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Efeitos do exercício físico após o tratamento com intenção curativa do câncer de mama: uma revisão sistemática e metanálise

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SUMÁRIO

Lista de abreviaturas utilizadas

CDSR: Cochrane Database of Systematic Reviews

DNA: ácido desoxirribonucleico

ECR: ensaio clínico randomizado

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer QLQ-C30

IGF-1: fator de crescimento semelhante a insulina tipo 1

IL-6: interleucina 6

IMC: índice de massa corporal

INCA: Instituto Nacional do Câncer

OMS: Organização Mundial da Saúde

PCR: proteína C reativa

TNF-alpha: fator de necrose tumoral alfa

SF-36: 36-Item Short Form Survey

SG: sobrevida global

SLR: Sobrevida livre de recorrência

SLP: Sobrevida livre de progressão

Resumo

Introdução: Revisão sistemática e metanálise são metodologias integradoras de estudos individuais resumindo seus resultados e aumentando o poder estatístico para responder questões clínicas.

Objetivo: investigar a efetividade de intervenções relacionadas a neoplasias ginecológicas, em especial avaliar a adjuvância do exercício físico no câncer de mama; a videolaparoscopia no tratamento de câncer de ovário precoce; e os derivados da platina na adjuvância do câncer de colo de útero precoce.

Materiais e Métodos: foram realizadas três revisões sistemáticas de ECRs para responder as questões de pesquisa. Metanálise foi realizada utilizando modelo de efeitos aleatórios. A execução seguiu as diretrizes preconizadas pela Colaboração Cochrare e a redação seguiu a diretriz PRISMA. A avaliação da qualidade da evidencia seguiu a metodologia GRADE.

Resultados: Sessenta estudos avaliaram exercício físico na adjuvância do câncer de mama. Apenas um apresentava mortalidade como desfecho com HR: 0,45; IC95% 0,21 – 0,97. Houve diminuição do peso (-1,36 kg; IC95% -2,51 a -0,21; p=0,02) e melhora de qualidade de vida (SMD 0,45; IC95% 0,20 a 0,69; p<0,01), porém existe viés de publicação e baixa qualidade metodológica das evidências. Encontramos 4 estudos avaliando quimioterapia com derivados da platina na adjuvância do câncer de colo de útero que demonstraram melhora da sobrevida em mulheres com fatores de risco para recorrência (HR=0,56; IC95%: 0,36 – 0,87), porém as custas de maior toxicidade. Não foram encontrados ECRs avaliando a videolaparoscopia no tratamento de câncer de ovário.

Conclusão: exercício físico demonstrou efeitos significativos em diversas medidas antropométricas e importante efeito em qualidade de vida. Um estudo apresentou efeitos positivos em SG. Quimioterapia à base de platina adicionado à radioterapia adjuvante pode melhorar a sobrevida em mulheres com câncer de colo do útero precoce e fatores de risco para recorrência. Não houve estudos para avaliação de videolaparoscopia no tratamento de câncer de ovário precoce.

Palavras-chave neoplasias da mama; neoplasia ginecológica; obesidade; exercício físico; revisão sistemática; metanálise.

Introduction: Systematic review and meta-analysis are integrative methodologies of individual studies summarizing their results and increasing statistical power to answer clinical questions.

Objective: to investigate the effectiveness of interventions related to gynecological neoplasias, in particular to evaluate the adjuvant of physical exercise in breast cancer; videolaparoscopy in the treatment of early ovarian cancer; and platinum derivatives in the adjuvant of early cervical cancer.

Materials and Methods: Three systematic reviews of RCTs were conducted to answer the research questions. Meta-analysis was performed using random effects model. The execution followed the guidelines recommended by Cochrare Collaboration and the writing followed the PRISMA guideline. The quality evaluation of the evidence followed the GRADE methodology.

Results: Sixty studies evaluated physical exercise in adjuvant breast cancer. Only one presented mortality as an outcome with HR: 0.45; 95% CI 0.21-0.97. There was a decrease in weight (-1.36 kg, 95% CI -2.51 to -0.21, p = 0.02) and

improvement in quality of life (MDS 0.45, 95% CI 0.20 to 0.69 , p <0.01), but there is publication bias and low methodological quality of the evidence. We found 4 studies evaluating chemotherapy with platinum derivatives in adjuvant cervical cancer that demonstrated improved survival in women with risk factors for recurrence (HR = 0.56, 95% CI: 0.36-0.87), but the costs of greater toxicity. We found no RCTs evaluating videolaparoscopy in the treatment of ovarian cancer.

Conclusion: physical exercise demonstrated significant effects on several anthropometric measures and an important effect on quality of life. One study had positive effects on OS. Platinum-based chemotherapy added to adjuvant radiotherapy may improve survival in women with early cervical cancer and risk factors for recurrence. There were no studies evaluating videolaparoscopy in the treatment of early ovarian cancer.

1. INTRODUÇÃO

O câncer de mama é a neoplasia maligna mais comum entre as mulheres no Brasil e em grande parte do mundo, inclusive nos países mais desenvolvidos, quando são excluídos os casos de câncer de pele não-melanoma. No Brasil, em 2016, foram estimados 57.960 novos casos da doença, o que representa uma incidência de 56,20 casos por 100 mil habitantes e 28,1% dos novos casos de câncer diagnosticados em mulheres naquele ano[1]. A mortalidade pelo câncer de mama, estimada em 13 casos/100 mil habitantes em 2014, é a primeira colocada no que diz respeito às mortes por câncer entre as mulheres brasileiras[2].

A incidência e a mortalidade fazem do câncer de mama um problema de saúde relevante. Associa-se a isto o fato de que, na maior parte dos casos novos diagnosticados, a doença se encontra em estágio localizado e passível de cura por meio de tratamento cirúrgico e complementar. Esta situação é o resultado de significativos avanços ocorridos no diagnóstico e no tratamento da doença e é algo bastante positivo, mas que cria um contingente crescente de mulheres sobreviventes de câncer de mama[3, 4]. Esta população tem diferentes necessidades médicas e sociais, as quais os diferentes sistemas de saúde muitas vezes não estão capacitados para atender[5]. De maneira progressiva estas pacientes irão demandar recursos e cuidados, o que exigirá mudanças importantes no planejamento dos serviços de saúde e no treinamento de profissionais[3, 5].

Assim como o câncer de mama, a obesidade também é um problema crescente que requer atenção. A prevalência de obesidade quase dobrou nas últimas duas décadas e, segundo a Organização Mundial da Saúde (OMS), em 2008, 10% dos homens e 14% das mulheres no mundo eram obesos[6]. No Brasil, de acordo com o inquérito Vigitel de 2013, a prevalência de obesidade em adultos chega a 17,4%[7]. A obesidade é multifatorial, mas o desequilíbrio entre as calorias ingeridas e o gasto energético é comum a todos os casos de obesidade. Apenas uma pequena porcentagem das pessoas obesas possui uma alteração genética isolada ou endócrina como causa primária da obesidade; assim, a maioria dos casos, é atribuída ao excesso de calorias e ao sedentarismo[8].

A prevalência de obesidade grave (graus II e III) é duas vezes maior em mulheres e a menopausa é um período ainda mais propício para o desenvolvimento desta comorbidade. Estudos mostram que mulheres eutróficas ou com sobrepeso ganham, em média, 5% de gordura em relação ao peso corporal prévio ao entrar na menopausa e este ganho se dá preferencialmente na gordura visceral do que no tecido adiposo subcutâneo. A gordura visceral está mais associada a desfechos cardiovasculares e à produção de citocinas pró-inflamatórias do que quando estocada em outros sítios[9]. A obesidade é também um fator de risco consolidado para o desenvolvimento de diversos tipos de câncer[10-12], bem como para o risco de recidiva e a morte após o tratamento[13].

O tecido adiposo gera um estado pró-inflamatório crônico, uma vez que até 40% do tecido pode conter macrófagos, além do próprio adipócito que produz citocinas. Indivíduos obesos tem níveis aumentados de fator de necrose

tumoral alfa (TNF-alpha), interleucina 6 e proteína C reativa, quando comparado com pessoas eutróficas[14], assim como leptina, que também funciona como marcador inflamatório e pode promover o desenvolvimento de neoplasia.

Não só a questão inflamatória, mas também o perfil hormonal da mulher com obesidade propicia ao desenvolvimento de neoplasia. Diversos hormônios estão alterados nesta população: *insulin-like growth fator 1* (IGF-1), insulina e leptina estão aumentados e estes hormônios podem promover o desenvolvimento de células anômalas (alteração na molécula de DNA, bloqueando mecanismos de apoptose). O tecido adiposo é o principal sítio de produção estrogênica e androgênica nas mulheres após a menopausa. O aumento de esteroides sexuais de forma crônica, como vemos na obesidade, causa estimulação constante de seus receptores na mama e no endométrio, aumentando o risco destas neoplasias[15].

Mais da metade das mulheres diagnosticadas com câncer de mama experimentam um aumento no peso corporal associado à menopausa e relacionado à quimioterapia e ao tratamento hormonal[16]. Há evidências de que mulheres obesas e mulheres que ganham peso após o diagnóstico tem um risco aumentado de recorrência da doença e de morte quando comparadas com mulheres de peso normal[17-21]. Os benefícios decorrentes da prática de exercícios físicos e de outros cuidados com a saúde buscando prevenir o ganho de peso vão além da redução do risco de recorrência, sendo também essenciais para a manutenção da saúde mental e da qualidade de vida[22, 23].

A perda de peso intencional traz benefícios concretos e é diretamente proporcional aos ganhos: quanto maior a perda de peso, maior o benefício; perdas de peso tão pequenas quanto 2% do peso inicial já podem ter impacto nas comorbidades associadas à obesidade[8].

O estudo ‘Study of Women’s Health Across the Nation’ mostrou que a atividade física regular foi associada com mudanças benéficas na composição corporal e distribuição de gordura nas mulheres na pós-menopausa[24]. Em alguns estudos observacionais, as mulheres com índice de massa corporal (IMC) aumentado apresentaram o dobro do risco de recorrência de neoplasia de mama em 5 anos e um risco 60% maior de morte em 10 anos em comparação com mulheres de peso normal[21]. Embora nem todos os estudos tenham demonstrado a mesma associação[25], estudos de intervenção mostraram de maneira consistente que medidas direcionadas à redução do peso em sobreviventes de câncer de mama trazem efeitos positivos no preparo físico e na qualidade de vida dessas pacientes[26, 27].

Dieta e alimentação, assim como o peso, tem relação com o risco de morte e recidiva das pacientes com câncer de mama[28-31]. Restrição energética na dieta pode reduzir o peso corporal e induzir um efeito positivo no bem-estar psicológico em mulheres obesas e sobreviventes de câncer de mama[32-35]. Intervenções para perda de peso com redução da ingestão de gorduras para 18-25% das calorias totais também pode provocar uma redução significativa nos níveis séricos de estrogênio em mulheres na pré e pós-menopausa[36]. No entanto, os dados associando perda de peso induzida pela dieta com mortalidade por câncer de mama são pouco consistentes[29, 37].

A atividade física regular pode ajudar a controlar o peso corporal e já demonstrou reduzir o risco de câncer de mama[38-43]. Estudos recentes sugerem que atividade física também pode reduzir pela metade o risco de morte em pacientes com câncer de mama[44]. O estudo de coorte *Nurses' Health Study*, um dos maiores estudos na área, demonstrou que mulheres fisicamente ativas em uma coorte de 2987 pacientes com câncer de mama inicial tinham metade do risco de recorrência e morte do que as sedentárias[44]. Porém, estudos randomizados não foram conclusivos a respeito[45].

Evidências de ECRs relacionando a prática de exercícios físicos com redução do risco de recidiva e morte por câncer de mama não são consistentes. No entando, recomenda-se que as sobreviventes da doença evitem o sedentarismo e busquem exercitar-se regularmente devido ao potencial desta prática ajudar na manutenção de um peso saudável, melhorar a condição física e a tolerância aos tratamentos por parte das pacientes[3, 46].

A atividade física regular também pode ter um efeito positivo sobre o estado psicológico de saúde assim como na qualidade de vida nas pacientes sobreviventes de câncer de mama[47-49]. Pacientes fisicamente ativas apresentam uma melhor funcionalidade física, maior resistência e força, menos ansiedade, depressão e fadiga[50-52].

No entanto, existe uma grande dificuldade em orientar exercício físico para essas pacientes, já que é uma intervenção que se apresenta de diversas formas e pode ser realizada em diversos graus de intensidade. Nessa situação a fragilidade de pacientes com câncer pode se apresentar como um empecilho

para que o oncologista clínico prescreva esse tipo de intervenção na falta de evidências científicas que embasem essa conduta.

Pela relevância do tema, torna-se justificável um estudo que analise a atividade física como intervenção para pacientes sobreviventes de câncer de mama já que essa é uma intervenção barata, de fácil aplicabilidade e praticamente isenta de contraindicações ou efeitos adversos. A importância dessa intervenção deve ser avaliada em relação ao seu impacto no perfil hormonal e inflamatório, qualidade de vida, medidas antropométricas, e, principalmente recidiva e mortalidade.

2. OBJETIVOS

2.1 Objetivo geral:

Nesse estudo, temos como objetivo avaliar os efeitos do exercício físico somado ou não a intervenções dietéticas no peso, na qualidade de vida e nos desfechos de sobrevida de pacientes após o tratamento do câncer de mama estágio clínico I a III, com intenção curativa.

2.2 Objetivos específicos

a) Avaliar as diferentes estratégias de promoção de exercícios físicos para pacientes com câncer de mama após tratamento curativo

b) Contribuir para uma melhor compreensão dos efeitos do exercício físico neste grupo de pacientes

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3 ARTIGOS CIENTÍFICOS

3.1 Artigo I

Effects of physical exercise after treatment of early breast cancer: systematic review and meta-analysis

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ABSTRACT

PURPOSE: The existing randomized clinical trials are inconclusive regarding the role of physical exercise in anthropometric measurements, quality of life survival outcomes in women with early stage breast cancer after therapy. Our aim was to conduct a systematic review and meta-analysis to assess the effects of physical exercise (with or without) dietary interventions after treatment of early stage breast cancer.

METHODS: We conducted a systematic review and meta-analysis. Electronic databases (Pubmed, Embase, Cochrane Library) were searched looking for Randomised clinical trials (RCT) that compared physical exercise interventions (counseling or structured programs with supervised / individualized exercise sessions) with usual care in women that underwent curative treatment for breast cancer. The primary outcomes considered were: overall survival and disease-free survival (5 years after treatment or until the maximum follow-up study). The secondary outcomes were: weight loss (kg), BMI (kg/m^2), waist-hip ratio, percentage of body fat (%) and quality of life.

RESULTS: We found 60 RCTs, and only one randomized clinical trial showed overall survival (OS) and progression-free survival data; the HR for mortality was 0.45 (95% CI 0.21-0.97) for the group that had exercise orientation for 8 months, when compared to the group that had usual care. Physical exercise showed significant effect in weight reduction (-1.36 kg, 95% CI -2.51 to -0.21, p = 0.02), BMI (-0.89, 95% CI -1.50 to -0.28, p <0.01) and percentage of body fat (-1.60 percentage points, 95% CI -2.31 to -0.88, p <0.01); there was an increase in the quality of life (standardized mean difference of 0.45, 95% CI

0.20 to 0.69, p <0.01). Publication bias was found for all outcomes except for the reduction of fat percentage and for the mental domain of quality of life.

CONCLUSION: We found only one study showing with positive effects of physical exercise in OS. In general we found articles with heterogeneous types of intervention, but with significant effects on several anthropometric measures and on quality of life although these effects may be associated with a significant publication bias or poor methodological quality of the trials concerning this intervention. PROSPERO registry for this study: CRD42014008743.

INTRODUCTION

Breast cancer is the most common malignant neoplasm among women in much of the world, even in more developed countries, when cases of non-melanoma skin cancer are excluded. Incidence and mortality make breast cancer a very important health problem. This is associated with the fact that the majority of newly diagnosed cases are in early stages, which are highly curable with surgical and adjuvant treatment. This is the result of significant advances in the diagnosis and treatment of the disease. At the same time, high rates of cure leads to a growing contingent of women survivors of breast cancer[3, 4]. This is a population with different medical and social needs, to which the different health systems are not trained nor prepared to attend[5]. Caring for breast cancer survivors is therefore a matter of growing importance for health professionals.

There is evidence that obese women and women who gain weight after breast cancer diagnosis have twice the risk of and recurrence d breast cancer in 5 years and 60% higher risk of death over 10 years, when compared to women normal weight[17-21]. More than half of women diagnosed with breast cancer experience an increase in body weight associated with menopause and related to chemotherapy and hormonal treatment[16]. In this setting, regular physical activity can help control body weight and has already been shown to reduce the risk of breast cancer[38-43]. Recent studies suggest that physical activity can also halve the risk of death in patients with breast cancer[44]. The Nurses' Health Study, one of the largest cohort in the field, showed that physically active women (from 2987 patients with early breast cancer) had half the risk of recurrence and death when compared to sedentary women[44].

Unlike studies involving chemotherapeutic treatments, physical exercise studies are consistently smaller, with shorter follow-up and different assessments regarding the type of physical exercises whether aerobic or strength exercises. In addition, the existing randomized clinical trials were inconclusive regarding the role of this intervention in anthropometric measurements or quality of life outcomes[45].

In this study we aim to conduct a systematic review and meta-analysis to assess the effects of physical exercise (with or without dietary interventions) in body composition, quality of life and survival in women after treatment of early stage breast cancer.

METHODS

Protocol and registration

We conducted this systematic review and meta-analysis using a previously published protocol[53] (PROSPERO registry number CRD42014008743) for the research question related to physical activity. We conducted this systematic review according to the Cochrane Handbook for Systematic Reviews of Interventions[54] and reported the manuscript according to PRISMA recomendations[55].

Data sources and searches

The following electronic databases were used to evaluate the indexed literature: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. We conducted the electronic search and up to July 2017; it was limited to papers in English (see Appendix for more details). We have also searched grey literature in annals of major meetings and ongoing studies at ClinicalTrials.gov.

Study Selection

We included randomized trials that evaluated physical exercise interventions (counseling or structured programs with supervised/individualized exercise sessions). The intervention should have been compared with usual care in women undergoing treatment for breast cancer from clinical stages I to III in the last 6 months to 5 years. We included studies that performed the intervention after the end of adjuvant treatment (excluding hormone therapy). We excluded studies that applied the intervention after first 5 years from the diagnosis.

The following primary outcomes were considered in the evaluation of the studies: overall survival and disease-free survival (5 years after treatment or until the maximum follow-up study). The secondary endpoints were: weight loss (kg), BMI (kg/m²), waist-hip ratio, percentage body fat (%) and quality of life. Adverse events, such as exercise-induced lesions, were also been considered.

The evaluation of titles and abstracts for potentially eligible studies was conducted in paired and independently. Inclusion and data extraction were conducted for the full texts in the same manner, using a standardized form. Disagreement was solved through discussion.

Data extraction

The data used for meta-analysis and comparison between usual care and intervention were the final values of the groups after the intervention, since these were the data most frequently found. This method was used to minimize the number of errors and minimize the need for imputations. In the studies that presented only the values of the difference between final results and initial results, the final values were calculated from a simple sum of the variation with the initial value. In this case the values of the standard deviations used were the same as the initial values of the variables. We preferred the EORTC QLQ-C30 quality of life score, since this was the most frequently used instrument among the studies. For studies such as Harrigan 2016[56], Demark-Wahnefried 2014[57] and Vallance 2007[58] with two or more intervention groups the data from all intervention groups were combined into a single group. Finally, some values of standard deviation of the quality of life data were not described by the authors in their works (Herrero 2006[59], Lee 2014[60], Heim 2007[61], Rogers 2009[62], Baruth 2015[63] and Fields 2016[64]); in this cases the standard deviation was used as a weighted mean of the other studies that used the same scale.

Quality assessment

We also carried out a paired methodological quality evaluation of the individual studies, according to the Cochrane Handbook of Systematic Reviews[54] using the Cochrane risk of bias tool. Disagreement was solved through discussion. The overall quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE)[65], and verified by a third reviewer. The quality of evidence was classified as 'high', 'moderate', 'low' or 'very low'.

Data synthesis and analysis

The data were combined using the random-effect meta-analysis model, with DerSimonian-Laird estimator as variance estimator. We estimated the treatment effect using the mean difference (MD) as summary measure for continuous outcomes. For continuous outcomes presented in different scales, we used the standardized mean difference (SMD). Data were presented with 95% confidence intervals (CI). All analyzes were performed using software R, version 3.3.2, *meta* packages version 4.8-4.

Statistical heterogeneity was assessed in each meta-analysis using the statistics I^2. Heterogeneity was considered substantial if the I^2 was greater than 50%. Heterogeneity was explored through subgroup analysis. We assessed publication bias using funnel plot and the Egger test. A significant publication bias was considered if $P<0.10$. We estimated the effect of publication bias on the interpretation of results by a trim-and-fill computation.

RESULTS

Literature search

In total, 19,987 titles were located, of which 3,553 were duplicates. In the review of titles and abstracts 16,434 studies were excluded 291 were fully read for assessment of eligibility. After that, 169 studies were excluded, and 60 studies entered the phase of data extraction. The flow-chart of the search is presented in Figure 1 and the initial characteristics of the studies are presented in Table 1.

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Anderson 2015 (Australia)[66]	12-week program instructions and healthy lifestyle readings, with a book containing weekly exercise planning and special parts to record data on diet, aerobic exercise, strength exercises, pelvic floor exercises, weight, waist circumference, and climacteric symptoms and diary supply to help participants achieve their goals	3	3	51	48.9
Baruth 2015 (USA)[63]	Home walking program for 12 weeks. First a face-to-face orientation session on exercise and week 1, 2, 4, and 10 week guidelines	3	3	32	56.7
Cadmus 2009 (USA)[67]	Supervised exercises 3x / week plus exercises on their own 2x / week; heart rate monitoring during sessions with a goal of maintaining between 60-80% of the expected maximum frequency	6	6	75	56.0
Campbell 2017 (Canada)[68]	150 min per week of aerobic activity (moderate to vigorous): two 45-minute sessions at a research facility gym and 2 30-minute sessions of unsupervised exercise of patient preference	6	6	19	52.6
Casla 2015 (Spain)[69]	Exercise program consisted of supervised exercise sessions twice a week (aerobic + resistance) with progressive increase of intensity. Patients also received nutritional guidance	3	3	94	47.9
Courneya 2003 (Canada)[70]	Training 3x / week on ergonomic bikes for 15 weeks. Duration of training gradually increased and intensity was adjusted according to the ventilatory equivalent for carbon dioxide	3.75	3.75	52	58.7
Daley 2007 (UK)[71]	Moderate intensity exercises 3x / week for 8 weeks lasting 50 minutes under the supervision of a specialist	2	2	72	51.4
De Luca 2016 (Italy)[72]	Two weekly sessions of 90 minutes, corresponding to 10 minutes of warm-up (onset) and cooling (final) followed by 40 minutes of resistance exercise followed by 30 minutes of aerobic exercise for 24 weeks. The exercises were progressive during the protocol	6	6	20	48.8

Table 1: Characteristics of the included studies.

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Demark-Wahnefried 2014 (USA)[57]	Individualized books with guidelines for weight loss and dietary changes followed by six leaflets over a year. Patients in the two intervention groups received individualized information or individualized information plus information about other participants in the group	12	12	68	61.3
Demark-Wahnenfried 2015 (USA)[73]	Physical exercise group sessions of 1 hour/week for 4 months, then sessions of 15/15 days and then monthly for one year, as well as telephone and e-mail between sessions. They also received dietary information on diet to physical exercise	12	24	692	56.1
Do 2015 (South Korea)[74]	Heating, aerobic exercise, strength exercise, core stability exercise and cooling 5x / week for 4 weeks under the supervision of a physical therapist	1	1	62	47.5
Duijts 2012 (Netherlands)[75]	Unsupervised exercises, at home, lasting 2.5-3 hours per week for 12 weeks aiming to achieve 60-80% Karvonen. Physiotherapist assisted the patient to choose the most appropriate exercise modality (bicycle, running, swimming)	3	6	207	47.7
Fairey 2003 (Canada)[76]	Treadmill 3x / week in ergometers at a VO2 of 70-75%. Exercise started for 15 minutes in the first 3 weeks and progressed in 5 minutes every 3 weeks to 35 minutes.	3.75	3.75	52	58.7
Fields 2016 (UK)[64]	Nordic walks (two-stick walk) supervised by the first ones for 12 weeks. Exercise was a group under supervision at weeks 1-6 with gradual increase in frequency in weeks 7-12 the patients were instructed to perform 4 sessions of 30 minutes per week on their own	3	3	40	62.0
Fillion 2008 (Canada)[77]	Supervised walk for one hour associated with management sessions for fatigue symptoms once a week for 4 weeks. Patients were given a heart monitor (Polar) to receive objective feedback from walking	1	4	87	52.7

Table 1: Characteristics of the included studies (continued).

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Galiano-Castillo 2016 (Spain)[78]	Three sessions of 90 minutes per week on non-consecutive days for 8 weeks. Exercises consisted of an aerobic part and a part of resistance	2	6	81	48.0
Ghavami 2017 (Turkey)[79]	Moderate-intensity aerobic exercise sessions under supervision 3-5 days per week throughout 24 weeks. Each session comprised a 10-minute light aerobic exercise and a gentle range of motion exercises (warm-up period), followed by 30 minutes of aerobic exercise at an intensity of 70%–85% of maximum heart rate and a reduction of caloric intake to 600 kcal below calculated energy requirements	6	6	80	49
Giallauria 2015 (Italy)[80]	Aerobic training with treadmill or bicycle 3x / week for 3 months and after 1x / week for another 9 months; patients also received information leaflets on exercise, diet and weight loss with a goal of performing exercises for 210 minutes per week. Patients also participated in feeding classes and meetings	12	12	51	52.5
Goodwin 2014 (USA, Canada)[26]	Patients received in the whole 19 connections over 24 months with guidelines on reduction of caloric intake, weight loss, increase in the amount of vegetables and fruits consumed and reduction in fats; goal of gradual increase in the practice of aerobic physical exercises to a goal of 150 to 200 min per week; between 30 and 60 minutes	24	24	338	61.2
Greenlee 2013 (USA)[81]	Patients were enrolled in a physical training center where they were recommended to attend 5x / week; strength and aerobic exercises for 15-30 min per session; also received dietary recommendations in a nutrition course	6	12	42	51.3
Guinan 2013 (Ireland)[82]	Aerobic exercises (biking, treadmill, rowing) supervised 2x / week + exercises at home up to 5x / week. Lesson duration and intensity increased every two weeks	2	3	26	48.7

Table 1: Characteristics of the included studies (continued).

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Hagstrom 2016 (Australia)[83]	Resistance training 3x / week for 60 min for 16 weeks; movements with the use ofmachines in the first 8 weeks and movements without weights in the last 8 weeks	4	4	39	51.7
Harrigan 2016 (USA)[56]	Counseling by telephone (1) or live (2) focusing on weight loss: reduced caloric intake and moderate intensity exercise for 150 min / week; also received a book on the LEAN method of weight loss. Weekly meetings in the first month; biweekly in the second and third months; monthly thereafter	6	6	66	58.6
Hayes 2017 (Australia, New Zealand)[84]	Described as a translational exercise intervention delivered either face-to-face or over the telephone	8	101	337	Not described
Heim 2007 (Germany)[61]	Brochure and guidelines on stretching and muscle exercises; instructions for aerobic (walking), coordination and relaxation	During rehabilitation	3 months after finishing rehabilitation	63	Not described
Herrero 2006 (Spain)[59]	Three weekly sessions of 90 min with endurance and aerobic exercises	2	2	20	50.3
Irwin 2009 (USA)[85]	Supervised aerobic exercise 3x / week plus home exercise 2x / week; duration of 15-30 min according to tolerance; mode of exercise of the patient's preference,	6	6	75	56.0
Irwin 2013 (USA)[86]	Supervised aerobic and strength exercises 2x / week plus home exercises for 150 min / week. Intensity of the exercise was adjusted according to heart rate	12	12	121	61.5
Karimi 2013 (Iran)[87]	Aquatic aerobic exercises 4x / week lasting 40 to 80 minutes per session	1.5	1.5	20	Not described
Kim 2011 (South Korea)[88]	Patients received counseling by phone, book and a prescription of diet and exercise. The goal was to perform exercises 5x / week for at least 30 min	3	6	45	45.4

Table 1: Characteristics of the included studies (continued).

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Kim 2017 (South Korea)[89]	Three times a week of warm-up consisting whole body stretching and flexibility exercises for 10 min followed by step aerobics for 20 min followed by the strength training using body weight and elastic bands for 20 min. The exercise intensity and the resistance of elastic band were progressively increased. At the end of the session, subjects performed cool-down involving easy walking and stretching exercises for 10 min	3	3	24	52
Kwiatkowski 2013 (France)[90]	Admission to a SPA for 2 weeks, where two hours of physical activity (strength, resistance, elasticity and water aerobics) were performed daily. They also received baths, massages, prepared diet and aesthetic care	0.5	12	222	52.0
Lahart 2016 (UK)[91]	Stimulating exercise; phone call at the end of the first, second and third month to maintain exercise; leaflet by mail at the end of the fourth and the fifth month with encouragement to practice. Order to maintain the practice of exercises 3-5x / week for 30 min at least. Patients also received a brochure with information and a DVD.	6	6	80	53.2
Lee 2014 (South Korea)[60]	Self-management web-based exercise and diet program. The intervention incorporates strategies of transtheoric model as stage of change, process of change, balance of decision or self-efficiency	3	3	59	42.1
Ligibel 2008 (USA)[92]	Strength and cardiovascular training at home for 16 weeks. Two weekly training sessions of 50 min supervised strength + 1 cardiovascular training of 90 min weekly at home	4	4	100	52.3

Table 1: Characteristics of the included studies (continued).

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Matthews 2007 (USA)[93]	Guided home walks on a 30 min visit, followed by short phone calls after 1, 2, 4, 7 and 10 weeks. Hiking in the first 4 weeks 3x / week (20-30min / session); at weeks 5 to 7, 4x / week (30-40min / session); in the last 5 weeks, 5x / week (30-40min / session) at moderate intensity	3	3	36	52.9
Mefferd 2007 (USA)[94]	Cognitive-behavioral group therapy, physical activity and dietary guidelines. Physical activity: promotion and encouragement of daily aerobic exercises, with progression of time and intensity. Strength exercises 2-3 x per week. Providing a pedometer to encourage and record physical activity on a daily basis	4	4	76	56.3
Milne 2008 (Australia)[95]	3 times per week supervised physical activity sessions in rehabilitation clinic. The program contains aerobic / cardiovascular and endurance, as well as stretching	3	6	58	55.2
Nuri 2012 (Iran)[96]	Supervised walking program for two times per week in a time-progressive duration protocol plus 60 minutes resistance training during the 15 weeks of intervention	3.75	3.75	29	58.3
Nyrop 2017 (USA)[97]	Participants were asked to walk on their own or with others at a pace that was safe, comfortable, and sustainable for 150 minutes per week	1.5	1.2	29	63.8
Ohira 2006 (USA)[98]	Supervised strength and resistance training exercises using resistance machines and free weights for thorax muscles, back, shoulders and arms as well as the buttocks, hips and thighs. In addition, participants were taught stretching exercises to perform before and after each weight training session	6	6	81	53.1

Table 1: Characteristics of the included studies (continued).

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Pakiz 2011 (USA)[99]	Cognitive-behavioral therapy based on 24 group sessions for weight loss. Weekly for 4 months and monthly up to 12 months. Aim to promote regular physical activity and reduce caloric intake to facilitate weight loss	4	4	68	56.0
Pinto 2005 (USA)[100]	Participants received instructions on how to exercise at moderate intensity, heart rate monitoring, and how to perform warm-up and cooling after exercise. Received pedometer and exercise table. Oriented to exercise for at least 10 min 2x per week, with gradual increase up to 30min 5x per week at the end of 12 weeks. Weekly phone calls from the team to monitor. They received weekly workout tips	3	9	86	53.2
Rahnama 2010 (Iran)[101]	60 minutes of resistance exercise (weight lifting) 2x in the week + walks (minimum time 25min) 2x in the week (alternate days)	3.75	3.75	29	Not described
Reeves 2017 (Australia, USA)[102]	Participants received detailed workbook of lifestyle recommendations, monitoring diary, digital scales, calorie count book and 16 phone calls (by lifestyle coaches, nutritionists specializing in motivation for physical training), calorie deficit diet of 2000kJ, orientation for increase walks to at least 30min / day and a pedometer	6.5	6	90	55.7
Rock 2015 (USA)[27]	Weekly meetings of 1 hour in the first 4 months, then every 15 days for another 2 months and after monthly; in the meetings were taught exercises and provided guidance as to achievement. Orientation of 60 minutes / day. Diet recommendation with caloric deficit of 500-1000kcal	24	24	692	56.0
Rogers 2009 (USA)[62]	Goal of reaching 150 minutes of moderate intensity walking per week. Participants attended 6 group sessions for time management, importance of physical activity and behavioral change and goals. They also attended 12 supervised exercise sessions and 3 session sessions with exercise specialists	3	3	41	52.7

Table 1: Characteristics of the included studies (continued).

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Roveda 2016 (Italy)[103]	A program conducted by 2 sport therapy experts and included 2 sessions of 1-hour brisk walking per week for three months	3	3	40	56.8
Saarto 2012 (Finland)[104]	Supervised on-site training and home-based exercise counseling. The supervised training was 1x / week, with up to 15 individuals and was performed circuit training and aerobic with walking, with progressive intensity. The home part could be walks, Nordic walks, step exercises or jump (patient preference), oriented to perform preferably 3x / week and at least 2x / week	12	12	473	52.3
Schmitz 2005 (USA)[105]	In the first 3 months of intervention: supervised exercises with trainer enabled in groups of maximum 4 people. In the other 3 months, participants were encouraged to continue performing physical activity on their own	6	12	81	53.1
Scott 2013 (UK)[106]	Three sessions per week supervised 30 minutes of aerobic exercise plus 10-15 minutes of muscle strengthening, using free weight. In addition, consultation with nutritionist for a caloric deficit of 600 kcal / day	6	6	90	55.7
Sheppard 2016 (USA)[107]	Supervised 30 minutes physical activity group sessions and 60 minutes educational sessions every two weeks comprising. On weeks when participants did not meet as a group they had individual telephone coaching sessions led by a trained survivor coach.	3	3	22	54.7
Shobeiri 2016 (Iran)[108]	Exercises of 40-60 min 2x per week for 10 weeks involving the HEATING (5-10min walk slow and moderate stretching), moderate aerobic exercise (15 minutes of slow walking, stretching and specific movements of the arms and shoulders) and 5 min of cooling down (slow walk). Increase of 2% of aerobic exercise time each week, resulting in 35min in the tenth week	2.5	2.5	53	43.0

Table 1: Characteristics of the included studies (continued).

Study ID	Description of intervention	Duration of intervention (months)	Follow up (months)	Number of participants	Mean Age
Speck 2010 (USA)[109]	Group instructions 2x / week for 90 minutes for 13 weeks followed by a further 13 weeks of 2x / week exercises without supervision. Sessions included stretching, cardiovascular warm-up, abdominal and back strengthening exercises, and weight lifting	12	12	234	56.5
Sturgeon 2016 (USA)[110]	The exercise component required 160 min/week of exercise (3 days/week of progressive resistance exercise, 2 days/week of interval aerobic exercise, and 1 day/week of active recovery aerobic exercise)	12	12	35	46.1
Swisher 2015 (USA)[111]	Supervised exercise of moderate intensity for 3x/ week in physical activity environment and other 2x/ week in home environment without supervision. Consultation with nutritionist with dietary guidelines of caloric reduction	3	3	28	53.7
Thomas 2017 (USA)[112]	Twice-weekly supervised resistance training (total body program for the lower and upper extremities) and 150 minutes of moderate-intensity aerobic at home (brisk walking on a treadmill or outside, but cycle ergometers and elliptical trainers were permitted). Exercise started at 50% of predicted maximal heart rate (220-age) and was gradually increased to approximately 60% to 80% of predicted maximal heart rate (verified by heart rate monitors)	12	12	121	61.2
Tirado-Gomez 2015 (Spain)[113]	Study of three groups in which one received written materials adapted to the culture of the patient with orientation of physical exercise, another group receiving materials not adapted to their culture and a placebo group	4	4	38	58.0
Vallance 2007 (Canada)[58]	The participants received a standard public health recommendation for physical activity (PA), previously developed breast cancer–specific PA print materials, a step pedometer, or a combination of breast cancer–specific print materials and step pedometers	3	3	190	57.0
Winters-Stone 2013 (USA)[114]	Participants received supervised classes (30-60 / minutes) 2 days / week and were instructed to repeat at home 1x / week for 12 months. The intervention group performed resistance activities with weights (shin guards and weight vests, dumbbell, kettlebell, barbells) with 8-15x repetition orientation and modulation of weight depending on individual capacity	12	12	71	46.6

Table 1: Characteristics of the included studies.

Study characteristics

The total number of patients in all of the studies was 6,303. The follow-up ranged from 1 to 101 months and the duration of the intervention ranged from 4 weeks to 24 months. The mean age of the patients across the trials was 47.4 years and the time from breast cancer surgery or from finishing the adjuvant treatment to intervention ranged from 1 month to 4 years. We found multiple types of physical exercise interventions but the most frequent modality was structured or individualized programs (found in 41 trials).

Outcomes

We found only one trial that reported disease-free survival in an abstract. This was an Australian trial that randomized 337 women 6 weeks after surgery for breast cancer to 8 months of physical exercise counseling (either in person or by telephone) or to usual care. After a follow-up of 101 months, the HR for overall survival in the intervention groups compared to placebo was 0.45 (95% CI 0.21-0.97); there was no difference in disease-free survival between the groups (HR 0.66 [95 % IC 0.38-1.17]). Despite not establishing causality, the study suggests the potential of physical activity to influence survival.

For the secondary outcomes we found that physical exercise interventions, whether by orientation or by structured programs promote statistically significant weight reduction in breast-cancer patients (-1.36 kg; 95% CI -2.51 to -0.21; $p = 0.02$; $I^2 = 17\%$; very low quality of evidence) (Figure 2) and BMI reduction (-0.89; CI 95% -1.50 to -0.28; $p < 0.01$; $I^2 = 51\%$; low quality of evidence) especially for the exercise counseling group (Figure 3). Physical exercise also showed a statistically significant

decrease of -1.60 in body fat percentage points (95% CI -2.31 to -0.88; p<0.01; I^2 = 28%; low quality of evidence) especially in the structured or individualized exercise program (Figure 4).

The overall quality of life was significantly modified by physical exercise interventions showing a standardized mean difference of 0.45 (95% CI 0.20 to 0.69, p <0.01; I^2 = 83%; very low quality of evidence) (Figure 5). The same can be said about the effect on the physical domain of quality of life, showing a standardized mean difference of 0.51 (95% CI 0.23 to 0.79; p <0.01; I^2 = 86%; very low quality of evidence) (Figure 6) and the mental domain, showing a standardized mean difference of 0.28 (95% CI 0.06 to 0.50; p = 0.013; I^2 = 71%; very low quality of evidence) in favor of the intervention groups (Figure 7). No significant effect of physical exercise could be seen on HOMA-IR (-0.03; 95% CI -0.20 to 0.13; p = 0.68)(see supplementary material).

We performed subgroup analysis for all the anthropometric outcomes according to type of intervention and for the different quality of life scales (as seen in Figures 2-7). Meta-regression analysis showed no association between duration of intervention and all outcomes.

The Egger test showed significant publication bias for all outcomes, except for fat percentage reduction or the mental domain of quality of life. Funnel plots for all the outcomes can be seen in Figure 8. Trim-and-fill computation resulted in loss of statistical significance when publication bias was corrected. After this correction the effect of the intervention on weight was -0.18 (95% CI -1.52 to 1.15), on BMI was -0.04 (95% CI -0.67 to 0.60), on the general quality of life was 0.08 (95% CI -0.2 to 0.36) and on physical quality of life was 0.09 (95% CI -0.22 to 0.40)

Quality evaluation

The risk of bias according to Cochrane risk of bias tool is presented in Figure 9 and 10. Serious methodological flaws were found such as poor randomization methods and poor outcome assessments. Noteworthy most of the studies were relatively small and just one study, published as an abstract, evaluated outcomes such as overall mortality or disease-free survival[84]. The GRADE summary of findings table is shown in Figure 11.

Discussion

The diagnosis of breast cancer affects patients' quality of life and have long lasting consequences. Both the diagnosis itself and the treatments that those patients are submitted have significant influence in mental and physical health for years to come. The incidence of breast cancer in its earlier stages is increasing because of improved screening. In the same way, treatments for the disease are becoming more effective, and so the number of survivors is expected to increase in the next years[115]. Many of these women might live for many years and have time to develop chronic conditions just as the general population[116]. Therefore, high quality evidence for survivorship guidance will be necessary. Physical activity is key to improve health and quality of life in any population, and here it is not an exception.

Our goal was to collect the best evidence regarding the impact of physical activity on the body composition and quality of life of patients who had been treated for breast cancer with curative intent. We have searched for randomized clinical trials only, considering them to be the best source of evidence for the question. To avoid confusion regarding quality of life, we excluded trials that assessed patients during treatment with chemotherapy or radiation; the included patients may have been receiving adjuvant hormone therapy. Also, trials evaluating patients with metastatic disease were not

included, considering that treatment goals and prognosis are significantly different in more advanced stages of the disease. We may say that we have collected the best evidence about this issue.

The results of this meta-analysis demonstrated a significant decrease in body weight, BMI as well as an improvement in quality of life outcomes, but a serious bias effect was demonstrated. Publication bias was found in almost all outcomes and it is a concern regarding physical activity trials, since all of them lost statistical significance after correction.

We found only one study that described overall survival and progression-free survival: it was from an Australian population of 337 newly diagnosed breast cancer women and it showed lower mortality rates in the physical activity group[84].

Nonetheless, our meta-analysis has several limitations. First, most of the studies included were small and many of them had significant methodological flaws. Some studies had reducing pain as main outcome in users of aromatase-inhibitors, such as Nyrop 2017[97] and Fields 2016[64], so some selection bias was expected from this populations. Second, the interventions were very different among the studies, making it very difficult to select any one of them as the best. It was also not possible to determine if any of the interventions should have been considered ineffective at all. Third, quality of life outcomes were assessed using different scales, which may influence the results. Finally, long-term data is seldom available, and conclusions about the possible impact in outcomes such as overall survival or disease-free survival are not possible. High quality, randomized trials with larger number of patients are required, and patients should be followed for longer periods of time to assess if the benefits of the interventions are long lasting or temporary.

It is also worth commenting that the studies included were broadly heterogeneous, they varied about the type of intervention (counseling, face-to-face orientation, practicing, phone call orientation) and we cannot classify all these

interventions under the same label, once they are not equivalent. This study shows that any intervention toward encouraging physical activity is valid, promotes good life habits that might affect the quality of life, the metabolic profile and mortality.

With all the limitations considered, clinical trials of physical activity as an intervention for breast cancer survivors is still highly justifiable, especially because exercise is a cheap intervention, easy to apply and practically has no contraindications and adverse effects. Even though a strong and solid evidence relating physical activity and reduced risk of recurrence and death from breast cancer is lacking, survivors are oriented to avoid a sedentary lifestyle and seek to exercise regularly. The potential benefits of this practice can help maintaining a healthy weight, improve fitness and tolerance to treatment, stimulate healthy lifestyles and prevent other chronic diseases for which this population is particularly vulnerable.

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Appendix

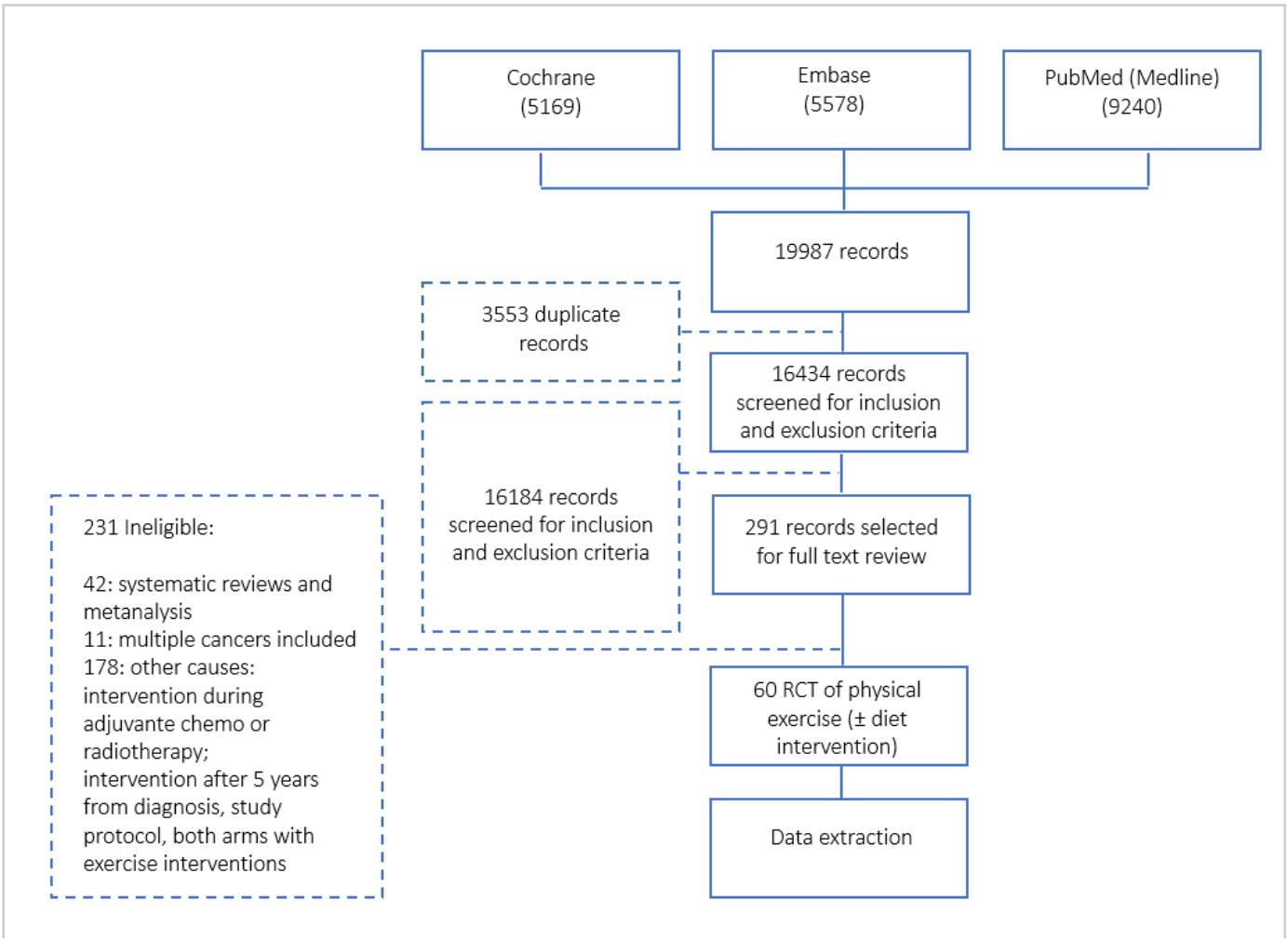


Figure 1: Study flow-chart

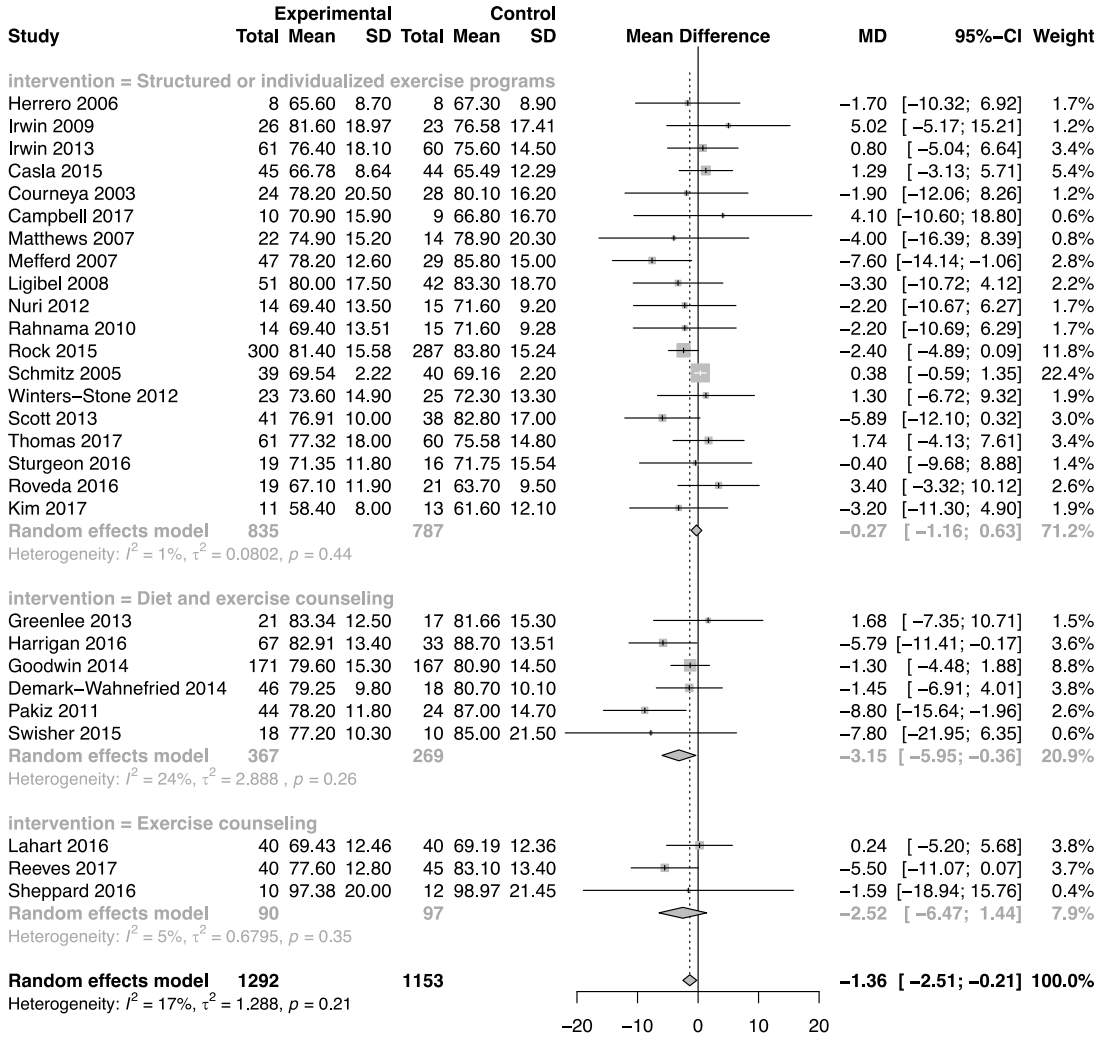


Figure 2: Forest plot for weight reduction

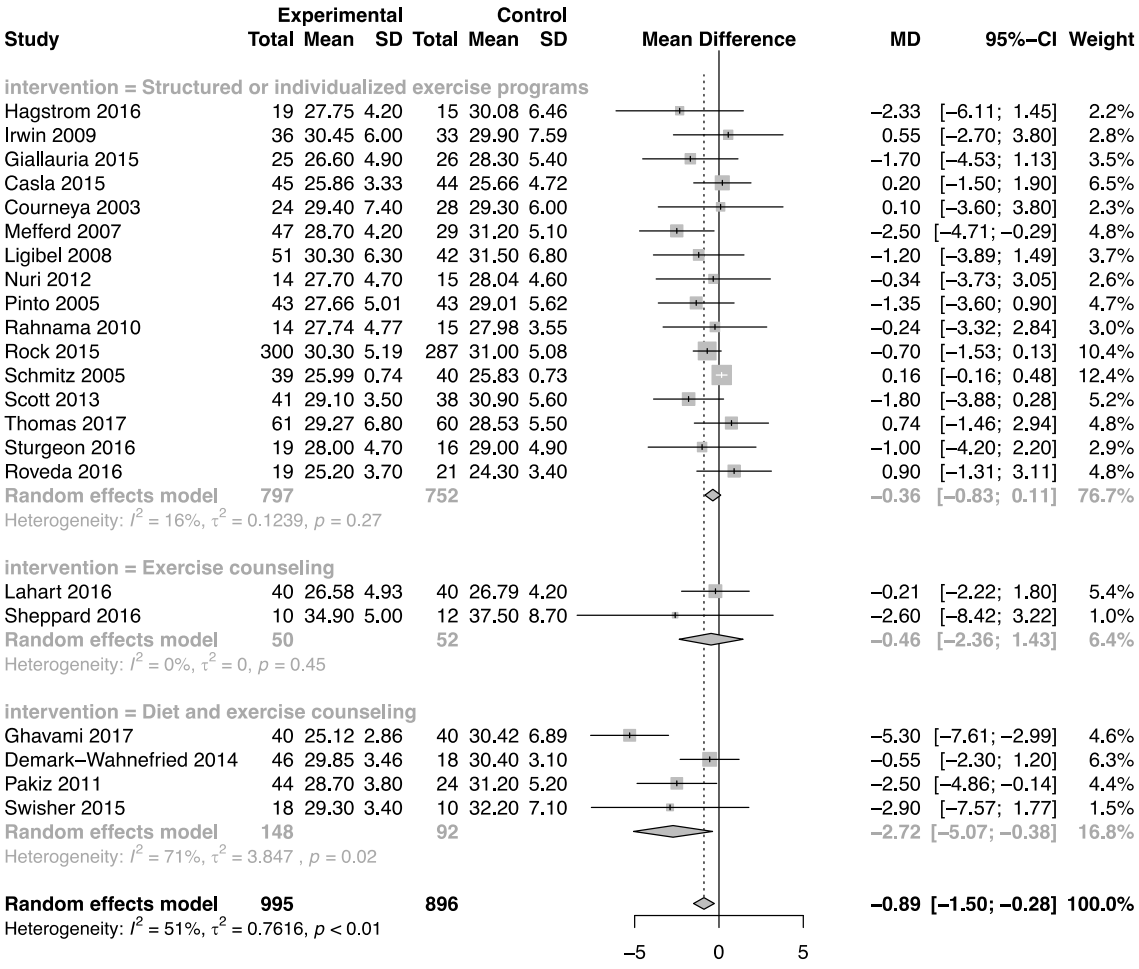


Figure 3: Forest plot for BMI reduction

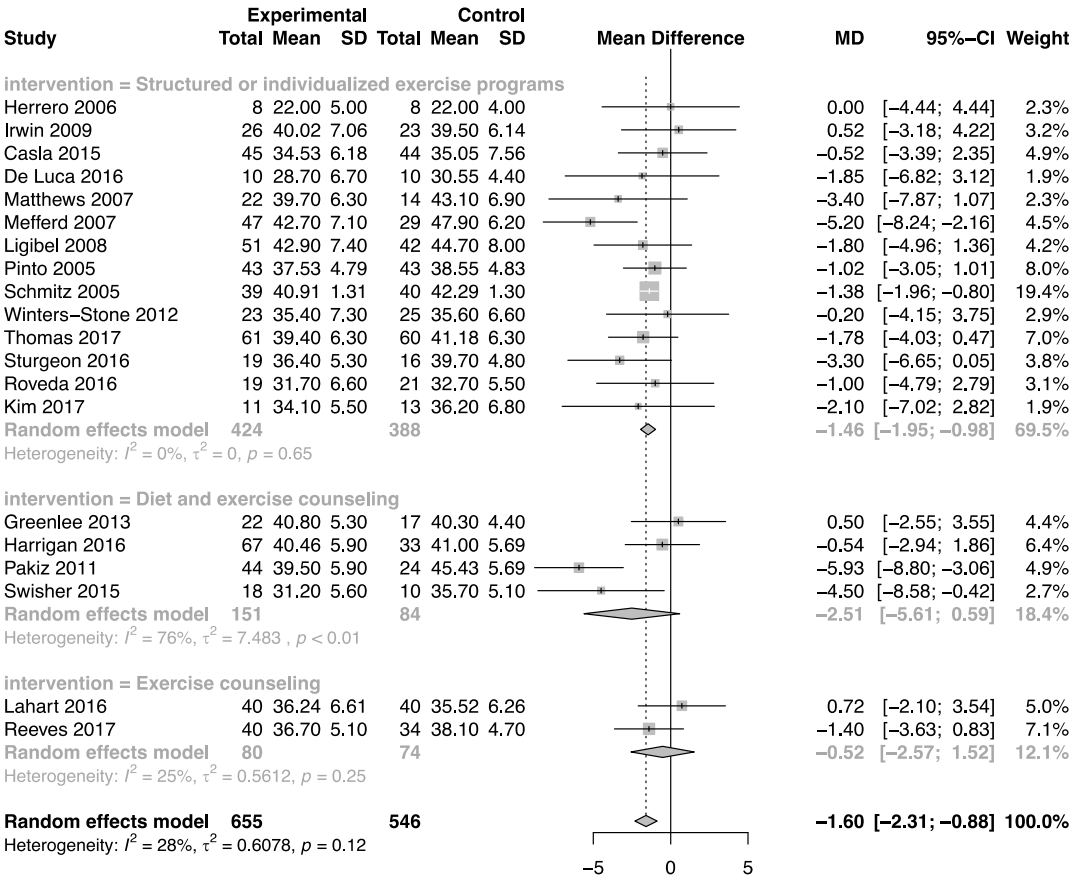


Figure 4: Forest plot for fat percentage reduction

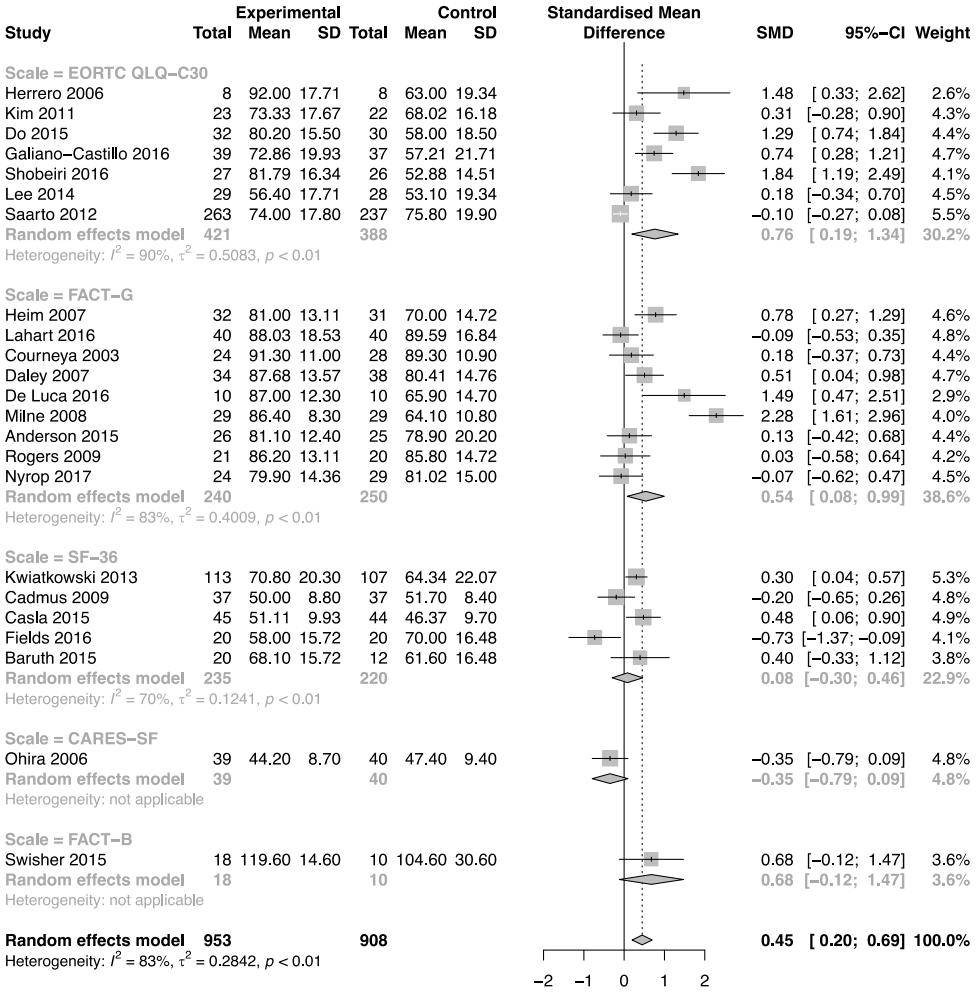


Figure 5: Forest plot for quality of life (general) for different scales

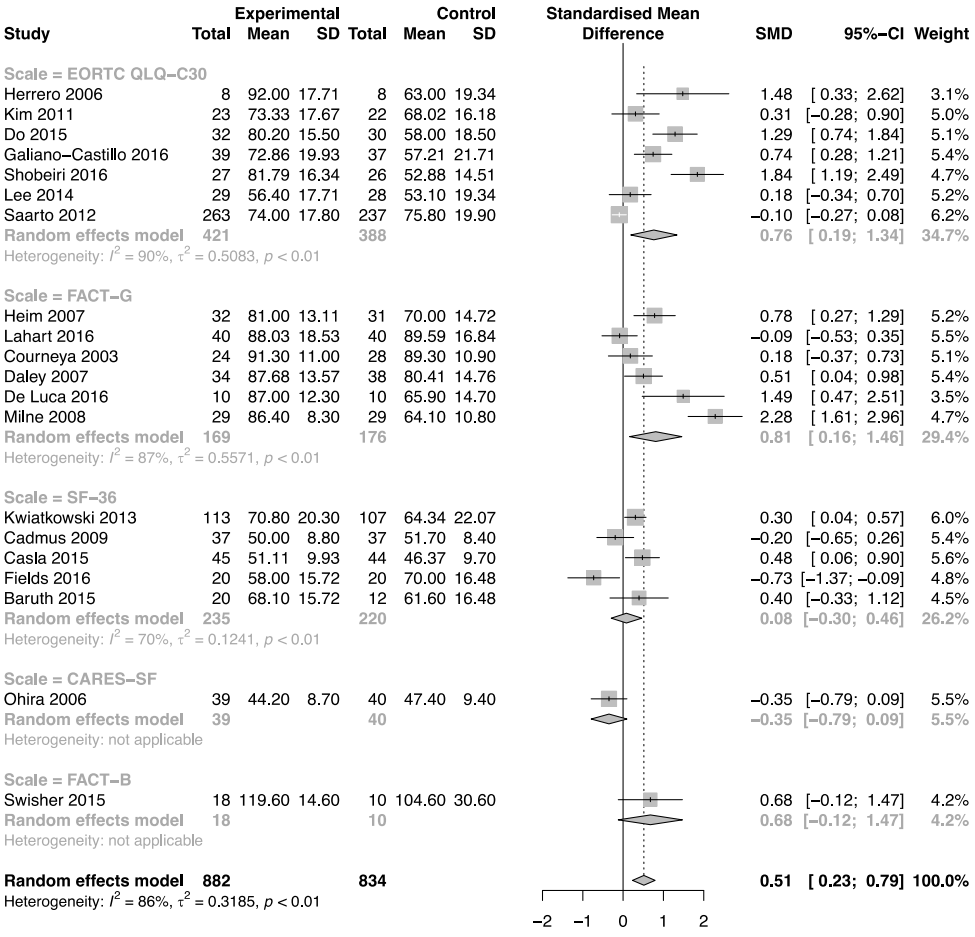


Figure 6: Forest plot for quality of life (physical) for different scales

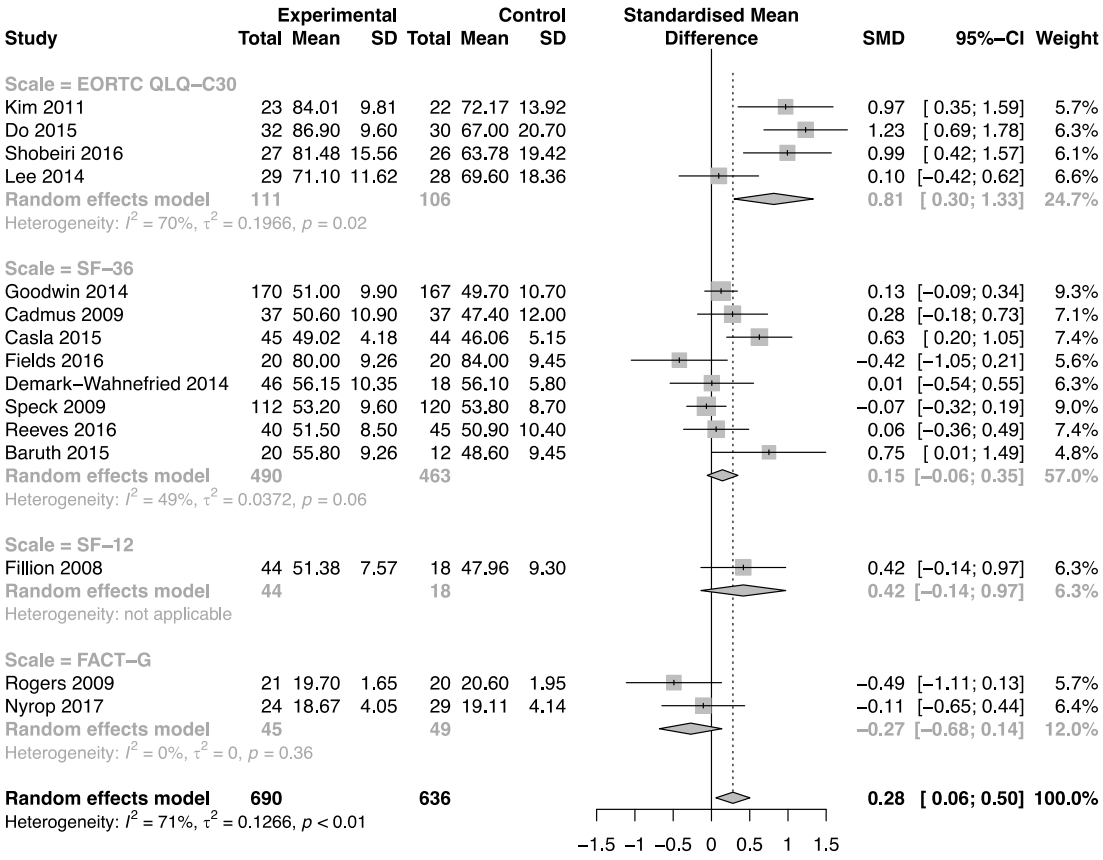


Figure 7: Forest plot for quality of life (mental) for different scales

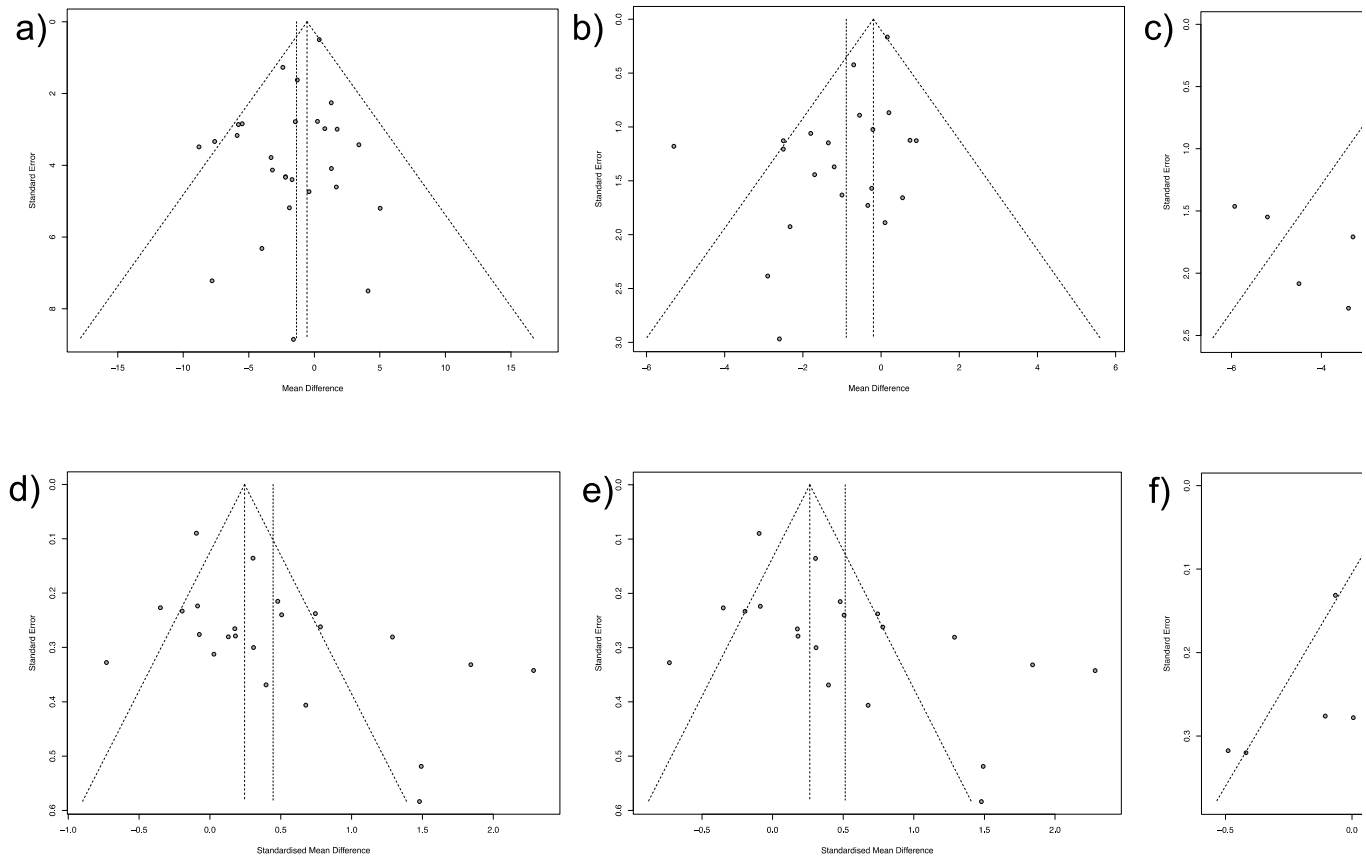


Figure 8: Funnel plots for all outcomes: a) weight; b) BMI; c) fat percentage; d) quality of life (general); e) quality of life (physical); f) quality of life (mental)

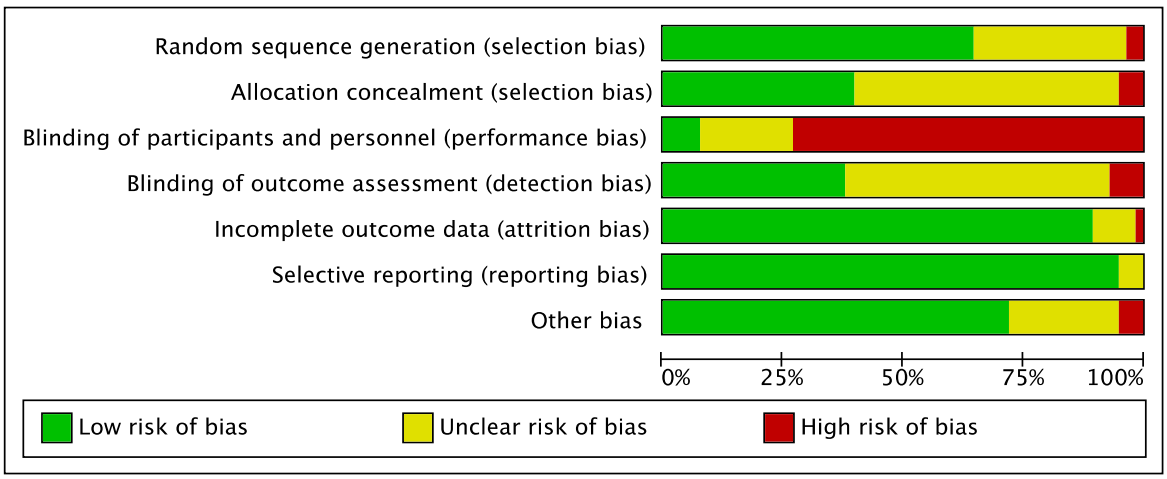


Figure 9: Risk of bias graph

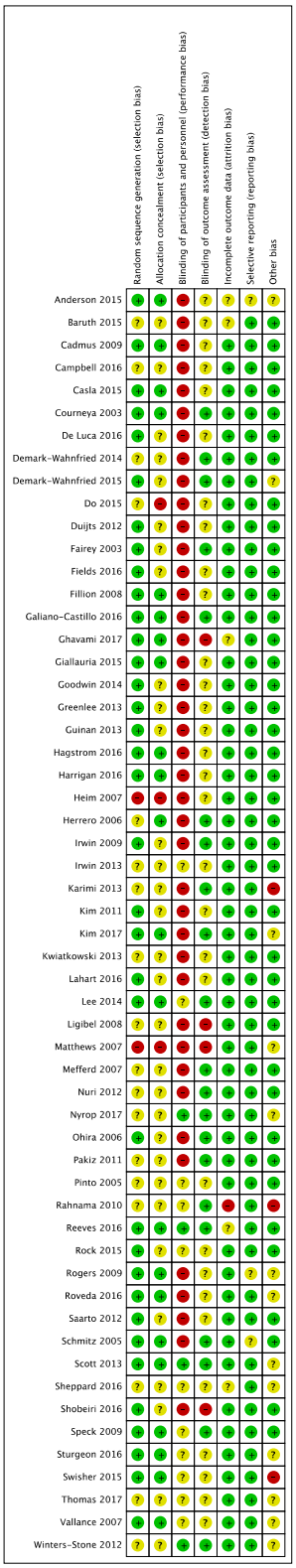


Figure 10: Risk of bias summary

Physical exercise compared to not realize physical exercise for breast cancer

Bibliography:

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with not realize physical exercise	Risk difference with Physical exercise
Weight	2445 (24 RCTs)	⨁◯◯◯ VERY LOW a,b,c,d	-	The mean weight was **0** kg	MD **1.36 kg lower** (2.51 lower to 0.21 lower)
Body mass index	1891 (19 RCTs)	⨁⨁◯◯ LOW d	-	The mean body mass index was **0**	MD **0.89 lower** (1.5 lower to 0.28 lower)
Body fat percentage	1201 (16 RCTs)	⨁⨁◯◯ LOW b,e	-	The mean body fat percentage was **0** % points	MD **1.6 % points lower** (2.31 lower to 0.88 lower)
Quality of life - General	1861 (22 RCTs)	⨁◯◯◯ VERY LOW a,d,f	-	-	SMD **0.45 SD higher** (0.2 higher to 0.69 higher)
Quality of life - physical	1716 (20 RCTs)	⨁◯◯◯ VERY LOW a,d,f,g	-	-	SMD **0.51 SD higher** (0.23 higher to 0.79 higher)
Quality of life - mental	1326 (14 RCTs)	⨁◯◯◯ VERY LOW a,f,g	-	-	SMD **0.28 SD higher** (0.06 higher to 0.5 higher)

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

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **HR:** Hazard Ratio

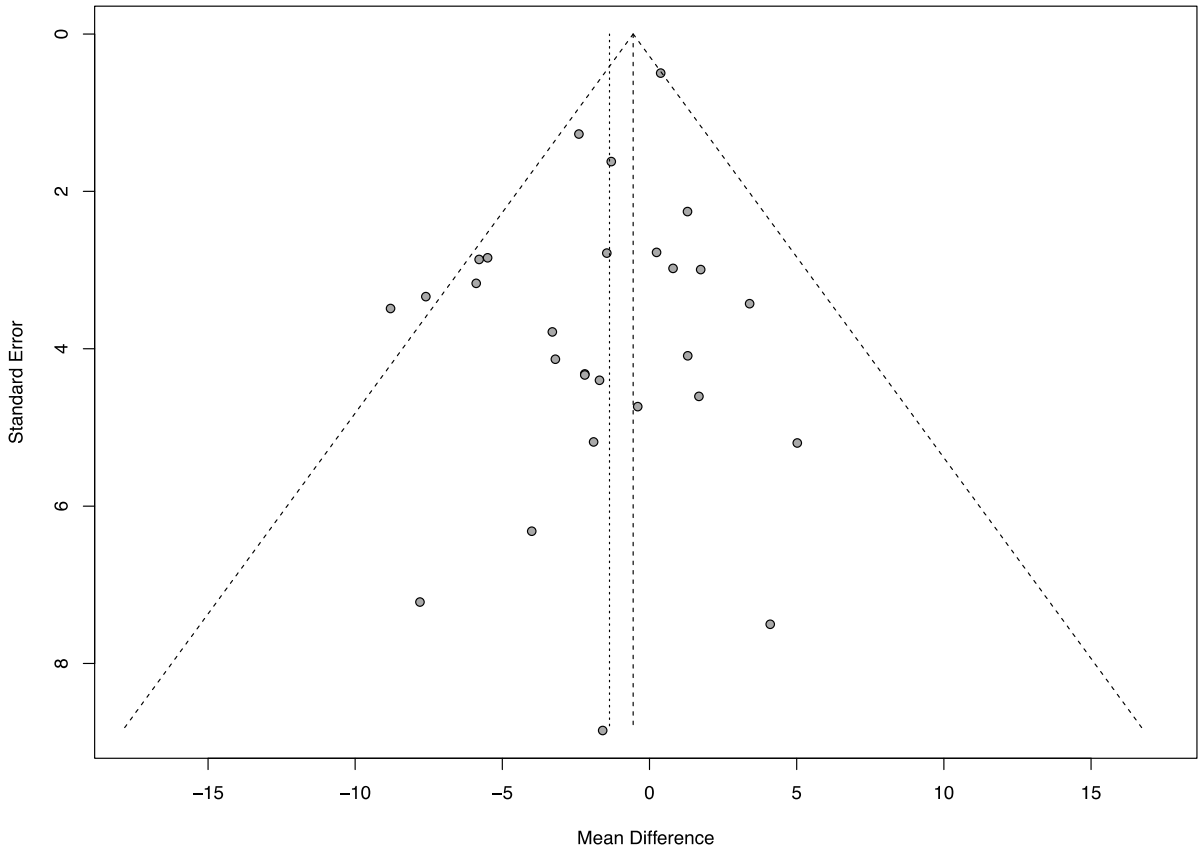
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

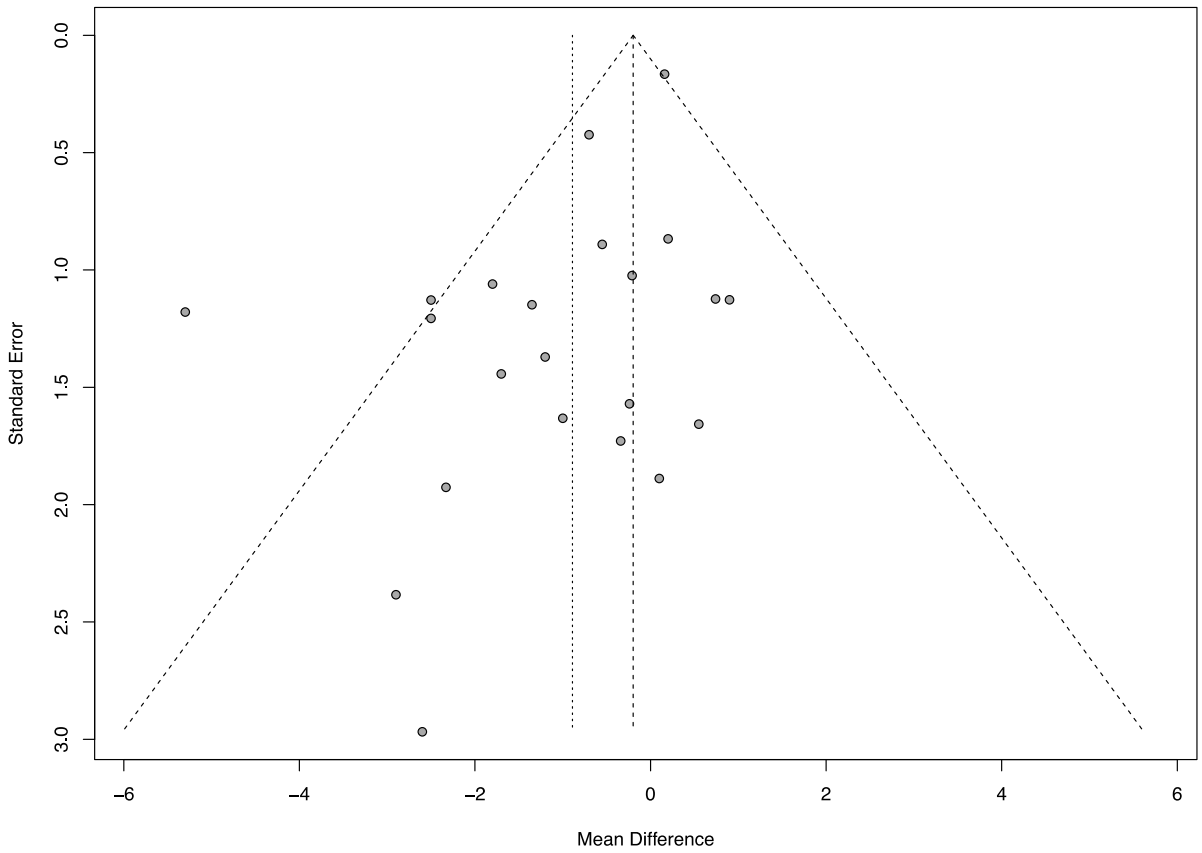
a. Impact on outcome varied greatly across studies.
b. Interventions varied widely across different studies. Interventions, in general, not tailored for the target patients. Excercise adherence unknown.
c. Confidence interval ranging from important effect (-1.5) to no clinical significant effect (-0.28)
d. Publication bias detected through Egger test. Trim and fill computation resulted in loss of statistical significance.
e. Confidence interval ranging from important effect (-2.31) to no clinical significant effect (-0.88)
f. Confidence intervals varied greatly across studies and across the different quality of life scales
g. Outcome assessed through different quality of life scales

Figure 11: GRADE summary

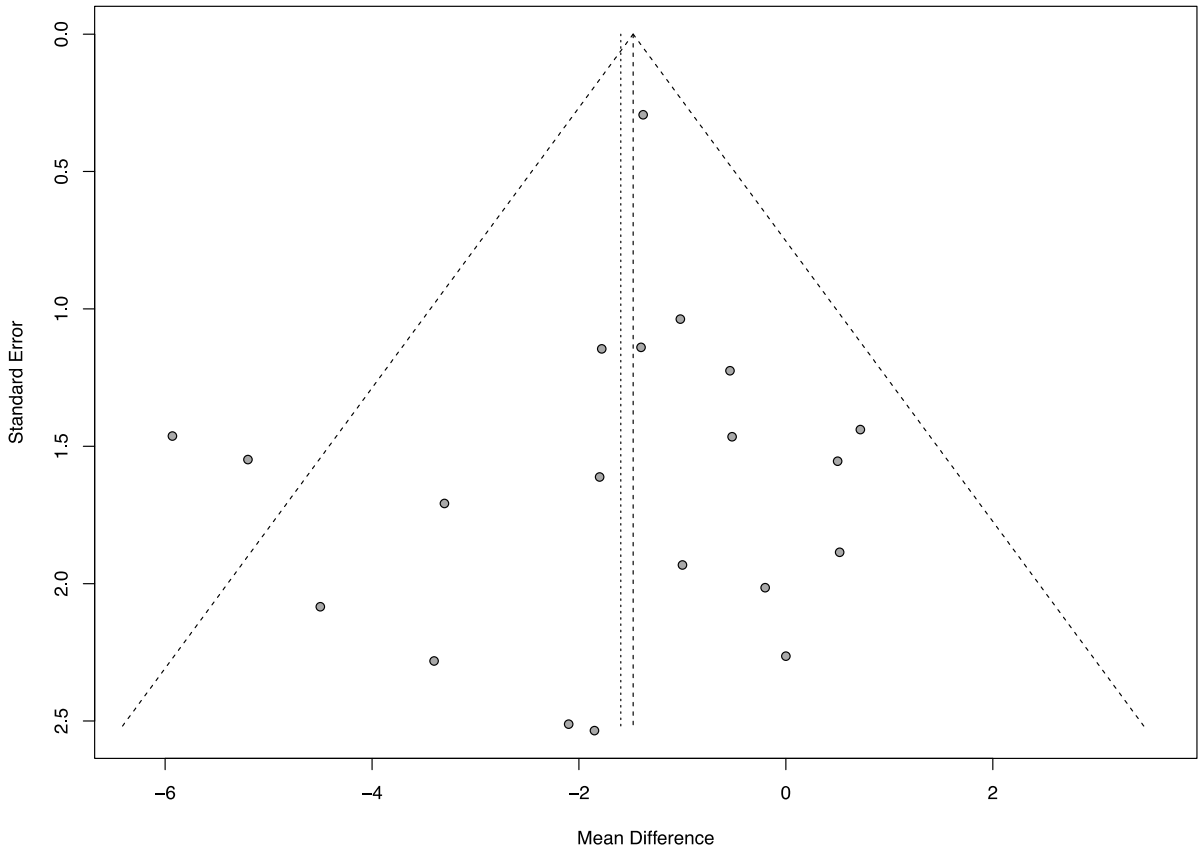
Supplementary Material



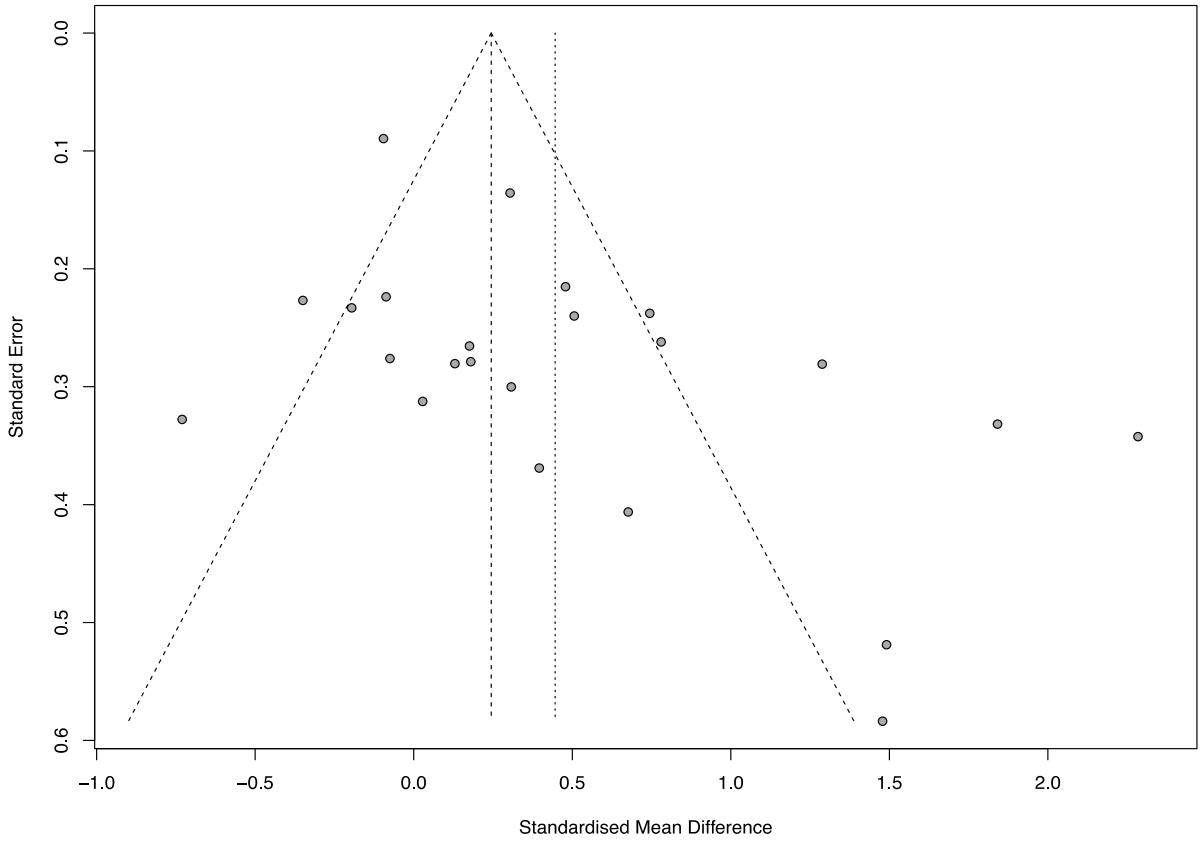
Funnel plot of publications regarding weight



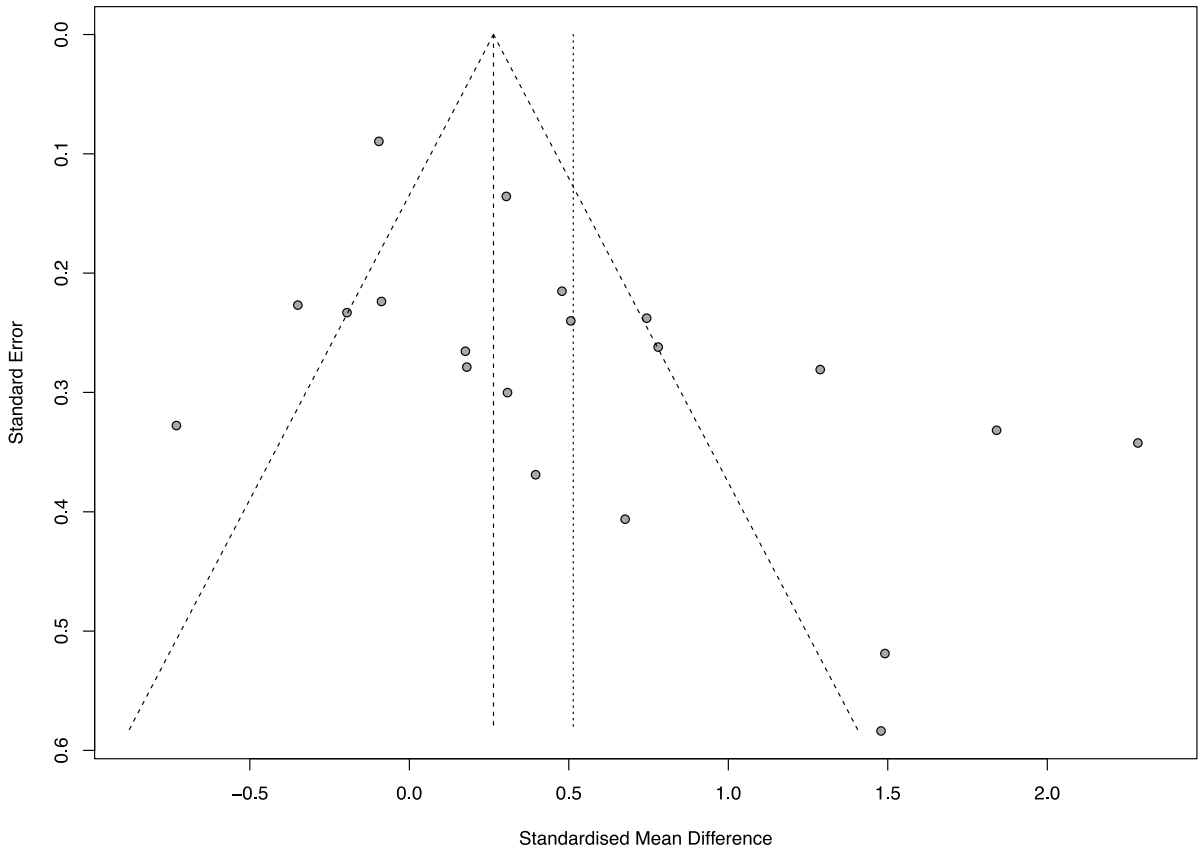
Funnel plot of publications regarding BMI



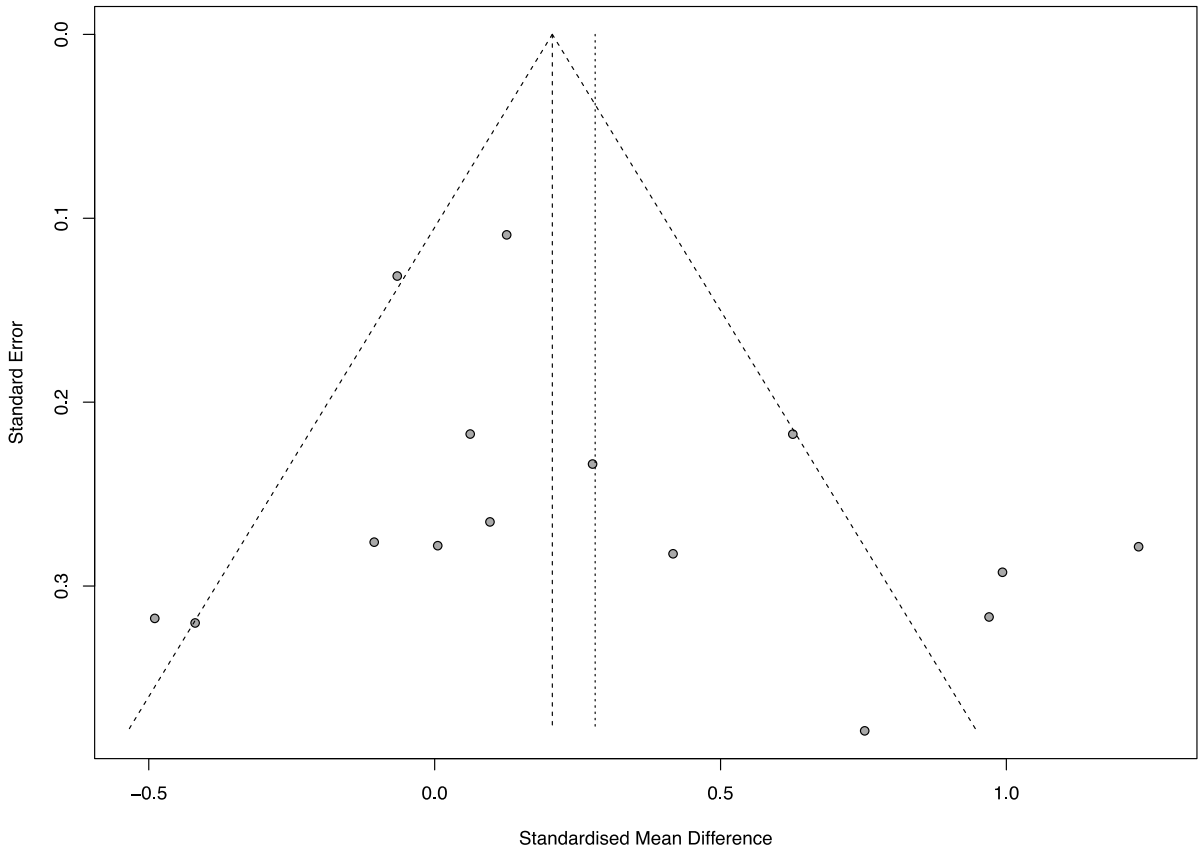
Funnel plot of publications regarding fat percentage



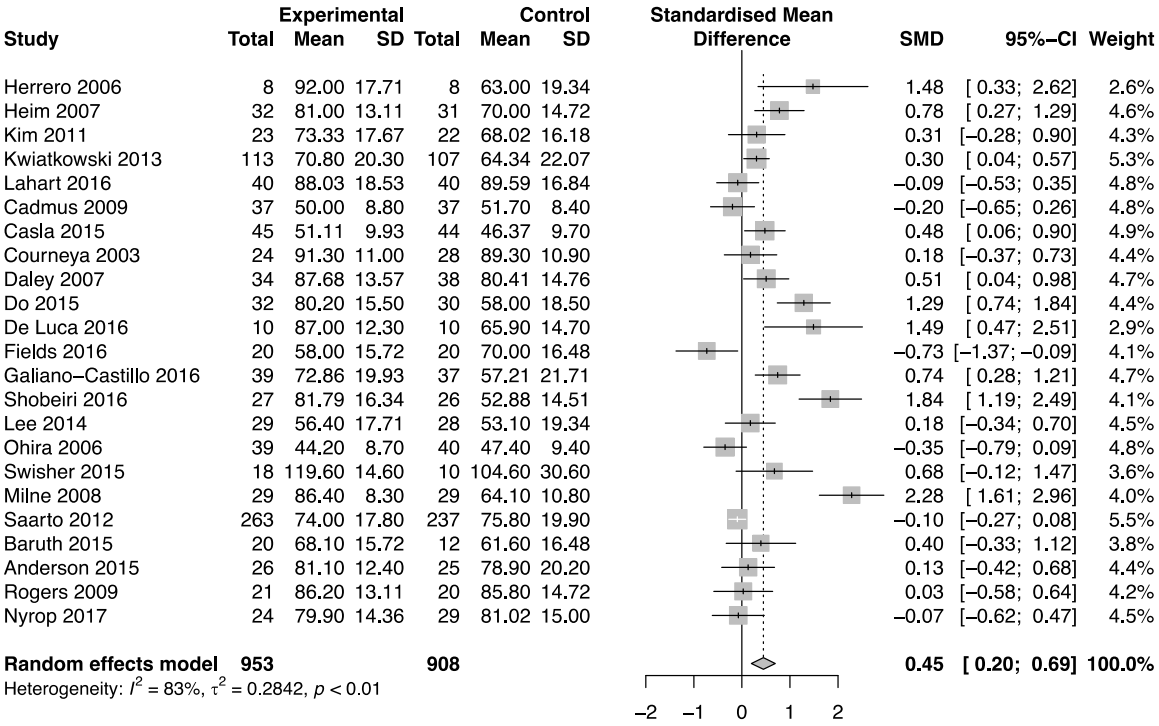
Funnel plot of publications regarding quality of life (general)



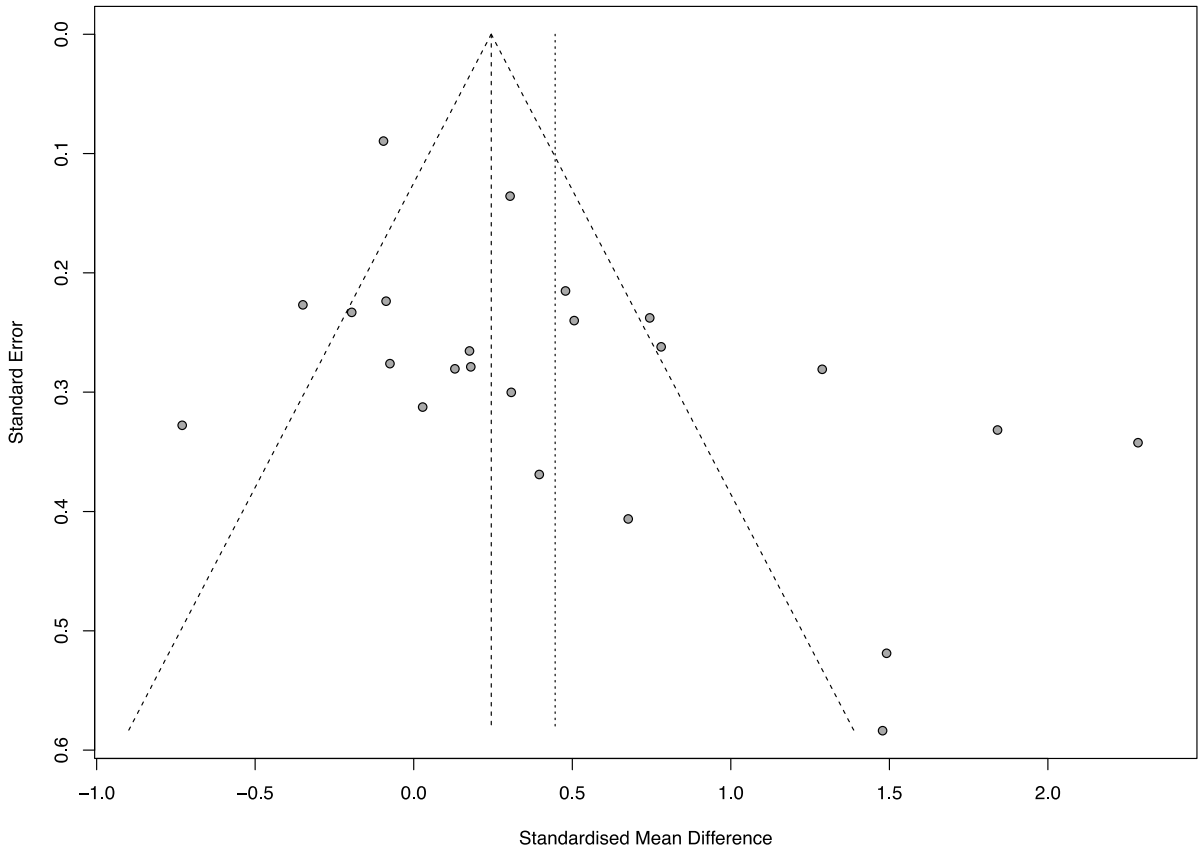
Funnel plot of publications regarding quality of life (physical)



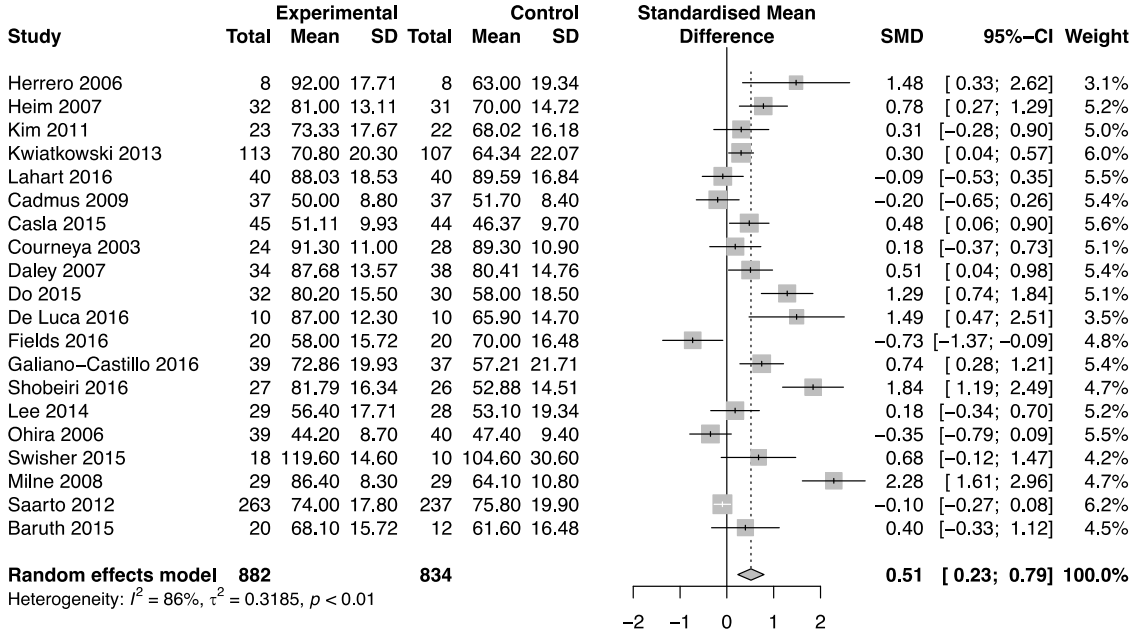
Funnel plot of publications regarding quality of life (mental)



Forest plot for quality of life (general)



Funnel plot of publications regarding quality of life (general)



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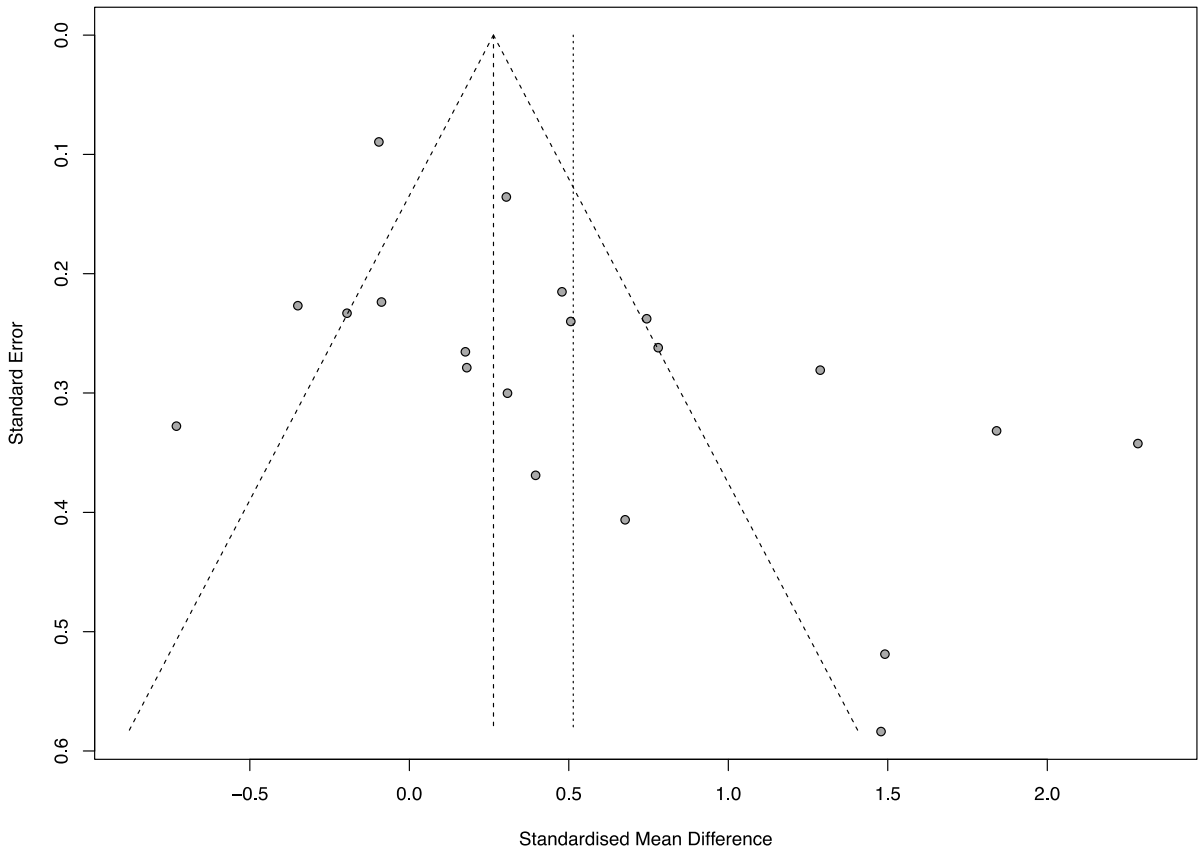

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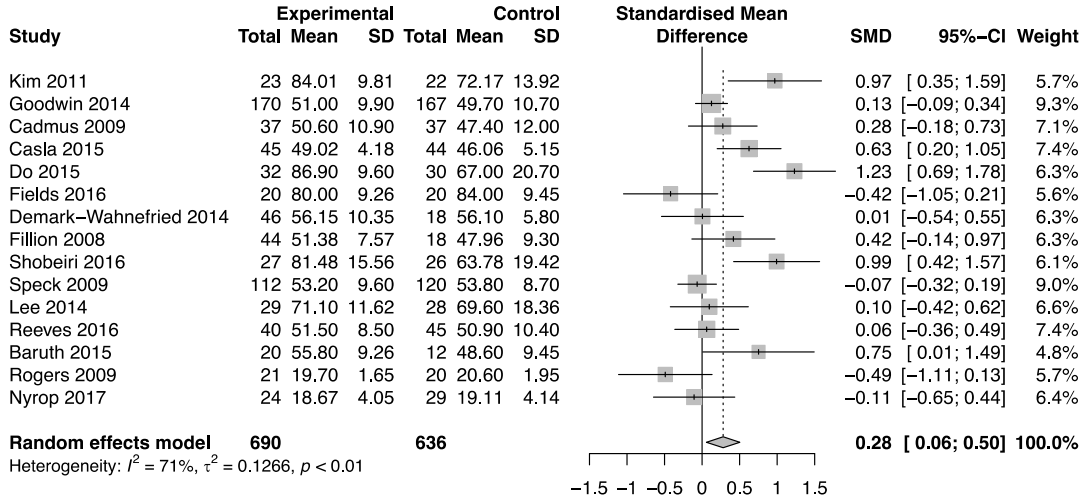
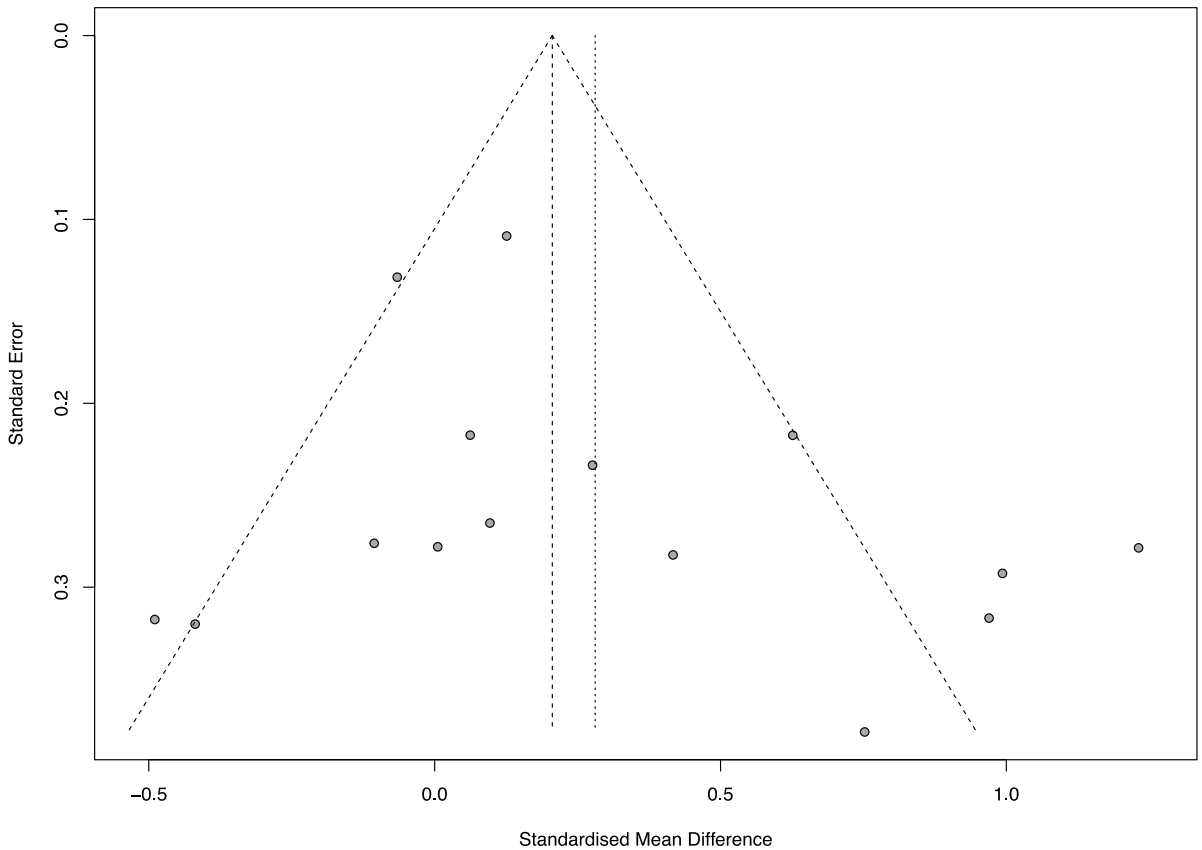


Forest plot for quality of life (mental)



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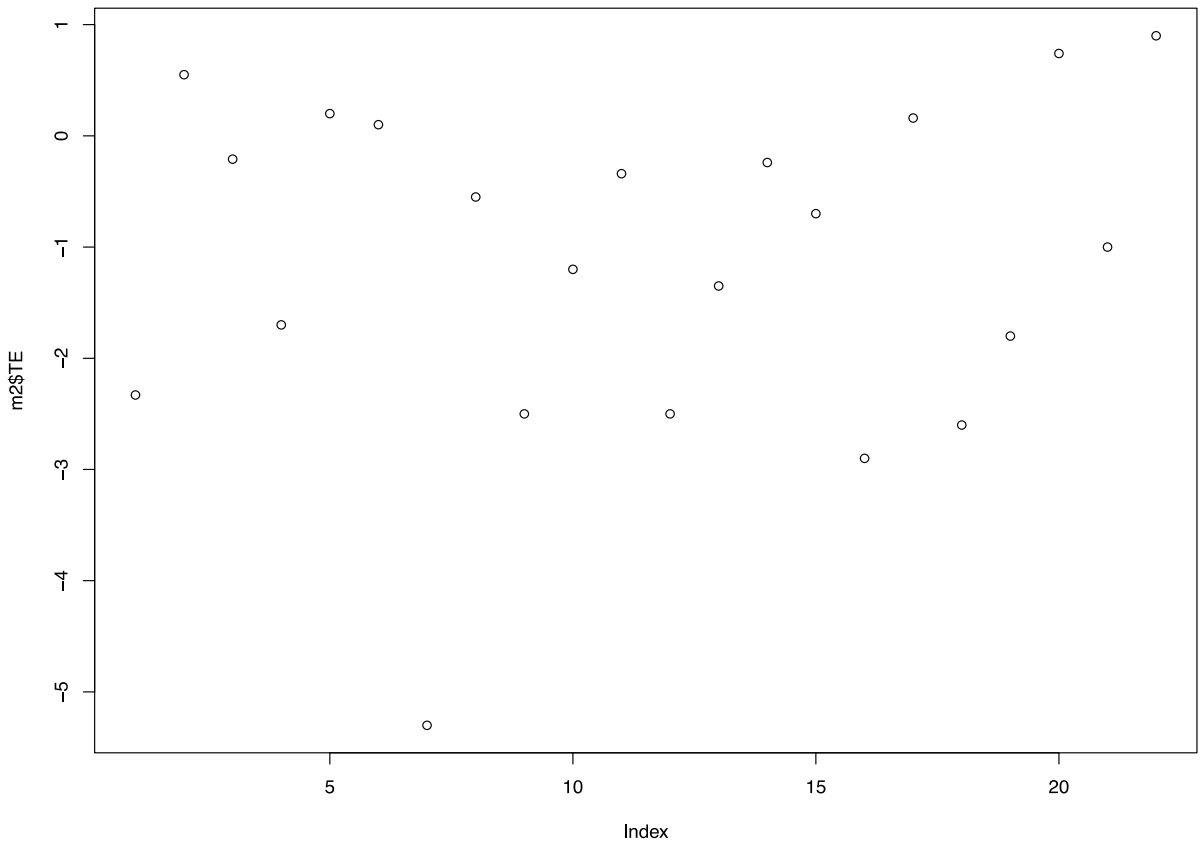
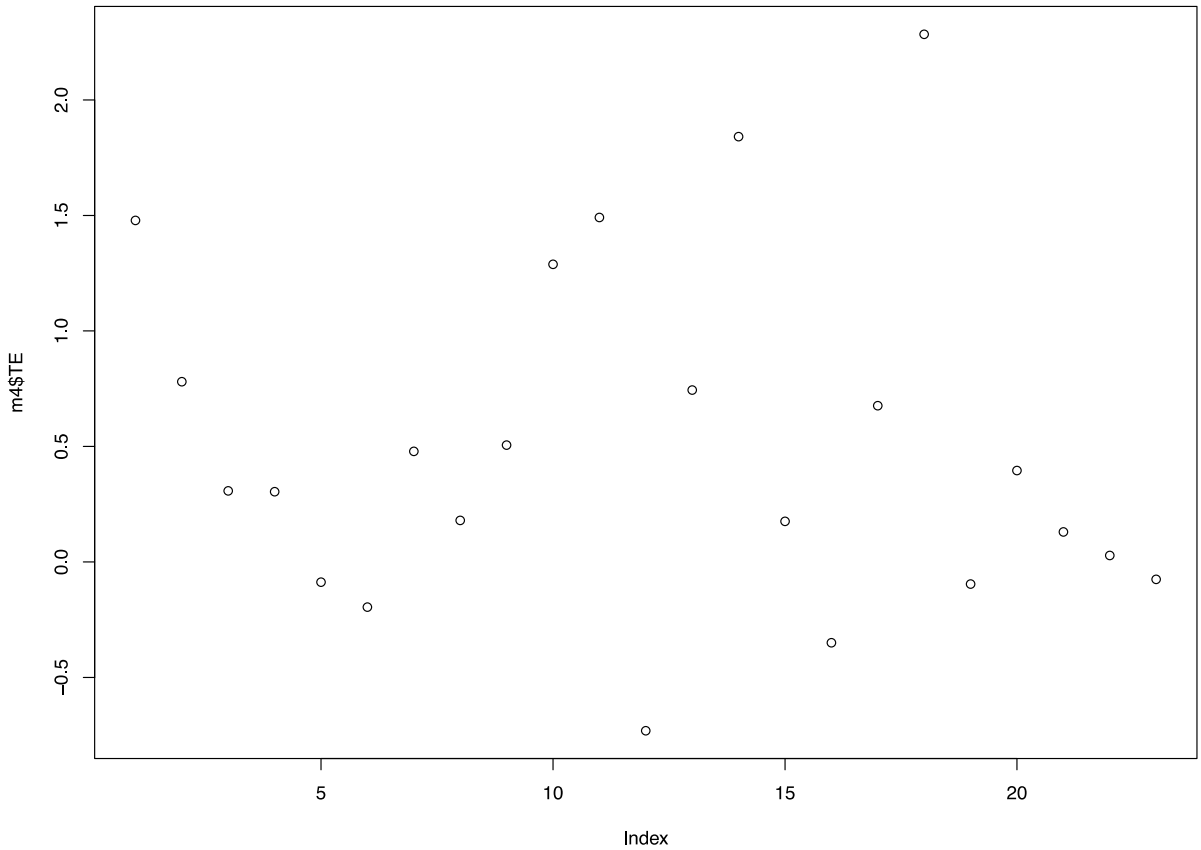
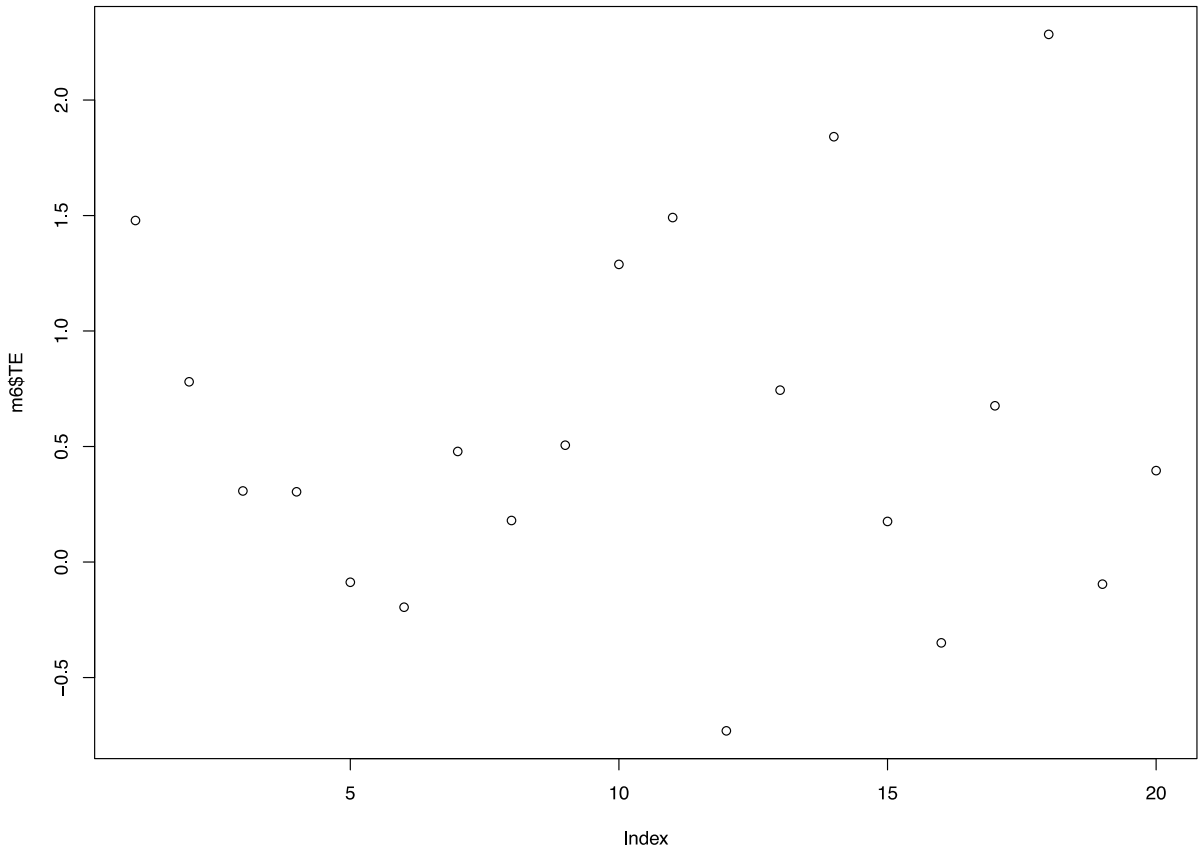


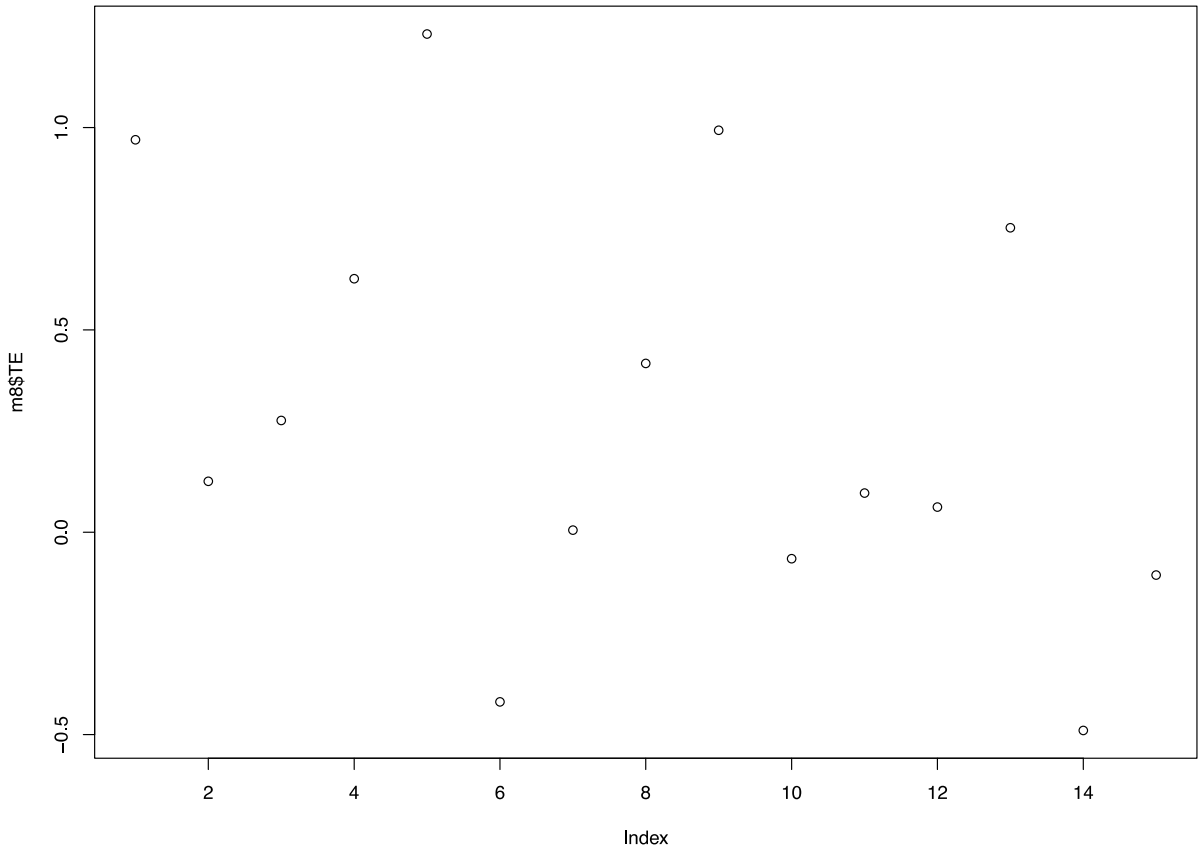
Bubble plot for the relation of BMI and duration of the physical exercise intervention



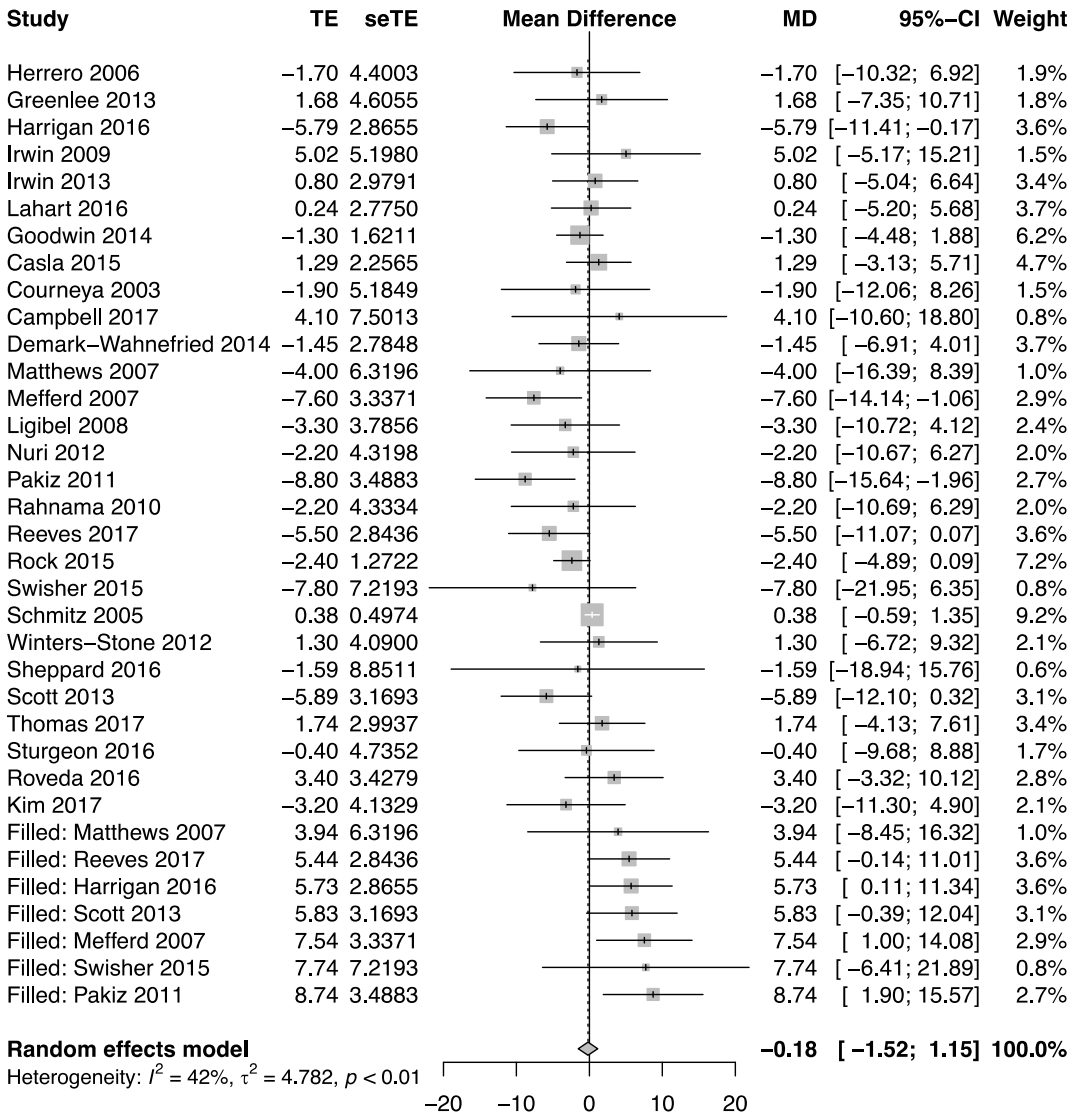
Bubble plot for the relation of quality of life (general) and duration of the physical exercise intervention



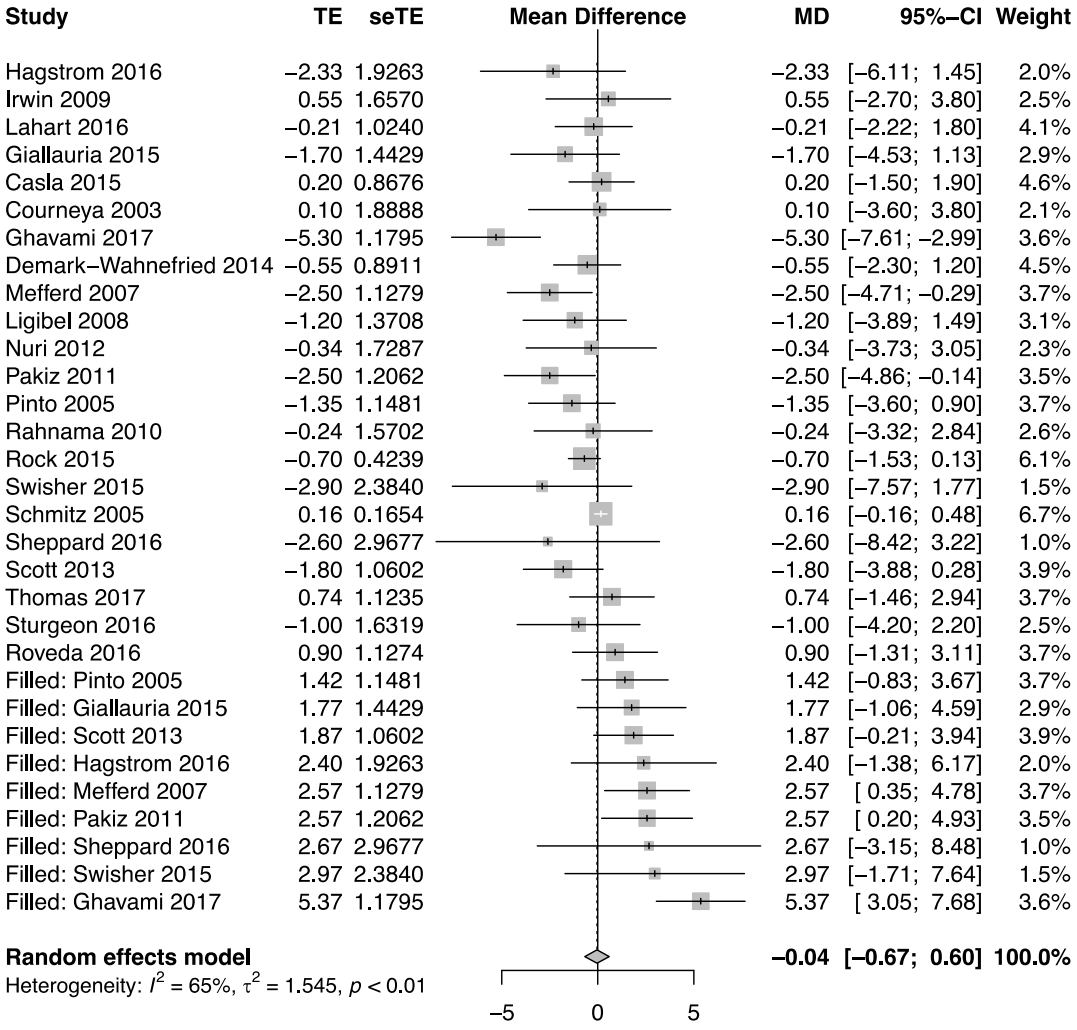
Bubble plot for the relation of quality of life (physical) and duration of the physical exercise intervention



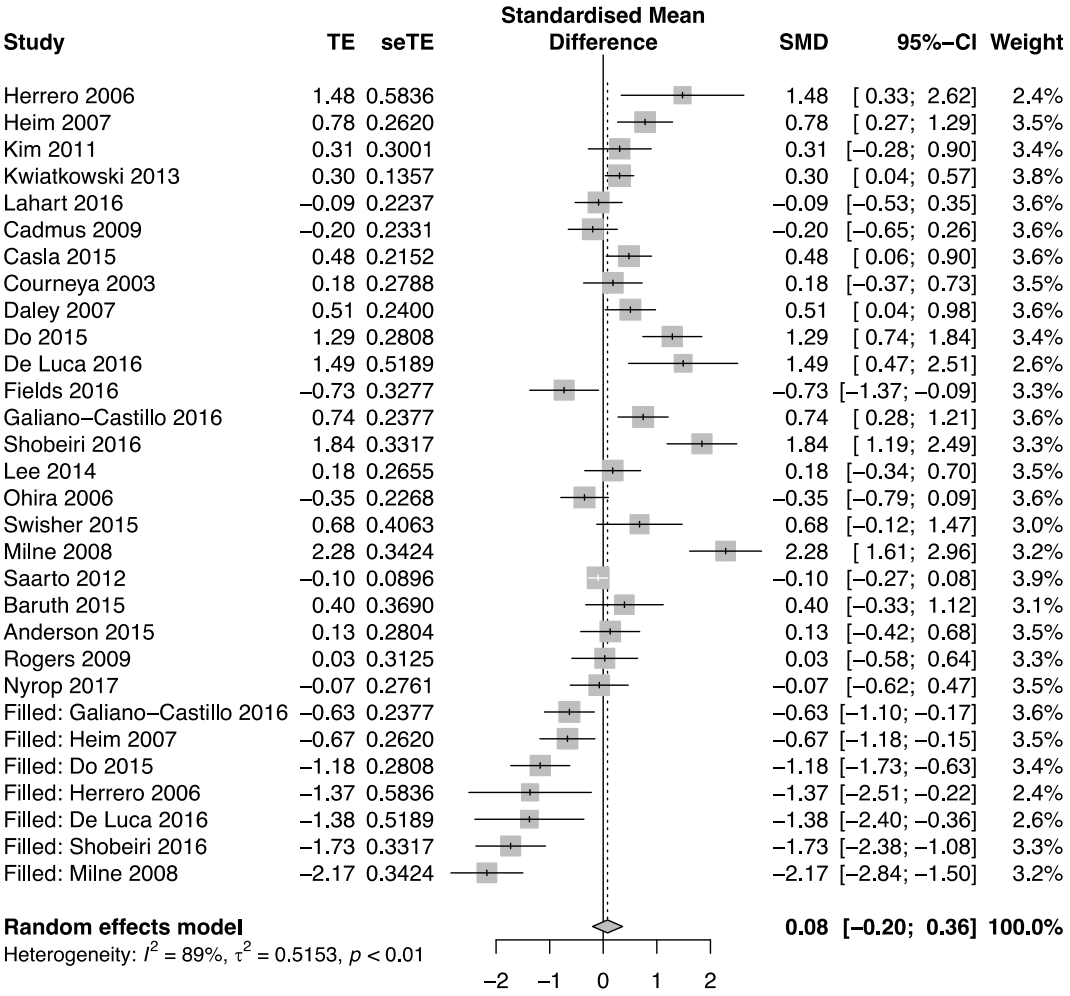
Bubble plot for the relation of quality of life (mental) and duration of the physical exercise intervention



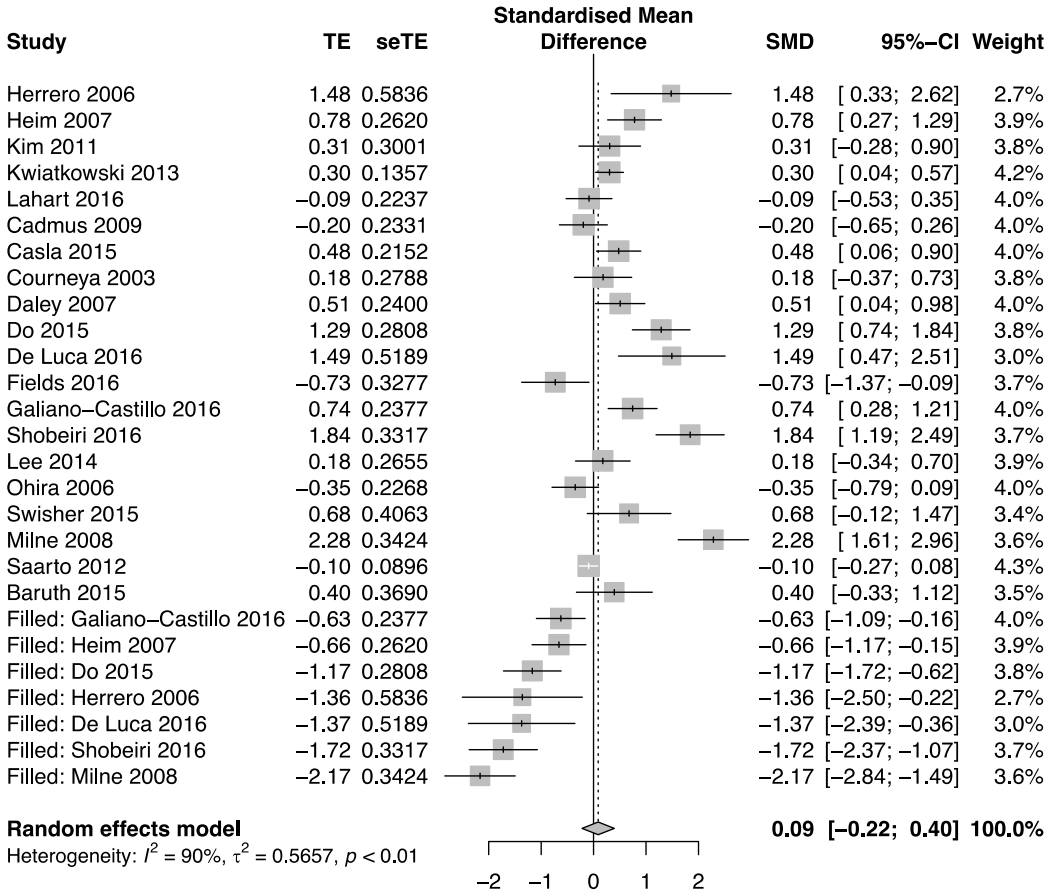
Trim-and-fill forest plot for weight



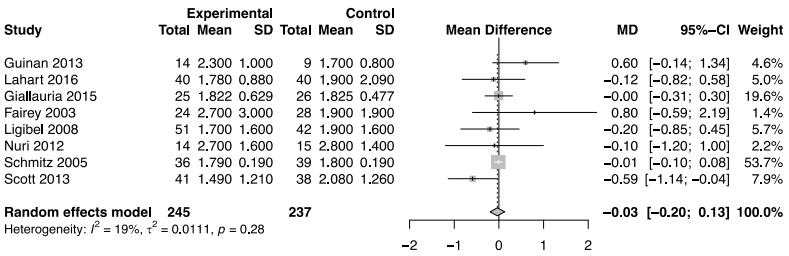
Trim-and-fill forest plot for BMI



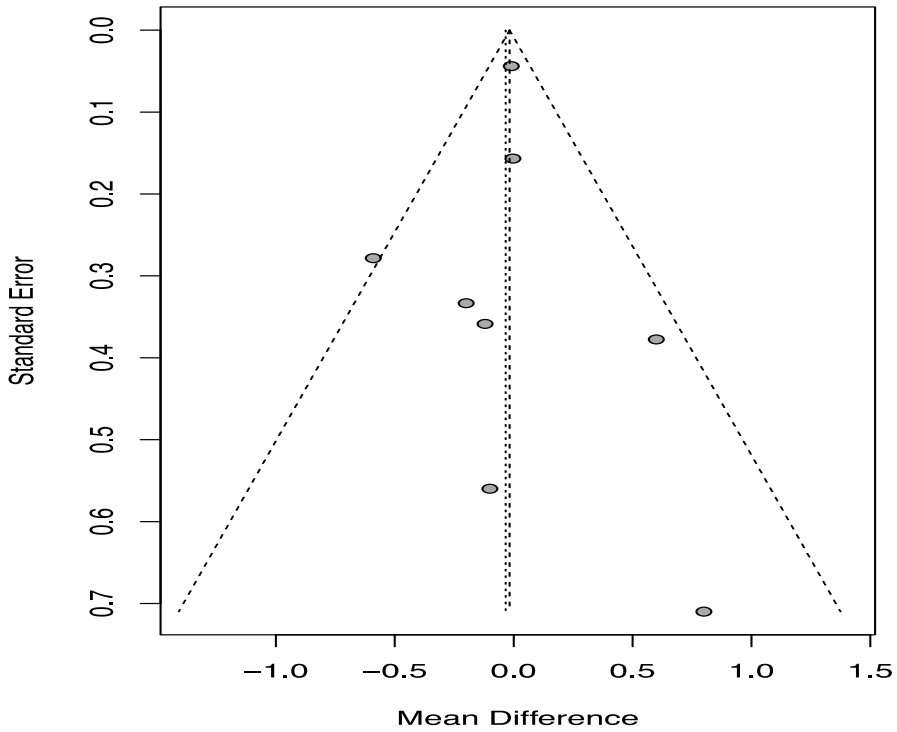
Trim-and-fill forest plot for quality of life (general)



Trim-and-fill forest plot for quality of life (physical)



Forest plot for HOMA-IR



Funnel plot for HOMA-IR

ELETRONIC SEARCH STRATEGY

CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees

#2 breast near cancer*

#3 breast near neoplasm*

#4 breast near carcinom*

#5 breast near tumour*

#6 breast near tumor*

#7 breast near malignan*

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 MeSH descriptor: [Health Behavior] explode all trees

#10 MeSH descriptor: [Health Promotion] explode all trees

#11 MeSH descriptor: [Exercise] explode all trees

#12 MeSH descriptor: [Exercise Therapy] explode all trees

#13 MeSH descriptor: [Sports] explode all trees

#14 MeSH descriptor: [Physical Fitness] explode all trees

#15 MeSH descriptor: [Diet Therapy] explode all trees

#16 MeSH descriptor: [Feeding Behavior] explode all trees

#17 MeSH descriptor: [Diet] explode all trees

#18 MeSH descriptor: [Physical Education and Training] explode all trees

#19 MeSH descriptor: [Life Style] explode all trees

#20 MeSH descriptor: [Health Education] explode all trees

#21 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 (lifestyl* or life styl*):ti,ab,kw

#23 (health* near (behav* or educ* or promot*)):ti,ab,kw

#24 (exercis* or physic* activit* or exert* or physic* fit* or sport*):ti,ab,kw

#25 (walk* or jog* or swim* or bicyc* or cycling or weight lift* or gymnastic or danc*):ti,ab,kw

#26 ((strength or resistance or circuit or enduran* or aerob* or physic* or fit*) next train*):ti,ab,kw

#27 (nutri* or diet*):ti,ab,kw

#28 #22 or #23 or #24 or #25 or #26 or #27

#29 #21 or #27

#30 #8 AND #29

MEDLINE (OVID)

#1 exp breast neoplasms/

#2 exp breast/

#3 breast.tw.

#4 2 or 3

#5 exp neoplasms/

#6 exp lymphedema/

#7 exp radiotherapy/

#8 or/5-7

#9 4 and 8

#10 (breast adj25 neoplasm$).tw,ot.

#11 (breast adj25 cancer$).tw,ot.

#12 (breast adj25 tumour$).tw,ot.

#13 (breast adj25 tumor$).tw,ot.

#14 (breast adj25 carcinoma$).tw,ot.

#15 (breast adj25 adenocarcinoma$).tw,ot.

#16 (breast adj25 ductal).tw,ot.

#17 (breast adj25 infiltrating).tw,ot.

#18 (breast adj25 lobular).tw,ot.

#19 (breast adj25 medullary).tw,ot.

#20 exp mammary neoplasms/

#21 (mammary adj25 neoplasm$).tw,ot.

#22 (mammary adj25 cancer$).tw,ot.

#23 (mammary adj25 tumour$).tw,ot.

#24 (mammary adj25 tumor$).tw,ot.

#25 (mammary adj25 carcinoma$).tw,ot.

#26 (mammary adj25 adenocarcinoma$).tw,ot.

#27 (mammary adj25 ductal).tw,ot.

#28 (mammary adj25 infiltrating).tw,ot.

#29 (mammary adj25 lobular).tw,ot.

#30 (mammary adj25 medullary).tw,ot.

#31 exp mastectomy/

#32 or/10-31

#33 1 or 9 or 32

#34 exp Health Behavior/

#35 exp Health Promotion/

#36 exp exercise/

#37 exp exercise therapy/

#38 exp Sports/

#39 exp Physical Fitness/

#40 exp Diet Therapy/

#41 exp Feeding Behavior/

#42 exp Diet/

#43 exp "Physical Education and Training"/

#44 exp Life Style/

#45 exp Health Education/

#46 (lifestyl$ or life styl$).tw,ot.

#47 (health$ adj6 (behav$ or educ$ or promot$)).tw,ot.

#48 (exercis$ or physic$ activit$ or exert$ or physic$ fit$ or sport$).tw,ot.

#49 (walk$ or jog$ or swim$ or bicyc$ or cycling or weight lift$ or gymnastic or danc$).tw,ot.

#50 ((strength or resistance or circuit or enduran$ or aerob$ or physic$ or fit$) adj6 train$).tw,ot.

#51 (nutri$ or diet$).tw,ot.

#52 or/34-51

#53 Randomized Controlled Trials as Topic/

#54 randomized controlled trial/

#55 Random Allocation/

#56 Double Blind Method/

#57 Single Blind Method/

#58 clinical trial/

#59 clinical trial, phase i.pt

#60 clinical trial, phase ii.pt

#61 clinical trial, phase iii.pt

#62 clinical trial, phase iv.pt

#63 controlled clinical trial.pt

#64 randomized controlled trial.pt

#65 multicenter study.pt

#66 clinical trial.pt

#67 exp Clinical Trials as topic/

#68 (clinical adj trial$).tw

#69 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw

#70 PLACEBOS/

#71 placebo$.tw

#72 randomly allocated.tw

#73 (allocated adj2 random$).tw

#74 or/53-73

#75 case report.tw

#76 letter/

#77 historical article/

#78 or/75-77

#79 74 not 78

#80 33 and 52 and 79

EMBASE (OVID)

#1 exp breast neoplasms/

#2 exp breast/

#3 breast.tw.

#4 2 or 3

#5 exp neoplasms/

#6 exp lymphedema/

#7 exp radiotherapy/

#8 or/5-7

#9 4 and 8

#10 (breast adj25 neoplasm$).tw,ot.

#11 (breast adj25 cancer$).tw,ot.

#12 (breast adj25 tumour$).tw,ot.

#13 (breast adj25 tumor$).tw,ot.

#14 (breast adj25 carcinoma$).tw,ot.

#15 (breast adj25 adenocarcinoma$).tw,ot.

#16 (breast adj25 ductal).tw,ot.

#17 (breast adj25 infiltrating).tw,ot.

#18 (breast adj25 lobular).tw,ot.

#19 (breast adj25 medullary).tw,ot.

#20 exp mammary neoplasms/

#21 (mammary adj25 neoplasm$).tw,ot.

#22 (mammary adj25 cancer$).tw,ot.

#23 (mammary adj25 tumour$).tw,ot.

#24 (mammary adj25 tumor$).tw,ot.

#25 (mammary adj25 carcinoma$).tw,ot.

#26 (mammary adj25 adenocarcinoma$).tw,ot.

#27 (mammary adj25 ductal).tw,ot.

#28 (mammary adj25 infiltrating).tw,ot.

#29 (mammary adj25 lobular).tw,ot.

#30 (mammary adj25 medullary).tw,ot.

#31 exp mastectomy/

#32 or/10-31

#33 1 or 9 or 32

#34 exp Health Behavior/

#35 exp Health Promotion/

#36 exp Exertion/

#37 exp exercise/

#38 exp exercise therapy/

#39 exp Sports/

#40 exp Physical Fitness/

#41 exp Diet Therapy/

#42 exp Feeding Behavior/

#43 exp Diet/

#44 exp "Physical Education and Training"/

#45 exp Life Style/

#46 exp Health Education/

#47 (lifestyl$ or life styl$).tw,ot.

#48 (health$ adj6 (behav$ or educ$ or promot$)).tw,ot.

#49 (exercis$ or physic$ activit$ or exert$ or physic$ fit$ or sport$).tw,ot.

#50 (walk$ or jog$ or swim$ or bicyc$ or cycling or weight lift$ or gymnastic or danc$).tw,ot.

#51 ((strength or resistance or circuit or enduran$ or aerob$ or physic$ or fit$) adj6 train$).tw,ot.

#52 (nutri$ or diet$).tw,ot.

#53 or/34-52

#54 Clinical trial/

#55 Randomized controlled trial/

#56 Randomization/

#57 Single blind procedure/

#58 Double blind procedure/

#59 Crossover procedure/

#60 Placebo/

#61 Randomi?ed controlled trial$.tw.

#62 Rct.tw.

#63 Random allocation.tw.

#64 Randomly allocated.tw.

#65 Allocated randomly.tw.

#66 (allocated adj2 random).tw.

#67 Single blind$.tw.

#68 Double blind$.tw.

#69 ((treble or triple) adj (blind$)).tw.

#70 Placebo$.tw.

#71 Prospective study/

#72 Or/54-71

#73 Case study/

#74 Case report.tw.

#75 Abstract report/

#76 letter/

#77 Or/73-76

#78 72 not 77

#79 32 and 53 and 78

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Adjuvant platinum-based chemotherapy for early stage cervical cancer (Review)

Falcetta FS, Medeiros LRF, Edelweiss MI, Pohlmann PR, Stein AT, Rosa DD

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[Intervention Review]

Adjuvant platinum-based chemotherapy for early stage cervical cancer

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ABSTRACT

Background

This is the second updated version of the original Cochrane review published in the Cochrane Library 2009, Issue 3.

Most women with early cervical cancer (stages I to IIA) are cured with surgery or radiotherapy, or both. We performed this review originally because it was unclear whether cisplatin-based chemotherapy after surgery, radiotherapy or both, in women with early stage disease with risk factors for recurrence, was associated with additional survival benefits or risks.

Objectives

To evaluate the effectiveness and safety of adjuvant platinum-based chemotherapy after radical hysterectomy, radiotherapy, or both in the treatment of early stage cervical cancer.

Search methods

For the original 2009 review, we searched the Cochrane Gynaecological Cancer Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library 2009, Issue 1), MEDLINE, Embase, LILACS, BIOLOGICAL ABSTRACTS and CancerLit, the National Research Register and Clinical Trials register, with no language restriction. We handsearched abstracts of scientific meetings and other relevant publications. We extended the database searches to November 2011 for the first update and to September 2016 for the second update.

Selection criteria

Randomised controlled trials (RCTs) comparing adjuvant cisplatin-based chemotherapy (after radical surgery, radiotherapy or both) with no adjuvant chemotherapy, in women with early stage cervical cancer (stage IA2-IIA) with at least one risk factor for recurrence.

Data collection and analysis

Two review authors extracted data independently. Meta-analysis was performed using a random-effects model, with death and disease progression as outcomes.

Main results

For this second updated version we identified only one small trial reporting grade 4 toxicity results, without disease-free or overall survival data with a median follow-up of 16 months.

From the first updated version, we identified three trials that were ongoing, and remain so in 2016.

Four trials including 401 women with evaluable results with early cervical cancer were included in the meta-analyses. The median follow-up period in these trials ranged from 29 to 42 months. All women had undergone surgery first. Three trials compared chemotherapy combined with radiotherapy versus radiotherapy alone; and one trial compared chemotherapy followed by radiotherapy versus radiotherapy alone. It was not possible to perform subgroup analyses by stage or tumour size.

Compared with adjuvant radiotherapy, chemotherapy combined with radiotherapy significantly reduced the risk of death (two trials, 297 women; hazard ratio (HR) = 0.56, 95% confidence interval (CI): 0.36 to 0.87) and disease progression (two trials, 297 women; HR = 0.47, 95% CI 0.30 to 0.74), with no heterogeneity between trials (I^2 = 0% for both meta-analyses). Acute grade 4 toxicity occurred significantly more frequently in the chemotherapy plus radiotherapy group than in the radiotherapy group (three trials, 321 women; risk ratio (RR) 6.26, 95% CI 2.50 to 15.67). We considered the evidence for all three outcomes to be of a moderate quality, using the GRADE approach due to small numbers and limited follow-up in the included studies. In addition, it was not possible to separate data for bulky early stage disease.

In the one small trial that compared adjuvant chemotherapy followed by radiotherapy with adjuvant radiotherapy alone there was no difference in disease recurrence between the groups (one trial, 71 women; HR = 1.34; 95% CI 0.24 to 7.66) and overall survival was not reported. We considered this evidence to be of a low quality.

No trials compared adjuvant platinum-based chemotherapy with no adjuvant chemotherapy after surgery for early cervical cancer with risk factors for recurrence.

Authors' conclusions

The addition of platinum-based chemotherapy to adjuvant radiotherapy (chemoradiation) may improve survival in women with early stage cervical cancer (IA2-IIA) and risk factors for recurrence. Adjuvant chemoradiation is associated with an increased risk of severe acute toxicity, although it is not clear whether this toxicity is significant in the long term due to a lack of long-term data. This evidence is limited by the small numbers and low to moderate methodological quality of the included studies. We await the results of three ongoing trials, which are likely to have an important impact on our confidence in this evidence.

PLAIN LANGUAGE SUMMARY

Adjuvant (supplementary treatment after initial treatment) platinum-based anti-cancer drugs for early stage cervical cancer

Background

Cervical cancer is the second most common cancer among women. Most women with early stage cervical cancer (stages I to IIA) are cured with surgery or, radiotherapy, or both. Radiotherapy uses high energy x-rays to damage tumour cells. Chemotherapy (anti-cancer) drugs use different ways to stop tumour cells dividing so they stop growing or they die.

Review question

We undertook this review because it was unclear whether chemotherapy with a drug called cisplatin offered additional benefits or risks to women with early stage cancer with risk factors for recurrence, when given after surgery, after radiotherapy, or both. (Risks for recurrence include tumour spread to the lymph nodes, spread into the lymph and blood vessels, tumour depth of more than 10 mm, microscopic invasion of the connective tissues next to the womb, non-squamous type of cancer, and when it is unlikely that surgery has removed all the tumour cells).

Main Findings

In this review, we analysed data from four small trials of unclear quality. It was not possible to separate data of bulky early stage disease (stage IB2 and IIA lesions greater than 4 cm) from the overall results. We found limited evidence to suggest that the addition of cisplatin chemotherapy to radiotherapy prolongs survival (time to death) and delays progression of the cancer when given after surgery to women with cervical cancer stage IA2 to IIA with risk factors for recurrence. The combined therapy was associated with more severe side effects than radiotherapy alone.

Quality of the Evidence

This evidence is limited by the small numbers and moderate quality methodological quality of included studies.

What are the conclusions?

We conclude that it seems appropriate to offer these women chemotherapy plus radiotherapy after surgery, however, more evidence regarding the relative benefits and risks is needed; this will hopefully be provided by the results of three ongoing trials.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Radiotherapy plus chemotherapy compared with **radiotherapy for early stage cervical cancer**

Patient or population: patients with early stage cervical cancer
Settings: inpatient or outpatient
Intervention: radiotherapy plus chemotherapy
Comparison: radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiotherapy	Radiotherapy pluschemotherapy			
Death from all causes Follow-up: 42 months	**310 per 1000**[1]	**188 per 1000** (125 to 276)	**HR 0.56** (0.36 to 0.87)	297 (2 studies)	⊕⊕⊕◯ **moderate**[2]
Disease progression Follow-up: 42 months	**353 per 1000**[1]	**185 per 1000** (122 to 275)	**HR 0.47** (0.3 to 0.74)	297 (2 studies)	⊕⊕⊕◯ **moderate**[2]
Grade 4 toxicity[3]	**26 per 1000**	**182 per 1000** (72 to 454)	**RR 6.26** (2.50 to 15.67)	321 (3 studies)	⊕⊕⊕◯ **moderate**[2]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Due to censoring and differing levels of follow-up combined figures from the two studies were not used. Peters 2000 explicitly reported four-year survival rate and carried substantially more weight in the meta-analysis, therefore we used the numbers from this trial.

[2] Trial of Peters 2000 was reported early because interim analysis showed benefit of radiotherapy plus chemotherapy.

[3] The results from radiotherapy plus chemotherapy and chemotherapy plus radiotherapy followed by consolidation chemotherapy in the Sun 2015 trial were analysed together for the outcome of grade 4 toxicity.

BACKGROUND

This is the second update of the original review that was published in the *Cochrane Database of Systematic Reviews,* 2009, Issue 3.

Description of the condition

Despite significant advances in the screening and treatment of cervical dysplasia, cervical cancer is the fourth most common cancer in women (GLOBOCAN 2012). Worldwide, there are more than 500,000 new cases of cervical cancer each year, accounting for around 8% of all cancers diagnosed in women. A woman's risk of developing cervical cancer by the age of 75 ranges from 0.9% in more developed countries to 1.6% in less developed countries; the risk of dying from cervical cancer is 0.3% and 0.9% in more- and less developed countries, respectively. Worldwide, over 260,000 women die from cervical cancer every year; over 230,000 of these deaths being in less developed countries. In Europe, about 60% of women with cervical cancer survive five years after diagnosis (EUROCARE 2014).

The International Federation of Gynecology and Obstetrics (FIGO) staging of cervical cancer, determined at the time of primary diagnosis, is summarised in Table 1 (Benedet 2003).

Description of the intervention

Most women with early lesions (stages I to IIA) are cured with surgery or radiotherapy alone. However, patients who present with metastatic disease or locally advanced lesions are at a significant risk of recurrence and account for most cervical cancer deaths (Im 2002). These deaths occur despite current surgical and radiotherapy protocols, often as a direct result of local or in-field treatment failure (Im 2002).

The treatment of women with stage IA1 or micro-invasive cervical cancer usually consists of local excision (a loop or cone biopsy), or a simple hysterectomy. Women with stage IA2 to IIA lesions require either radical hysterectomy with bilateral pelvic lymph node dissection or radiotherapy, combining whole pelvic teletherapy with brachytherapy. There is a trend to increased use of primary radiotherapy with increased stage of disease (Benedet 2003). These treatments (radical surgery and radiotherapy) are considered equally effective with respect to local control and survival if lesions are small and nodal metastasis are absent (Holtz 2002); however, for bulky early lesions (IB2 and IIA), chemoradiation (as primary treatment or after surgery) is considered to be more effective in improving survival and reducing recurrence than radiotherapy alone (CCCMAC 2010).

Disease control for early lesions with risk factors such as lymph node metastasis, lymphovascular space invasion, depth invasion more than 10 mm, parametrial invasion (Ho 2004; Lai 1999; Park 1997), non-squamous histology (Ikeda 1994) and positive surgical margins (Rushdan 2004) is difficult. Retrospective studies analysing the outcome of high-risk women after adjuvant radiotherapy found that radiotherapy decreased the incidence of local recurrence with little or no effect on overall survival (OS) (Kinney 1989; Monk 1994). These findings are supported by a Cochrane review (Rogers 2012). Furthermore, many women with these risk factors are at increased risk for subclinical dissemination of the disease, which will not be affected by radiotherapy directed to the pelvis. To eradicate micrometastases, Wertheim 1985 added chemotherapy to radiotherapy, with an apparent improvement in survival rates when compared to historical controls. Cisplatin-based regimens, evaluated on the basis of shrinkage of the tumour, are the most effective chemotherapy regimens (Morton 1996; Park 1997).

The complete response rate to primary treatment of early stage disease ranges from 70% to 90%, with an overall five-year survival for stage I disease in excess of 90% (Benedet 2003). Adjuvant therapies may improve survival but are associated with several adverse effects and toxicities. Early morbidity from radiotherapy is most frequently seen in the rectosigmoid (around 60%) with proctitis, tenesmus, diarrhoea, fistula, stenosis and ulceration. In one third of patients, toxicity within the urinary bladder such as cystitis, fistula, ulceration and contracted bladder may occur. Local dermal toxicity (oedema, erythema, pigmentation, fibrosis and ulceration) is reported in 20% of patients and gynaecological toxicity (vaginitis, dryness, narrowing, shortening, dyspareunia, necrosis or ulceration of the cervix, uterus infection, pyometra, hematometra, perforation of the uterus and necrosis of the uterus) in 10%. Furthermore, there is a 5% chance of developing late pelvic complications following intra-cavitary and external beam radiotherapy (EBRT), the most frequent being cystitis and proctitis (Maduro 2003). Reviews of chemoradiation in the treatment of locally advanced cervical cancer have shown greater acute haematological and gastro-intestinal toxicity in the combination arm (CCCMAC 2010; Green 2005).

Why it is important to do this review

There is no consensus about the place of chemotherapy in the adjuvant treatment of early stage (stages I to IIA) cervical cancer (Curtin 1997; Kato 1994; Lin 1998; Lin 2000; Mossa 2003; Nitz 1994; Thomas 1996). Adding therapies also adds potential adverse effects and toxicities. We aimed to help clarify the risks and benefits of adjuvant chemotherapy for early cervical cancer by performing this systematic review. Adjuvant radiotherapy for early cervical cancer is the subject of a separate Cochrane review (Rogers 2012), as is chemoradiation for locally advanced cervical cancer (CCCMAC 2010).

OBJECTIVES

To evaluate the effectiveness and safety of adjuvant platinum-based chemotherapy after radical hysterectomy (RH), radiotherapy, or both in the treatment of early stage cervical cancer (stages IA2 to IIA). The main outcomes of interest are survival and disease recurrence.

METHODS

Criteria for considering studies for this review

Types of studies

The review was restricted to randomised controlled trials (RCTs). We excluded trials with quasi-randomised designs (e.g. participants assigned to treatment arms on the basis of date of birth, clinic id-number or surname).

Types of participants

Women with stage IA2 to IIA cervical cancer defined as follows, according to FIGO staging (Benedet 2003; Pecorelli 2009).

- Stage IA2: invasive cancer identified only microscopically, with stromal invasion more than 3 mm and not more than 5 mm with a horizontal spread of 7 mm or less.
- Stage IB1: preclinical lesions higher than stage IA or clinical lesions 4 cm or less.
- Stage IB2: clinical lesions > 4 cm but confined to the cervix.
- Stage IIA: cervix cancer extends beyond the cervix but not to the parametrium, pelvic wall or lower third of the vagina.

We planned to subgroup women by stage and we excluded studies that only included women with bulky lesions (IB2 and IIA, 4cm or more) as we considered these lesions to be 'locally advanced'. We included studies where participants with at least one of the following risk factors for recurrence were included:

- lymph node metastasis;
- lymphovascular space invasion;
- depth invasion more than 10 mm;
- microscopic parametrial invasion;
- non-squamous histology;
- positive surgical margins.

Types of interventions

We only included studies that addressed chemotherapy in the adjuvant setting i.e. post-surgery or post-radiotherapy (or in combination with radiotherapy). Chemotherapy regimens without platins were excluded. Comparisons were restricted to those that compared an intervention with a control that was similar in all respects, except that chemotherapy was not included in the treatment regimen.

The following comparisons were included.

- Radical hysterectomy (RH) *with* adjuvant radiotherapy *compared with* RH and adjuvant radiotherapy plus chemotherapy (= adjuvant chemoradiation, where chemotherapy may be given before, after or in combination with radiotherapy).
- RH alone *compared with* RH and adjuvant chemotherapy.
- Primary radiotherapy *compared with* primary radiotherapy and adjuvant chemotherapy.

Types of outcome measures

Primary outcomes

- Overall survival (OS), defined as the time from randomisation until death (from any cause).
- Progression-free survival (PFS), defined as the time from randomisation until disease progression or death (by any cause).

Secondary outcomes

- Local recurrence, defined as the time from randomisation until loco-regional progression or recurrence, or death (by any cause).
- Distant recurrence, defined as the time from randomisation until distant progression or recurrence, or death (by any cause).
- Quality of life (QoL) using a validated scale.

Adverse events: type and severity of acute and late toxicity grades 3 and 4 (according to the ECOG Common Toxicity Criteria) (CTCAE 4.0).

Search methods for identification of studies

Electronic searches

For the first version of this review, we conducted the following searches to identify all published and unpublished RCTs, without language restrictions: Specialised Register (SR) of the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers (CGNOC), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, 2009, Issue 1, MEDLINE (January 1990 to 2009), Embase (January 1990 to 2009), LILACS (January 1990 to 2009), BIOLOGICAL ABSTRACTS (January 1990 to 2009) and Cancerlit (January 1990 to 2009). See Appendix 1 for the MEDLINE and Embase search strategies used. The search strategies were developed and executed by the author team for the original review.

The first updated version of the review searches of the SR, CENTRAL, MEDLINE, Embase and LILACS (Appendix 2) were performed in November 2011 by the CGNOC Information Specialist, who also searched the MetaRegister (http://www.controlled-trials.com/mrct/) for ongoing trials.

For this second updated version, searches of CENTRAL, MEDLINE and Embase were performed in September 2016 by the CGNOC Information Specialist.

Searching other resources

For the first version of the review, we handsearched the abstracts of scientific meetings and the citation lists of included studies and other relevant publications. In addition, we attempted to contact experts in the field to identify further reports of trials. We handsearched conferences reports from January 1990 to January 2009 in the following sources: Gynecologic Oncology, International Journal of Gynecological Cancer, British Journal of Cancer, British Cancer Research Meeting, Annual Meeting of the International Gynecologic Cancer Society, Annual Meeting of the American Society of Gynecologic Oncologist, Annual Meeting of European Society of Medical Oncology (ESMO), and the Annual Meeting of the American Society of Clinical Oncology (ASCO). We did not handsearch conference reports for the first or second update, however, the updated electronic search strategies were designed to include any published abstracts.

Data collection and analysis

Selection of studies

For the orginal version of the review, two review authors (DDR, LRM) undertook study selection and extracted data independently to assess whether the studies met the specified inclusion criteria. Any discrepancies were resolved by a third and a fourth review author (ATS, MCB). The review authors were blind to names of authors, institutions and journals. For this second updated version, two review authors selected the studies (FSF, DDR) as described in the inclusion criteria.

Data extraction and management

For the included studies in the original version of the review, five review authors (DDR, LRM, MCB, MIE, ATS) independently abstracted the following data to specifically designed, data collection forms: characteristics of patients and interventions, study quality, endpoints and deviations from protocol (Table 2; Table 3; Table 4; Table 5; Table 6). Differences between review authors were resolved by discussion or by appeal to a third review author if necessary. When necessary, we sought additional information from the principal investigator of the trial concerned. For this second updated version of the review, two review authors (FSF, DDR) extracted data from the one new included study.

For time-to-event (survival) data, we extracted the log of the hazard ratio (HR) [log(HR)] and its standard error from trial reports. If these were not reported, we digitised the published Kaplan-Meier survival curves using Adobe Photoshop (Adobe 2007) and noted the minimum and maximum duration of follow-up, in order to estimate the log(HR) and its standard error using the methods of Parmar 1998. We performed these calculations in Stata 9 (StataCorp 2005), using a specially written program, which yielded the reported log(HR) and variance when used on the data presented in Table V of Parmar 1998. If possible, we also extracted the log-rank or Cox P value, and number of observed events by treatment arm, in order to make alternative estimates of the log(HR) and its standard error (Parmar 1998).

For one trial for which unpublished individual patient data were available (Protocol CE3005), we used Cox regression to estimate log(HR) and its standard error for overall and recurrence-free survival, both unadjusted and adjusted for age (McCullagh 1989).

For dichotomous outcomes (adverse events), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio (RR).

Assessment of risk of bias in included studies

We assessed the risk of bias in included RCTs using Cochrane's tool in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of the following domains.

1) Random sequence generation

We assessed the randomisation of participants to intervention groups as follows.

- Low risk: e.g. a computer-generated random sequence or a table of random numbers.
- High risk: e.g. date of birth, clinic id-number or surname (quasi-randomised).
- Unclear risk: e.g. not reported.

2) Allocation concealment

We assessed the concealment of allocation sequence from treatment providers and participants as follows.

- Low risk: e.g. where the allocation sequence could not be foretold.
- High risk: e.g. allocation sequence could be foretold by patients, investigators or treatment provider.
- Unclear risk: e.g. not reported.

3) Blinding

We assessed the blinding of outcome assessors as follows.

- Low risk if outcome assessors were adequately blinded.
- High risk if outcome assessors were not blinded to the intervention that the participant received.
- Unclear if this was not reported or unclear.

4) Incomplete outcome data

We recorded the proportion of participants whose outcomes were not reported at the end of the study; we noted if loss to follow-up was not reported.

We assessed loss to follow-up as follows.

- Low risk if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
- High risk if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
- Unclear risk, if loss to follow-up was not reported.

5) Selective reporting of outcomes

We assessed whether studies are free of selective outcome reporting as follows.

- Low risk: e.g. if all outcomes that are specified above and also pre-specified in the study were reported in the study.
- High risk: e.g. if it was suspected that outcomes had been selectively reported.
- Unclear risk: e.g. It is unclear whether outcomes had been selectively reported.

6) Other potential threats to validity

We assessed whether studies were apparently free of other problems that could have put them at a high risk of bias using the following categories.

- Low risk.
- High risk.
- Unclear risk.

Measures of treatment effect

We used the following measures of the effect of treatment.

- For time-to-event (survival and disease progression) data, we used the log of the HR and its standard error, if possible.
- For dichotomous outcomes (adverse events), we used the RR.

Dealing with missing data

We attempted to extract data on the outcomes only among participants who were assessed at endpoint. We did not impute missing outcome data. Where possible, all data extracted on effectiveness were those relevant to an intention-to-treat (ITT) analysis and data on adverse events were those relevant to the treatments which patients actually received.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of forest plots, by the I^2 statistic which estimates of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001).

Assessment of reporting biases

We were unable to assess reporting bias as only four studies were included.

Data synthesis

The outcomes were pooled statistically using random-effects methods (DerSimonian 1986). For time-to-event data, we pooled the log(HRs) using the generic inverse variance facility of RevMan 5.1 (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

We planned to subgroup analyses by tumour stage and size as follows:

- early stages: IA2, IB1 and IIA less than 4 cm;
- bulky early stages: IB2 and IIA more than 4 cm.

In addition, where possible, we planned to stratify cervical cancer by histology:

- epidermoid or squamous carcinoma;
- adenocarcinoma;
- adenosquamous carcinoma;
- other types.

Sensitivity analysis

We performed sensitivity analysis, using estimates of HRs (i) calculated using alternative methods proposed by Parmar 1998 for one study (Peters 2000) and (ii) adjusted for age for another study (Protocol CE3005). If sufficient trials had been available, we also planned to perform sensitivity analyses, excluding studies which did not report adequate (i) concealment of allocation, (ii) blinding of the outcome assessor.

RESULTS

Description of studies

Results of the search

For the original review, the search strategy identified 716 unique records. The title and abstract screening of these references identified 50 studies as potentially eligible for this review. The full text screening of these 50 studies excluded 47 for the reasons described in the table Characteristics of excluded studies. The remaining three RCTs met our inclusion criteria and are described in the table Characteristics of included studies.

The first updated search identified 1034 records (excluding 166 duplicates) including three ongoing trials identified in the online register of controlled trials (MetaRegister). Of the 12 records that we screened for relevance, we found no new trials to include. However, we added the three ongoing trials to the Ongoing studies section (GOG 0263; Hong 2013; NCT 00806117) and requested the full text of one record (an abstract; Zola 2003), which we subsequently excluded. A summary of the ongoing studies may be found in Characteristics of ongoing studies.

In this second updated search, we identified 1095 records (excluding 195 duplicates). Of the 22 records that we screened for relevance we found two trials that met the inclusion criteria (Sun 2015 and Liu 2014). The trial by Liu 2014 was reported as an abstract with insufficient information and the principal investigator did not respond to our attempt to obtain the correct data for this meta-analysis. we excluded this study. All of the three ongoing trials added in the first update are still recruiting patients (GOG 0263; Hong 2013; NCT 00806117).

Included studies

We included four RCTs, which included a total of 435 women but only 268 women with evaluable results.

1) Peters 2000: 268 women with clinical stage IA2, IB or IIA carcinoma of the cervix treated by surgery were randomised to receive either adjuvant pelvic radiotherapy or pelvic radiotherapy plus four cycles of chemotherapy with cisplatin and 5-fluorouracil. After randomisation, 25 (9%) women were deemed ineligible and so 243 women were assessed: 116 in the radiotherapy-only arm and 127 in the radiotherapy and chemotherapy arm. In the radiotherapy-only arm, three women refused radiotherapy and one was not treated because of physician discretion; in the radiotherapy plus chemotherapy arm, one woman was not treated due to a surgical complication, five women refused chemotherapy and four women refused both chemotherapy and radiotherapy. Accrual took place between 1991 and 1996 in the US. Women were followed up for a median of 42 months.

2) Tattersall 1992: 71 women with clinical stage IB or IIA treated by radical hysterectomy were randomised to receive either pelvic radiotherapy (n = 37) or three cycles of chemotherapy with cisplatin, vinblastine and bleomycin followed by pelvic radiotherapy (n = 34). One woman randomised to receive radiotherapy alone refused all treatment and two women randomised to receive chemotherapy plus radiotherapy refused chemotherapy. Accrual of women took place between May 1985 and November 1990 in Australia. Women were followed up for a median of 30 months.

3) Protocol CE3005: Women with clinical stage IB or IIA were randomised to receive either adjuvant radiotherapy and chemotherapy (n = 27) or adjuvant radiotherapy only (n = 30).Three women were not followed up after randomisation: one in the radiotherapy plus chemotherapy arm and two in the radiotherapy-only arm. Hence 26 and 28 women were evaluated in the radiotherapy plus chemotherapy and radiotherapy-only arms, respectively. Accrual of women took place between September 1988 and October 1995 in the UK. Patients were followed up for a median of 29.5 months.

4) Sun 2015: 39 women with clinical stage IB1 or IIA2 were randomised to receive adjuvant radiotherapy and chemotherapy (n = 15), chemoradiotherapy plus consolidation chemotherapy (n = 5) or adjuvant radiotherapy only (n = 13). Six of all the included patients did not complete the allocated therapy (15%). Thirty-three patients completed the protocol and were evaluated: 13 in the radiotherapy and chemotherapy, 15 in the concomitant radiotherapy and chemotherapy arm and five in the chemoradiotherapy plus consolidation chemotherapy arm. Accrual of women took place between September 2011 and August 2013 in China. Patients were followed up for a median of 16 months.

All the included studies enrolled women with stage IB2 and IIA lesions (potentially larger than 4 cm). Although we intended to perform subgroup analyses by stage and tumour size, it was not possible to separate the data accordingly.

Outcomes

Peters 2000 reported overall survival (OS) but Tattersall 1992 did not. Peters 2000 reported progression-free survival (PFS); Tattersall 1992 reported disease-free survival (DFS). Sun 2015 only reported toxicity results due to a median follow-up of 16 months.

Peters 2000 reported the hazard ratios (HRs) for both OS and DFS, but not their variance. However, the reported HRs compared radiotherapy alone with radiotherapy plus chemotherapy, whereas, we required the converse comparison (with radiotherapy alone as the reference group) and this could not be estimated. Tattersall 1992 did not report HRs.

Both Peters 2000 and Tattersall 1992 presented Kaplan-Meier plots (and therefore the maximum duration of follow-up) for the endpoints which they considered, based on analysis of women in the groups to which they were randomised. We estimated the minimum duration of follow-up for both studies, digitised the survival plots and used Parmar's methods (Parmar 1998) to estimate the log(HR) and its variance for both trials. Peters 2000 reported the number of events in each treatment group and a P value from Cox regression, so we additionally used these data to provide another estimate of the log(HR) and its variance for this trial.

For Protocol CE3005, individual patient data were available, giving: date of birth, date of randomisation, date of death and whether death was due to the primary tumour, date of disease recurrence and toxicities.

Details on the type and severity of acute toxicity grades 3 and 4 were reported in three studies (Peters 2000; Protocol CE3005; Sun 2015).

Excluded studies

In total, we excluded 65 studies for the reasons described in the Characteristics of excluded studies table.

Eight papers found were reviews on the proposed subject (Hansgen 2001; Koh 2000; Lai 1999; Lu 2000; Morton 1996; Park 1997; Roth 1994; Shimizu 1995). Twenty-three studies were retrospective (Buxton 1990; Frigerio 1994; Harrand 2013; Ikeda 1994; Killackey 1993; Kim 2007; Lin 1998; Lin 2000; Mossa 2003; Nakamura 2014; Ng 1995; Park 2001; Park 2012; Ryu 2005; Sivanesaratnam 1987; Sivanesaratnam 1989; Sivanesaratnam 1998; Wada 1995; Wen 2013; Wertheim 1985; Yessaian 2004; Yoon 2014; Zhang 2012); seven were non-randomised clinical trials (Argenta 2006; Dimpfl 1996; Lahousen 1990; Lai 1989; Linghu 2003; Russel 1995; Zanetta 1995); six were phase II studies (Hansgen 2002; Rushdan 2004; Lee 2013; McCaffrey 2011; Strauss 2002; Wang 2015) and three were phase I studies (Schwarz 2011; Shu 2015; Watanabe 2006).

The chemotherapeutic regimen of the intervention group did not include cisplatin in five studies (Blohmer 2001; Kato 1994; Lahousen 1999; Richter 1982; Yamamoto 2004). Two studies evaluated chemotherapy (and not radiotherapy) in the control arm (Curtin 1996; Lahousen 1999). Seven trials were excluded because they included women with stage IIB or more in the analyses (Chatterjee 2013; Iwasaka 1998; Kemnitz 1991; Kim 2007; Lahousen 1999; Morris 1999; Yamamoto 2004) and these data could not be separated.

A multicentre Italian RCT (abstract only) of 204 women compared adjuvant chemotherapy with adjuvant radiotherapy (Zola 2003) in early invasive cervical cancer. Three-year follow-up showed no significant differences in survival and recurrence between the two interventions.

In one study, more than 70% of participants were lost after randomisation (Lai 1998). The protocol MRC CE04/EORTC55954 was excluded since it closed due to lack of accrual and the investigators did not reply our e-mails. On the clinicaltrials.gov web-site the trial is listed as completed since July 2012.

In the second update one randomised trial (Liu 2014) was excluded because it did not report the number of patients allocated to each one of the three groups or their outcomes (DFS, OS) or toxicity). The first author did not respond to our attempt to obtain the correct data from this study. A second RCT (Pu 2013) was excluded because both the intervention group and the control group received cisplatin, since the trial was comparing the inclusion of docetaxel in the adjuvant setting; as was another RCT (Sehouli 2012) that compared single-agent cisplatin and radiotherapy with paclitaxel, carboplatin and radiotherapy. One study (Rogers 2012) was a meta-analysis of adjuvant radiotherapy and chemoradiation therapy after surgery.

Risk of bias in included studies

The risk of bias in included studies is summarised in Figure 1 and Figure 2: most of the methodological quality criteria were unclear.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

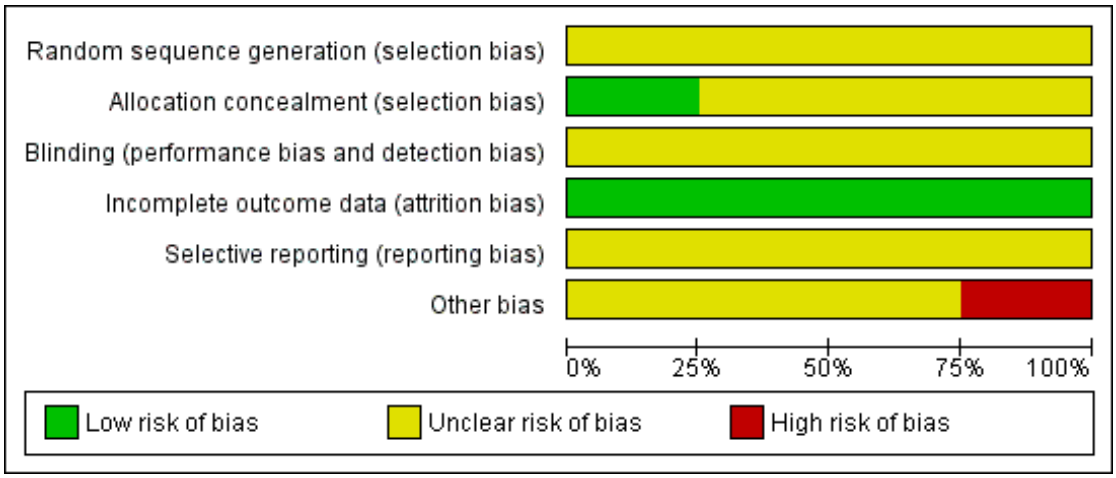
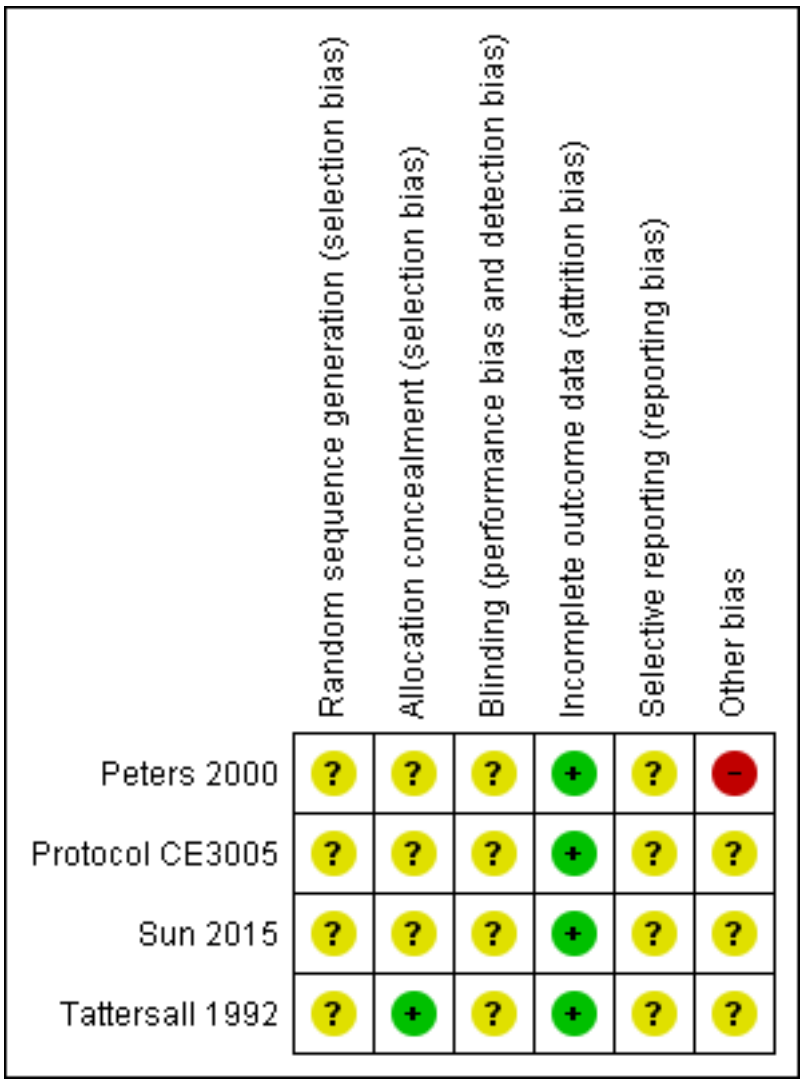


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

None of the four trials described randomisation adequately. Concealment of allocation was adequate in one study (Tattersall 1992), but was not described in the other three studies (Peters 2000; Protocol CE3005; Sun 2015).

Blinding

Blinding of the outcome assessors was not described in any of the four included studies.

Incomplete outcome data

Tattersall 1992 did not report loss to follow-up. Peters 2000 did not assess 25 (9%) of the 268 randomised patients as they were deemed ineligible after randomisation, but the numbers of ineligible patients were not reported by treatment arm. This study did not report any further loss to follow-up. Protocol CE3005 did not follow up 1/27 (4%) women in the radiotherapy plus chemotherapy arm and 2/30 (7%) women in the radiotherapy-only arm; reasons for loss to follow-up were not available. Sun 2015 did not report recurrence-free survival and OS because of a median follow-up of only 1 months.

Selective reporting

It was unclear whether the studies reported all the outcomes that they assessed.

Other potential sources of bias

Early reporting of findings

The report of Peters 2000 was based on an interim analysis of the data which rejected the null hypothesis of no benefit of chemotherapy. Another study was closed early due to lack of accrual (Protocol CE3005).

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

Adjuvant radiotherapy and chemotherapy versus adjuvant radiotherapy (comparison 1)

Death

Peters 2000 reported the Cox hazard ratio (HR) comparing overall survival (OS) in the radiotherapy group with that in the radiotherapy plus chemotherapy group to be 1.96 (P = 0.007). We estimated the log (HR) comparing OS in the radiotherapy plus chemotherapy group with that in the radiotherapy group and its variance using two of Parmar's methods: see Table 7. In the primary meta-analysis, we used the values estimated from the Kaplan-Meier plots, i.e. a HR of 0.57 (95% confidence interval (CI) 0.33 to 0.96). For Protocol CE3005, we estimated the HR comparing the risk of death in the radiotherapy plus chemotherapy group with that in the radiotherapy group using Cox regression, both unadjusted and adjusted for the age of the participants: see Table 7. In the primary meta-analysis, we used the unadjusted value, i.e. a HR of 0.55 (95% CI 0.25 to 0.1.20).

Meta-analysis of these two studies, which assessed a total of 297 participants, found that women who received radiotherapy plus chemotherapy had a significantly lower risk of death than women who received radiotherapy alone: the pooled HR was 0.56 (95% CI 0.36 to 0.87) with no heterogeneity between the trials (I^2 = 0%) - see Analysis 1.1; *moderate-quality evidence*. Sensitivity analyses, using the alternative Parmar estimates of HRs for the trials of Peters 2000 and age-adjusted estimates for the Protocol CE3005 trial, resulted in a similar estimate of the HR: 0.52 (95% CI 0.34 to 0.80).

As only two studies were included in this meta-analysis, we did not construct a funnel plot or perform sensitivity analyses around quality.

Disease progression

Peters 2000 reported the Cox HR comparing disease progression in the radiotherapy group with that in the radiotherapy plus chemotherapy group to be 2.01 (P = 0.003). We estimated the log(HR) comparing disease progression in the radiotherapy plus chemotherapy group with that in the radiotherapy group and its variance using two of Parmar's methods: see Table 7. In the primary meta-analysis, we used the values estimated from the Kaplan-Meier plots, i.e. a HR of 0.48 (95% CI 0.27 to 0.84). For Protocol CE3005, we estimated the HR comparing the risk of disease recurrence in the radiotherapy plus chemotherapy group with that in the radiotherapy group using Cox regression, both unadjusted and adjusted for the age of the participants: see Table 7. In the primary meta-analysis, we used the unadjusted value, i.e. a HR of 0.46 (95% CI 0.21 to 0.99).

Meta-analysis of these two studies found that women who received radiotherapy plus chemotherapy had a significantly lower risk of disease progression than women who received radiotherapy alone: the pooled HR was 0.47 (95% CI 0.30 to 0.74), with no heterogeneity between the trials (I^2 = 0%) - see Analysis 1.2; *moderate-quality evidence*. Sensitivity analyses, using the alternative Parmar estimates of HRs for the trials of Peters and age-adjusted estimates for the Protocol CE3005 trial, resulted in a similar estimate of the HR: 0.48 (95% CI 0.32 to 0.72).

Adverse events

In the study of Peters 2000, toxicity was only assessed in women who received the treatment to which they were randomised: thus 122 and 112 women were assessed for toxicity in the combination (chemotherapy plus radiotherapy) and radiotherapy-only arms, respectively. There were 27 episodes of grade 4 toxicity in 21 patients in the combination arm, most of which were haematological, and four episodes of grade 4 toxicity in four patients in the radiotherapy-only arm. There was one late death in a patient treated with radiotherapy alone that may have been treatment-related. The numbers of women in each arm who experienced grade 3 toxicities were not reported.

In the Protocol CE3005, there were 37 episodes of grade 3 toxicities in 15 women in the combination arm (23 of alopecia, 13 of nausea and vomiting and one of mild somnolence or agitation) and 13 episodes of grade 4 toxicities in eight women in the combination arm (10 of alopecia, two of nausea and vomiting and one of infection). No episodes of toxicity of grade 3 or higher were reported in the radiotherapy-only arm.

In the study of Sun 2015 there were seven episodes of grade 3 toxicities in 13 women in the radiotherapy arm (most of which were haematological, one of diarrhoea, one nausea/vomiting, one genitourinary), and no grade 4 toxicity. There were 13 grade 3 toxicities episodes in 15 women in the chemoradiotherapy arm (mostly haematological) and seven episodes of grade 4 toxicities (five of neutropenia, one of thrombocytopenia, and one of diar-

rhoea). There were nine grade 3 toxicities episodes in five women in the chemoradiotherapy plus consolidation chemotherapy arm (most of which were haematological) and three episodes of grade 4 toxicities (all haematological), five of neutropenia, one of thrombocytopenia, and one of diarrhoea).

The pooled risk ratio (RR) comparing grade 4 toxicities in the combination and radiotherapy arms was 6.26 (95% CI 2.50 to 15.67) (three studies, 321 women, with no heterogeneity between the trials (I^2 = 0%), indicating a significantly higher risk of a severe adverse event among women receiving chemotherapy plus radiotherapy than among those receiving radiotherapy alone - see Analysis 1.3; *moderate-quality evidence*.

Adjuvant chemotherapy followed by radiotherapy versus adjuvant radiotherapy (comparison 2)

Disease recurrence

From the Kaplan-Meier plots presented by Tattersall 1992, we estimated the HR comparing the risk of disease recurrence in the chemotherapy followed by radiotherapy group with that in the radiotherapy group to be 1.34 (95% CI 0.24 to 7.66), indicating no significant difference between the treatment groups - see Analysis 2.1; *low-quality evidence*.

Long-term toxicities and quality of life

None of the included studies (for comparison 1 and 2) reported data on long-term toxicities or quality of life (QoL).

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Chemotherapy followed by radiotherapy compared with **radiotherapy for early stage cervical cancer**

Patient or population: patients with early stage cervical cancer
Settings: inpatient or outpatient
Intervention: chemotherapy followed by radiotherapy
Comparison: radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiotherapy	Chemotherapy followed by radiotherapy			
Disease progression Follow-up: median 30 months	**297 per 1000**	**376 per 1000** (81 to 933)	**HR 1.34** (0.24 to 7.66)	71 (1 study)	⊕⊕◯◯ **low**[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** Hazard ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Imprecision in point estimate for Tattersall 1992, indicated by large CI due to low number of women with disease progression. This uncertainty means we are unsure whether to use radiotherapy alone or sequentially in combination with chemotherapy.

DISCUSSION

Summary of main results

We found four randomised controlled trials (RCTs) of the following comparisons: adjuvant chemotherapy plus radiotherapy versus adjuvant radiotherapy (three trials enrolling 364 women of whom 321 (88%) were assessed) and adjuvant chemotherapy followed by radiotherapy versus adjuvant radiotherapy (one trial assessing 71 women). All included trials used chemotherapy regimens consisting of cisplatin alone or in combination with other agents and all included women who had undergone surgery. No trials compared adjuvant chemotherapy after surgery with no adjuvant chemotherapy.

Heterogeneous evidence from two small trials showed that the addition of chemotherapy to the radiotherapy regimen reduced the risk of death by between 13% and 64% and reduced the risk of disease progression by between 26% and 70% (Summary of findings for the main comparison). This corresponds to an absolute benefit in overall survival (OS) of 12% and in progression-free survival (PFS) of 16%.

Overall, the risk of severe adverse events was significantly higher among women who received radiotherapy and chemotherapy than among those who received radiotherapy alone.

The trial comparing adjuvant chemotherapy followed by radiotherapy versus radiotherapy alone (Tattersall 1992) found little difference in outcomes between the two treatment groups (Summary of findings 2); it should be noted that in this trial chemotherapy was given sequentially and not in combination with radiotherapy.

Overall completeness and applicability of evidence

One important observation is that the studies analysed in this systematic review included women with bulkier disease (stage IB2 and IIA). Nowadays, it is widely accepted that these women should not be treated primarily with surgery as concurrent chemoradiation improves OS and PFS of women with locally advanced cervical cancer (CCCMAC 2010; Green 2005). It is possible that the exclusion of women with bulky early lesions from the trials could alter these results.

Chemotherapy toxicity may delay radiotherapy, which may be harmful, since local disease control has been shown to fall by up to 1% per day if treatment is prolonged beyond seven weeks (Perez 1995). We were unable to analyse late toxicity as this was not reported by the included trials. While acute side effects are generally of short duration and resolve with medical management (Morris 1999), the late complications of radiotherapy can lead to damage which can be difficult to reverse, and may permanently impair quality of life (QoL). As data on late morbidity are sparse, there is insufficient evidence to say whether it increases with combined therapy (CCCMAC 2010; Green 2005).

We were unable to obtain data about QoL. Increasing interest in the systematic assessment of QoL in cancer patients using standardised, self-administered instruments has emerged over the past two decades, and has become an important focus in the evaluation of the benefit of newer therapies (Ganz 1994; Sloan 2002).

We found no trials comparing platinum-based chemotherapy with no platinum-based chemotherapy after surgery, or after primary radiotherapy, for early cervical cancer. Such trials would not be ethical in high-risk patients as, even although adjuvant radiotherapy has not been shown to improve survival in these women (Rogers 2012), chemoradiation has been shown to improve survival compared with radiotherapy in locally advanced disease (CCCMAC 2010). Ongoing studies in this field, comparing chemoradiation with primary radiotherapy for early cervical cancer without high-risk factors (Hong 2013), and comparing chemoradiation with radiotherapy after surgery in women with intermediate- and high-risk factors (GOG 0263; NCT 00806117), should further elucidate the role of platinum-based chemotherapy in this disease.

Quality of the evidence

It is unclear whether the PFS reported by Peters 2000 is the same as the disease-free survival (DFS) reported by Curtin 1996 and Tattersall 1992 and disease recurrence reported by Protocol CE3005 (Altman 1995). It should be noted that neither trial comparing radiotherapy plus chemotherapy with radiotherapy alone reported allocation concealment, which could have introduced bias. None of the included trials reported blinding of outcome assessors, which could have introduced bias in the assessment of disease progression; hence the meta-analysis of deaths is likely to have greater validity than that of disease progression. Inadequate concealment of allocation and lack of blinding are often associated with an exaggeration of the effects of treatment (Moher 1998; Schulz 1995). None of the trials provided information about QoL.

The trials of Peters 2000 and Protocol CE3005 provide consistent evidence about overall and PFS, however, we downgraded this evidence due to the small size of the trials and the limited period of follow-up. Further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates. In particular, the trial of Tattersall 1992 may have yielded an inconclusive result because it was so small that it did not have adequate statistical power. It is possible that the limited number of patients enrolled in these studies could be due to the low incidence of cervical cancer in the countries (Australia, UK, USA) in which these trials were conducted. In Australia (SACR 2003), the incidence of cervical cancer is declining. Only 43 new cases of invasive cervical cancer were diagnosed in 2001. The incidence of cervical cancer was reduced by 38% between the years of 1997 to 1999, in comparison with the period of 1977 to1981 (SACR 2001). In addition, the incidence in 2001 showed a 25%

reduction when compared with the incidence seen in 1998 to 2000. This downward trend is attributed mostly to the screening and detection of precursor lesions, and their early treatment. The same has occurred in the USA, where the incidence of cervical cancer declined from 13 cases/100,000 women per year in 1975 to 1979 to eight cases/100,000 women in the year 2000 (NCI 2004). In developing countries, on the other hand, the numbers are markedly different, with incidences of cervix cancer as high as 58 cases/100,000 women per year and 31 cases/100,000 women per year in Bolivia and Brazil, respectively (PAHO 2003). Therefore, large multicentre RCTs should include centres in developing countries, where there is a higher prevalence of this disease.

Potential biases in the review process

A comprehensive search was performed, including searches of conference abstracts and clinical trial registers for unpublished results; and all studies were sifted and data extracted by at least two review authors independently for the first version of this review. We restricted the included studies to RCTs as they provide the best evidence available. Hence, we have attempted to reduce bias in the review process.

The greatest potential bias in this review was that the report of Peters 2000 was based on an interim analysis of the data which rejected the null hypothesis of no benefit of chemotherapy and so may over-estimate the benefit of the combination of radiotherapy and chemotherapy. We know of no other potential biases in the review process.

Agreements and disagreements with other studies or reviews

Our findings regarding both the benefits and harms of chemotherapy are consistent with those of other reviews. Similar results were found in a systematic review of concurrent chemoradiation for locally advanced cancer of the uterine cervix (stage IB to IVA), giving an absolute benefit of 10% in OS and of 13% in PFS (Green 2005). In the meta-analysis of Green 2005, acute toxicity, predominantly haematological and gastro-intestinal, was increased in the combined arms (concomitant chemoradiation) of all trials evaluating locally advanced cervical cancer. The CCCMAC 2010 review of individual patient data found an absolute OS benefit of chemoradiation versus radiotherapy of 6% ($P < 0.001$) in locally advanced cervical cancer. Furthermore, they found that the earlier stage lesions may be associated with a greater benefit (10% for stage IA to IIA).

AUTHORS' CONCLUSIONS

Implications for practice

Women with operable early stage cervical cancer (IA2 to IIA) may benefit from the addition of cisplatin-based chemotherapy to adjuvant radiotherapy. However, since subgroup analyses according to stage and size were not possible, it is not clear that the survival benefits apply equally to all early stage lesions. Severe acute toxicities are more likely to occur with chemoradiation than with radiotherapy alone. There is insufficient evidence on late toxicity.

Implications for research

There are very few trials in this area due to difficulties in accrual. We identified three ongoing trials: one trial comparing primary radiotherapy with primary chemoradiation in stage IB to IIB cervical cancer with no high-risk factors (Hong 2013) and two multicentre trials comparing adjuvant chemoradiation with adjuvant radiotherapy in stages I to IIA with intermediate- and high-risk factors (GOG 0263; NCT 00806117). In addition to these ongoing trials, RCTs comparing adjuvant platinum-based chemotherapy with adjuvant radiotherapy and/or chemoradiation for early invasive cervical cancer would be helpful to our understanding of the treatment options for this condition. Such trials should be stratified by FIGO stage and should include evaluation of QoL and toxicity. Since cervical cancer is much more prevalent in developing countries, researchers should collaborate with centres in these regions.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Peters 2000

Methods	RCT
Participants	Country: USA Enrolled 268 patients, stage IA2, IB or IIA Underwent radical hysterectomy and pelvic lymphadenectomy. Ineligible 15 Assessed 243 (91%)
Interventions	Chemotherapy plus radiotherapy versus radiotherapy Arm 1: chemotherapy began on day 1 of radiotherapy and consisted of cisplatin 70 mg/m^2 by 2-hour intravenous infusion given on day 1 and 5-FU 1000 mg/m^2 per day given as a 96-hour continuous infusion on days 1 to 4. The second cycle of chemotherapy began on day 22, and the third and fourth cycles of chemotherapy were scheduled after completion of radiotherapy, to begin on days 43 and 64. Arm 2: consisted of 1.7 Gy per day on days 1 to 5 each week, for a total of 29 fractions (49.3 Gy); pelvic radiotherapy was given to a standard four-field box. Patients with positive high common iliac lymph nodes also received treatment to a para-aortic field with a dose of 1.5 Gy per day on days 1 to 5 of each week, for a total of 30 fractions. The radiation source of treatment was 4MeV or more. Brachytherapy was not permitted
Outcomes	Overall survival Progression-free survival Grade 3/4 toxicity
Notes	Statistics on survival: Cox HR and P value. Kaplan-Meier survival plots; minimum follow-up estimated from dates of accrual and date of interim analysis. No. of deaths and disease recurrences by treatment arm. The estimated 4-year survival was 81% for chemotherapy plus radiotherapy and 71% for radiotherapy only. The estimated 4-year progression-free survival for patients receiving chemotherapy plus radiotherapy was 80%, versus 63% for patients receiving radiotherapy alone. Median follow-up: 42 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported, "Patients were randomised to either pelvic radiotherapy or pelvic radiotherapy with four cycles of chemotherapy"
Allocation concealment (selection bias)	Unclear risk	Not reported.

Peters 2000 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For all survival outcomes: % analysed: 243/243 (100%) For toxicity: % analysed: 234/243 (96%) Chemotherapy + radiotherapy group: 122/127 (96%) Radiotherapy group: 112/116 (97%) "122 patients assessable for toxicity in the chemotherapy+ radiotherapy arm ... 112 patients randomised to RT alone and assessable for toxicity"
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	High risk	Based on an interim analysis of the data which rejected the null hypothesis of no benefit of chemotherapy

Protocol CE3005

Methods	RCT
Participants	Country: UK Enrolled 57 patients, stage IB or IIA Underwent primary surgery Assessed 54 (95%)
Interventions	Arm A: External beam pelvic radiotherapy (EBRT). Arm B: Adjuvant chemotherapy with bleomycin plus ifosfamide plus cisplatin plus external beam radiotherapy
Outcomes	Survival, recurrence and toxicity.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.

Protocol CE3005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	For all outcomes: % analysed: 54/57 (95%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to permit judgement.

Sun 2015

Methods	RCT
Participants	Country: China Enrolled 39 patients, stage IA2, IB or IIA Underwent radical hysterectomy and pelvic lymphadenectomy with or without para-aortic lymphadenectomy via laparotomy or laparoscopy Assessed 33 (84%)
Interventions	Radiotherapy versus radiotherapy plus chemoradiotherapy versus chemoradiotherapy plus consolidation chemotherapy Arm 1 (radiotherapy): 3D-CRT pelvic radiation, 95%CTV DT 45Gy/25f. Radiation field includes tumour bed and regional lymph nodes area. Upper border was considered as branching of abdominal aorta; lower border was considered as the inferior margin of obturator foramen. The radiation fields go down along the iliac vessels (including regions of 7 mm out of the iliac vessels) and include the tumour bed region. Arm 2 (chemoradiotherapy): radiotherapy as described for Arm 1 plus topotecan 0.75 mg/m² intravenously during 30 minutes on the days 1, 2 and 3 and cisplatin 25 mg/m2² intravenously for days 1,2 and 3. Chemotherapy will be carry out in the 2nd and 6th week of radiation therapy Arm 3 (chemoradiotherapy plus consolidation chemotherapy): radiotherapy as described for Arm 1 plus topotecan 0.75 mg/m² intravenously during 30 minutes on the days 1, 2 and 3 and cisplatin 25 mg/m2² intravenously for days 1,2 and 3. Chemotherapy will be carry out in the 2nd and 6th week of radiation therapy. The consolidation chemotherapy regimen was delivered in the 4th and 8th week after radiation therapy and consisted of the same regimen already described
Outcomes	Toxicity.
Notes	Closed ahead of schedule with median follow-up of 16 months because of severe haematologic toxicity

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.

Sun 2015 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only reported toxicity outcomes, the median follow-up of 16 months did not permit conclusions about recurrence-free survival or overall survival
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Not reported

Tattersall 1992

Methods	RCT
Participants	Country: Australia 71 patients, stage IB or IIA Underwent primary surgery
Interventions	Radiotherapy alone versus chemotherapy followed by radiotherapy Arm 1: chemotherapy with cisplatin 50 mg/m^2, vinblastine 4 mg/m^2, and bleomycin 15 mg all given IV on day 1. Bleomycin 15 mg was given intramuscularly on days 8 and 15 and the cycle was repeated on day 22. The chemotherapy was given by a total of 3 cycles. Pelvic radiotherapy began during the eighth week after initiating chemotherapy. Arm 2: each institution entering patients on the trial had their protocol for pelvic radiotherapy, but the study did not describe it. Although there were variations in treatment between institutions, a total of 40 to 55 Gy was given to the whole pelvis over 4 to 5 weeks
Outcomes	Disease-free survival.
Notes	Statistics on survival. Kaplan-Meier survival plots; minimum follow-up estimated from dates of accrual and date of submission of manuscript Median follow-up 30 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It is unclear how patients were assigned to groups and if minimisation was used, "patients were stratified prior to randomisation according to the clinical stage, and according to the institution"

Tattersall 1992 (*Continued*)

Allocation concealment (selection bias)	Low risk	Concealment of allocation was satisfactory, "randomisation was accomplished by telephone to the trial centre"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	% analysed: 71/71 (100%).
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

HR: hazard ratio
IV: intravenous
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Argenta 2006	Not an RCT. Included 21 women with stage IB-IV.
Blohmer 2001	The chemotherapeutic regimen of the intervention group did not include cisplatin
Buxton 1990	Retrospective study.
Chatterjee 2013	RCT of 80 patients comparing adjuvant chemotherapy for stage IB to IIIB cervical carcinoma. The chemotherapy regimen of the intervention group consisted of cisplatin and 5-FU
Curtin 1996	Not an RCT.
Dimpfl 1996	Non-randomised clinical trial.
Frigerio 1994	Retrospective study.
Hansgen 2001	Review.
Hansgen 2002	Phase II study; included stage IIB patients in the analysis.
Harrand 2013	Retrospective study.

(*Continued*)

Ikeda 1994	Retrospective study.
Iwasaka 1998	Included stage IIB patients in the analysis.
Kato 1994	The chemotherapeutic regimen of the intervention group did not include cisplatin
Kemnitz 1991	The study included stage IIB patients in the analysis.
Killackey 1993	Retrospective study.
Kim 2007	Retrospective study. Included patients with stage IIB cervical cancer
Koh 2000	Review.
Lahousen 1990	Non-randomised study.
Lahousen 1999	The control arm had received only chemotherapy as adjuvant treatment; the chemotherapeutic regimen of the intervention group did not include cisplatin; the study included stage IIB patients in the analysis
Lai 1989	Non-randomised study.
Lai 1998	More than 70% of patients were lost after randomisation.
Lai 1999	Review.
Lee 2013	Phase II study.
Lin 1998	Retrospective study.
Lin 2000	Retrospective study.
Linghu 2003	Not an RCT. Study of neoadjuvant chemotherapy.
Liu 2014	RCT of 564 patients with stage IB1 to IIA2 cervical carcinoma with high-risk features comparing three groups: 1. Radiotherapy; 2. Radiotherapy with weekly cisplatin; 3. Paclitaxel and cisplatin every three weeks followed by radiochemotherapy with the same regimen. The authors did not report the number of patients allocated for each one of the three groups, doses of chemotherapy regimens, outcomes (DFS, OS or toxicity) for each group. No difference for DFS was found
Lu 2000	Review.
McCaffrey 2011	Phase II study.
Morris 1999	The study included stage IIB patients in the analysis.
Morton 1996	Review.

(*Continued*)

Mossa 2003	Retrospective study. Included patients with stage IIB cervical cancer
MRC CE04/EORTC55954	Study closed due to lack of accrual. Investigators did not reply our e-mails
Nakamura 2014	Retrospective study.
Ng 1995	Retrospective study.
Park 1997	Review.
Park 2001	Retrospective study.
Park 2012	Retrospective study
Pu 2013	RCT of 320 patients comparing two adjuvant chemotherapy regimens for stage IB to IIA cervical carcinoma. Included patients with high-risk features. Control group consisted of single-agent cisplatin and radiotherapy and the intervention group consisted of docetaxel, cisplatin and radiotherapy
Richter 1982	The chemotherapeutic regimen of the intervention group did not include cisplatin
Rogers 2012	A meta-analysis of adjuvant radiotherapy and chemoradiation therapy after surgery for early cervical cancer that found only two trials that did not adressed the subject of chemotherapy
Roth 1994	Review.
Rushdan 2004	Phase II study.
Russel 1995	Non-randomised study.
Ryu 2005	Retrospective study.
Schwarz 2011	Phase I-II study.
Sehouli 2012	An open-label RCT of 271 patients comparing two adjuvant chemotherapy regimens for stage IB to IIB cervical carcinoma. Included patients with high-risk features. Control group consisted of single-agent cisplatin and radiotherapy and the intervention group consisted of paclitaxel, carboplatin and radiotherapy
Shimizu 1995	Review.
Shu 2015	Phase I study of one cycle of cisplatin and paclitaxel before, two cycles concurrent with intensity-modulated radiotherapy (IMRT) and one cycle after IMRT as adjuvant treatment to stage IB-IIA cervical cancer with high-risk factors in women that underwent radical hysterectomy and pelvic lymphadenectomy
Sivanesaratnam 1987	Retrospective study.

(*Continued*)

Sivanesaratnam 1989	Retrospective study.
Sivanesaratnam 1998	Retrospective study.
Strauss 2002	Phase II study.
Wada 1995	Retrospective study.
Wang 2015	Phase II study.
Watanabe 2006	Phase I study.
Wen 2013	Retrospective study. Included patients with stage IIB cervical cancer
Wertheim 1985	Retrospective study.
Wolfson 2012	Description of an appropriateness criteria to adjuvant radiotherapy in stage I and II cervical carcinoma
Yamamoto 2004	The study included stage IIB patients in the analysis; the chemotherapeutic regimen of the intervention group did not include cisplatin
Yessaian 2004	Retrospective study.
Yoon 2014	Retrospective study. Included patients with advanced stage disease
Zanetta 1995	Non-randomised study.
Zhang 2012	Retrospective study. Included patients with stage IIB cervical cancer
Zola 2003	RCT that randomised 199 women after radical hysterectomy and pelvic lymphadenectomy to receive EBRT or platinum-based chemotherapy. After 3 years there was no difference in survival between the two treatment groups

DFS: disease-free survival
EBRT: External beam pelvic radiotherapy
OS: overall survival
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

GOG 0263

Trial name or title	GOG 0263 and NCT01101451 Radiation therapy with or without chemotherapy in patients with stage I or stage II cervical cancer who previously underwent surgery
Methods	Multicentre RCT.
Participants	Women with intermediate-risk factors stage I-IIA cervical cancer after treatment with radical hysterectomy
Interventions	Arm 1: external beam (EBRT) or intensity-modulated radiotherapy (IMRT) 5 days a week for 5.5 weeks Arm 2: weekly cisplatin plus radiotherapy as per arm 1
Outcomes	Primary: RFS Secondary: OS, adverse effects, toxicity and QoL
Starting date	April 2010
Contact information	Sang Y. Ryu, MD, Principal Investigator, Korea Cancer Center Hospital Wui-jin Koh, MD, Fred Hutchinson Cancer Research Center
Notes	

Hong 2013

Trial name or title	NCT00846508 Cisplatin-based chemoradiation versus radiotherapy for cervical cancer and with a clinically-defined good prognosis
Methods	Single-blind RCT.
Participants	208 women with stage IB - IIB cervical cancer who have no LN or systemic metastases
Interventions	Arm 1: Primary radiotherapy Arm 2: radiotherapy plus 6 x weekly cisplatin (40 mg/m^2)
Outcomes	Primary: survival and toxicity. Secondary: molecular markers associated with radiosensitivity and distant metastases
Starting date	February 2009; recruiting.
Contact information	Ji-Hong Hong, Department of Radiation Oncology, LIN KOU Chang Gung memorial Hospital, Taiwan
Notes	

NCT 00806117

Trial name or title	NCT 00806117 A multicentre trial of benefits of adding post-surgery chemotherapy for cervical cancer
Methods	Single-blind phase III multicentre RCT underway in Guangzhou Province, China
Participants	990 women with stage IB-IIA cervical cancer with risk factors for recurrence, and who have undergone radical surgery
Interventions	Radiotherapy, cisplatin and cisplatin plus paclitaxel. Three groups will be compared: radiotherapy versus chemoradiation (concurrent) versus chemoradiation (sequential)
Outcomes	Primary: distant metastasis-free survival; disease-free survival Secondary: OS
Starting date	February 2008; recruiting.
Contact information	Jihong Liu, Ph.D. tel: 86-20-8734-3102; Liujih@mail.sysu.edu.cn He Huang, Ph.D. tel: 86-20-8734-3104; huangh@sysucc.org.cn
Notes	

OS: overall survival
QoL: quality of life
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Radiotherapy plus chemotherapy versus radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes	2	297	HR (Random, 95% CI)	0.56 [0.36, 0.87]
2 Disease progression	2	297	HR (Random, 95% CI)	0.47 [0.30, 0.74]
3 Grade 4 toxicity	3	321	Risk Ratio (M-H, Random, 95% CI)	6.26 [2.50, 15.67]

Comparison 2. Chemotherapy followed by radiotherapy versus radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease progression	1		HR (Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Radiotherapy plus chemotherapy versus radiotherapy, Outcome 1 Death from all causes.

Review: Adjuvant platinum-based chemotherapy for early stage cervical cancer

Comparison: 1 Radiotherapy plus chemotherapy versus radiotherapy

Outcome: 1 Death from all causes

Study or subgroup	RT+CT N	RT N	log [HR] (SE)	HR IV,Random,95% CI	Weight	HR IV,Random,95% CI
Peters 2000	127	116	-0.5677 (0.2692)		68.9 %	0.57 [0.33, 0.96]
Protocol CE3005	26	28	-0.6016 (0.4005)		31.1 %	0.55 [0.25, 1.20]
Total (95% CI)	**153**	**144**			**100.0 %**	**0.56 [0.36, 0.87]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 2.59 (P = 0.0096)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Radiotherapy plus chemotherapy versus radiotherapy, Outcome 2 Disease progression.

Review: Adjuvant platinum-based chemotherapy for early stage cervical cancer

Comparison: 1 Radiotherapy plus chemotherapy versus radiotherapy

Outcome: 2 Disease progression

Study or subgroup	RT+CT N	RT alone N	log [HR] (SE)	HR IV,Random,95% CI	Weight	HR IV,Random,95% CI
Peters 2000	127	116	-0.7369 (0.2883)		65.5 %	0.48 [0.27, 0.84]
Protocol CE3005	26	28	-0.7844 (0.3975)		34.5 %	0.46 [0.21, 0.99]
Total (95% CI)	**153**	**144**			**100.0 %**	**0.47 [0.30, 0.74]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 3.23 (P = 0.0012)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Radiotherapy plus chemotherapy versus radiotherapy, Outcome 3 Grade 4 toxicity.

Review: Adjuvant platinum-based chemotherapy for early stage cervical cancer

Comparison: 1 Radiotherapy plus chemotherapy versus radiotherapy

Outcome: 3 Grade 4 toxicity

Study or subgroup	RT+ CT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Peters 2000	21/122	4/112		78.2 %	4.82 [1.71, 13.61]
Protocol CE3005	8/26	0/28		10.7 %	18.26 [1.11, 301.35]
Sun 2015	10/20	0/13		11.1 %	14.00 [0.89, 220.15]
Total (95% CI)	**168**	**153**		**100.0 %**	**6.26 [2.50, 15.67]**

Total events: 39 (RT+ CT), 4 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.20$, df = 2 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 3.92 (P = 0.000090)

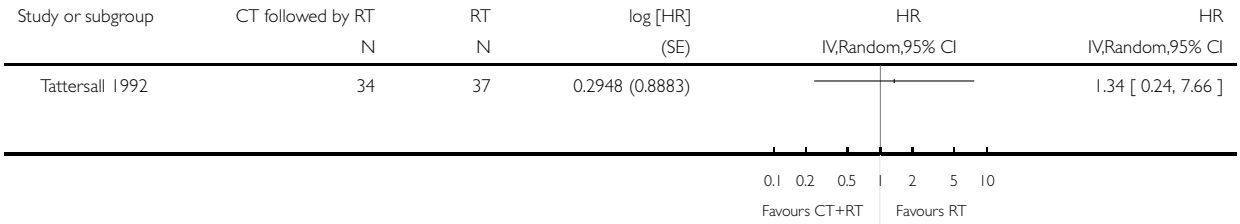
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Chemotherapy followed by radiotherapy versus radiotherapy, Outcome 1 Disease progression.

Review: Adjuvant platinum-based chemotherapy for early stage cervical cancer

Comparison: 2 Chemotherapy followed by radiotherapy versus radiotherapy

Outcome: 1 Disease progression



ADDITIONAL TABLES

Table 1. FIGO staging of cervical cancer

Stage 0	Carcinoma in situ, cervical intraepithelial neoplasia Grade III
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded). Ia Invasive carcinoma which can be diagnosed only by microscopy. All macroscopically visible lesions - even with superficial invasion - are allotted to Stage Ib carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0mm and a horizontal extension of not >7.0 mm. Depth of invasion should not be > 5.0mm taken from the base of the epithelium of the original tissue - superficial or glandular. The involvement of vascular spaces - venous or lymphatic - should not change the stage allotment. Ia1 Measured stromal invasion of not >3.0mm in depth and extension of not >7.0 mm. Ia2 Measured stromal invasion of >3.0mm and not > 5.0 mm with an extension of not >7.0 mm. Ib Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than Stage Ia. Ib1 Clinically visible lesions not > 4.0 cm. Ib2 Clinically visible lesions > 4.0 cm.
Stage II	Cervical carcinoma invades beyond uterus, but not to the pelvic wall or to the lower third of vagina. IIa No obvious parametrial involvement. IIb Obvious parametrial involvement.

Table 1. FIGO staging of cervical cancer (*Continued*)

Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to other cause. IIIa Tumor involves lower third of the vagina, with no extension to the pelvic wall. IIIb Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV. IVa Spread of the growth to adjacent organs. IVb Spread to distant organs.

FIGO nomenclature (Montreal, 1994) from Benedet 2003.

Table 2. Critical review form: randomised studies

No.	Question	Yes/No
1.	Was the assigned treatment adequately concealed prior to allocation?	
2.	Were the outcomes of patients who withdrew or were excluded after allocation described and included in an "intention-to-treat" analysis?	
3.	Were the withdrawals < 15% of the study population?	
4.	Were the inclusion and exclusion criteria for entry clearly defined?	
5.	Were the care programmes, other than the trial options, identical?	
6.	Were there any checks to ensure compliance to treatment?	
7.	Were the outcome assessors blind to assignment status?	
8.	Were the outcome measures used clearly defined?	
9.	Were the accuracy, precision, and observer variation of the outcome measure adequate?	
10.	Was the timing of the outcome measure appropriate?	
11.	Were the outcome measure clearly reported?	

Table 3. Were interventions defined adequately?

No.	Question	Answer
1.	Method of randomisation, in order of preference, as follows: (i) third party randomisation (pharmacy, computer or telephone) (ii) true randomisation (opaque numbered envelope or register)	
2.	Study design (i) duration of follow-up (ii) type of follow-up (iii) presence or absence of blinding to allocation	
3.	Size of study (i) number of women recruited (ii) number of women randomised (iii) number of women excluded (iv) number of women withdrawn and lost to follow-up (v) number of women analysed	
4.	Study setting (i) single-centre or multi-centre (ii) location (iii) timing and duration	
5.	Analysis (i) whether 'intention-to-treat' analysis was performed by authors	
6.	Criteria for adjuvant treatment (i) lymph node metastasis (ii) lymphovascular space invasion (iii) depth invasion more than 10 mm (iv) parametrial invasion (v) non-squamous histology (vi) positive surgical margins	

Table 4. Data extraction: characteristics of the study participants

No.	Question	Answer
1.	Baseline characteristics (i) stage of early cervix cancer by FIGO (ii) age (iii) previous treatments and surgery (iv) how were found participants (v) reason to exclusion participants	

Table 5. Data extraction: intervention

No.	Question	Answer
1.	Number of cycles and type of chemotherapy	
2.	Duration of radiotherapy	

Table 6. Data extraction: outcomes

No.	Question	Answer
1.	Overall survival at 5 years	
2.	Progression-free survival	
3.	Local recurrence (local, distant or local and distant)	
4.	Acute and late toxicity grades 3 and 4 (according to the ECOG Common Toxicity Criteria)	

Table 7. Radiotherapy and chemotherapy versus radiotherapy: hazard ratios in included trials

Outcome	Study	Comparison	ln(HR)	SE[ln(HR)]	HR (95% CI)	Notes
Death						
	Peters 2000	radiotherapy vs. radiotherapy+chemotherapy	0.67	NR	1.96	Cox HR, reported in paper
		radiotherapy+chemotherapy vs. radiotherapy	-0.57	0.27	0.57 (0.33 to 0.96)*	Estimated from Kaplan-Meier plots
		radiotherapy+chemotherapy vs. radiotherapy	-0.71	0.26	0.49 (0.43 to 0.56)	Estimated from Cox P value and total number of deaths
	Protocol CE3005	radiotherapy+chemotherapy vs. radiotherapy	-0.60	0.25	0.55 (0.25 to 1.20)*	Unadjusted HR from Cox regression
		radiotherapy+chemotherapy vs. radiotherapy	-0.53	0.27	0.59 (0.27 to 1.32)	HR from Cox regression, adjusted for age.

Table 7. Radiotherapy and chemotherapy versus radiotherapy: hazard ratios in included trials (*Continued*)

Disease progression	Peters 2000	radiotherapy vs. radiotherapy+chemotherap	0.70	NR	2.01	Cox HR, reported in paper
		radiotherapy+chemotherap vs. radiotherapy	-0.74	0.29	0.48 (0.27 to 0.84)	Estimated from Kaplan-Meier plots*
		radiotherapy+chemotherap vs. radiotherapy	-0.74	0.25		Estimated from Cox P value and total number of deaths
	Protocol CE3005	radiotherapy+chemotherap vs. radiotherapy	-0.78	0.20	0.46 (0.21 to 0.99)*	Unadjusted HR from Cox regression
		radiotherapy+chemotherap vs. radiotherapy	-0.76	0.21	0.47 (0.21 to 1.03)	HR from Cox regression, adjusted for age.

* = used in primary meta-analysis; NR = Not reported

APPENDICES

Appendix 1. Original search strategies 2009

MEDLINE

1. Randomized controlled trial.pt.
2. Controlled clinical trial.pt.
3. Randomizes controlled trials/
4. random allocation/
5. double -blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt.
9. exp clinical trials/
10. (clin$ adj25 trial$).ti,ab,sh.
11. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or masks$)).ti,ab,sh.
12. placebos/
13. placebo$.ti,ab,sh
14. random$.ti,ab,sh.
15. Research design/
16. or/8-15
17. (animal not human).sh

18. 16 not 17
19. comparative study.sh
20. exp evaluation studies
21. follow up studies.sh
22. prospective studies
23. (prospectiv$ adj5 (stud$ or trial$)).tw
24. or/19-23
25. 24 not 17
26. exp Cervix Neoplasms/
27. (cervi$ adj5 tumo?r).tw
28. (cervi$ adj5 neoplas$).tw
29. (cervi$ adj5 cancer$).tw
30. (cervi$ adj5 carcino$).tw
31.exp Cervix Diseases/
32. early cancer.tw.
33. or/26-32
34. exp chemotherapy/
35. exp radiotherapy/
36. chemotherapy.tw
37. radiotherapy.tw
38. or/ 34-37
39. 33 and 38
40. 18 and 24 and 33 and 39

Embase

1. Controlled study/or Randomized Controlled trial/
2. double blind procedure/
3. single blind procedure/
4. drug comparison/
5. placebo/
6. random$.tw,hw,mf.
7. placebo$.tw,hw,mf.
8. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw,hw,mf.
9. (comparativ$ adj5 trial$).tw,hw,mf.
10. (clinical adj5 trial$).tw,hw,mf.
11. follow up studies.tw,hw,mf.
12. prospective studies
13. (prospectiv$ adj5 (stud$ or trial$)).tw
14. or/ 1-14
15. animal/ not (human/ and animal/)
16. 14 not 15
17. exp Cervix Neoplasms/
18. (cervi$ adj5 tumo?r).tw
19. (cervi$ adj5 neoplas$).tw
20. (cervi$ adj5 cancer$).tw
21. (cervi$ adj5 carcino$).tw
22. exp Cervix Diseases/
23. early cancer.tw.
24. exp chemotherapy/
25. exp radiotherapy/
26. chemotherapy.tw
27. radiotherapy.tw
28. or/ 17-23
29. 24 or 26

30. 25 or 27
31. 16 and 28 and 29 and 30
32. radiation therapy.tw.
33. 30 or 33
34. 16 and 28 and 29 and 33

Appendix 2. Search strategies for updates

MEDLINE Ovid

1 Uterine Cervical Neoplasms/
2 (cervi* adj5 (cancer* or tumor* or tumour* or malignan* or carcinoma* or neoplas*)).mp.
3 1 or 2
4 Chemotherapy, Adjuvant/
5 exp Antineoplastic Agents/
6 Antineoplastic Combined Chemotherapy Protocols/
7 chemotherap*.mp.
8 drug therapy.fs.
9 4 or 5 or 6 or 7 or 8
10 exp Radiotherapy/
11 radiotherap*.mp.
12 radiation.mp.
13 irradiat*.mp.
14 radiotherapy.fs.
15 10 or 11 or 12 or 13 or 14
16 exp Surgical Procedures, Operative/
17 (surg* or hysterectom*).mp.
18 surgery.fs.
19 16 or 17 or 18
20 15 or 19
21 3 and 9 and 20
22 randomized controlled trial.pt.
23 controlled clinical trial.pt.
24 randomized.ab.
25 placebo.ab.
26 clinical trials as topic.sh.
27 randomly.ab.
28 trial.ti.
29 22 or 23 or 24 or 25 or 26 or 27 or 28
30 21 and 29

key:

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

Embase OVID

1 exp uterine cervix tumor/
2 (cervi* adj5 (cancer* or tumor* or tumour* or malignan* or carcinoma* or neoplas*)).mp.
3 1 or 2
4 exp chemotherapy/
5 dt.fs.
6 chemotherap*.mp.
7 4 or 5 or 6
8 exp radiotherapy/
9 radiotherap*.mp.

10 radiation.mp.
11 irradiat*.mp.
12 rt.fs.
13 8 or 9 or 10 or 11 or 12
14 exp surgery/
15 (surg* or hysterectom*).mp.
16 su.fs.
17 14 or 15 or 16
18 13 or 17
19 3 and 7 and 18
20 crossover procedure/
21 double-blind procedure/
22 randomized controlled trial/
23 single-blind procedure/
24 random*.mp.
25 factorial*.mp.
26 (crossover* or cross over* or cross-over*).mp.
27 placebo*.mp.
28 (double* adj blind*).mp.
29 (singl* adj blind*).mp.
30 assign*.mp.
31 allocat*.mp.
32 volunteer*.mp.
33 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 19 and 33

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

CENTRAL

#1 MeSH descriptor Uterine Cervical Neoplasms explode all trees
#2 cervi* near/5 (cancer* or tumor* or tumour* or malignan* or carcinoma* or neoplas*)
#3 (#1 OR #2)
#4 MeSH descriptor Chemotherapy, Adjuvant, this term only
#5 MeSH descriptor Antineoplastic Agents explode all trees
#6 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols, this term only
#7 chemotherap*
#8 Any MeSH descriptor with qualifier: DT
#9 (#4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Radiotherapy explode all trees
#11 radiotherap*
#12 radiation
#13 irradiat*
#14 Any MeSH descriptor with qualifier: RT
#15 (#10 OR #11 OR #12 OR #13 OR #14)
#16 MeSH descriptor Surgical Procedures, Operative explode all trees
#17 surg* or hysterectom*
#18 Any MeSH descriptor with qualifier: SU
#19 (#16 OR #17 OR #18)
#20 (#15 OR #19)
#21 (#3 AND #9 AND #20)

LILACS

(MH:"uterine cervical neoplasms" or (cervi$ and (cancer$ or tumor$ or tumour$ or malignan$ or neoplas$ or carcinoma$))) and (MH:"chemotherapy, adjuvant" or (adjuvant and chemotherap$))

WHAT'S NEW

Date	Event	Description
23 November 2016	Amended	Author contact details updated.

HISTORY

Date	Event	Description
19 September 2016	New search has been performed	Literature searches updated 8 September 2016.
19 September 2016	New citation required but conclusions have not changed	One small randomised controlled trial (Sun 2015) included with only toxicity outcomes. An additional 17 trials excluded. Conclusions remain unchanged
16 May 2012	Amended	Author listing amended
25 April 2012	New citation required but conclusions have not changed	Review updated: Twelve records screened: one study was added to 'excluded studies' (Zola 2003) and three studies added to 'ongoing studies' (Hong 2013; GOG 0263; NCT 00806117). Conclusions unchanged.
8 November 2011	New search has been performed	Search updated (MEDLINE, EMBASE, CENTRAL, LILACS and SR) rendering 1,197 records (1,031 records after de-duplication, plus three ongoing studies)

CONTRIBUTIONS OF AUTHORS

- Daniela Rosa: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods and search strategy.
- Frederico Falcetta: Took the lead in writing the updated version of the review.
- Lidia Medeiros: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods and search strategy.
- Maria Isabel Edelweiss: Took the lead in writing the protocol, developed background and initial objectives.
- Mary Bozzetti: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods and search strategy.
- Paula Pohlmann: Developed background, initial objectives, selection criteria, methods and search strategy.

- Airton Stein: Contributed to background section, selection criteria, initial objectives, methods and search strategy.

- Heather Dickinson (co-author of original review): Performed data extraction and all the statistical analyses, wrote the results section, revised the review for important intellectual content.

DECLARATIONS OF INTEREST

None to declare.

SOURCES OF SUPPORT

Internal sources

- CAPES, Brazil.

External sources

- Department of Health, UK.
UKNHS Cochrane Collaboration programme Grant Scheme CPG-506

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following were specified in the protocol but not implemented because of the small number of included studies:

- For continuous outcomes (e.g. quality of life (QoL) measures), we planned to pool the mean differences between the treatment arms at the end of follow-up using the mean difference method if all trials measured the outcome on the same scale, or using the standardised mean difference method otherwise. If standard deviations of final values were not available, we planned to use change scores (the difference between final value and baseline value) if their standard deviations were available.

- If there was evidence of substantial heterogeneity (e.g. $I^2 > 50\%$), we planned to investigate and report the possible reasons for this. If it was inappropriate to pool the data because of clinical or statistic heterogeneity then we planned to exclude outlying studies from the meta-analysis or conduct a systematic review without a meta-analysis.

- If sufficient trials were available, we planned to examine funnel plots corresponding to meta-analysis of the primary outcome in order to assess the potential for publication bias. If these plots suggested that treatment effects might not be sampled from a symmetric distribution, as assumed by the random-effects model, we planned to perform further meta-analyses using fixed-effect models.

The following 'Risk of bias' criteria were not specified in the protocol, but included in the review as they are now recommended for all Cochrane reviews.

Selective reporting of outcomes

We coded whether studies are free of selective outcome reporting as follows.
- Yes: e.g. if all outcomes that are specified above and also pre-specified in the study were reported in the study
- No
- Unclear

Other potential threats to validity

We assessed whether studies were apparently free of other problems that could have put them at a high risk of bias.

- Yes
- No
- Unclear

The other 'Risk of bias' items now follow RevMan5 format, but are equivalent to those specified in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Chemotherapy, Adjuvant [methods]; Cisplatin [administration & dosage]; Fluorouracil [administration & dosage]; Hysterectomy; Neoplasm Staging; Platinum Compounds [*therapeutic use]; Radiotherapy, Adjuvant; Randomized Controlled Trials as Topic; Survival Analysis; Uterine Cervical Neoplasms [*drug therapy; pathology; radiotherapy; surgery]

MeSH check words

Female; Humans

Cochrane Library

Cochrane Database of Systematic Reviews

Laparoscopy versus laparotomy for FIGO stage I ovarian cancer (Review)

Falcetta FS, Lawrie TA, Medeiros LRF, da Rosa MI, Edelweiss MI, Stein AT, Zelmanowicz A, Moraes AB, Zanini RR, Rosa DD

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[Intervention Review]

Laparoscopy versus laparotomy for FIGO stage I ovarian cancer

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ABSTRACT

Background

This is an updated version of the original review that was first published in the Cochrane Database of Systematic Reviews 2008, Issue 4. Laparoscopy has become an increasingly common approach to surgical staging of apparent early-stage ovarian tumours. This review was undertaken to assess the available evidence on the benefits and risks of laparoscopy compared with laparotomy for the management of International Federation of Gynaecology and Obstetrics (FIGO) stage I ovarian cancer.

Objectives

To evaluate the benefits and harms of laparoscopy in the surgical treatment of FIGO stage I ovarian cancer (stages Ia, Ib and Ic) when compared with laparotomy.

Search methods

For the original review, we searched the Cochrane Gynaecological Cancer Group Trials (CGCRG) Register, Cochrane Central Register of Controlled Trials (CENTRAL 2007, Issue 2), MEDLINE, Embase, LILACS, Biological Abstracts and CancerLit from 1 January 1990 to 30 November 2007. We also handsearched relevant journals, reference lists of identified studies and conference abstracts. For the first updated review, the search was extended to the CGCRG Specialised Register, CENTRAL, MEDLINE, Embase and LILACS to 6 December 2011. For this update we searched CENTRAL, MEDLINE, and Embase from November 2011 to September 2016.

Selection criteria

Randomised controlled trials (RCTs), quasi-RCTs and prospective cohort studies comparing laparoscopic staging with open surgery (laparotomy) in women with stage I ovarian cancer according to FIGO.

Data collection and analysis

There were no studies to include, therefore we tabulated data from non-randomised studies (NRSs) for discussion as well as important data from other meta-analyses.

Main results

We performed no meta-analyses.

Authors' conclusions

This review has found no good-quality evidence to help quantify the risks and benefits of laparoscopy for the management of early-stage ovarian cancer as routine clinical practice.

PLAIN LANGUAGE SUMMARY

Laparoscopy versus laparotomy (open surgery) for early-stage ovarian cancer

Background

Stage I ovarian cancer is diagnosed when the tumour is confined to one or both ovaries, without spread to lymph nodes or other parts of the body. Approximately 25% of women with ovarian cancer will be diagnosed at an early stage, thus the diagnosis often occurs due to an accidental finding. The intention of surgical staging is to establish a diagnosis, to assess the extent of the cancer and to remove as much tumour as possible. The latter is particularly important as women with ovarian cancer survive for longer when all visible tumour has been removed.

Review question

We conducted this review in an attempt to clarify whether laparoscopy (keyhole surgery) is as safe and effective as laparotomy (open surgery) for early-stage ovarian cancer. We intended to include only high-quality studies that compared the two types of surgery. We wanted to know whether women having laparoscopy survived as long as those having open surgery and whether there were differences in the time it took for the cancer to get worse. We were also interested to see how these different surgeries compared with regard to blood loss and other complications.

Main findings and quality of the evidence

We search the literature from 1990 to 2106. Unfortunately, we were unable to find any high-quality randomised trials comparing these approaches.

BACKGROUND

Description of the condition

This is the second updated version of the original review that was first published in the Cochrane Database of Systematic Reviews 2008, Issue 4.

Ovarian cancer is the eighth most common cancer in women worldwide (Jemel 2011). A woman's risk of developing ovarian cancer before the age of 75 ranges from 0.5% in developing countries to 1% in developed countries (GLOBOCAN 2008; Jemel 2011). Just over a third of women with ovarian cancer are alive five years after diagnosis (EUROCARE 2003), largely because most women with ovarian cancer are diagnosed when the cancer is already at an advanced stage (Jemal 2008). International Federation of Gynaecology and Obstetrics (FIGO) stage I ovarian cancer (limited to the ovaries) is diagnosed in approximately 20% to 33% of women with ovarian cancer in developed countries (Maringe 2012) and diagnosis is usually made by accidental discovery at sonography, computerised tomography (CT scanning) or during laparoscopy. The incidence of accidental discovery of ovarian cancer at laparoscopy has been estimated to range from 0.65% (Wenzl

1996) to 0.9% (Muzii 2005) of premenopausal women and 3% of postmenopausal women who undergo the procedure for an adnexal mass (Muzii 2005), but may be higher depending on the selection criteria applied.

Most cancers of the ovary are epithelial (90%) with histological subtypes including serous (35%), endometrioid (10%), borderline (16%), mucinous (8%), clear cell (4%), undifferentiated and mixed epithelial (Kosary 2007). In general, the prognosis of ovarian tumours depends on the FIGO stage, tumour grade, histological subtype, age and the volume of residual disease after surgery (Benedet 2000), however for stage I tumours the most important prognostic indicators are considered to be the degree of differentiation (grade) and the occurrence of tumour rupture (Vergote 2001).

The standard management of women with ovarian cancer is comprehensive surgical staging by laparotomy, a midline abdominal incision that allows exposure of the entire abdomen. Comprehensive surgical staging includes a total hysterectomy, bilateral salpingo-oophorectomy, removal of all obvious sites of tumour, aspiration of cytological washings or ascites, omentectomy, retroperitoneal (pelvic and para-aortic) lymph node dissection or sampling and biopsy of all suspicious-looking areas including mesentery, liver and diaphragm (Benedet 2000; Schorge 2012). Systematic retroperitoneal lymph node dissection (RLND) may improve survival in stage I ovarian cancer by detecting microscopic disease (Chan 2007), and is considered a standard procedure in some centres (Schorge 2012), however the UK National Institute for Clinical Excellence (NICE) guidelines currently do not recommend RLND in stage I disease (NICE 2011).

A meta-analysis of four randomised controlled trials (RCTs) of adjuvant platinum-based chemotherapy, which included data from the International Collaborative Ovarian Neoplasm 1 (ICON1) trial (Trimbos 2003) and the Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial (Trimbos 2004), found that adjuvant chemotherapy significantly improved overall survival (OS) and progression-free survival (PFS) in women with early ovarian cancer (Winter-Roach 2012). However, it was considered not to be necessary in women with comprehensively staged, stage Ia or 1b grade 1 to 2 tumours, as subgroup analyses suggested that women who were optimally staged were unlikely to benefit from adjuvant chemotherapy. Hence, comprehensive surgical staging has an important impact on the subsequent management of women with early ovarian cancer, with adjuvant chemotherapy indicated when staging is considered to be inadequate (Elit 2004; Winter-Roach 2012).

Description of the intervention

The intention of surgical staging is to establish a diagnosis, to assess the extent of the disease and to remove as much gross tumour as possible (Schorge 2012). Surgical staging of ovarian cancer by laparoscopy is the same intra-abdominal procedure as that performed by laparotomy except that it involves two or more, much smaller, abdominal incisions, through which laparoscopic instruments are then inserted. Specimen retrieval bags are used to prevent spillage and possible seeding of cyst contents and to avoid contact with incision (port) sites. Cysts may be aspirated within the retrieval bag, or morcellated if solid, to facilitate extraction through the port sites (Ghezzi 2007). Larger specimens, like omentum, may be extracted through the vagina with the uterus after hysterectomy (Lee 2011; Park 2008a).

How the intervention might work

Several non-randomised studies (NRSs) in early ovarian cancer have reported that laparoscopic surgical staging is a safe and technically feasible procedure (Colomer 2008; Ghezzi 2009; Nezhat 2009; Park 2008b; Park 2010). The possible advantages of laparoscopy include smaller incisions, less blood loss, faster recovery, shorter hospital stay, fewer complications, less postoperative infection and a better visualisation of the tumour inside the abdomen as the laparoscopy image can be magnified (Gad 2011; Ghezzi 2007; Lee 2011). In addition, the shorter recovery period following laparoscopy means that chemotherapy can be commenced sooner compared with laparotomy (Ghezzi 2007; Nezhat 2009), potentially resulting in a favourable effect on survival.

However, laparoscopy has been associated with a higher rate of intraoperative cyst rupture for apparently benign (Muzii 2005) and borderline tumours (Fauvet 2005), which may result in upstaging of the unexpected ovarian cancer from stage Ia or 1b to Ic (Muzii 2005). It has been argued that some aspects of comprehensive surgical staging, particularly RLND, may be technically difficult to achieve via laparoscopy and, therefore, that laparoscopy should be restricted to women with pre-operative evidence of benign conditions only (Vergote 2004). Other disadvantages of laparoscopy may include longer operating times and the possibility of port-site metastases, although the risk of the latter in early disease is considered to be low (Schorge 2012). Furthermore, to facilitate laparoscopy, CO_2 is commonly used for pneumoperitoneum and has been shown to lower the peritoneal pH (Bergstrom 2008; Kuntz 2000), which may activate enzymes that increase tumour cell mitosis and growth factor production. In addition, mechanical damage to the mesothelium may occur with prolonged laparoscopic surgery, thereby increasing the risk of metastases in the abdominal cavity (Greene 1995; Volz 1999).

Why it is important to do this review

Laparoscopic surgical staging of stage I ovarian cancer remains controversial as it is unclear how the risks and benefits of this procedure compare with the conventional open approach by laparotomy. Both earlier versions of this systematic review, published

in 2008 and in 2013, found insufficient evidence to evaluate laparoscopy for the management of early ovarian cancer as routine clinical practice. We continue to update this review with the aim of clarifying and consolidating the available evidence regarding this alternative surgical approach.

OBJECTIVES

To evaluate the benefits and harms of laparoscopy in the surgical treatment of FIGO stage I ovarian cancer (stages Ia, Ib and Ic) when compared with laparotomy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs. We also considered prospective cohort studies where the results had been adjusted for the baseline case mix using multivariate analyses, and excluded those with historical (non-concurrent) controls.

Types of participants

Women with stage I ovarian cancer defined by FIGO as follows.

1. Stage Ia: unilateral tumours
2. Stage Ib: bilateral tumours
3. Stage Ic: identified tumour spillage, tumour capsular penetration, positive peritoneal cytology

Types of interventions

Surgical staging via laparoscopy (experimental group) versus laparotomy (control group) for stage I ovarian cancer

Types of outcome measures

Primary outcomes

- Overall survival (OS)
- Progression-free survival (PFS)

Secondary outcomes

- Operating time
- Intraoperative tumour rupture
- Pelvic and para-aortic lymph node yield
- Size of omental specimen
- Estimated blood loss and the need for blood transfusion
- Comprehensive staging achieved by the allocated procedure (conversion to laparotomy)
- Surgical complications (immediate and delayed) including: injuries to the bladder, ureter, blood vessels, nerves, small bowel and colon; febrile morbidity; intestinal obstruction; haematomas and infections
- Length of hospital stay
- Time to adjuvant chemotherapy
- Systemic complications
- Abdominal wall recurrence: laparoscopy (port sites) and laparotomy (midline incision)
- Quality of life

Search methods for identification of studies

Electronic searches

We conducted searches to identify all published and unpublished RCTs and NRSs that compared laparoscopy and laparotomy for stage I ovarian cancer. The search strategies identified studies in all languages and, when necessary, we translated non-English language papers so that they could be fully assessed for potential inclusion in the review.

For the original review, we searched the Cochrane Gynaecological Cancer Review Group (CGCRG) Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL 2007, Issue 2), MEDLINE (January 1990 to November 2007), Embase (1990 to November 2007), LILACS (1990 to November 2007), Biological Abstracts (1990 to November 2007) and CancerLit (1990 to November 2007).

For the first updated version, we extended these searches to 6 December 2011.

For this second updated version of the review we extended the search to 7 September 2016. Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 9), MEDLINE (November 2011 to August week 4 2016), Embase (2011 week 48 to 2016 week 36). See Appendix 1, Appendix 2, and Appendix 3 for search strategies.

Searching other resources

We handsearched the citation lists of relevant publications and included studies, and contacted experts in the field to identify further trials. For the original review we also handsearched the following conferences and publications: *Gynecologic Oncology*, *International*

Journal of Gynaecological Cancer, *British Journal of Cancer*, British Cancer Research Meeting, Annual Meetings of the International Gynaecologic Cancer Society, Annual Meetings of the American Society of Gynecologic Oncologists, Annual Meetings of the European Society of Medical Oncology (ESMO), and Annual Meetings of the American Society of Clinical Oncology (ASCO).

Data collection and analysis

Selection of studies

Two review authors sifted the searches and identified potentially eligible studies. All authors assessed the methodology of these potentially eligible studies according to the specific inclusion criteria. Review authors were not blind to the authors, institutions or journals of potentially relevant studies.

Data extraction and management

No studies fulfilled the inclusion criteria for the original review or both the updated versions. For future versions of this review, two review authors will independently extract data from included trials to a pre-designed data collection sheet that includes the following information.

- *Study methodology*: description of randomisation, blinding, number of study centres, study duration, length of follow-up and number of study withdrawals.
- *Participants*: number, mean age, mean risk score.
- *Intervention*: type of intervention, dose and schedule.
- *Outcomes:*
    - we will extract data to allow for intention-to-treat (ITT) analysis where possible;
    - for dichotomous outcomes (e.g. number of lymph nodes, complications or deaths), we will extract outcome rates to estimate a risk ratio (RR);
    - for continuous outcomes (e.g. quality of life (QoL) measures and duration of treatment), we will extract means and standard deviations (SD) to estimate a mean difference (MD);
    - for time-to-event outcomes (e.g. OS), we will extract the log of the hazard ratio (log(HR)) and its standard error (SE) from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its SE Parmar's methods (Parmar 1998).

Assessment of risk of bias in included studies

For future versions of this review, we will assess the risk of bias in included studies using Cochrane's 'Risk of bias' tool (Higgins 2011) and the following criteria:

- selection bias: random sequence generation and allocation concealment;
- performance bias: blinding of participants and personnel (patients and treatment providers);
- detection bias: blinding of outcome assessment;
- attrition bias: incomplete outcome data;
- reporting bias: selective reporting of outcomes;
- other possible sources of bias.

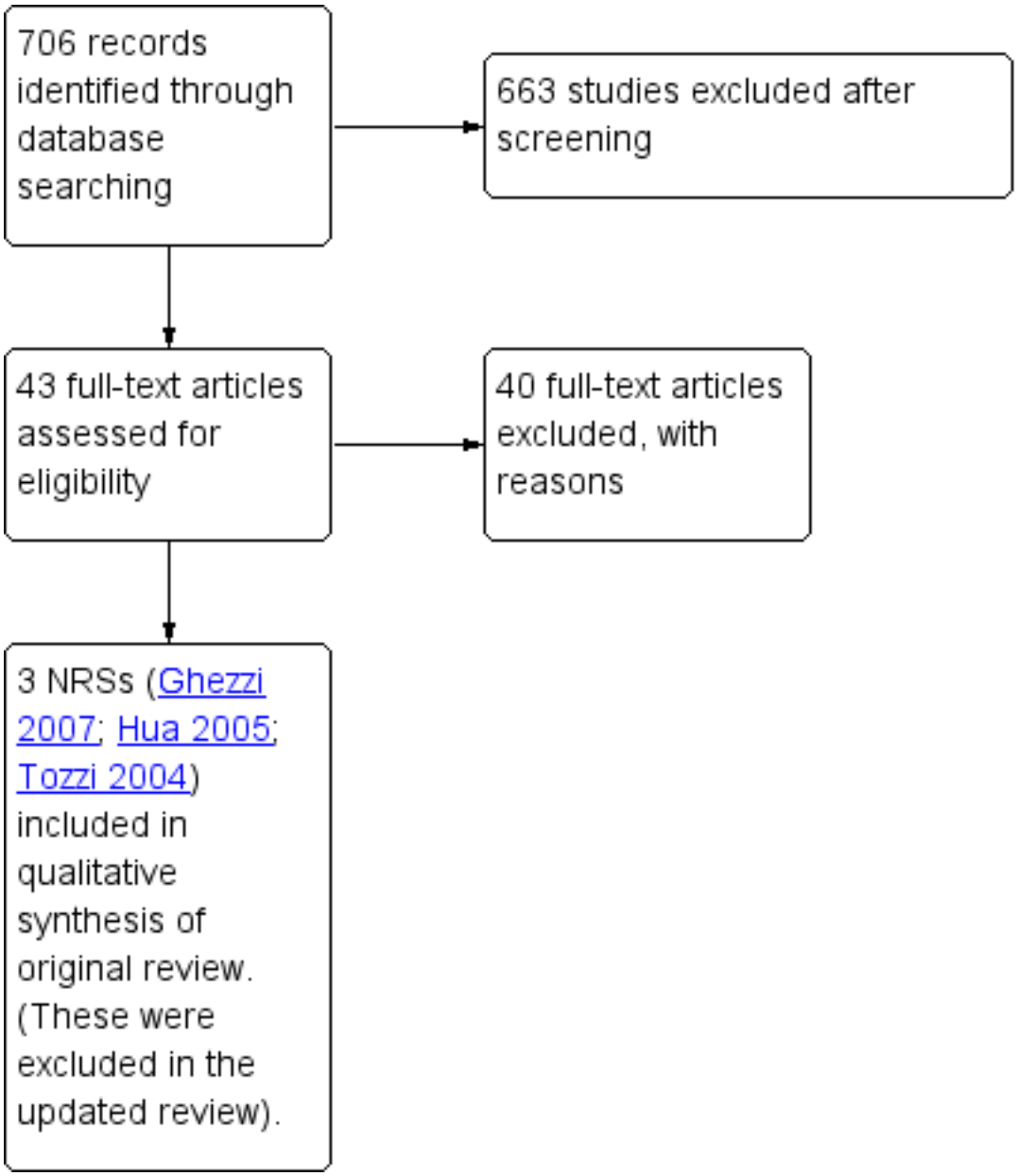
RESULTS

Description of studies

Results of the search

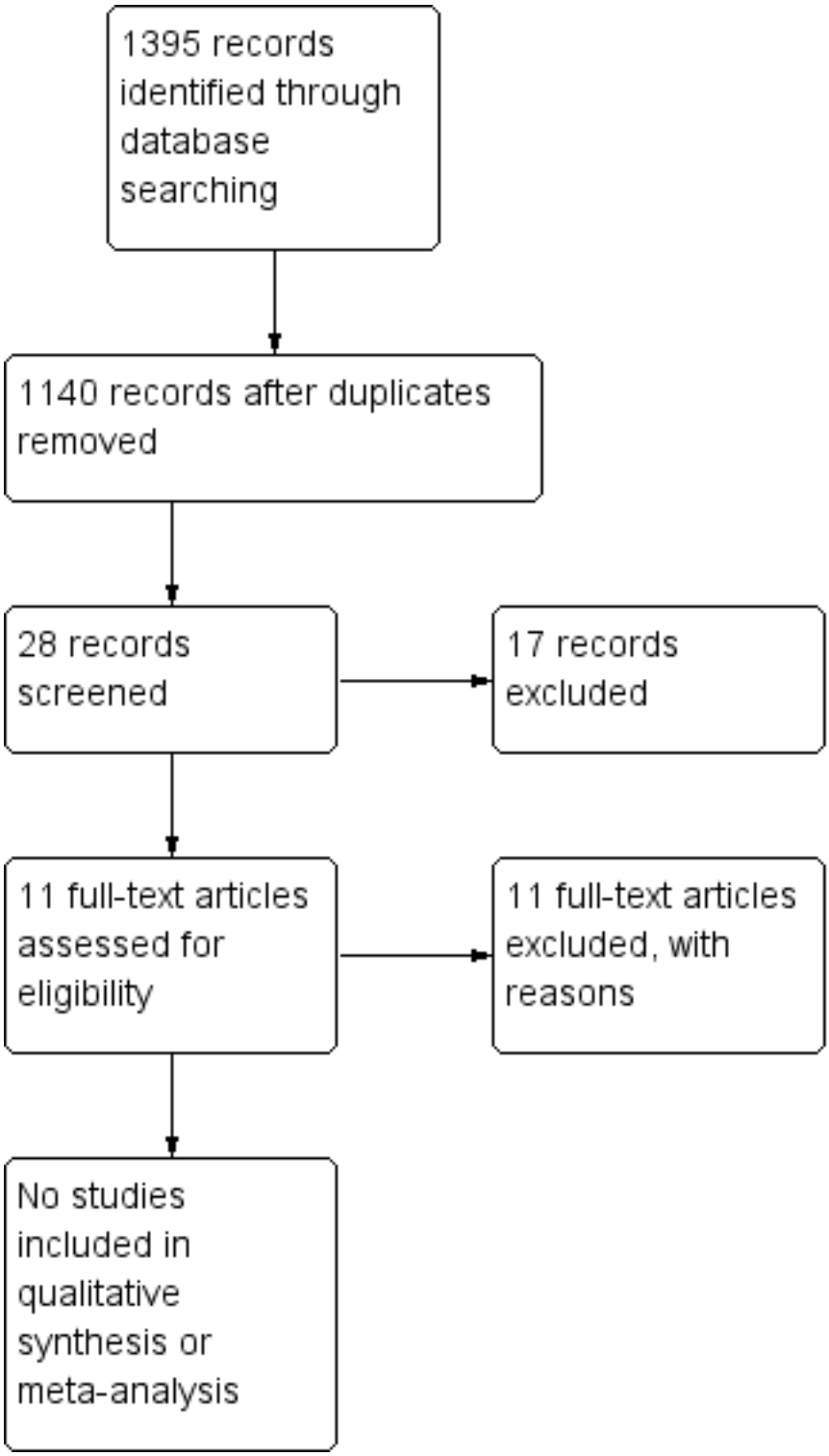
The original search identified 706 citations, of which we retrieved 43 for detailed examination. We subsequently excluded 40 of these records and three NRSs (two case-control studies and one case series) were included in the original review (Ghezzi 2007; Hua 2005; Tozzi 2004; Figure 1). For this updated review, we excluded these NRSs but tabled their findings with other similar studies that were identified by the updated search (see Differences between protocol and review).

Figure 1. Study flow diagram of original search 17 May 2007



From the first updated search we identified 1395 records (1140 after de-duplication), 28 of which we screened for possible relevance. Of these, 11 new studies were identified for classification (Chen 2010; Chi 2005; Colomer 2008; Ghezzi 2009; Lee 2011; Nezhat 2009; Park 2008a; Park 2008b; Park 2010; Park 2011a; Wu 2010; Figure 2). Park 2008b, Park 2010 and Park 2011a are extensions of the same series.

Figure 2. Study flow diagram of updated search 30 November 2011



From the second updated search we identified 1806 records (1530 after de-duplication), 32 of which we screened for possible relevance. Of these, 21 new studies were identified for classification (Bae 2014; Bogani 2014; Brockbank 2013; Ditto 2014; Ditto 2015; Gallotta 2016; Hong 2011; Kim 2014; Kobal 2013; Koo 2014; Leblanc 2014; Liu 2014; Lu 2014; Lu 2015; Minig 2015; Montanari 2013; Moon 2012; Park 2011b; Park 2013; Yoon 2011; Zhang 2015).

Included studies

There were no studies that met the inclusion criteria.

Excluded studies

Altogether we excluded 87 studies. None of these studies met the inclusion criteria in Types of studies. We have summarised the results of the relevant case series, case-control studies and retrospective cohort studies in three tables: Table 1, Table 2 and Table 3, respectively. None of the comparative NRSs reported adjusting results for baseline characteristics and we considered all of them to be at a high risk of selection bias and other bias (e.g. outcome assessment bias).

We included in the second update of this analysis 4 meta-analyses relevant for the subject in matter (Bogani 2014; Lu 2015; Park 2013; Zhang 2015) shown in Table 4.

Risk of bias in included studies

Not applicable.

Effects of interventions

There were no studies to include, therefore no meta-analyses could be performed. Table 2 and Table 3 present the available data from the case-control and retrospective studies to date as well as the relevant information from the four meta-analyses.

DISCUSSION

Stage I ovarian cancer is a rare disease and the use of laparoscopy for surgical staging is a relatively new field of clinical study, therefore data are scarce. UK guidelines on the management of ovarian cancer do not consider laparoscopy as an approach to the surgical staging of early ovarian cancer (NICE 2011); however, the German Gynaecological Oncology Group (AGO) have cautiously included the option of this procedure in their guidelines, for selected patients and only when performed by expert laparoscopic oncology surgeons, pending further evidence (Mettler 2009). The NCCN in its recent guidelines (NCCN 2016) suggest open laparotomy as the chosen surgical procedure for this pathology.

Summary of main results

We found no randomised controlled trials (RCTs) to include in this review and from which to compare the risks and benefits of laparoscopy with the conventional open approach. Existing non-randomised evidence comparing these interventions is extremely limited and is particularly at risk of selection bias. We considered including case-control non-randomised studies (NRSs) in meta-analyses, however sample sizes were small, none of these studies reported performing statistical adjustments for baseline case mix using multivariate analyses (e.g. age, final FIGO stage, grade, tumour size, co-morbidity and adjuvant chemotherapy), the duration of follow-up varied widely, and the primary outcomes of this review (overall survival (OS) and progression-free survival (PFS)) were not consistently reported.

Overall completeness and applicability of evidence

Survival

According to Surveillance Epidemiology and End Results (SEER; Kosary 2007), five-year OS rates for stage Ia, Ib and Ic ovarian adenocarcinoma (excluding borderline tumours) are about 94%, 91% and 80%, respectively. However, survival data relating to the surgical approach (laparoscopy versus laparotomy) in the existing literature are extremely limited: comparative studies of laparoscopy versus laparotomy for early ovarian cancer to date include three case-control studies (Table 2; Chi 2005; Ghezzi 2007; Hua 2005) and five retrospective cohort studies (Table 3; Lee 2011; Park 2008a; Park 2008b; Park 2010; Park 2011a), three of which are expansions of the same case series (Park 2008b; Park 2010; Park 2011a). Of these eight studies, six reported survival data but the length of follow-up varied widely or was not reported. Lee 2011 reported higher PFS rates in the laparoscopy group (100% for laparoscopy versus 91% for laparotomy) and did not report OS, however median follow-up was much shorter in the laparoscopy group compared with the laparotomy group (12 versus 25 months) and mean tumour size was significantly larger in the laparotomy group (P = 0.01). Park 2011a reported OS of 89% and 86% for laparoscopy and laparotomy, respectively and PFS rates of 78% in each group, but did not report the duration of follow-up in each group. Ghezzi 2007 reported 100% OS in both groups, however the median duration of follow-up differed substantially between

the groups (16 months in the laparoscopy group compared with 60 months in the laparotomy group).

Two studies conducted in women with early ovarian cancer (Park 2008a; Wu 2010) have reported unfavourable survival outcomes with laparoscopy. In Park 2008a (OS = 88% in the laparoscopy group versus 100% in the laparotomy group; Table 3), one woman who was diagnosed with FIGO stage Ia grade 1 ovarian cancer was shown to have severely disseminated disease at seven months and died of the disease 15 months later; the other woman had stage Ia grade 2 ovarian cancer at laparoscopy and developed recurrence at the vaginal stump. The extent of laparoscopy surgical staging was considered sufficient in the latter case, the tumour was not ruptured and retrieval bags were used. Wu 2010 reported data from a cohort of women with stage 1 ovarian cancer treated between 1984 and 2006 and found that those in whom the initial surgical approach was laparoscopic had significantly worse PFS and OS than those who underwent laparotomy (OS hazard ratio (HR) = 3.52), however, comprehensive staging was not the purpose of the laparoscopy in most of these women, therefore these results are difficult to interpret. In general, we consider the available survival data to be of a very low quality, hence it is not possible draw any conclusions regarding the relative effect of laparoscopic surgical staging compared with laparotomy on ovarian cancer survival from the existing literature.

Feasibility

Measures of the technical feasibility of laparoscopy have included pelvic and para-aortic lymph node yields, the size of the omental specimen, operating times and intra-operative tumour spillage. All case-control and cohort studies identified have reported statistically similar yields of retroperitoneal lymph nodes between their laparoscopy and laparotomy groups. Only two comparative studies (Chi 2005; Park 2008b) have reported mean omental specimen volumes, which were not statistically significantly different. With regard to operating times, some studies report significantly longer times with laparoscopy (Chi 2005; Ghezzi 2007; Hua 2005; Lee 2011), whilst others have reported significantly shorter times with laparoscopy (Park 2008b; Park 2010; Park 2011a). These differences probably reflect differences in surgeons' skills and laparoscopic techniques between investigator teams.

Rupture or spillage of ovarian tumours during surgery has been reported to occur more frequently with laparoscopy than laparotomy (Romagnolo 2006) and has been identified as a prognostic indicator of disease-free survival (Vergote 2001). To date, six out of eight NRSs have compared rates of tumour spillage between laparoscopy and laparotomy groups (Hua 2005; Lee 2011; Park 2008a; Park 2008b; Park 2010; Park 2011a). Five of these studies reported no significant difference between the two groups, and one study (Lee 2011) reported a statistically significantly higher rate of spillage in the laparotomy group (0% versus 14.9%; P = 0.037), which also had a significantly larger mean tumour size compared with the laparoscopy group. The definitions of spillage vary and the distinction between tumour rupture and puncture is not detailed in most studies (Ghezzi 2009). To properly assess these outcomes, technique and definitions need to be clearly defined in future studies. However, these limited data suggest that laparoscopy staging of early ovarian cancer is technically feasible when performed by experienced laparoscopic gynaecology oncology surgeons.

An inherent shortcoming of laparoscopy for surgical staging is the inability to palpate lymph nodes and other peritoneal surfaces (Colomer 2008; Park 2008a), however Chi 2010 argues that intra-operative direct visualisation and evaluation of nodes by palpation is inherently subjective. In a recent prospective study of 111 women with apparent early ovarian cancer who underwent comprehensive staging by laparotomy that included retroperitoneal lymph node dissection (RLND), retroperitoneal nodal metastases were present in 13.5% of the women (Ditto 2012), which suggests that without RLND many women would be under-staged. However, systematic RLND may be associated with significant morbidity and is not a routine part of staging for early ovarian cancer in the UK, where clinical guidelines currently recommend retroperitoneal lymph node assessment with sampling of suspicious nodes (NICE 2011). Therefore, where RLND is not routine, lymph node palpation may play a crucial role in the decision-making process with regard to sampling. Another technically difficult part of the surgical staging procedure is the examination of the diaphragmatic peritoneum behind the liver and spleen and the dome of the liver (Park 2008a); this may be more difficult with laparoscopy, although it has been argued that isolated metastases to these areas are rare (Ghezzi 2009).

Safety

Surgical staging for ovarian cancer is a radical procedure that may be associated with severe intra-operative vascular, nerve, lymphatic, bowel and urinary tract complications. Common postoperative complications include wound infection, ileus, febrile morbidity and lymphoceles (Ghezzi 2007; Lee 2011; Park 2008a; Park 2008b). Three comparative studies in early ovarian cancer have reported significantly fewer postoperative complications with laparoscopy compared with laparotomy (Hua 2005; Lee 2011; Park 2011a). The following complications have been reported in the laparoscopy participants of studies in early ovarian cancer: umbilical hernias (Lee 2011), retroperitoneal haematoma (Ghezzi 2007), vascular injury (Colomer 2008; Ghezzi 2007; Park 2008b), lymphoceles (Lee 2011; Nezhat 2009), obturator nerve damage (Hua 2005), bowel injury or obstruction (Nezhat 2009; Park 2008a) and ureter injury (Park 2008b). Estimated blood loss (EBL) in all case-control (Table 2) and comparative cohort studies (Table 3) has been statistically significantly less than in the laparoscopy groups compared with laparotomy groups, with the exception of one study (Ghezzi 2007). In these studies, rates of blood trans-

fusion in laparoscopy groups ranged from 0% to 15%, whereas transfusions were necessary in up to 30% (Park 2010) of women who underwent laparotomy.

There have been several reports of the occurrence of abdominal wall metastases following laparoscopy for ovarian cancer (Childers 1994; Gleeson 1993; Leminen 1999). However, in the studies of laparoscopy in stage I ovarian cancer that have reported this outcome, no port-site metastases had occurred by the time of reporting in Chi 2005 (20 women), Park 2008a (17 women), Park 2008b (19 women), Nezhat 2009 (36 women) and Lee 2011 (26 women). Port-site metastases may be technique-related and limited mostly to patients with advanced disease (Chi 2005; Nezhat 2009). In a study of laparoscopic cytoreductive surgery for advanced ovarian cancer and in which no port-site metastases occurred, the authors attributed their results to a surgical technique that employed endoscopic bags to retrieve intact specimens and a layered closure of the trocar site (Nezhat 2010). Lee 2011 and Chi 2005 have also reported employing this technique to prevent port-site metastases.

Other outcomes

Lee 2011 evaluated the relative cost of laparoscopy compared with open surgery in women with early ovarian cancer and found that laparoscopy resulted in higher costs due to the cost of disposable instrumentation and direct material/operating room costs, but the cost of hospital stay was higher in the laparotomy group because the stay was longer. Where bed costs are higher, this difference in cost might be eliminated, however the median lengths of hospital stay in the laparotomy groups in most of the studies reporting this outcome seem excessive with a range of up to 14.5 days (Table 2; Table 3). Literature on the quality of life for women undergoing laparoscopy compared with laparotomy is scant, however Lee 2011 reported significantly lower postoperative pain scores in the laparoscopy group.

Agreements and disagreements with other studies or reviews

A meta-analysis of eight RCTs comparing laparoscopic surgical staging with laparotomy for endometrial cancer has shown the laparoscopic approach to be safe, with statistically significantly fewer postoperative complications than laparotomy, and similar rates of intra-operative complications (Zullo 2012). It is possible that similar conclusions may, in time, be drawn about laparoscopy and laparotomy for stage I ovarian cancer, however the evidence for this is not currently in the literature.

AUTHORS' CONCLUSIONS

Implications for practice

Due to technological advancements in instrumentation and an increase in laparoscopic surgical expertise, the role of laparoscopy in gynaecological cancers is expanding, however there is still wide regional variation in the laparoscopic skills and competence of gynaecological-oncology surgeons. We did not find any good evidence to recommend laparoscopy for the routine management of women with stage I ovarian cancer.

Implications for research

Survival data for patients with gynaecological malignancies managed by laparoscopy are still lacking. A major barrier to conducting randomised controlled trials (RCTs) in early ovarian cancer is the anticipated difficulty in recruiting sufficient numbers of participants (Ghezzi 2009). Other difficulties include standardising the quality of the surgery and the skill of the surgeons. Subsequent results from such trials may only be applicable to expert laparoscopic oncology surgeons. However, we understand, from a personal communication, that the Korean Gynecologic Oncology Group (KGOG) is currently developing a protocol for a RCT comparing laparoscopy with laparotomy for early ovarian cancer. Two recently reported Korean cohort studies (Lee 2011; Park 2011a) recruited 325 women between them within the same six-year period (2004 to 2010), suggesting that a multicentre RCT is feasible. Participating institutions should be subgrouped according to whether retroperitoneal lymph node dissection or lymph node assessment with sampling is performed routinely. Outcomes of RCTs should include overall and progression-free survival, complications (intra-operative and postoperative), the use of adjuvant chemotherapy, patient satisfaction, quality of life and costs. It would be helpful if costs are reported separately for the preoperative, intra-operative and postoperative periods.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amara 1996	A case series of 11 women with stage Ia to IIIc ovarian cancer who underwent laparoscopy staging
Bae 2014	A retrospective cohort study of laparoscopy (minimally invasive surgical approach) in 89 women with early ovarian cancer versus 105 women who underwent open surgery. There was no difference in progression-free survival or overall survival
Berman 2003	Narrative review
Bogani 2014	Case series with historical controls followed by a systematic review and meta-analysis. The conclusion was that patients in the laparoscopy group had lower blood loss, shorter length of hospital stay, and shorter time gap between surgery and chemotherapy, although they had longer operative time (see Table 2 and Table 4)
Bristow 2000	Narrative review
Brockbank 2013	A case series of 35 women who underwent laparoscopic surgical staging for apparent early ovarian cancer
Canis 1994	Narrative review
Canis 1997	A case series of 10 cases of laparoscopy for low malignant potential tumour and 15 cases of cancer, but stage not described
Canis 2000	A series of laparoscopy for 28 cases of cancer and borderline tumour; stage not described
Chapron 1998	Narrative review
Chen 2010	A case series of 43 women who underwent laparoscopic surgical staging for apparent early ovarian cancer (see Table 1)
Chi 2005	A retrospective case-control study of 50 women who underwent laparoscopic or open surgical staging for apparent early ovarian cancer (see Table 2)
Childers 1995	A prospective case series of second-look laparoscopy to evaluate both intraperitoneal cavity and retroperitoneal lymph nodes and laparoscopic surgical staging. 14 women underwent laparoscopic staging of apparent early ovarian cancer; metastatic disease was discovered in 8 of these women (see Table 1).
Childers 1996	A series of 138 cases of laparoscopy for suspicious ovarian masses (not surgical staging). Malignancies were discovered in 19 women
Colomer 2008	A prospective case series of laparoscopic surgical staging of 20 women with apparent early ovarian cancer (18 EOCs and 2 dysgerminomas) (see Table 1)

(*Continued*)

Covens 2012	A systematic review of the surgical management of suspicious adnexal mass. Included patients with suspicious early stage disease (stage I-II) as well as studies about frozen section diagnosis
Darai 1998	A retrospective case series of 25 women with borderline ovarian tumours
de Poncheville 2001	Retrospective study of surgery without para-aortic lymphadenectomy in stage I ovarian cancer. Investigators advocate surgery without lymphadenectomy for women with early ovarian cancer
Ditto 2014	Case-control study comparing fertility sparing surgery open or laparoscopic (n = 18) with radical surgery (n = 18). The authors concluded that fertility-sparing surgery in patients submitted to a comprehensive surgical staging yielded results similar to radical surgery
Ditto 2015	Case-control study comparing laparoscopic (n = 37) with open surgery (n = 37) in patients with apparent early ovarian cancer (results in Table 2)
Dottino 1999	Retrospective case series of 94 laparoscopic lymphadenectomies for gynaecological malignancies, including 14 women with ovarian cancer
Gallotta 2016	Case-control study comparing laparoscopic (n = 60) with laparotomic surgery (n = 120) in patients with apparent early ovarian cancer (results in Table 2)
Ghezzi 2007	A case-control study of 15 women who underwent laparoscopic staging for early ovarian cancer versus 19 historical controls who had open surgery (see Table 2)
Ghezzi 2009	A case series of 26 women who underwent laparoscopic staging for early ovarian cancer (see Table 1)
Goff 2006	Narrative review
Hong 2011	A case series of 35 laparoscopic versus laparotomy (see Table 3) for second look operations for ovarian cancer (see Table 3)
Hua 2005	A small, prospective, case-control study of 10 women who underwent laparoscopic staging for early ovarian cancer versus 11 women who underwent laparotomy (see Table 2). No adjustments were made for baseline case mix.
Iglesias 2011	Narrative review
Kadar 1995	Included other cancers (endometrial, cervical, ovarian)
Kim 2014	Retrospective case series of 113 laparoscopic versus laparotomy. Mean operation time longer for the laparoscopy group (not statistically significant), however the laparoscopy group had less blood loss, shorter time to adjuvant chemotherapy, lower operative complications, and shorter hospital stay (see Table 1).
Klindermann 1995	A survey conducted on laparoscopy in Germany
Kobal 2013	Retrospective case series of 28 laparoscopic versus laparotomy

(*Continued*)

Koo 2012	A retrospective case series of 262 pregnant women who underwent laparotomy (n = 174) or laparoscopic surgery (88) for adnexal masses
Koo 2014	Retrospective case series of 77 laparoscopic versus laparotomy for early stage ovarian cancer (stage I to II) (see Table 3)
Leblanc 2004	Cohort with other types of cancer (fallopian tube carcinoma) and in patients that were inadequately staged at the time of initial surgery for invasive ovarian carcinoma
Leblanc 2006	Narrative review
Leblanc 2014	Retrospective case series of laparoscopic staging paraaortic lymph node dissection (PALND) by two routes (extraperitoneal and transperitoneal) for gynaecologic cancers compared with laparotomic PALND. The author concluded that laparoscopic PALND is safe and the preferred approach is extraperitoneal since it yielded more lymph nodes compared with the transperitoneal approach
Lee 2011	A retrospective cohort study of laparoscopy in 26 women with early ovarian cancer versus 87 women who underwent open surgery (see Table 3). No adjustments were made for baseline case mix. Women in the laparotomy group had significantly larger tumours and longer follow-up
Liu 2014	Retrospective case series of 75 patients that underwent laparoscopy (35 patients) or laparotomy (40 patients) surgery for early ovarian cancer (stage I - II)(see Table 3)
Lu 2014	Retrospective case series of 92 patients that underwent laparoscopy vs laparotomy surgery for early ovarian cancer (stage I to II)
Lu 2015	A systematic review and meta-analysis of the surgical management of early ovarian cancer. Included non-randomised studies with a total of 591 patients. The authors concluded that the laparoscopic approach is associated with less intraoperative blood loss, lower postoperative complication rates, shorter postoperative hospital stays, and lower postoperative recurrence rates. There were no significant differences mortality, operative time, and number of lymph node harvested
Lécuru 2004	Retrospective study of 105 women who underwent surgery for stage I ovarian cancer. 14 underwent laparoscopy only, 13 had a laparoscopy converted to laparotomy and 78 had a laparotomy. Comprehensive staging was less frequent in the laparoscopy group
Maiman 1991	Members and candidate members of the Society of Gynecologic Oncologists responded to a survey concerning the "laparoscopy management of ovarian neoplasm subsequently found be malignant"
Malik 1998	Unexpected ovarian tumours were discovered in 11/292 women who underwent laparoscopy to evaluate adnexal masses
Maneo 2004	Criteria for exclusion: 62 patients had fertility-sparing after surgery
Manolitsas 2001	Narrative review
Mehra 2004	A prospective case series of 32 women with ovarian and other gynaecological cancers who underwent laparoscopic retroperitoneal para-aortic lymphadenectomy

(*Continued*)

Meinhold-Heerlein 2014	Narrative review
Minig 2015	Case-control study comparing laparoscopic (n = 50) with open surgery (n = 58) in patients with apparent early ovarian cancer (results in Table 2)
Montanari 2013	Series of cases
Moon 2012	Series of cases (see Table 1)
Nakayama 2015	Retrospective study comparing laparoscopy versus laparotomy for the treatment stage I - IV granulosa cell tumours
Nezhat 1992	A case series
Nezhat 2009	A case series of 36 women with early ovarian cancer who underwent complete laparoscopic staging (see Table 1)
Nezhat 2010	A case series of women with advanced ovarian cancer who underwent complete laparoscopic staging
Palomba 2010	Long-term follow-up of a randomised controlled trial comparing ultra-conservative fertility sparing surgery (bilateral cystectomy) with oophorectomy plus contra-lateral cystectomy in patients with bilateral borderline ovarian tumours
Park 2008a	A retrospective cohort study of 17 versus 19 women with early ovarian cancer who underwent laparoscopic staging and laparotomy respectively (see Table 3). No adjustments were made for baseline case mix.
Park 2008b	A retrospective cohort study of 19 versus 33 women with early ovarian cancer who underwent laparoscopic staging and laparotomy respectively (see Table 3)
Park 2010	An expansion of the earlier study (Park 2008b; see Table 3)
Park 2011a	An expansion of Park 2008b and Park 2010 retrospective studies (see Table 3)
Park 2011b	The same report as Park 2011a
Park 2013	A systematic review and meta-analysis of retrospective and observational studies of laparotomy versus laparoscopy in early ovarian cancer. The authors concluded that the overall incidence of conversion from laparoscopy to laparotomy was 3.7% the overall rate of recurrence in studies with a median follow-up period of 19 months was 9.9%
Parker 1990	This study only included women with benign ovarian cysts
Poilblanc 2012	Narrative review
Pomel 1995	A series of women with stage I ovarian carcinoma who underwent a laparoscopic procedure to complete their staging
Querleu 2003	A retrospective study of laparoscopic restaging of 30 women with borderline ovarian tumours

(*Continued*)

Querleu 2006a	Narrative review
Querleu 2006b	Many types of tumours (cervical, vaginal, endometrial and ovarian carcinoma)
Reich 1990	A case report
Romagnolo 2006	A case series where laparoscopy was performed for suspected borderline ovarian tumours, and included fertility-sparing procedures
Rouzier 2005	Narrative review
Satoh 2015	Protocol description for fertility-sparing surgery
Solima 2011	A retrospective study designed to evaluate the learning curve of para-aortic lymphadenectomy by laparoscopy and laparotomy in the setting of endometrial and early ovarian cancer
Spirtos 2005	A case series of laparoscopy for all stages of ovarian cancer and other types of cancers
Tozzi 2004	A case series of laparoscopic staging for early ovarian cancer (see Table 1)
Tozzi 2005	Narrative review
Trillsch 2013	Retrospective case series of 105 patients that underwent laparoscopy (44 patients) or laparotomy surgery (61 patients) for borderline ovarian tumours
Tropé 2006	Narrative review
Vaisbuch 2005	Narrative review
Vergote 2003	Narrative review
Vinatier 1996	Narrative review
Vizza 2012	Abstract with narrative review
Volz 1997	Narrative review
Wenzl 1996	A questionnaire was sent to all 97 Departments of Gynaecology in Austria to determine the frequency of discovering a malignant ovarian mass when laparoscopy is used to manage an adnexal mass
Wu 2010	A retrospective cohort study of laparoscopy versus laparotomy, however surgical staging was not always the aim of the initial laparoscopy
Yoon 2011	A case series 38 ovarian cancer patients. Seven cases (18%) were converted to conventional laparotomy
Zhang 2015	A systematic review and meta-analysis of laparotomy versus laparoscopy in early ovarian cancer. Included non-randomised studies. The authors found that laparoscopic surgery was associated with lower rates of complications and shorter postoperative hospital stays and no difference in the rates of recurrence (see

(*Continued*)

	Table 4).

EOC = epithelial ovarian cancer

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Case series of comprehensive laparoscopic staging of early ovarian cancer (including fallopian tube cancer)

	No. of women	Mean pelvic nodes (n)	Mean para-aortic nodes (n)	Mean para-aortic nodes and pelvic nodes (n)	Median follow-up (months)	Recurrences (n)	PFS (%)	OS (%)
Querleu 1994	8	-	8.6	-	-	-	-	-
Pomel 1995	8	7.5	8.5	-	-	-	-	-
Childers 1995	14	-	-	-	-	-	-	-
Tozzi 2004	24	19.4	19.6	-	46	2	92	100
Leblanc 2004	42	14	20	-	54	3/34 [1]	91	98
Colomer 2008	20	18	11.3	-	24.7	1	95	100
Ghezzi 2009	26	24.5	9.8	-	26.7	1	96	96
Nezhat 2009	36	14.8	12.2	-	55.9[2]	3	92	100
Chen 2010	43	16.6	6.5	-	24.7	3	93	-
Moon 2012	24	-	-	37.2	22.3	0	-	-
Montanari 2013	19	17	14	-	30	3	84	100
Brockbank 2013	35	6	5.6	-	18	2	94	100
Yoon 2011	38	-	-	29.46	-	-	-	-

Abbreviations: PFS = progression-free survival; OS = overall survival; n = number

[1]Leblanc 2004 reported recurrences in confirmed stage I women only, i.e. excluding 8 women who were upstaged|

[2]Mean follow-up.

Table 2. Case-control studies of laparoscopic surgical staging versus open surgical staging of early ovarian cancer

Study name	Hua 2005			Chi 2005			Ghezzi 2007			Bogani 2014*			Ditto 2015			Gallotta 2016			Minig 2015		
Period	2002-2004			2000-2003			2003-2006			2003-2010			Not described			2007-2013			2006-2014		
Design	Prospective cohort			Retrospective case-control			Case-control (with historical controls 1997-2003)			Case-control (with historical controls 1990-2003)			Case-control (with historical controls)			Case-control (with historical controls 2000-2011)			Retrospective case-control		
Intervention	**LPS**	**LPT**	P value	**LPS**	**LPT**	P value	**LPS**	**LPT**	P value	**LPS**	**LPT**	P value	**LPS**	**LPT**	P value	**LPS**	**LPT**	P value	**LPS**	**LPT**	P value
Number of wom	10	11	-	20	30	-	15	19	-	35	32	-	37	37	-	60	120		50	58	-
Mean age	40	42	-	47.3	50.6	0.31	55	61	0.05	52	56	0.35	-	-	-	48	55	**0.001**	-	-	-
BMI (kg/m²)	-	-	-	24.6	25.4	0.64	23.8	25.8	0.19	24.1	22.6	0.56	-	-	-	-	-	-	-	-	-
Mean operating time (min)	298	182	**< 0.05**	321	276	**0.04**	377	272	**0.002**	335	230	**<0.001**	213	212	0.74	NS	NS	**0.01**	222	214	0.482
Mean blood loss (mL) (SD)	280	346	**< 0.05**	235	367	**0.003**	250	400	0.28	300	400	0.28	157	442	**<0.001**	NS	NS	**0.032**	229	684	**<0.0001**

Table 2. Case-control studies of laparoscopic surgical staging versus open surgical staging of early ovarian cancer (*Continued*)

Blood transfusion n (%)	-	-	-	-	-	-	1 (6.7)	2 (10.5)	1.0	1 (3)	7 (22)	**0.02**	-	-	-	-	-	-	3 (6)	20 (34)	**<0.0001**
Pelvic lymph nodes n	25[1]	27[1]	NS	12.3	14.7	NS	25.2	25.1	0.96	22	15	0.002	15.8[1]	27.7[1]	**0.04**	16[1]	18	0.464	16	15	0.472
Para-aortic nodes n	-	-	-	6.7	9.2	NS	6.5	7	0.78	10	6	0.08	-	-	-	-	-	-	10	13	0.217
Omental specimen (cm^3)	-	-	-	186	347	0.09	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intraoperative tumour spill n (%)	0	0	-	-	-	-	3 (20)	2 (10.5)	0.63	6 (17)	4 (12)	0.59	-	-	-	-	-	-	-	-	-
Postoperative complica-	2 (20%[2]	7 (72.7%)	**<0.01**	0 (0)	3 (10)	-	2 (13.3%)	8 (42.1%)	0.13	1 (3)	9 (28)	**0.005**	-	-	-	-	-	-	14 (28)	22 (38)	0.275

Table 2. Case-control studies of laparoscopic surgical staging versus open surgical staging of early ovarian cancer (*Continued*)

tions n (%)																					
Hospital stay (days	-	-	-	3.1	5.8	**< 0. 001**	3	7	**0. 001**	4	6	**0. 03**	3.3	17	**<0. 001**	3	7	**0. 001**	2. 42	5. 67	**<0. 0001**
Final diagnosis = stage I, n (%)	-	-	-	-	-	-	11 (73. 3)	13 (68. 4)	-	20 (57)	17 (53)	0. 74	-	-	-	-	-	-	-	-	-
Tumour upstaged n (%)	0	0	-	-	-	-	4 (26. 7)	6 (31. 6)	1.0	6 (17)	3 (9)	NS	-	-	-	-	-	-	12 (24)	8 (14)	0. 173
Conversion to LPT, n	-	-	-	0	NA	-	0	NA	-	0	-	NA	-	-	-	-	-	-	1 (2%)	NS	-
Adjuvant chemotherapy, n (%)	-	-	-	-	-	-	11 (73. 3)	13 (68. 4)	-	32	24	0.1	-	-	-	42 (70)	NS	NS	37 (74)	34 (58. 5)	0. 093
Time to	-	-	-	-	-	-	-	-	-	22	30	**<0.**	-	-	-	-	-	-	37	41	0.

Table 2. Case-control studies of laparoscopic surgical staging versus open surgical staging of early ovarian cancer (*Continued*)

adjuvant chemotherapy (days												**001**								318
Median follow-up in mont (rang	-	-	-	-	-	-	16 (4-34)	60 (32-108)	-	64 (37-106)	100 (61-287)	**<0.001**	60.8	125.8	NS	38 (24-48)	NS		26	37	**0.004**
Port-site/abdominal wour metastasis, n	-	-	-	0	-	-	-	-	-	0	0	NA	-	-	-	0	NS	-	-	-	-
Recurrence n (%)	-	-	-	-	-	-	0	4 (21)	-	4 (11)	9 (28)	0.12	-	-	-	5 (8.3)	16 (13.3)	0.651	6 (12)	7 (12)	0.785
OS, n (%)	-	-	-	-	-	-	15 (100)	19 (100)	-	NS	NS	0.26	-[3]	-[3]	P > 0.2	55 (92)	109 (91)	0.719	-	-	-

Abbreviations: LPS = laparoscopy; LPT, laparotomy; BMI = body mass index; PFS = progression-free survival; OS = overall survival; n = number; NA = not applicable; SD = standard deviation; NS = not specified

[1]Lymph nodes not specified as pelvic or para-aortic in origin

[2]Right obturator nerve damaged and repaired in one patient

[3]Stated as survival outcomes

[4] Favouring the laparoscopic group

Table 3. Retrospective cohort studies of laparoscopic surgical staging versus open surgery for early ovarian cancer

Study name	Park 2008a			Park 2008b			Park 2010**			Park 2011a			Lee 2011			Koo 2014			Liu 2014			Hong 2011		
Study period	2004-2008			2004-2007			2004-2008			2004-2010			2005-2010			2006-2012			2002-2010			2000-2005		
Intervention	LPS	LPT	P value	LPS	LPT	P value	LPS	LPT	P value	LPS	LPT	P value	LPS	LPT	P value	LPS	LPT	P value	LPS	LPT	P value	LPS	LPT	P value
Number of women	17	19	-	19	33	-	40	76	-	84	128	-	26	87	-	24	53	-	35	40	-	18	17	-
Mean age (years)	43.2	48.9	0.155	43.9	45.4	0.614	-	-	NS	-	-	NS	42	44.4	0.437	45.8	48.4	0.246	51.09	50.78	NS	49	48	0951
BMI (kg/m²)	22.8	24.2	0.247	23.2	22.7	0.578	-	-	NS	-	-	NS	21.9	23.3	0.185	22.9	23.7	0.353	-	-	-	22	24	0.164
Mean operating time (min	303.8	290.4	0.706	221	275	**0.012**	230	278	**0.001**	207	262	**< 0.001**	228	184	**0.016**	192.9	224.1	0.127	209.71	200.50	NS	121	139	0.295
Mean blood loss (mL	231	505	**0.001**	240	569	**0.005**	301	494	**0.004**	252	454	**< 0.001**	230	475	**< 0.001**	697.9	972.6	0.127	197.14	345	NS	100	109	0.812
Blood transfu-	0 (0)	2 (11)	-	1 (5)	10 (30)	**0.04**	6 (15)	23 (30)	0.071	6 (13)	36 (28)	**0.012**	0 (0)	20 (23)	**0.006**	5 (20.8)	15 (28.3)	0.489	2 (5)	5 (12)	-	0	2 (12)	0.303

Table 3. Retrospective cohort studies of laparoscopic surgical staging versus open surgery for early ovarian cancer (*Continued*)

sion n (%)																								
Median pelvi lymp node n	13.7	19.3	0.052	27.2	33.9	0.079	-	-	NS	-	-	NS	23.5	22.8	0.867	26.8	27.8	0.721	-	-	-	-	-	-
Median para aortic node n	8.9	6.4	0.187	6.6	8.8	0.324	-	-	NS	-	-	NS	9.9	4.8	**0.003**	17.7	21.2	0.202	-	-	-	-	-	-
Omental specimen (cm³	-	-	-	160	274	0.113	-	-	NS	-	-	NS	-	-	-	-	-	-	-	-	-	-	-	-
Tumour size, mean (cm)	4.0	4.5	0.618	8.9	11.0	0.254	-	-	-	-	-	-	9.1	14.0	**0.010**	7.3	11.2	**0.001**	6.69	11.50	**<0.05**	-	-	-
Complications n (%)	0 (0)	4 (21)[1]	-	2[2]	9[1]	0.290	-	-	-	6 (7.1)	25 (19.5)	**0.013**	2	20[4]	-	-	-	-	4 (11.43)	5 (12.5)	NS	0	1 (6)	0 0.303
Return to bow	3.8	2.0	**< 0.001**	1.3	3.6	**< 0.001**	1.7	3.6	**< 0.001**	1.8	3.1	**< 0.001**	-	-	-	-	-	-	2.11	2.83	**<0.05**	-	-	-

Table 3. Retrospective cohort studies of laparoscopic surgical staging versus open surgery for early ovarian cancer (*Continued*)

mov mer (day																							
Hos· pi- tal stay (day	9.4	14.1	**0.002**	8.9	14.5	**0.002**	7.9	14.5	**0.002**	6.3	13.5	**< 0.001**	6.4	12.4	**< 0.001**	13.7	13.1	0.594	16.29	21.85	**<0.05**	5	9	**<0.001**
Fi- nal di- ag- no- sis = stage I, n	16 ³	13	-	15	26	0.936	-	-	-	-	-	-	25	82	0.212	20	43	-	30	33	NS	-	-	-
In- tra- op- er- a- tive tu- mou spill: n (%)	0	0	-	2	4	1.000	-	-	NS	-	-	NS	0	13 (14.9)	**0.037**	13 (54.2)	21 (39.6)	0.465	-	-	-	-	-	-
Ad- ju- vant che- mo- ther· apy, n (%)	10 (59)	17 (89)	0.196	15 (79)	26 (79)	-	-	-	-	-	-	-	17 (65.4)	65 (74.7)	0.453	21 (87.5)	48 (90.6)	0.48	30 (85.71)	36 (90)	NS	-	-	-
Tim (day	11.1	14.3	0.140	12.8	17.6	**0.049**	12.8	13.9	**< 0.001**	15.8	20.7	**< 0.**	8.5	10.	**0.007**	-	-	-	-	-	-	-	-	-

Table 3. Retrospective cohort studies of laparoscopic surgical staging versus open surgery for early ovarian cancer (*Continued*)

to adjuvant chemotherapy													**001**		3									
Upstage n (%)	1	6	0.092	4 (21)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6 (17.14)	9 (22.50)	NS	-	-	-
Conversion to LPT n	0	NA	-	1	NA	-	-	-	-	-	-	-	-	-	-	0	-	NA	-	-	-	-	-	-
Port-site/abdominal wound metastases	0	-	-	0	-	-	-	-	-	-	-	-	0	0	-	0	-	NA	-	-	-	-	-	-
Median follow-up in mon (rang	19 (5 to 56)	14 (5 to 61)	-	17 (2 to 40)	23 (1 to 44)	-	-	-	-	-	-	-	12 (1 to 42)	25 (1 to 74)	-	31.7 (ND	31.1 (ND	0.9	-	-	-	53 (9-84)	45 (18-84)	-
PFS n (%)	15 [5] (88)	19 (100	-	19 (100	33 (100	-	37 (92)	71 (93)	0.876	66 (78)	100 (78)	0.873	26 (100	79 (91)	0.195	22 (91.7)	51 (96.2)	0.585	-	-	NS	8 (80)	7 (63.6)	0.705

Table 3. Retrospective cohort studies of laparoscopic surgical staging versus open surgery for early ovarian cancer (*Continued*)

OS, n (%)	16 (94)	19 (100	-	19 (100	33 (100	-	38 (96)	71 (94)	0. 841	75 (89)	110 (86)	0. 731	-	-	-	23 (95. 8)	53 (100	NS	-	-	NS	-	-	-

Abbreviations: LPS = laparoscopy; LPT, laparotomy; BMI = body mass index; PFS = progression-free survival; OS = overall survival; n = number; NA = not applicable; NS = not specified; ND = not described

*Not included abstracts from conferences for lack of information

**These studies are expansions of the original data set (Park 2008b)

[1]Wound infections, fever, ileus

[2]Including one intra-operative great vessel injury repaired via a small abdominal incision

[3]All these women were staged Ia/b compared with only five Ia/b and eight Ic cases in the LPT group

[4] Including 10 lymphoceles in the LPT group. Two umbilical hernias occurred in the LPS group

[5] One woman diagnosed as FIGO stage Ia grade 1 had severely disseminated disease 7 months postoperatively and died of the disease 15 months later. The other woman was stage Ia grade 2 at LPS and developed recurrence at the vaginal stump

Table 4. Systematic reviews and meta analysis

	Zhang 2015		**Park 2013**		**Lu 2015**		**Bogani 2014**	
		P value		P value		P value		P value
Number of studies	8		11		11		6	
OR length of hospital stay	0.433 (0. 215-0.869)	**0.019**	-		-4.87 (-7.26, -2.47)**	**<0.00001**	-3.30 (-3.92, -2. 69)**	**<0.00001**
OR recurrence rates	0.707 (0. 245-2.037)	0.521	0.099 (0. 067-0.144)*	**<0.001**	0.32 (0.13-0. 82)	**0.02**	0.50 (0.21-1.21)	0.13
OR of upstaging rates	-	-	0.669 (0. 246-1.815)	0.430	-	-	0.70 (0.38-1.27)	0.24
OR intraoperative complications	-	-	-	-	1.34 (0.37-4. 93)	0.66	2.47 (0.50-12. 22)	0.27
OR postoperative complications	-	-	-	-	0.26 (0.13-0. 52)	**0.000**	0.25 (0.12-0.53)	**0.0003**

Table 4. Systematic reviews and meta analysis (*Continued*)

OR complications	0.433 (0.215-0.869)	**0.019**	-	-	-	-	-	-

*Event rate
**Mean difference

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Ovarian Neoplasms explode all trees
#2 ovar* near/5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan* or adenocarcinoma*)
#3 (#1 OR #2)
#4 MeSH descriptor Laparoscopy explode all trees
#5 laparoscop* or celioscop* or peritoneoscop* or (endoscop* near/5 abdom*)
#6 MeSH descriptor Laparotomy, this term only
#7 laparotom* or (abdom* near/5 (surg* or incision))
#8 (#4 OR #5 OR #6 OR #7)
#9 (#3 AND #8)

Appendix 2. MEDLINE search strategy

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan* or adenocarcinoma*)).mp.
3 1 or 2
4 exp laparoscopy/
5 (laparoscop* or celioscop* or peritoneoscop* or (endoscop* adj5 abdom*)).mp.
6 Laparotomy/
7 (laparotom* or (abdom* adj5 (surg* or incision))).mp.
8 4 or 5 or 6 or 7
9 3 and 8
10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 randomized.ab.
13 placebo.ab.
14 clinical trials as topic.sh.
15 randomly.ab.
16 trial.ti.
17 exp cohort studies/
18 exp case-control studies/
19 comparative study/
20 (cohort* or prospective* or retrospective* or control* or longitudinal or follow-up).mp.
21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 9 and 21

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

Appendix 3. Embase search strategy

1 exp ovary tumor/
2 (ovar* adj3 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan* or adenocarcinoma*)).ti,ab.
3 1 or 2
4 laparoscopy/
5 (laparoscop* or celioscop* or peritoneoscop* or (endoscop* adj3 abdom*)).ti,ab.
6 laparotomy/
7 (laparotom* or (abdom* adj3 (surg* or incision))).ti,ab.
8 4 or 5 or 6 or 7
9 exp controlled clinical trial/
10 cohort analysis/
11 exp case control study/
12 exp comparative study/
13 (randomized or randomly or trial* or cohort* or prospective* or retrospective* or control* or longitudinal or follow-up).ti,ab.
14 9 or 10 or 11 or 12 or 13
15 3 and 8 and 14
key: [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

F E E D B A C K

Definition of studies, 7 June 2015

Summary

Name: Alexander Melamed
Comment: The term "prospective case-control" is used in this study is confusing. Case-control studies by definition are retrospective. A case-control study is one where patients with and without an outcome of interest are identified, and the presence or absence of a putative causal exposure is investigated among these "cases" and "controls." Perhaps what the authors of this study are referring to is what would conventionally be called a cohort study. For a useful discussion of the confusion in regarding the terminology please see Marshall T. What is a case-control study? International Journal of Epidemiology 2004;33:612-617.
I agree with the conflict of interest statement below:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

The authors would like to thank Dr Melamed for taking the time to write, and we accept his suggestion. We have amended the term prospective case-control to prospective cohort studies throughout the review.

Contributors

Theresa A Lawrie on behalf of the author team.

WHAT'S NEW

Date	Event	Description
17 November 2016	Amended	Minor copy-edit changes

HISTORY

Date	Event	Description
17 October 2016	Amended	Additional author affiliations added.
9 September 2016	New citation required but conclusions have not changed	No studies identified for inclusion.
7 September 2016	New search has been performed	Literature searches updated September 2016.
16 June 2015	Feedback has been incorporated	Feedback received and responded too.
12 September 2012	New citation required but conclusions have not changed	Eleven newly identified studies excluded, no studies included. Conclusions unchanged
30 November 2011	New search has been performed	Search updated.

CONTRIBUTIONS OF AUTHORS

Lidia Medieros (LM), Daniela Rosa (DR), Mary Bozetti (MB), Maria Ines Rosa (MR), Alice Zelmanowicz (AZ) and Airton Stein (AS) contributed to the writing of the protocol and the original review. LM, DR, MR, MB and Maria Edelweiss sifted the searches, selected studies and extracted data for the original review (which included NRSs). Anaelena Ethur (AE) and Roselaine Zanini (RZ) contributed to the protocol and methods section. Tess Lawrie (TL) sifted the updated search and wrote the first draft of the updated review. Frederico Falcetta (FF) and DR wrote the draft of the second update of the review. All authors approved the final version.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the original review (Medeiros 2008), we included non-randomised studies (NRSs) and evaluated the quality of three studies (Ghezzi 2007; Hua 2005; Tozzi 2004) according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and NOS tools. For the updated review, these studies were excluded, but we tabulated and discussed the data with other NRSs.

INDEX TERMS

Medical Subject Headings (MeSH)

*Laparoscopy; *Laparotomy; Early Detection of Cancer [*methods]; Neoplasm Staging; Ovarian Neoplasms [pathology; *surgery]

MeSH check words

Female; Humans

4. CONSIDERAÇÕES FINAIS

Nosso objetivo era coletar as melhores evidências quanto ao impacto do exercício físico na composição corporal e na qualidade de vida de pacientes tratados com câncer de mama com intenção curativa. Buscamos apenas ensaios clínicos randomizados, considerando-os como a melhor fonte de evidência para a questão excluindo estudos que avaliaram pacientes durante o tratamento com quimioterapia ou radiação. Podemos dizer que reunimos as melhores evidências sobre essa questão demonstrando uma diminuição significativa no peso corporal, IMC, bem como uma melhoria nos resultados da qualidade de vida, porém com grande viés de publicação, que, quando corrigido diminuiu os efeitos dessa intervenção. Na nossa busca encontramos apenas um estudo que descreveu a sobrevida global e sobrevida livre de recidiva com efeitos positivos para o grupo de exercício físico.

Como conclusão podemos dizer que são necessários ensaios clínicos randomizados de melhor qualidade com um número maior de pacientes e com maior tempo de acompanhamento. Nosso este estudo mostra que qualquer intervenção para incentivar a atividade física é válida, promove bons hábitos de vida que possam afetar a qualidade de vida, o perfil metabólico e a mortalidade já que o exercício físico é uma intervenção barata, fácil de aplicar e praticamente não possui contraindicações. Embora não existam evidências fortes e sólidas relacionadas à atividade física e risco reduzido de recorrência e morte por câncer de mama, os sobreviventes estão orientados para evitar um estilo de vida sedentário e procuram exercitar-se regularmente.

Um novo trabalho considerando intervenções em dieta no câncer de mama pode completar a falta de evidências dos efeitos de modificações de estilo de vida para essa doença.