL was better with chemotherapy. Based on these trials, no conclusions can be made as to the QOL achieved with either treatment.

Accurate information about hormone receptor status is now routinely available for many women with metastatic breast cancer, and hormonal treatments have improved in their effectiveness in the last 10 years. In women with metastatic breast cancer where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy appears to be better, on the basis of the trials and outcomes in this review, except in the presence of rapidly progressive disease.

Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD002747. DOI: 10.1002/14651858.CD002747.

Treatments targeting blood vessels for metastatic breast cancer

Angiogenesis refers to the development of new blood vessels from the pre-existing beds containing the normal supply of blood vessels. Tumours are dependent on the formation of new blood vessels for their growth. Vascular-endothelial-growth-factor (VEGF) is a key molecule in promoting blood vessel growth. VEGF-targeting therapies are a new class of drugs designed to target a specific molecule. One of these drugs is bevacizumab (Avastin) which has been studied in clinical trials in metastatic breast cancer. Trials with other drugs are ongoing. Data are available from seven randomised trials, which evaluated the effect of bevacizumab on the primary endpoint in a total of 4032 patients with metastatic breast cancer. These patients were either-hormone receptor negative or had progressed on hormonal treatment. The primary end point was progression-free survival and secondary end points included overall survival, response rate measuring the change in size of the tumour, quality of life and toxicity of the treatment. Progression-free survival is considered a surrogate end point, i.e. a substitute for overall survival as an end point. The addition of bevacizumab to chemotherapy significantly prolongs progression-free survival and response rates in patients who have had previous chemotherapy and those who have not had previous chemotherapy for metastatic disease. The magnitude of this benefit is dependent on the type of chemotherapy used. Best results have been observed for the combination of weekly paclitaxel and bevacizumab in patients without prior chemotherapy for metastatic disease. Although progression-free survival was significantly longer with bevacizumab, there was no significant effect observed on either overall survival or quality of life. Quality of life is a direct measure of benefit to the patient. Adverse effects of bevacizumab in breast cancer are generally manageable, but may be serious and include increased frequencies of high blood pressure, blood clots in arteries and bowel perforations. However, overall rates of treatment-related deaths were lower in patients treated with bevacizumab. Because of the lack of effect on overall survival and quality of life, it is regarded as controversial whether bevacizumab is associated with a true patient benefit in spite of the increase in progression-free survival.

Wagner AD, Thomssen C, Haerting J, Unverzagt S. Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD008941. DOI: 10.1002/14651858.CD008941.pub2.

SUPPORTIVE AND FOLLOW-UP CARE

Online support groups for women with breast cancer

Review question

We reviewed the evidence for effects of online support groups for women with breast cancer on emotional distress, uncertainty, anxiety, depression and quality of life.

Background

Women with a diagnosis of breast cancer can be affected physically, psychologically and emotionally. They are uncertain about the future and may need information and support to help them cope with their condition. Increasingly, people with cancer are accessing the Internet to seek the information and support that they need; many join online support groups. At this time, we know little about how participation in online support groups psychologically and emotionally affects women with breast cancer.

Study characteristics

We conducted a systematic search of the literature with no restrictions on language or country. We included in this review six studies, with a total population of 492 women with breast cancer. Five of the six studies had small samples. Study participants were predominantly 'white', well-educated women with moderate to high income at any stage of breast cancer who were undergoing a range of treatments.

Online support groups in these six trials lasted six to 30 weeks and included eight to 15 members. Women participated in these groups between 1.5 and 2.5 hours per week. Investigators reported all trials in English and conducted their research in the USA.

Key results

None of the included trials measured emotional distress or uncertainty. Women who participated in online support groups showed no improvement in anxiety or quality of life when compared with those in control groups (which included women with similar characteristics who did not participate in online support groups). However, women who took part in online support groups showed a small to moderate reduction in depression when compared with those in control groups.

Results revealed no difference in depression between groups led by peers and those led by health professionals. However, women taking part in standard online groups (run by participants without prompting from health professionals) reported a greater reduction in depression and anxiety than those in other types of online groups (in which women were asked specifically by the health professional to respond to one another's need for support).

Quality of the evidence

Small studies of low or very low quality attributed mainly to poor study design and other shortcomings have provided evidence on the effectiveness of online support groups for women with breast cancer. Large, rigorous trials including ethnically and economically diverse participants are needed to provide robust evidence on the effectiveness of online support groups for women with breast cancer.

McCaughan E, Parahoo K, Hueter I, Northouse L, Bradbury I. Online support groups for women with breast cancer. Cochrane Database of Systematic Reviews 2017, Issue *3*. Art. No.: CD011652. DOI: 10.1002/14651858.CD011652.pub2.

Yoga for women with a diagnosis of breast cancer

What is the issue?

Breast cancer is the most common cancer among women worldwide. Although the number of women who survive breast cancer is increasing, those women often suffer from psychological or physical problems. We wanted to find out whether yoga can improve quality of life, mental health and symptoms related to cancer in women with a diagnosis of breast cancer. We included all forms of yoga but excluded multi-modal interventions such as mindfulness-based stress reduction.

Why does it matter?

Many women with a diagnosis of breast cancer try yoga as a means of coping with their symptoms. Thus, it is important to find out whether yoga can really help these women. It is also important to find out whether any risks are associated with practising yoga.

What did we find?

We found 24 studies that involved 2166 women. Our evidence is current to January 2016. We found that women in 11 studies had completed surgery, chemotherapy and radiotherapy; women in three studies were currently undergoing chemotherapy; and women in five studies were currently undergoing radiotherapy. Women in the remaining five studies were either undergoing treatment or were not. Studies used a variety of questionnaires to assess quality of life, depression, fatigue and/or sleep disturbances.

We found that yoga was more effective than no therapy in improving quality of life and reducing fatigue and sleep disturbances. We also found that yoga was better for reducing depression, anxiety and fatigue in women when compared with psychosocial or educational interventions such as counselling. We are fairly certain that these observed results are probably true. Yoga might be as effective as exercise in improving quality of life and reducing fatigue; we do not have enough data to be sure. Studies have poorly reported risks of yoga. However, we found no evidence of serious risks of yoga among women with a diagnosis of breast cancer. No studies have assessed effects of yoga in women given a diagnosis of breast cancer more than five years ago.

What does this mean?

Our findings indicate that women with a diagnosis of breast cancer can use yoga as supportive therapy for improving their quality of life and mental health, in addition to standard cancer treatments.

Cramer H, Lauche R, Klose P, Lange S, Langhorst J, Dobos GJ. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD010802. DOI: 10.1002/14651858.CD010802.pub2.

Home-based multidimensional survivorship programmes for breast cancer survivors

Background

The demands are growing for effective multidimensional survivorship programmes in women who have had breast cancer. This review was conducted to evaluate the effects of home-based multidimensional survivorship programmes on the quality of life in women who had completed primary treatment (surgery and/or chemotherapy and/or radiotherapy) for breast cancer in the previous 10 years.

Study characteristics

We found 26 studies with 2272 participants receiving home-based multidimensional survivorship programmes compared with control. The content and delivery approach of the home-based multidimensional survivorship programmes were diverse among the included studies. The survivorship programme could incorporate any combination of at least two of the three identified components: educational (such as the provision of information and advice on how to self-manage); physical (such as exercise or resistance training); and psychological (such as counselling and cognitive therapies). Most of the studies used usual care (routine medical follow-up services) as a comparator. A few studies used a lower level or different type of intervention (e.g. stress management or exercise) or attention control as the comparator.

The results revealed that home-based multidimensional survivorship programmes in breast cancer survivors appear to have a short-term beneficial effect of improving quality of life. Several other studies examined the effects of home-based multidimensional survivorship programmes on symptoms and psychosocial outcomes. Those breast cancer survivors who received home-based multidimensional survivorship programmes showed a reduction in fatigue, insomnia and anxiety, but the effect was in the short term. There was no difference between groups with respect to symptoms of depression, flushes and night sweats. We found that a group-based approach may be more effective than an individual-based approach to deliver the home-based multidimensional survivorship programmes. However, we found no evidence for a difference in quality of life with educational, psychological or physical components of the survivorship programmes.

Quality of evidence

The quality of evidence across studies for quality of life ranged from moderate to very low, meaning that in some cases we were fairly confident about the results (e.g. quality of life improvements) while in other cases we were uncertain about the results (e.g. reductions in fatigue, insomnia and anxiety).

Cheng KKF, Lim YTE, Koh ZM, Tam WWS. Home-based multidimensional survivorship programmes for breast cancer survivors. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD011152. DOI: 10.1002/14651858.CD011152.pub2.

Psychological interventions for women with metastatic breast cancer

Cancer that has spread beyond the breast (metastatic breast cancer) is frightening and distressing and can lead women to experience psychological symptoms, such as depression. There is a belief that these psychological symptoms can make the cancer worse. Treatment for psychological symptoms is sometimes offered to women with metastatic breast cancer, either individually or in a group. In 1989 one study examined the effect of this treatment, offered to a group of women, and it found that it led to them feeling psychologically better and living longer. Subsequent studies did not seem to replicate the findings from the 1989 study, causing uncertainty about the effects of psychological treatments for women with metastatic breast cancer.

This review examined the studies to date to see what effect psychological treatments had on women with metastatic breast cancer. We found 10 studies with a total of 1378 women with metastatic breast cancer. Three of the studies used a psychological treatment known as cognitive behavioural therapy (CBT), four studies used supportive-expressive group therapy (SEGT), while the remaining three studies used treatments that were delivered on an individual basis and were neither CBT nor SEGT.

We performed statistical analysis and found that the odds ratio (a measure of association between an intervention and an outcome) for survival of women with metastatic breast cancer one year after receiving psychological treatment was 1.46, suggesting that there was an association between the psychological treatment and improved survival. This finding was not found when looking at the odds ratio of survival at five years. We also found some evidence that psychological treatments in the short term (for example, one year) may produce a small reduction in pain and improve some psychological symptoms. However, making comparisons across these studies was difficult as they differed in their conduct, treatments and measures used. Moreover, we cannot rule out that the psychological treatments could also cause psychological harm.

Mustafa M, Carson-Stevens A, Gillespie D, Edwards AGK. Psychological interventions for women with metastatic breast cancer. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD004253. DOI: 10.1002/14651858.CD004253.pub4.

Use of psychological interventions in women diagnosed and under treatment for non-metastatic breast cancer

Review question

We reviewed the evidence for the effect of psychological interventions on the psychological impact, quality of life and survival among women with non-metastatic breast cancer (that is cancer that has not spread beyond the breast).

Background

Breast cancer is the most common cancer affecting women worldwide. Being a distressing diagnosis, considerable research has examined the psychological consequences of being diagnosed and treated for breast cancer. Breast cancer diagnosis and treatment can cause depression and anxiety and reduce quality of life. As a result, various psychological interventions have been utilised to help address the psychological distress experienced after a diagnosis of breast cancer.

Study characteristics

The evidence was current to May 2013. An intervention could be delivered in a group setting (group intervention), as one to one contact between a therapist and a patient (individual intervention) or in the form of couple therapy where the patient and her spouse attends the therapy sessions (couple intervention). The control group could receive educational leaflets or have access to seminars or relaxation classes. A comprehensive search of the literature was conducted and 28 studies comprising 3940 participants were included.

The majority (24 out of 28 studies) of interventions were based on cognitive behavioural therapy, which involves changing a person's thoughts and behaviour. Four studies used psychotherapy as the intervention. Generally, the methods for assessing outcomes (such as anxiety, depression, quality of life) after the intervention and the timing of these assessments were not uniform across studies.

Key results

Women who received cognitive behavioural therapy showed important reductions in anxiety, depression and mood disturbance, especially when it was delivered to groups of women. An improvement in quality of life was observed when women received individual cognitive behavioural therapy compared to the control group. The effects on survival were uncertain because the results were imprecise.

The four psychotherapy studies reported limited information for each outcome. Therefore no firm conclusion could be made about the efficacy of psychotherapy.

Adverse events were not reported in any of the included studies.

Further research should aim to provide evidence for people to make informed decisions about whether the effects of these treatments are sustainable after discontinuation of the therapy.

Quality of the evidence

The quality of evidence ranged from very low quality (for example for quality of life, individually delivered intervention) to moderate quality evidence (for mood disturbance). The interventions varied between studies as did the methods and timing of outcome measures and treatment received within the control groups.

Jassim GA, Whitford DL, Hickey A, Carter B. Psychological interventions for women with non-metastatic breast cancer. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD008729. DOI: 10.1002/14651858.CD008729.pub2.

Different follow-up strategies for women after breast cancer treatment

Review question

Whether an intensive follow-up decreases the number of recurrences or deaths and affects health-related quality of life (HRQoL) compared with a less intensive follow-up and whether a follow-up offered by specialists is different from that performed by family physicians.

Background

Follow-up after breast cancer is performed in order to check whether breast cancer has returned to the breast or other part of the body and to monitor side effects related to treatment. Follow-up may be performed by specialists or family physicians, regularly or on demand, and may be based on routine clinical visits (physical examinations and yearly mammography), or on a more intensive surveillance (laboratory tests and imaging examinations). The first update of this Cochrane review published in 2004 has shown that having more tests does not improve the length or quality of life in breast cancer survivors and a comparable effectiveness of follow up by specialist to that by primary physician. Moreover, additional screening tests could increase anxiety related to false positive results, unnecessary radiation exposure and health-related costs.

Study characteristics

A literature search up to July 2014 found five trials (involving 4023 women with a median follow-up variable from 16 to 120 months). Since the previous version of this Cochrane review in 2004, one new study has been published.

Key results

This review of trials found that follow-up programs based on a regular physical examination and a yearly mammogram appear to be as effective as the more intensive approaches and to have similar impact on HRQoL. No significant differences were found between follow-up performed by specialists or family physicians, regularly or on demand. These results should be interpreted with caution bearing in mind that these studies were conducted almost two decades ago; additional trials incorporating new biological knowledge and improved imaging technologies are needed.

Quality of the evidence

Allocation concealment was adequate in all but one trial; two trials were judged to be at low risk of selection bias; the blinding of the outcome assessor was not described in two trials. For one trial it was not possible to judge risk of bias because it reported no methodological information.

Moschetti I, Cinquini M, Lambertini M, Levaggi A, Liberati A. Follow-up strategies for women treated for early breast cancer. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD001768. DOI: 10.1002/14651858.CD001768.pub3.

Exercise for women receiving chemotherapy or radiation therapy or both (adjuvant therapy) for breast cancer

What is the issue?

In the past, women receiving cancer treatment were usually advised to rest and avoid physical activity. But, we now know that too much rest and too little physical activity can lead to muscle wasting. This reduces women's physical fitness level and may limit their regular activities. Women also often have other side effects that can affect their daily lives, such as extreme tiredness (fatigue), depression, and reduced mental functioning, for example being able to remember things or keep focused.

Why does it matter?

The side effects of breast cancer treatment can interfere with daily activities and return to work. It is important to learn of ways to reduce these side effects.

We asked if physical exercise during chemotherapy or radiation therapy or both helped to reduce treatment side effects. Side effects studied included tiredness, depression, and reduced physical fitness and mental functioning. We also studied general effects such as health-related, cancer-specific, and cancer site-specific quality of life. Questionnaires for cancer-specific quality of life ask questions that are important for patients with cancer in general, for example about pain or nausea. Cancer site-specific quality of life is measured with questionnaires that ask women with breast cancer about topics that are especially important to them, for example about breast symptoms or body image. We only included questionnaires that have been shown to be reliable.

We found 32 studies involving 2626 women. The included studies were published up through March 2015. Not all studies considered all of these potential side effects. Combining the results of these studies suggests that physical exercise probably improves physical fitness and slightly lessens fatigue. These studies also suggest that physical exercise probably results in little or no improvement in cancer specific quality of life and depression. Exercise may improve mental function and slightly improve cancer site-specific quality of life, although the quality of the evidence was low for both of these outcomes. It may result in little or no improvement in health-related quality of life, however the quality of evidence was low for this outcome. The quality of evidence may have been low because many of the studies did not have enough participants to observe small differences and because results may be biased due to people assessing the outcomes knowing which participants were in the control group. Importantly, physical exercise did not harm most women. Very few women experienced discomfort or pain in their arms or legs.

What does this mean?

It appears that exercise during cancer treatment can help lessen fatigue and improve physical fitness. It probably results in little or no improvement in cancer-specific quality of life and depression. It is unknown whether it helps for other side effects. At least nine current studies will help to answer the question if and how much exercise helps with the mentioned side effects and other side effects.

Furmaniak AC, Menig M, Markes MH. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD005001. DOI: 10.1002/14651858.CD005001.pub3.

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