Efficacy of Interventions for Prevention of Chemotherapy-induced alopecia: A Systematic Review and Meta-Analysis

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A brief description of the novelty and impact of this paper

There are numerous trials aimed at preventing chemotherapy-induced alopecia (CIA). However to date, data on comparisons of the different interventions to prevent CIA are lacking, and no meta-analyses have been published on this topic. We believe that the current

meta-analysis is the first comprehensive meta-analysis on this issue, and that this paper will help clinicians, researchers, and policy makers provide the affected patients with useful information regarding the efficacy of preventive treatments for CIA.

ABSTRACT

Chemotherapy-induced alopecia (CIA) is a highly distressing event for cancer patients, and hence, we here aimed to assess the efficacy of various interventions in the prevention of CIA. We searched PubMed, EMBASE, and the Cochrane Library, from 20 June 2013 through 31 August 2013. Two of the authors independently reviewed and selected clinical trials that reported the efficacy of any intervention for prevention of CIA compared with that of controls. Two authors extracted data independently on dichotomized outcome in terms of CIA occurrence. Relative risks (RRs) and 95% confidential intervals (CIs) were calculated for efficacy of CIA prevention by using random-effect or fixed-effect models. Out of 691 articles retrieved, a total of 8 randomized controlled trials and 9 controlled clinical trials involving 1098 participants (616 interventions and 482 controls), were included in the final analyses. Scalp cooling, scalp compression, a combination of cooling and compression, topical minoxidil, and *Panicum miliaceum* were used as interventions. The participants were mainly breast cancer patients receiving doxorubicin- or epirubicin-containing chemotherapy. Scalp cooling, which is the most popular preventive method, significantly reduced the risk of CIA (RR = 0.38, 95% CI = 0.32-0.45), whereas topical 2% minoxidil and other interventions did not significantly reduce the risk of CIA. No serious adverse effects associated with scalp cooling were reported. Our results suggest that scalp cooling can prevent CIA in patients receiving chemotherapy. However, the long-term safety of scalp cooling should be confirmed in further studies.

INTRODUCTION

Chemotherapy-induced alopecia (CIA) is a common and stressful adverse effect associated with chemotherapy.[1] CIA generally starts at 1–3 weeks after the first cycle of chemotherapy, and is aggravated after subsequent cycles.[2] Fortunately CIA is spontaneously recovered after 3-6 months in usual cases.[3] However, not a few patients suffer from permanent CIA, and many patients experience changes in hair color, texture, and growth rate even after re-growth of hairs.[4] The occurrence and severity of CIA is dependent on the chemotherapeutic dose, administration schedule, and other protocols.[5] Various cytotoxic chemotherapeutics can cause CIA. The chemotherapeutics target all rapidly proliferating cells, and consequently damage not only tumor cells but also the hair follicles. At any given time, approximately 90% of the hair follicles in the human scalp are in the anagen stage, and these hair matrix cells proliferate fast. The apoptosis of these cells caused by cytotoxic chemotherapeutics results in hair shedding, which is called anagen effluvium.[6]

Although CIA is generally reversible 3-6 months post-chemotherapy, it commonly causes psychosocial stress to the patients, including negative changes in body image, sexuality, self-esteem, and disturbances in social relationships. The fear of hair loss and the associated distress may even result in cancer patients refusing proper chemotherapy treatment.[7]

Many interventions, such as scalp cooling, scalp compression with tourniquet, and various medications have been proposed to prevent CIA.[8] Among these, scalp cooling is the most widely used.[9] Scalp cooling by cooling devices was first introduced in the 1970s as a treatment for CIA.[10] The mechanism of scalp cooling for CIA can be explained in 2 ways: (1) by vasoconstriction, resulting in decreased blood flow to the hair follicles during chemotherapeutic infusion and thereby interrupting the uptake of the cytotoxic agents in the hair follicles; and (2) by lessening biochemical activity, with hair follicles with reduced

biochemical activity being less likely to be damaged by chemotherapeutics.[11]

The external carotid artery is the source of blood supply to the scalp tissue, and can be blocked by external pressure.[12] Scalp compression with tourniquets is simple, and one of the earliest proposed methods for preventing CIA. This method involves an inflatable tourniquet used to reduce the blood supply to the scalp during the time of peak plasma concentration of chemotherapeutics. It can be used alone or in combination with scalp cooling.[13,14] However, this methods seems to be rarely used for prevention of CIA at the present time, and the method alone has not been studied clinically since 1978.[15]

Minoxidil is a US Food and Drug Administration (FDA) approved, effective, and safe topical treatment for patterned alopecia, which modulates the hair cycle by prolongation of the anagen stage in mouse models.[16] Topical 2% minoxidil has been reported to result in early recovery from CIA in breast cancer patients receiving adjuvant chemotherapy, and in gynecologic cancer patients receiving cyclophosphamide, doxorubicin, and cisplatin.[17] However, its preventive efficacy for CIA is still questionable.[15,18]

Calcitriol (1,25-dihydroxyvitamin D3), has various effects on keratinocytes: it arrests the cell cycle progression by DNA synthesis inhibition, and induces cell differentiation.[6] Calcitriol has been demonstrated to prevent CIA caused by cyclophosphamide, etoposide, and doxorubicin-cyclophosphamide combination therapy in neonatal rats.[19] However, in humans, no obvious protective effects have been described.[20,21]

Moreover, experimental data have suggested that the pineal hormone melatonin can prevent chemotherapy-induced production of free radicals, which play a role in the damaging of hair follicles.[22] In addition, various cytokines, growth factors, and antioxidants have been investigated for the prevention and treatment of CIA. However, most of these have only been tested in animal models.[4, 23]

Currently, data on comparisons of these different measures are lacking, and to our knowledge,

no meta-analysis has been published on this topic. This is needed in order to suggest the most evidence-based, effective, and safe treatment to physicians. Hence, the aim of this meta-analysis was to investigate the clinical efficacies of the various available interventions for the prevention of CIA

MATERIAL AND MEHODS

Literature search and selection criteria

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 20 June 2013 through 31 August 2013, using search terms related to chemotherapy-induced alopecia (*chemotherapy, alopecia, and hair loss*) and its preventive methods (*scalp cooling, scalp hypothermia, hypothermic cap, minoxidil, calcitriol, dihydroxyvitamin D3, and Vitamin D*). Moreover, we reviewed the bibliographies of relevant articles to locate additional publications. The search was restricted to human studies and English literatures, but not restricted to publication date.

Two of the authors (H Shin and DH Kim) independently established the eligibility of the studies retrieved from the databases and bibliographies. First, the titles and abstracts of the searched articles were evaluated. Full-text articles were reviewed when abstracts did not reveal contents about inclusion and exclusion criteria. Subsequently, we evaluated the full text of selected articles and determined their eligibility for this study. Disagreements between evaluators were resolved by discussion. We included randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that reported the efficacy of any intervention for prevention of CIA compared with that of controls (placebo or no treatment), and excluded the studies if they included patients with scalp irradiation or scalp metastases. If data were duplicated or shared in more than 1 study, the first published, larger, or more comprehensive study was included in the analysis.

Assessment of the risk of bias

Two of the authors (H Shin, DH Kim) independently assessed the risk of bias of each article by using the Cochrane Collaboration's Risk of Bias tool.[24] We evaluated the risk of bias

during the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, analysis of incomplete outcome data, selective reporting, and in other areas. All these were categorized as "yes" (low risk of bias), "unclear," or "no" (high risk of bias). The graphs showing the results were made using Review Manager, Version 5.1.7 (Nordic Cochrane Center, Copenhagen, Denmark).

Primary outcomes

In trials of CIA prevention, clinical efficacy was measured by different criteria. The primary outcome of interest was dichotomized in terms of prevention failure, which was defined as the occurrence of CIA, as assessed by the investigators or patients. In this meta-analysis, we defined the prevention failure as the occurrence of WHO grade III - IV alopecia according to the WHO criteria (0: no change; I: minimal hair loss, II: moderate, patch alopecia; III: complete but reversible alopecia; IV: complete and irreversible alopecia) or wearing a wig.[25] These criteria were used by Katsimbri et al., and are generally accepted.[10] When our definition of CIA occurrence in this meta-analysis was different from the criteria used in the original studies, we extracted data according to our own criteria regardless of the original criteria in the trial.

Adverse effects

Adverse effects of CIA prevention therapy were classified as local or systemic discomfort. In some studies, the effects of the underlying cancer on the treatment were also evaluated. These are described qualitatively in the Results section.

Data extraction

Data were extracted from included studies independently by 3 authors (H Shin, SJ Jo, and

DH Kim). The included articles were read in detail, and relevant information was summarized in the data sheets, including: study name (publication year and the first author), type of study design, CIA prevention therapy, country, numbers and descriptions of subjects (age, gender, underlying cancer), chemotherapy regimen, observation period, the original criteria defining CIA occurrence in each article, numbers of CIA occurrence in intention-to-treat population, and adverse effects. An intention-to-treat analysis was planned, and we attempted to include dropouts in the analysis of dichotomous variables.

Main and subgroup analyses

The occurrence of CIA was used as the main outcome measure to calculate the relative risk. We investigated the association between the preventive methods and CIA events in patients treated with chemotherapy. Regarding the scalp cooling method, we further conducted subgroup meta-analyses by type of study design (RCTs vs. CCTs), gender ratios of the study populations (mixed gender vs. female populations), chemotherapeutic agents (doxorubicin, epirubicin, docetaxel, etc.), type of underlying cancer (breast cancer, mixed group of cancer, etc.), year of publication (before 1999 vs. after 2000), and country where the study was conducted (Europe vs. non-Europe).

Statistical analysis

We calculated the relative risks (RRs) with 95% confidence intervals (CIs) by using crude 2×2 tables on the basis of intention-to-treat analyses from the original publications except articles that described only per-protocol populations.[14,26] For the test of heterogeneity, we utilized Higgins I^2, which measures the percentage of total variation across trials.[27] I^2 was calculated as follows:

$$I^2 = 100\% \times (Q - \mathrm{df})/Q,$$

where Q is Cochran's heterogeneity statistic, and df indicates the degrees of freedom. Negative values of I^2 are set to zero. I^2 ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity). To calculate pooled RRs with 95% CIs, both the fixed-effects and random-effects models were used. An I^2 value >50% was considered as substantial heterogeneity.[28] When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported. We used the Stata SE version 12.0 software package (Stata Corp, College Station, Texas, USA) for statistical analysis. Publication bias was assessed by using Begg's funnel plot and Egger's test. If publication bias existed, the Begg's funnel plot was asymmetric or the *P* value was <0.05 by the Egger's test, and the Trim and Fill method was subsequently used for adjustment.[29]

RESULTS

Literature Search and Study Selection

Fig. 1 shows a flow diagram depicting how we identified the relevant clinical trials. By searching 3 databases (i.e. PubMed, EMBASE, the CENTRAL) and by hand-searching relevant bibliographies, a total of 691 articles were identified. After excluding 52 duplicated articles, 2 of the authors independently reviewed and excluded an additional 585 articles that did not satisfy the pre-determined selection criteria based on each article's title and abstract. We reviewed the full texts of the remaining 54 articles and excluded 38 articles because of the following reasons: trials not related to the subject of this study (n = 2); non-controlled trials (n = 11); identical trials with the same population (n = 2); review articles or comments (n = 16); and trials reporting insufficient data (n = 7). The excluded 7 trials reporting insufficient data seemed eligible for the inclusion criteria at first, but data could not be extracted because of the following reasons: trials not showing dichotomous variables as a primary outcome (n = 2);[17,21] a trial reporting percentage data which were not calculated into the exact number of subjects (n = 1),[30] and trials using a different WHO grade to define CIA (n = 4).[20,22,31,32] As mentioned in the Methods section, when the criteria used in the original studies differed from our definition of CIA occurrence in this meta-analysis, we used our own criteria and extracted data regardless of the original criteria used in the trials.[7,13,14,18,26,33,34] However, those 4 studies[20,22,31,32] did not show sufficient results to extract the required data and were hence excluded from this meta-analysis. A clinical trial to test ammonium trichloro (dioxethylene-O,O'-) tellurate (AS101) hair growth cycle modifiers, was eligible, but the percentage data did not transformed integer value, a number of patients we sought.[30] Therefore, we excluded it from the final analysis. In addition, 1 article was added through manual search of the bibliographies of relevant articles,[14] resulting in a total of 17 trials being

included in the meta-analysis and analyzed to calculate the RRs (Fig. 2).[1,7,8,13,14,16,18,26,33-41]

General characteristics of included studies

Table 1 shows the general characteristics of the 17 trials included in the final analysis.[1,7,8,13,14,16,18,26,33-41] Scalp cooling was investigated in 10 studies,[1,7,8,26,34,36 37,39-41] scalp compression in 1 study,[14] a combination of cooling and compression in 3 studies,[13,33,35] and topical minoxidil in 2 studies.[16,18] *Panicum miliaceum* was investigated once.[38] One study was a randomized, double-blind, placebo-controlled trial,[16] 7 were open-label, randomized controlled trials,[1,7,13,14,33,35,36] and 9 were non-randomized controlled clinical trials.[8,18,26,32,34, 37-42] All studies were prospective. The countries where the studies were conducted included Italy (n = 4),[26,35,36,38] USA (n = 4),[7,13,14,18] UK (n = 3),[1,34,37] Netherlands (n = 2),[8,40] Argentina (n = 1),[16] Iran (n = 1),[39] Ireland (n = 1),[33] and Switzerland (n = 1).[41]

All 17 trials involved a total of 1098 participants (616 in the intervention groups and 482 in the control groups). The number of participants in each study ranged from 6 to 266. The underlying cancers of the patients were mainly breast cancer, and other solid cancers such as gynecologic, gastrointestinal tract, lung, and prostate cancers. Twelve studies included patients treated with doxorubicin- or epirubicin-containing chemotherapy,[1,8,13,14,16,18,26,33-37] and 2 studies included patients treated with cyclophosphamide or docetaxel-containing chemotherapy not including doxorubicin or epirubicin.[7,41] The remaining 3 studies included patients treated with either doxorubicin- or epirubicin-containing chemotherapy, or miscellaneous chemothepeutics.[38-40] The dosage of doxorubicin ranged between 30-70 mg/m^2.[8,13,14,16,18,26,33,35,36]

Development of CIA was assessed by WHO criteria in 6 studies,[1,26,34,38,39,41] necessity of head-covering in 7 studies, [6,12,15,34-36,39] area of hair loss in 3 studies[13,17,32] and by hair count in 1 study.[7] Among the 6 studies using the WHO criteria, 4 studies considered grade 3 and over

as significant alopecia,[1,38,39,41] 1 study considered grade 2 and over as significant alopecia,[26] and 1 study just showed the result of grading.[34]

Scalp cooling Ten studies used scalp cooling to prevent CIA.[1,7,8,26,34,36,37,39-41] Scalp cooling was performed by wearing a cooling cap, which is made with soft thermoabsorbent material. The cooling cap was fully refrigerated below 0°C before application and applied to the scalp 10-30 min before chemotherapeutic agent administration until 0-90 min post-treatment. No scalp cooling studies used sham devices, but rather compared the treatment with 'no intervention'. Only 3 of the 10 studies used randomization for assignment of participants.[1,7,36]

Scalp compression One RCT evaluated the efficacy of tourniquet for the prevention of CIA.[14] The intervention induced scalp ischemia just prior to, during, and after chemotherapeutic agent injections by means of a tourniquet inflated above systolic blood pressure. The control group did not receive intervention for CIA prevention.

Scalp cooling and compression Three RCTs investigated the efficacy of scalp cooling combined with tourniquet.[13,33,35] The cooling cap was fastened to the scalp together with the tourniquet. Unlike the use of tourniquet only, however, the tourniquet was not fastened tight to occlude arterial circulation, but was instead applied longer.

Topical minoxidil/Phytotherapeutic agents Two studies tested 2% topical minoxidil.[16,18] The solution was applied twice daily between 1-14 days prior to the first chemotherapy cycle to the end of the study. One study was performed as double-blind, RCT design,[16] and the other as an open-label, split test without placebo.[18] One study tested a phytotherapeutic agent (*Panicum miliaceum*) administered orally to participants during chemotherapy.[38]

Risk of bias in included studies

Eight studies were described as randomized.[1,7,13,14,16,33,35,36] Additionally, no studies, except

1,[16] were blinded for participants and assessing researchers. Ten studies had incomplete outcome data due to drop-out of participants.[1,8,14,18,34-37,40,41] The results are summarized in the Fig. 3, and in Supplemental eFig. 1.

Preventive efficacy of interventions for CIA

In the control groups, 75.9% of patients (365 of 481) suffered CIA, whereas only 28.7% of patients (177 of 616) experienced CIA in the experimental group. The CIA-prevention rates during chemotherapy ranged between 10.0-100.0% in the intervention groups (mean prevention rate = 65.2%, standard deviation (SD) = 29.0%), and from 0.0% to 66.7% in the control groups (mean prevention rate = 27.2%, SD = 23.4%).

Scalp cooling The meta-analysis by type of intervention showed various efficacy of each intervention. Scalp cooling, the most common preventive method, significantly reduced the development of CIA (RR = 0.38, 95% CI = 0.32-0.45, I^2 = 73.8%, P < 0.001, Fig. 2A).[1,7,8,26,34,36,37,39-41] However, Begg's funnel plot was asymmetrical (Fig. 4B). P for bias was 0.108 in Egger's test. Publication bias was adjusted using the Trim and Fill method, which suggested that 4 studies were missing, and the adjusted RR was 0.45 (95% CI = 0.33-0.62). Sensitivity analysis (each study sequentially excluded) revealed that the result was robust and not dependent on any individual study. When the Macduff et al. study[1] was excluded, the heterogeneity decreased (I^2 = 46.3%) (Supplemental eTable 1).

The other methods The study using scalp compression was not significant (RR = 0.33, 95% CI = 0.02-5.97, Fig. 2B), whereas scalp cooling combined with compression significantly reduced the development of CIA (RR = 0.54, 95% CI = 0.39-0.74, I^2 = 87.9%, P < 0.001, Fig. 2C). Neither topical 2% minoxidil nor *Panicum miliaceum* significantly reduced the development of CIA (RR = 0.96, 95% CI = 0.77-1.21, I^2 = 0.0%, P = 0.902, Fig. 2D and RR = 0.65, 95% CI = 0.42-1.00, Fig. 2E, respectively).

Subgroup analysis of scalp cooling prevention for CIA

The scalp cooling method was the most common and effective among the investigated methods, and we performed a subgroup analysis for the scalp cooling studies (Table 2).

Subgroup meta-analysis by type of study design demonstrated significant efficacy of scalp cooling for the prevention of CIA in both RCTs and CCTs, regardless of the gender of study population, the underlying cancer, the year of publication, and the country where the study was conducted. When analyzed for the chemotherapeutic regimen, scalp cooling was found to significantly prevent CIA induced by doxorubicin- and epirubicin-containing regimens, docetaxel, and the various combination regimens, with the exception of combination therapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).[7]

Adverse events

Most of the adverse events were not serious. Intolerable coldness and headaches were commonly reported in the scalp cooling studies, with incidence rates of 4.0–33.3%. Despite these adverse events not being serious, many participants dropped out of the trials. One case of chest pain was reported during the treatment with scalp cooling.[1] The treatment was discontinued for this patient, although it was uncertain whether the chest pain was related to the scalp cooling or not. An overview of adverse events reported in the included studies is provided in Supplemental eTable 2.

DISCUSSION

The efficacy of scalp cooling for CIA has been previously reported in numerous studies. However, most of those studies were uncontrolled, small-sized, with poor values.[9] The sale of scalp cooling devices was banned by the US FDA in 1990, because of lack of evidence of its safety and effectiveness.[43] However, studies on scalp cooling for CIA were performed up until recently. Hence, we here performed a comprehensive systematic review and meta-analysis to examine the efficacy of interventions aimed at preventing CIA, focusing particularly on the scalp cooling method.

We did our best to fulfill most of the methodological criteria for meta-analyses.[44] A comprehensive search of the published articles was performed using different databases, as shown in Fig. 1. Most subjects included in this analysis were female, which can be attributed to breast cancer being the most common underlying cancer in these studies. Additionally, a study evaluating the experience of chemotherapy in postmenopausal women with breast cancer showed that many women felt that hair loss was a worse experience than the loss of a breast,[45] suggesting that women may be more concerned by CIA than men.

The risk of bias was rather high in many of the included studies. Most studies did not perform randomization or used a double-blind approach. Moreover, the application of intervention was determined by the patients and not by investigators in many trials, and, unlike other treatments, scalp cooling is hard to perform in a double-blinded fashion.

In our analysis, scalp cooling reduced the relative risk of CIA about one-third. Combining of scalp compression and cooling also showed effectiveness, but the RR of this method was not lower than that of scalp cooling only, suggesting that there were no synergistic effects. Scalp compression only, topical 2% minoxidil, and a phytotherapeutic agent failed to show significant prevention for CIA. However, it should be noted that the insignificant results were

from only 1 or 2 studies, and thus, more clinical studies to investigate these other preventive methods for CIA are needed.

Because of the significant efficacy of scalp cooling observed in our analysis, we subsequently focused on scalp cooling trials. Publication bias was suspected in the analysis of scalp cooling studies, and after the adjustment of publication bias, the preventive efficacy of scalp cooling was slightly decreased, but still significant. Moreover, the scalp cooling studies showed significant heterogeneity. When excluding the Macduff et al. study,[1] the heterogeneity was decreased to I^2 = 46.3%, as determined using post hoc sensitivity analysis. In the subgroup analysis, all subgroups by study design, gender of study population, chemotherapeutic agents, underlying cancer, year of publication, or conducting country, showed significant reductions of the relative risk for CIA development, except 1 trial using CMF as the chemotherapeutic agents,[7] suggesting that these moderating factors generally do not influence the preventive efficacy of scalp cooling for the treatment of CIA. Although the intradermal temperatures during scalp cooling is known to affect the protective effects on hair loss,[46] none of the studies analyzed provided that information.

Sorting by chemotherapeutic agents was hard since a wide variety of agents were used. Four major chemotherapeutic agents are antimicrotubule agents like docetaxel, alkylating agents like cyclophosphamide, topoisomerase inhibitors like doxorubicin, and antimetabolites like 5-fluorouracil. Combination with several agents or radiation usually induces more severe CIA. We regarded doxorubicin, daunorubicin, epirubicin, docetaxel, and cyclophosphamide as the main chemotherapeutic agents inducing CIA in this analysis.[4,47] Doxorubicin, which is one of the most common causes of CIA, was significantly prevented from causing CIA by scalp cooling. The observed heterogeneity was further reduced by performing the subgroup analysis excluding the Macduff et al. study.[1] The results of this analysis are described in Supplemental eTable 3.

Scalp cooling was generally well tolerated but contraindicated in cases with cold sensitivity, cold agglutinin disease, cryoglobulinemia, and cryofibrinogenemia.[9] Furthermore, some authors have reported a potential risk of scalp metastases after scalp cooling.[48] Thus, it is advised that scalp cooling systems should not be used in patients with circulating malignant cells, such as leukemia or lymphoma, who are receiving chemotherapy with curative intent.[9] If used in patients with solid tumors with strong skin metastatic potential, such as breast, lung, or gastric cancer, special attention should be paid to monitoring the scalp for evidence of disease.[49] However, one previous article described that no patients treated with scalp cooling manifested scalp metastases after a median follow-up of 14 months (maximum follow-up, 2.5 years) from the end of chemotherapy.[31] Additionally, 2 studies included in this analysis also reported no occurrence of scalp metastases among participants who had used the cooling cap after 12 and 17-month follow-up periods, respectively.[7,40]

It has moreover been suggested that liver function is important for the success rate of scalp cooling, since patients with abnormal liver function have impaired metabolism of chemotherapeutics, resulting in high plasma concentration of the chemotherapeutics,[9,10] and thereby increasing the risk of treatment failure. However, many of the analyzed studies did not describe the liver functions of their subjects, and some studies excluded patients with liver problems.[20,35]

Although scalp cooling is contraindicated in patients with circulating malignant cells, these patients are in dire need of CIA prevention because they commonly develop permanent CIA after high-dose chemotherapy for bone-marrow transplantation.[50] Recently, several novel methods other than physical interventions have been tested. Those were drug-specific antibodies, hair growth cycle modifiers, cytokines, growth factors, antioxidants, cell cycle / proliferation modifiers, or inhibitors of apoptosis.[4] Because rapid cell proliferation in hair follicles seems to be responsible for the development of CIA, inhibition of cell proliferation

would be a proper strategy to protect hair follicles against CIA. For example, epidermal growth factor which induces a catagen phase of hair follicles was beneficial for the prevention of CIA in the mice model.[23]

This meta-analysis has several limitations. The populations of some of the included studies were relatively small, and the risk of bias in the analyzed studies was generally high. Although we here detected a significant benefit of scalp cooling for prevention of CIA, the protocols and devices used for scalp cooling differed somewhat between the studies. In addition, we used the crude relative risk as the main outcome. In order to get a more valid result, confounding variables should be well controlled. Among included 17 studies, four studies confirmed statistically the similarity of such confounding variables[7,8,40,41], nine RCTs conducted a random allocation of participants [1,13,14,16,18,33,35,36,38], and two studies commented the similarity of the covariates between the two groups.[26,37] However, the other two studies did not describe adjusting the confounding variables.[32,37] None of them did conduct a generalized linear regression model in order to adjust the confounding variables such as age, gender, cancer type, and chemotherapeutic regimens. For the purpose of overcoming the limitations regarding this issue, we conducted subgroup analyses for scalp cooling studies.

We here found that there is clinical evidence for the use of scalp cooling to prevent CIA in patients receiving chemotherapy. Especially, scalp cooling should be the recommended intervention for prevention of CIA in breast cancer patients undergoing doxorubicin, epirubicin, or docetaxel-containing chemotherapy regimens. On the other hand, topical 2% minoxidil and other methods currently lack clinical evidence for the prevention of CIA. Serious adverse effects of scalp cooling were not reported in any of the trials included in this analysis. The long term safety of scalp cooling needs to be confirmed by further trials and systematic reviews.

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TABLES

Table 1. Characteristics of trials included in the final meta-analysis (n = 17)

Study name	Country	Study Design	Participants	Gender ratio of participants (M:F)	Chemotherapy regimen	Intervention vs. control	Observation period	No. of CIA occurrence /No. of participants	
								Intervention group	Control group
Scalp cooling (n = 10)									
Villani et al., 1986[26]	Italy	CCT	36 patients with gynecological cancer	0:36	DX (6 cycles)	Applying cooling cap (20 min before drug administration, until 30 min post-treatment) vs. no treatment	During chemotherapy	1/18	6/18
Robinson et al., 1987[34]	UK	CCT	32 patients with breast cancer	0:32	Epirubicin every 3 week (mean 4 cycles)	Applying cooling cap (15-20 min before drug administration, until 45 min post-treatment) vs. no treatment	During chemotherapy	1/22	5/10
Parker et al., 1987[7]	USA	RCT	14 patients with stage IV breast cancer	0:14	CMF every 3 week (at least 7 cycles)	Applying cooling cap (10 min before drug administration, until 60 min post-treatment) vs. no treatment	During chemotherapy	0/6	7/8
Giaccone et al., 1988[36]	Italy	RCT	39 patients with mainly breast cancer and other miscellaneous cancers,	2:37	DX every 3 to 4 week (at least 2 cycles)	Applying cooling cap (10 min before drug administration, until 30 min post-treatment) vs. no treatment	During chemotherapy	11/23	15/16
Peck et al., 2000[37]	UK	CCT	15 patients with breast cancer	0:15	FEC every 4 week (6 cycles)	Applying cooling cap (a total of 2 hours and 10 minutes every session) vs. no treatment	Until 1 month after the final chemotherapy	2/10	5/5
Macduff et al., 2003[1]	UK	RCT	30 patients with breast cancer	NA (female dominant)	Epirubicin and docetaxel every 3 week (6 cycles)	Applying cooling cap (15 min before drug administration, until 45 min post-treatment) vs. no treatment	During chemotherapy	12/16	14/14
Mols et al., 2009[8]	Netherlands	CCT	266 patients with breast cancer.	NA (female dominant)	One of the followings every 3 week: AC, FEC, FAC, or TAC (4-6 cycles)	Applying cooling cap (the protocol of applying: NA) vs. no treatment	Until 3 weeks after the final chemotherapy	30/98	145/168
Kargar et al., 2011[39]	Iran	CCT	63 patients with cancer (the detailed diagnosis: NA)	23:40	One of the followings every 3 week: taxol, ABVD, BEP, or CHOP (6 cycles)	Applying cooling cap (15 min before drug administration, until treatment end) vs. no treatment	During chemotherapy.	15/31	24/32
Van Den Hurk et al., 2012[40]	Netherlands	CCT	85 patients with solid tumor (breast, lung, ovary, prostate, or gastrointestinal cancer)	NA (female dominant)*	Docetaxel alone or in combination with other agents. (carboplatin, herceptin, doxorubicin, or capecitabine) every 3 week (at least 2 cycles)	Applying cooling cap (30 min before drug administration, until 90 min post-treatment) vs. no treatment	During chemotherapy	10/65	11/20

Study name	Country	Study Design	Participants	Gender ratio of participants (M:F)	Chemotherapy regimen	Intervention vs. control	Observation period	No. of CIA occurrence /No. of participants	
								Intervention group	Control group
Betticher et al., 2013[41]	Switzerland	CCT	238 patients solid tumor (breast, lung, prostate cancer, etc.)	133:105	Docetaxel every week or 3 week (6-9 cycles)	Applying cooling cap (15 min before drug administration, until 90 min post-treatment) vs. no treatment	During chemotherapy	31/199	21/39
Scalp compression (n = 1)									
Lovejoy et al., 1979[14]	USA	RCT	6 patients with cancer (the detailed diagnosis: NA)	NA	DX every 3 week (at least 2 cycles)	Applying scalp tourniquet inflated to a pressure of 50 mmHg above systolic blood pressure (prior to, during, and for 15 min after doxorubicin injections) vs. no treatment	During chemotherapy	0/3	1/3
Scalp cooling and compression (n = 3)									
Edelstyn et al., 1977[33]	Ireland.	RCT	77 patients cancer (the detailed diagnosis: NA)	NA	DX (number of cycle: NA)	Applying cooling cap with a stockinette bandage (10 min before drug administration, until 30 min post-treatment) vs. no treatment	NA	13/40	23/37
Kennedy et al., 1983[13]	USA	RCT	19 patients with mainly breast cancer and other miscellaneous cancer without scalp irradiation	6: 13	Doxorubicin alone or AC every 3 to 4 week (1-6 cycles)	Applying cooling cap with a tourniquet (10 min before drug administration, until 30 min post-treatment) vs. no treatment	During chemotherapy	9/10	9/9
Satterwhite et al., 1984[35]	Italy	RCT	26 patients with mainly breast cancer and other miscellaneous cancer	NA (female dominant)*	DX (1–10 cycles)	Applying cooling cap with a tourniquet (15 min before drug administration, until 60 min post-treatment) vs. no treatment	During chemotherapy	3/13	12/13
Topical minoxidil (n = 2)									
Granai et al., 1991[18]	USA	CCT	10 patients with gynecologic cancer	0:10	DX (number of cycle: NA)	Applying topical 2% minoxidil twice daily from 1-2 weeks prior to the first chemotherapy cycle vs. no treatment (Split test: each patient served as her own non-treatment control	During chemotherapy	5/10	5/10
Rodriguez et al., 1994[16]	Argentina	RCT	48 patients with mainly breast cancer and other miscellaneous cancer.	0:48	Doxorubicin alone, DX or FAC every 3 to 4 week (1–2 cycles)	Applying topical 2% minoxidil twice daily from 24 hours prior to the first chemotherapy cycle vs. placebo	During chemotherapy	21/24	22/24

Study name	Country	Study Design	Participants	Gender ratio of participants (M:F)	Chemotherapy regimen	Intervention vs. control	Observation period	No. of CIA occurrence /No. of participants	
								Intervention group	Control group
Others (n = 1)									
Gardani et al., 2007[38]	Italy	CCT	84 patients with advanced solid tumor (breast cancer, lung cancer, etc.)	NA	Cisplatin-containing or anthracycline (doxorubicin or epirubicin)-containing chemotherapy. (number of cycles: NA)	*Panicum miliaceum* 300mg/day p.o. medication from 7 days before chemotherapy to the end of the chemotherapy vs. no treatment	NA	13/28	40/56

No.: number; RCT: randomized controlled trial; CCT: controlled clinical trial; NA: not available; USA: United States of America; F: female; M: male; WHO: World Health Organization; UK: United Kingdom, IV: intravenous; p.o: per os; 5-FU: 5-fluorouracil; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AC: doxorubicin and cyclophosphamide; BEP: bleomycin, etoposide, and cisplatin; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; DX: doxorubicin in combination with other chemotherapeutic agents; ECF: epirubicin, cisplatin, and 5-fluorouracil; EP: etoposide and cisplatin; FEC: 5-fluorouracil, epirubicin, and cyclophosphamide; FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; TAC: docetaxel, doxorubicin, and cyclophosphamide; The measure of age is a years old.;* The article showed the gender ratio of per-protocol population, not intention-to-treat population.

Table 2. Subgroup meta-analyses by various factors for the efficacy of scalp cooling prevention for chemotherapy-induced alopecia

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Scalp cooling[1,7,8,26,34,36,37,39-41]	10	0.38 (0.32-0.45)	73.8%	Random effects
Study design				
RCT[1,7,36]	3	0.54 (0.40-0.72)	71.4%	Random effects
CCT[8,26,34,37,39-41]	7	0.35 (0.29-0.43)	47.4%	Fixed effects
Gender of study population				
Only female[7, 26,34,37]	4	0.15 (0.06-0.36)	0.0%	Fixed effects
Mixed gender[36,40,41]	3	0.34 (0.26-0.46)	49.7%	Fixed effects
Not available[1, 8,39]	3	0.44 (0.36-0.55)	88.5%	Random effects
Chemotherapeutic agents				
Doxorubicin-containing regimen[26,36]	2	0.42 (0.26-0.69)	33.3%	Fixed effects
Epirubicin-containing regimen[1,34,37]	3	0.48 (0.34-0.68)	84.6%	Random effects
Docetaxel[40,41]	2	0.29(0.20-0.41)	0.0%	Fixed effects

CMF[7]	1	0.09 (0.01-1.26)	-	-
Mixed regimen[8,39]	2	0.40 (0.31-0.52)	80.2%	Random effects
Underlying cancer				
Breast cancer[1,7,8,34,37]	5	0.37 (0.29-0.47)	84.6%	Random effects
Mixed group of cancer[26,36,40,41]	4	0.33 (0.25-0.44)	36.3%	Fixed effects
Not available[39]	1	0.63 (0.41-0.94)	-	-
Year of publication				
Before 1999[7,26,34,36]	4	0.30 (0.18-0.49)	61.9%	Random effects
After 2000[1,8,37,39-41]	6	0.40 (0.33-0.48)	81.5%	Random effects
Country				
Europe[1,8,26,34,36,37,40,41]	8	0.36 (0.30-0.44)	76.7%	Random effects
Non-Europe[7,39]	2	0.51 (0.33-0.78)	62.2%	Random effects

RCT: randomized controlled trial; CCT: controlled clinical trial; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil

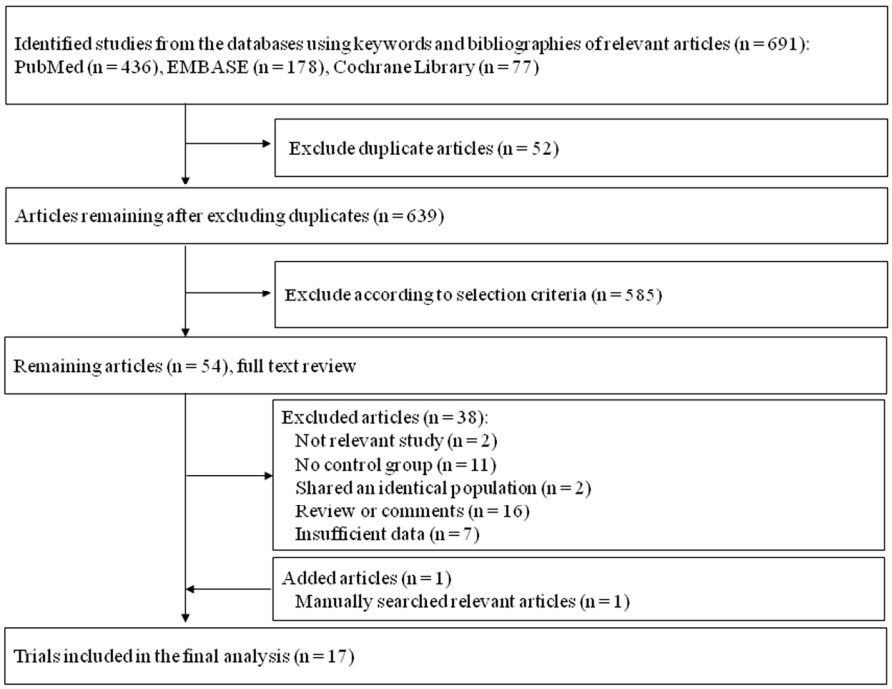

Figure 1. Flow diagram for identification of relevant studies
170x127mm (300 x 300 DPI)

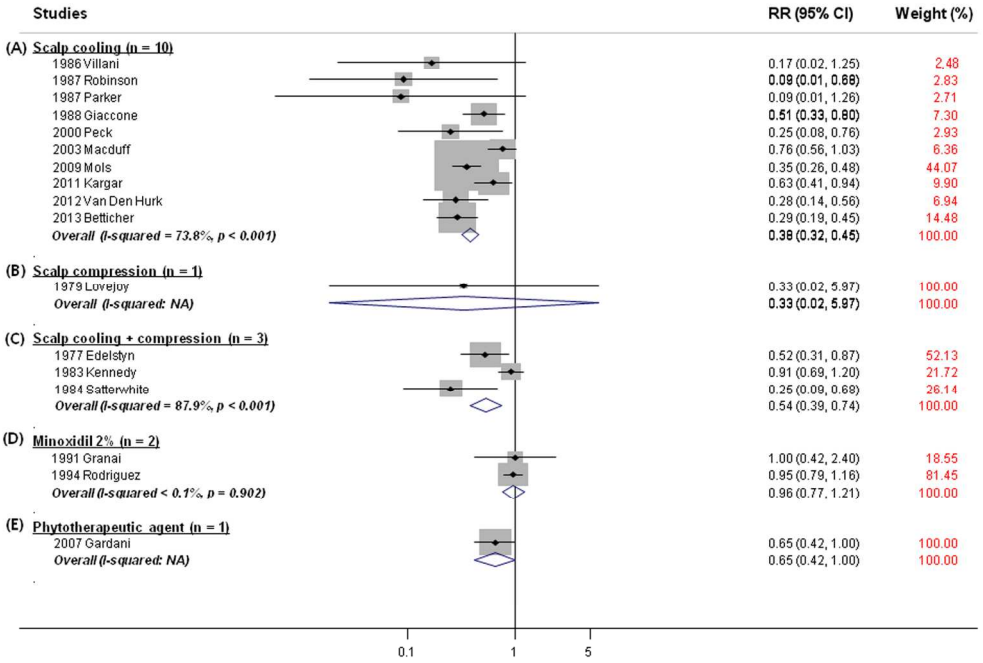

Figure 2. Efficacy of prevention for CIA development in the random-effects meta-analysis of prospective CCTs and RCTs

/ Legend /
RR indicates relative risk; CI, Confidence Interval; Horizontal lines, 95% CIs; gray boxes, the weight of each study; Diamond data markers represent each overall RR and 95% CI for the outcome of interest.
170x127mm (300 x 300 DPI)

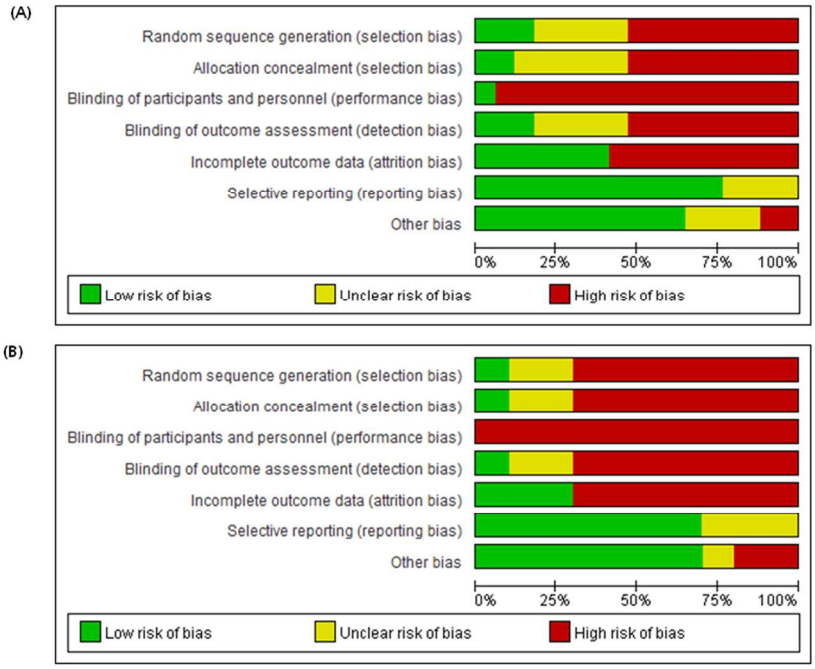

Figure 3. Risk-of-bias graph. (A) All included CCTs and RCTs. (B) Only scalp cooling studies.
170x127mm (300 x 300 DPI)

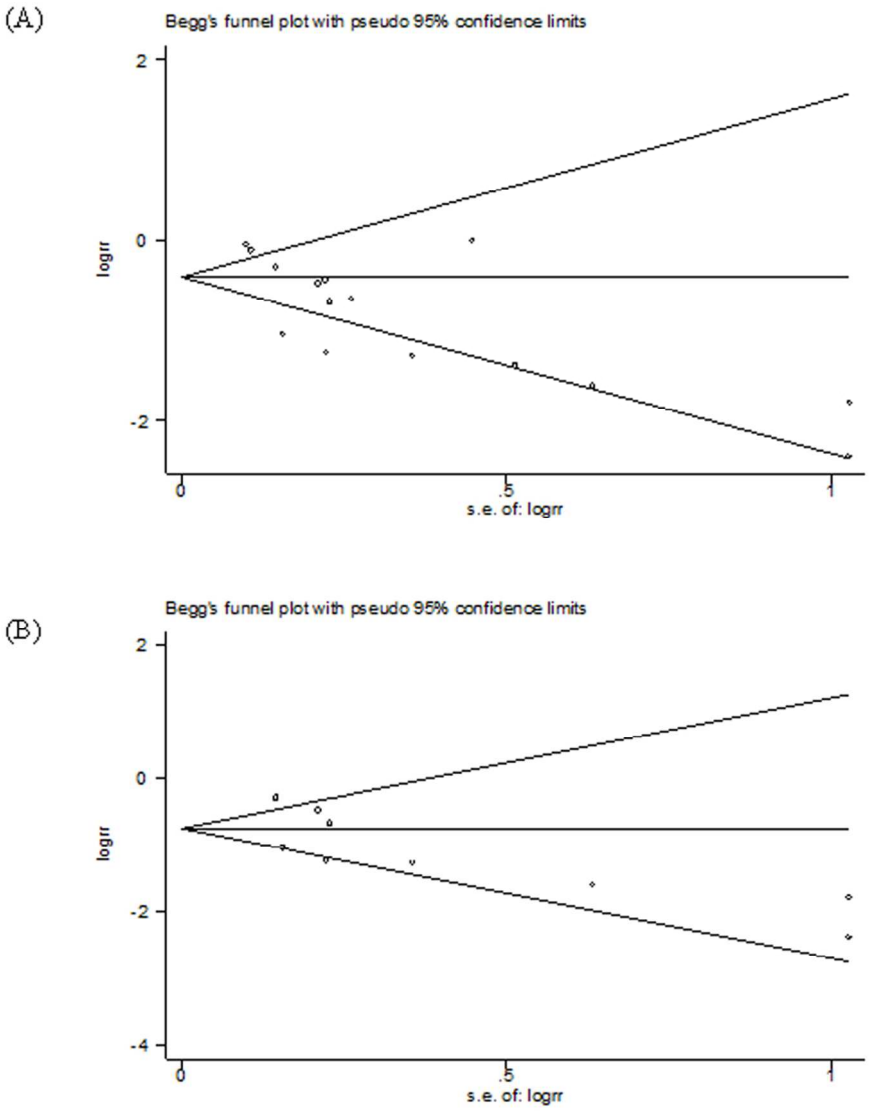

Figure 4. Begg's funnel plot of studies reporting on the preventive effects against CIA included in the meta-analysis. (A) All studies (n = 17). (B) Scalp cooling studies only (n = 10)
85x106mm (300 x 300 DPI)

SUPPLEMENTS (online only figures and tables)

eFigure 1. Risk of bias summary: the authors' judgments about each risk of bias item

eTable 1. Post hoc sensitivity analysis for scalp cooling study (n = 10, each study excluded)

Excluded study	Subjects number	I^2 (%)	RR	95% CI	*P*-value
Villani et al., 1986[26]	781	75.7	0.39	0.33 - 0.46	< 0.001
Robinson et al., 1987[34]	785	74.3	0.39	0.33- 0.47	< 0.001
Parker et al., 1987[7]	803	75.0	0.39	0.33- 0.47	< 0.001
Giaccone et al., 1988[36]	778	76.6	0.37	0.31 - 0.45	< 0.001
Peck et al, 2000[37]	802	75.9	0.39	0.32 - 0.46	< 0.001
Macduff et al., 2003[1]	787	46.3	0.36	0.29 - 0.43	< 0.001
Mols et al., 2009[8]	551	74.1	0.40	0.33 - 0.49	< 0.001
Kargar et al., 2011[39]	755	75.3	0.36	0.29 - 0.43	< 0.001
Van Den Hurk et al., 2012[40]	732	75.3	0.39	0.33 - 0.47	< 0.001
Betticher et al., 2013[41]	579	73.5	0.40	0.33 - 0.48	< 0.001

eTable 2. Adverse events of preventive treatments for chemotherapy-induced alopecia

	Adverse effect	No. of adverse events in experimental group /No. of the participants in experimental group (%)
1977 Edelstyn[33]	NA	NA
1979 Lovejoy[14]	NA	NA
1983 Kennedy[13]	Discomfort during the intervention	3/10 (30%)
1984 Satterwhite[35]	Headache, coldness, heaviness	NA
1986 Villani[26]	Headache	NA
1987 Parker[7]	Headache	2/6 (33.3%)
1987 Robinson[34]	Discomfort during the intervention	2/22 (9.1%)
1988 Giaccone[36]	Headache, coldness	4/23 (17.4%)
1991 Granai[18]	None	–
1994 Rodriguez[16]	None	–
2000 Peck[37]	Anxiety, coldness, headache, nausea	NA
2003 Macduff[1]	Dizziness; Chest pain	Dizziness: 1/10 (10.0%); Chest pain: 1/10 (10.0%)
2007 Gardani[38]	Mild constipation	NA
2009 Mols[8]	Headache	–
2011 Kargar[39]	Headache	12/98 (12.2%)
2012 Van Den Hurk[40]	Coldness	6/65 (9.2%)
2013 Betticher[41] _ENREF_39	Coldness	8/199 (4.0%)

No.: number; NA: not available

eTable 3. Efficacy of scalp cooling prevention for CIA in subgroup meta-analyses by various factors (excluding 1 heterogenic study[1])

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Scalp cooling[7,8,26,34,36,37,39-41]	9	0.36 (0.29-0.43)	46.3%	Fixed effects
Study design				
RCT[7,36]	2	0.40 (0.24-0.65)	60.1%	Random effects
CCT[8,26,34,37,39-41]	7	0.35 (0.29-0.43)	47.4%	Fixed effects
Gender of study population				
Only female[7,26,34,37]	4	0.15 (0.06-0.36)	0.0%	Fixed effects
Mixed gender[36,40,41]	3	0.34 (0.26-0.46)	49.7%	Fixed effects
Not available[8,39]	2	0.40 (0.31-0.52)	80.2%	Random effects
Chemotherapeutic agents				
Doxorubicin-containing regimen[26,36]	2	0.42 (0.26-0.69)	33.3%	Fixed effects
Epirubicin-containing regimen[34,37]	2	0.17 (0.06-0.46)	0.0%	Fixed effects
Docetaxel[40,41]	2	0.29(0.20-0.41)	0.0%	Fixed effects
CMF[7]	1	0.09 (0.01-1.26)	-	-
Mixed regimen[8,39]	2	0.40 (0.31-0.52)	80.2%	Random effects
Underlying cancer				
Breast cancer[7,8,34,37]	4	0.32 (0.24-0.43)	2.0%	Fixed effects
Mixed group of cancer[26,36,40,41]	4	0.33 (0.25-0.44)	36.3%	Fixed effects
Not available[39]	1	0.63 (0.41-0.94)	-	-
Year of publication				
Before 1999[7,26,34,36]	4	0.30 (0.18-0.49)	61.9%	Random effects
After 2000[8,37,39-41]	5	0.37 (0.30-0.45)	54.2%	Random effects
Country				
Europe[8,26,34,36,37,40,41]	7	0.33 (0.27-0.41)	10.3%	Fixed effects
Non-Europe[7,39]	2	0.51 (0.33-0.78)	62.2%	Random effects

RCT: randomized controlled trial; CCT: controlled clinical trial; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
1977 Edelstyn
1979 Lovejoy
1983 Kennedy
1984 Satterwhite
1986 Villani
1987 Parker
1987 Robinson
1988 Giaccone
1991 Granai
1994 Rodriguez
2000 Peck
2003 Macduff
2007 Gardani
2009 Mols
2011 Kargar
2012 Van Den Hurk
2013 Betticher