Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Alopecia during chemotherapy is a distressing side effect of chemotherapy and affects a patient's quality of life. A systematic review and meta-analysis of randomized controlled trials comparing scalp cooling with no scalp cooling using Cochrane methodology was undertaken. Meta-analysis of scalp cooling studies showed a significant reduction in alopecia. Scalp cooling should be presented as an option to patients.

Background: Alopecia is a side effect of chemotherapy and affects a patient's quality of life. Cooling the scalp during chemotherapy might reduce alopecia. The objective of this systematic and meta-analysis was to examine the effects of scalp cooling on the end point of alopecia in randomized controlled trials. **Materials and Methods:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Electronic searches of databases were undertaken through February 2017. In addition other sources were searched. All languages were considered for evaluation. Data were collected and evaluated using a data collection form. Assessment of biases was undertaken using Cochrane methods. When studies could be combined, binary outcomes were evaluated using risk ratio assessment and continuous outcomes were assessed using mean difference (MD). Confidence intervals (CIs) were included and heterogeneity using the I^2 statistic. Grading of Recommendations, Assessment, Development, and Evaluation assessments were also made. **Results:** Ten studies were included in the analysis comprised of 654 patients. Most were patients with breast cancer 432 patients [66%] mainly receiving anthracyclines. For the binary outcome of $< 50\%$ versus $> 50\%$ alopecia, the use of scalp cooling reduced relative risk (RR) of alopecia by 43% (RR, 0.57; 95% CI, 0.45-0.72; $I^2 = 11\%$; $P < .00001$). For ordinal outcomes (alopecia on a scale of 0-3), use of scalp cooling significantly reduced alopecia (MD, −0.80; 95% CI, −1.19 to −0.41; $I^2 = 0\%$; $P < .0001$). The quality of the evidence was graded as moderate. **Conclusion:** This systematic review and meta-analysis supports the use of scalp cooling to prevent alopecia in patients with solid tumors undergoing chemotherapy.

Clinical Breast Cancer, Vol. 18, No. 1, 19-28

Keywords: Alopecia, Breast cancer, Chemotherapy, Scalp cooling

Introduction

Alopecia is a common side effect of chemotherapy and has significant psychosocial and quality of life (QoL) issues, most especially for women. Alopecia consistently ranks among the top most distressing side effects of chemotherapy.[1] Further, those experiencing high distress because of alopecia are more likely to have poorer body image, lower psychosocial well-being (including lower social, physical, cognitive, role, and emotional functioning) and are more likely to have depression.[2] Significant progress has been made in treating many of the side effects of chemotherapy (including emesis, infection, thrombosis, pain, and bone marrow suppression).[3] To date however, progress in preventing alopecia has not been as significant.

Chemotherapy agents that commonly cause alopecia include: anthracycline antibiotics (doxorubicin, epirubicin), microtubule antagonists (paclitaxel, docetaxel, eribulin, ixabepilone), and alkylating agents (ifosfamide, cyclophosphamide, etoposide). These drugs can be used alone, or in combination over several courses of treatment as treatment for solid and nonsolid tumors.[3] Chemotherapy induced alopecia (CIA) is dose- and schedule-dependent,

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Submitted: Dec 7, 2016; Revised: Apr 4, 2017; Accepted: Jul 16, 2017; Epub: Aug 10, 2017

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http://dx.doi.org/10.1016/j.clbc.2017.07.012

with alopecia usually occurring 7 to 14 days after the first dose of chemotherapy, although lower doses of chemotherapy given more frequently might cause delayed alopecia.[4]

Chemotherapy agents generally target rapidly proliferating cells such as hair follicles, causing apoptosis. Most hair follicle cells represent keratinocytes (epidermal cells) within the epithelial matrix of the hair follicle, which proliferate rapidly. Because chemotherapy does not discriminate between tumor cells (which also proliferate rapidly) and keratinocytes, these cells are also damaged causing the hair shafts to fall out.[3]

Scalp cooling has been widely used to decrease CIA. There are several mechanisms that have been postulated as to how scalp cooling prevents CIA.[5] These include cutaneous vasoconstriction leading to a decrease in the concentration of chemotherapy in the scalp, decrease in cellular uptake of chemotherapy by the hair follicle, and reduction in the hair follicle metabolic rate.[5]

Scalp cooling has been used in the clinic since the late 1970s. Current devices include caps frozen to very low temperatures (eg, −18°C to −25°C), then placed on the head before, during, and after chemotherapy treatment; the caps must be changed every 30 minutes because they thaw (Penguin Cold Caps). Although this technology has been reported to be effective in preventing alopecia,[6] it requires refrigeration for storage as well as freezing before use, and support with changing the caps every 30 minutes during and after treatment. Newer self-contained technologies use a machine to cool and circulate a glycol-based fluid in channels within a cap, allowing the scalp temperature to be controlled and maintained throughout the treatment course. These systems include the DigniCap Scalp Cooling System (Dignitana) and the Orbis (Paxman).

There are several systematic review articles and technology assessments that have examined the use of scalp cooling during chemotherapy.[2,4,7-12] This systematic review and meta-analysis adds additional information in several areas. Only one of the previously published reviews performed a systematic review and meta-analysis.[11] This review included nonrandomized trials (NRTs), which possibly overestimated the true effect of scalp cooling in preventing alopecia, depending on chemotherapy regimen and intensity. Other reviews included small nonrandomized single cohort studies with older chemotherapy regimens that reported scalp cooling using a variety of techniques; some of which were ineffective in preventing alopecia.[13,14] Measures of alopecia and hair preservation varied widely, including subjective assessments by providers or use of wigs. Last, none of the reports have examined the available data using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] A comprehensive review of randomized trials is important because at least one major patient advocacy group in the United States has stated that controlled studies on scalp cooling have produced conflicting results.[16]

In this review, using PRISMA guidelines, we undertake a systematic review of randomized controlled trials (RCTs) and perform meta-analyses on similar outcomes. The main objective of this review was to determine whether the use of scalp cooling versus no scalp cooling in RCTs (in aggregate) significantly reduced alopecia when used with chemotherapy regimens for cancer.

Materials and Methods

Randomized controlled trials that investigated the effect of scalp cooling versus no scalp cooling in patients receiving chemotherapy were included. Quasi-RCTs, that is, trials in which participants were allocated according to date of birth, day of the week, medical record number, month of the year, or order of inclusion in the study (eg, alternation), were included only in the absence of RCTs. Since RCT's were identified in the systematic searches, quasi-RCT's were not included. All languages were considered.

Any type of scalp cooling system was included in the analysis. Each scalp cooling system as treatment was in place approximately 15 to 20 minutes before, during, and 30 to 60 minutes after chemotherapy.

The primary outcome measure evaluated was the extent of alopecia during and after chemotherapy regimens for treating cancer. The more common means for evaluating alopecia was using a grade scale from 0 to 3, with a grade of "0" being no alopecia (0% alopecia); a grade of "1" being $>$ 0% to $<$ 25% alopecia (minimal alopecia); grade of "2" being $>$ 25% to $<$ 50% alopecia (moderate alopecia) and; a grade of "3" being $>$ 50% alopecia (severe alopecia requiring a wig).[17-20] A variation on this without the grade scale, using only percentages of alopecia (0%-25%, 26%-50%, 51%-75%, $>$ 75%) was used by Kennedy et al.[21] Other methods used in evaluating the extent of alopecia included: the number of hairs lost after 15 days past each chemotherapy treatment (number of hairs collected over a 2-week period after the 15th day of chemotherapy treatment),[22] and the categories of: none, minimal, moderate, and severe alopecia.[23]

Secondary outcomes were noted such as adverse events, which included headache, cold sensation, and intolerability of cold cap (with requirement for removal), and QoL and were evaluated.

Searches

Electronic searches performed were:

- The Cochrane Database of Systematic Reviews (searched November 11, 2015), which also included:
  - The Cochrane Central Register of Controlled Trials (2015, Issue 3)
- Centre for Reviews and Dissemination
  - The Database of Abstracts of Reviews of Effects (2015, Issue 1)
  - The National Health Service Economic Evaluation Database (NHS EED; 2014, Issue 1)
  - The NHS EED (up to March 2015)
- Ovid MEDLINE (1970 to March 11, 2017)
- Ovid MEDLINE (in-process and other non-indexed citations, October 23, 2015)
- Network Digital Library of Theses and Dissertations (searched November 10, 2015)
- ClinicalTrials.gov (searched November 10, 2015)

The following search terms were used with these electronic searches: ((((scalp) and cool*) AND hair) and loss) and chemotherapy.

Other sources searched were manufacturer Web sites for scalp cooling systems used in preventing alopecia on March 11, 2017. These manufacturer Web sites included Dignitana (Dignitana AB, Sweden),

Paxman scalp cooling system (Paxman Coolers Limited), Chemocold cap (Chemotherapy Cold Caps, Inc), Penguin Cold Caps, and Elasto-Gel Cold Caps (Southwest Technology Inc.).

Technology assessment Web sites were searched on November 12, 2015 and included: Center for Technology Assessment Forum, Blue Cross Blue Shield Technology Evaluation Center Assessment, National Institute for Health and Clinical Excellence, and the Canadian Agency for Drugs and Technology in Health.

Patient advocacy/support group Web sites were searched on November 14, 2015. These Web sites included the American Cancer Society and the National Breast Cancer Foundation.

Manual searches of the reference sections of reviews and systematic reviews with or without meta-analyses of scalp cooling systems were searched on November 11, 2015. Manual searches of the reference sections of RCT reports were searched on November 11, and November 19, 2015.

Last, the following journal Web sites were also searched on February 24, 2017 (all dates):

- *Journal Clinical Oncology*
- *European Journal Cancer*
- *European Journal Cancer Care*
- *Cancer Journal*
- *Cancer Nursing Journal*
- *Cancer Nursing Practice*
- *Oncology Nursing Forum*
- *Journal of the American Medical Association*

Two review authors independently screened the titles and abstracts of all studies identified in the search. Upon the agreement of both review authors, full-text versions were obtained of all studies identified as potentially relevant, and 2 review authors assessed them independently against the inclusion criteria. Any disagreement(s) between the 2 review authors were resolved by discussion. A data extraction form was developed (Appendix A). One review author extracted the data and a second review author validated the extracted data. If a study had more than 1 publication, we considered all versions to maximize data extraction, and identified the primary publication, along with the secondary references. Studies that required translation were performed by one of the authors (J.V.).

Two review authors independently assessed each included study using the Cochrane Collaboration tool for assessing risk of bias.[24] This tool addresses 6 specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues (eg, extreme baseline imbalance; see Appendix B for details of the criteria on which judgements were based). We assessed blinding and completeness of outcome data for each outcome separately. A 'risk of bias' table for each eligible study was also completed. Any disagreement(s) among the review authors were discussed to achieve a consensus.

Assessment of risk of bias was evaluated using a 'risk of bias' summary figure, which presents all of the judgements in a cross-tabulation of study by entry.

Funnel plots were used to help in the assessment of reporting and selection bias, and the plots were examined for evidence of potential publication/location bias (high vs. low impact journals, and country publication bias). If asymmetry existed in the funnel plots, selection bias was examined further.

An assessment of studies other than RCTs (ie, quasi-RCTs) was undertaken using the same criteria. However no quasi-RCTs were included because of the identification of RCTs. The results of the 'risk of bias' assessment were incorporated into the review through systematic narrative description and commentary about each of the domains, leading to an overall assessment of the risk of bias of the included studies and a judgement about the internal validity of the results.

The results of binary outcomes were summarized descriptively (eg, $>$ 50% or $<$ 50% alopecia) and treatment comparisons were presented as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). For continuous data (eg, grading of alopecia from 0 to 3; no alopecia to $>$ 50% alopecia), the mean difference (MD) was used when trials measured outcomes in the same way, and the standardized MD (Hedges adjusted g) when trials used different methods to measure the same outcomes.[25] The results of the treatment effect are reported in the Results section. In cases in which studies could not be combined for meta-analysis purposes, the statistics from those singular studies are reported.

The I^2 statistic was used to determine statistical heterogeneity and to determine appropriateness of meta-analysis. The heterogeneity thresholds described in the *Cochrane Handbook for Systematic Reviews of Interventions* were used to identify the levels of heterogeneity in the trials. These thresholds are: 0% to 40% (might not be important); 30% to 60% (might represent moderate heterogeneity); 50% to 90% (might represent substantial heterogeneity); and 75% to 100% (considerable heterogeneity).[23] If the I^2 value was $>$ 60%, a sensitivity analyses was undertaken in an attempt to identify studies that were most likely to be causing the problem. If there were only a few such studies, and they could be identified, the reasons for their difference were explored and a determination for the appropriateness of removing them was made. When appropriate, a meta-analysis excluding these studies[23] was performed.

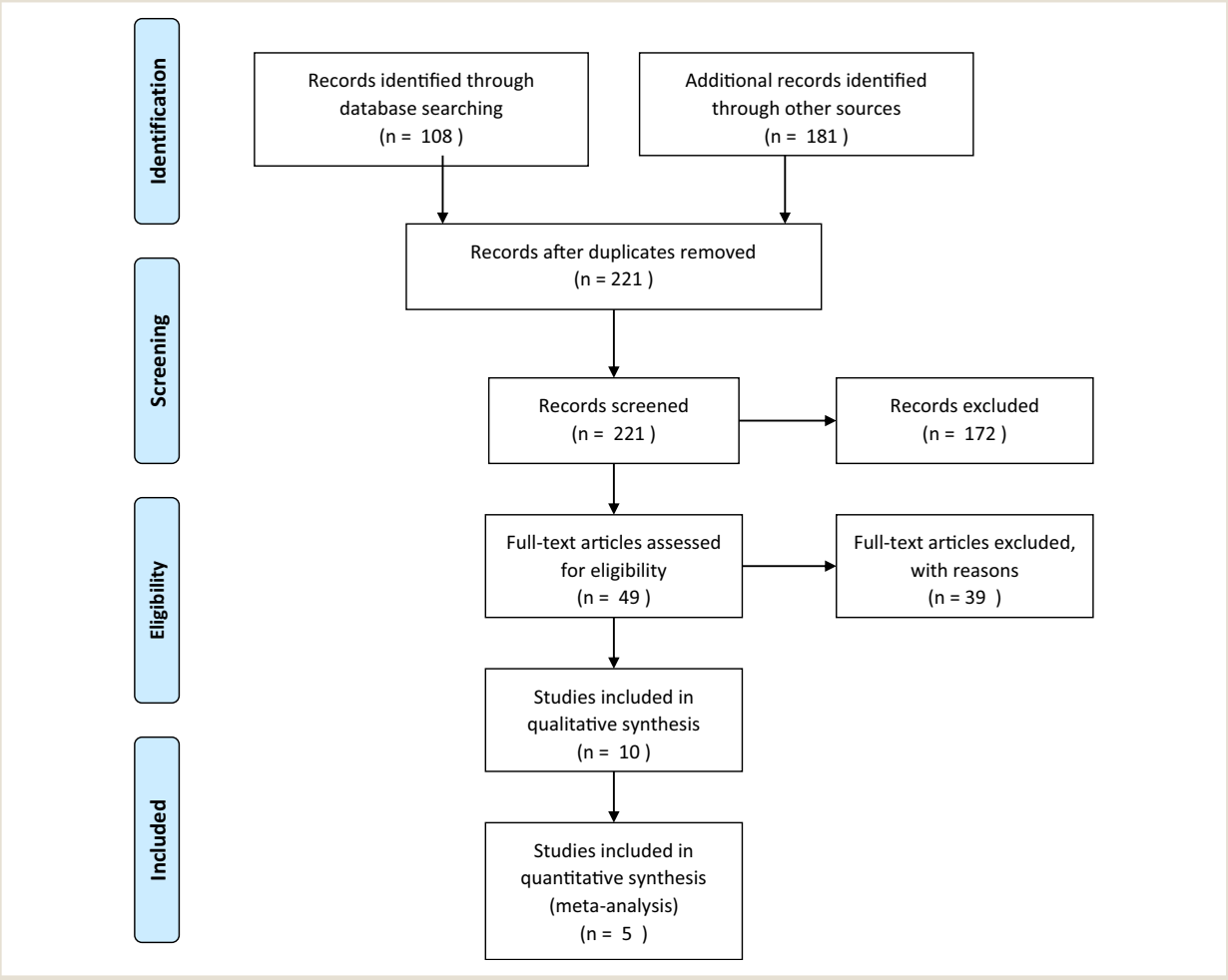
When possible, studies that were similar were grouped together. A fixed-effect meta-analysis was used first. In the absence of heterogeneity ($I^2 = 0\%$), or in the presence of low heterogeneity ($I^2 < 40\%$), in the initial fixed-effect model, the observed difference was assumed to be solely due to chance and used only in a fixed-effect model. If heterogeneity was moderate in the fixed-effect model ($I^2 > 40\%$ and $\leq 60\%$) a random-effects model was used when heterogeneity could not be readily explained, otherwise a fixed-effect model[23] was used.

Last, a Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) summary of findings table was used in assessing the evidence using GRADEpro 3.6 software.[26]

Results

The electronic searches identified a total of 108 potentially relevant reports. A total of 20 abstracts were screened of which 12 studies were obtained for full review. Searching other sources identified 181 potentially relevant reports. After duplicates were removed, a total of 221 abstracts were screened of which 49 studies were obtained for full review (see the PRISMA Flow Diagram [Figure 1] for the total number of records identified, duplicated removed, records screened, and full articles assessed for eligibility).

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram for Scalp Cooling



There were 10 studies included in the review that met the criteria for eligibility. Six of the studies were performed in Europe[16,18,22,27,28] and 4 were performed in the United States.[19-21,29] Two of these studies were a multicenter study[18,28] with the remainder being single-center. All of these studies except for 2 used older scalp cooling technology (eg, frozen caps) rather than the more recent technologies such as for example, DigniCap Scalp Cooling System (Dignitana) or Orbis (Paxman). Two studies used the Paxman system.[18,28] Most patients in all of these studies were treated with anthracyclines (doxorubicin, epirubicin or taxanes)[16,18,19,22,26,27] for several cycles. See Table 1 for the breakdown of cancer therapies and cancer types.[17-23,27-29]

Six of the studies compared scalp cooling with no scalp cooling.[16,18,19,21,27] Three of the studies compared one scalp cooling system with another.[18,22,26] The van den Hurk et al[28] study specifically examined the amount of time, after intravenous chemotherapy administration, that a scalp cooling system could be worn (20 vs. 45 minutes) and compared their efficacy on reducing alopecia. Also see the *Characteristics of studies* section (Appendix C) for more detail on the types of patients included from each study.

Twenty-four studies were excluded with reasons.[6,14,30-51] All except for 1 study[40] were not an RCT. Lovejoy[41] was an RCT except that it examined the use of a "head tourniquet" versus no head tourniquet in reducing the blood flow to the head in preventing alopecia during chemotherapy and thus was excluded (see Appendix D for more detail on excluded studies).

Although randomization was stated in the Materials and Methods section to prevent selection bias, in only 4 of the RCTs was the method of randomization clear.[18,19,22,28] Further, it was clear in only 1 trial[28] the point at which patients were randomized and when treatment began to prevent selection bias (ie, concealment). In all cases because of the use of a scalp cooling system versus none or versus another, the patients and clinicians performing scalp cooling knew the group to which the patient was allocated. Most importantly, there was 1 trial in which the clinician evaluating for alopecia was blinded to the treatment arm.[18] Further, there were 5 trials[17,18,21,22] in which there were incomplete data (attrition) on the end point of alopecia. Last, in 1 trial the end point of alopecia as identified in the methods section was only partially reported on in the results section.[29] Overall, most studies had an unclear risk of bias, with approximately equal numbers between low and high risk of bias. The risk of bias summary and risk of bias graph are shown in Figures 2 and 3, respectively.

Table 1 Treatments and Dosages According to Cancer Type

Study	Number of Patients	Scalp Cooling Method Used	Treatment (Cancer Therapies)	Number of Treatments	Cancer Type
Dougherty[27]	48	Gel cap	Doxorubicin and/or epirubicin	Unclear	Mainly breast cancer (statistics not available)
Dougherty[23]	170	Chemocap and Gel cap	Epirubicin or doxorubicin, fluorouracil, cyclophosphamide	Unclear	Breast cancer
Edelstyn et al[17]	87	Cryogel bag	Doxorubicin, vincristine, 5-fluorouracil, chlorambucil, methotrexate	1	Breast cancer
Giaccone et al[18]	35	Spenco Hypothermia Cap	Cyclophosphamide, 5-fluoroouracil, vincristine, cisplatin, carboplatin, mitomycin	2	Advanced or metastatic cancer: breast, 91%; ovary 9%
Kennedy et al[21]	19	Chemocap	Cyclophosphamide, doxorubicin	6	Metastatic cancer: breast 53%; gastric 15%; lymphoma 11%; sarcoma 11%; pancreatic 5%; mesothelioma 5%
Macduff et al[19]	17	Gel cooling cap	Epirubicin with docetaxel	6	Breast cancer
Nangia et al[29]	142	Paxman scalp cooling system	51 With doxorubicin and cyclophosphamide; 43 with docetaxel and cyclophosphamide; 32 with docetaxel with carboplatin and trastuzumab; 10 with paclitaxel; 3 with docetaxel; 2 with docetaxel with pertuzumab and trastuzumab; 1 with paclitaxel with carboplatin	4	Stage I and II breast cancer
Parker[22]	14	Spenco Hypothermia Cap	Cyclophosphamide with methotrexate and 5-fluourouracil	Minimum of 7 treatments	Stage IV breast cancer
Satterwhite and Zimm[20]	25	Chemocap	All with doxorubicin with combinations of 16 and Cytoxan (cyclophosphamide); Cytoxan, vincristine, cisplatin, 5-fluourouracil/mitomycin C; dacarbazine, Velban (vinblastine)/thiotepa/ fluoxymesterone	Average of 2 treatments	Breast 36%; stomach 16%; lung 12%; all others 40%
van den Hurk et al[28]	97	Paxman scalp cooling system	Docetaxel	Unclear	Unclear

The total number of patients was 654, and 523 (80%) had breast cancer.

There was a significant effect of scalp cooling in reducing alopecia (eg, patients generally requiring a wig; RR, 0.54; 95% CI, 0.46-0.63; $I^2 = 11\%$; $P < .00001$; Figure 4). In other words, the risk of significant alopecia was reduced by 46% with scalp cooling relative to no scalp cooling during chemotherapy.

When examining the effect of scalp cooling on an ordinal scale from grade 0 to 3; with grade "0" no alopecia; grade "1" 0% to 25% alopecia; grade "2" 26% to 50% alopecia, and grade "3" > 50% alopecia, it was found that the use of scalp cooling significantly reduced the grade of alopecia (MD, −0.80; 95% CI, −1.19 to −0.41; $I^2 = 0\%$; $P < .0001$; Figure 5).

Despite the presence of biases and the small study sizes, the intervention effect is fairly symmetrical when plotting the studies examined as shown in the Figure 4 analysis and as can be seen in the funnel plot (Figure 6).

Only 1 study reported on QoL assessments using the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire−Core 30, Hospital Anxiety and Depression Scale, and Body Image Scale.[28] In examining between group differences using the Kruskal−Wallis test, there was no statistical difference on any of these instruments.

Adverse events/side effects as an end point were identified in only 1 of the methods sections of the included studies.[28] They were reported in the results sections of 4 studies.[17-19,21] These side effects included as the main adverse event headache: 4 patients of 19,[17] 2 of 6,[21] 12 of 101,[28] and in 2 studies no statistics were available.[18,19]

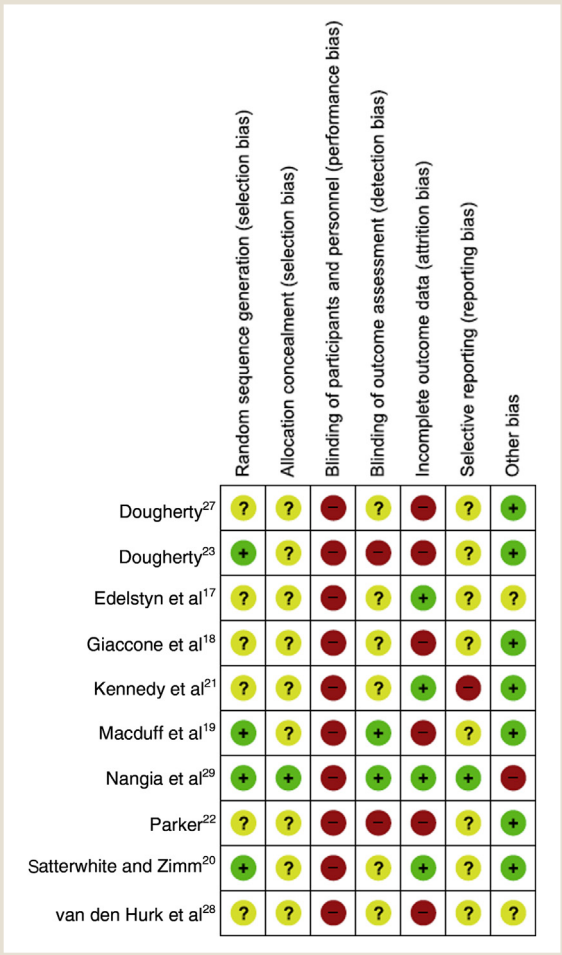
Last, a GRADE assessment (Table 2) was regarded as moderate, namely, that the confidence in the estimate of the effect might change but that there is likely an effect of scalp cooling in reducing alopecia from chemotherapy.

Discussion

Scalp cooling to prevent alopecia during chemotherapy for cancer has been examined extensively in the literature—in reviews,[3,4,6,8-11] technology assessments,[7] and in numerous observational studies. In most cases, it has shown a positive effect in reducing CIA. However, to date no one has examined its effect specifically in high-quality studies (ie, RCTs) and using meta-analysis statistical techniques. This systematic review and meta-analysis shows similar findings compared with previous reviews, technology assessments, and observational studies.

One of the concerns with scalp cooling is that its use would be associated with an increased risk of subsequent metastases to the scalp. This concern arises from the concept that reduced blood flow to the scalp from cooling would decrease exposure of the scalp to chemotherapy drugs, creating a site of potential risk for recurrence. This has also been studied extensively in longitudinal studies on the longer-term effect of scalp cooling on scalp metastases[5,52,53] and were found not to increase the risk of scalp metastasis. In one study,

Figure 2 Risk of Bias Summary



at a median follow-up of at least 5.4 years in a large series of patients with early stage breast cancer including those using or not using scalp cooling, the incidence of scalp metastases was 1.1% in those using scalp cooling versus 1.2% in those who did not use scalp cooling.[5] Two additional studies, including one study that examined numerous observational, autopsy studies[51] and the Munich cancer registry showed no statistical difference in the incidence of scalp metastases between scalp cooled (0.04%-1%) and non−scalp-cooled (0.03%-3%) patients with breast cancer. Last, in a retrospective analysis of more than 1300 patients with breast cancer, it was found that there was no difference in overall mortality between scalp cooled and non−scalp-cooled patients followed for at a median of 6.3 and 8.0 years (adjusted hazard ratio, 0.89; 95% CI, 0.60-1.17; $P = .49$).[54] Although the RCTs reported in this article did not include long-term follow-up, and therefore did not specifically report the incidence of scalp metastases, the studies outlined previously provide evidence to refute any potential risk of worse cancer outcome associated with scalp cooling to prevent CIA; specifically in patients with breast cancer.

One of the main issues with CIA is its effect on a patient's QoL. As mentioned previously, hair loss ranks among the most distressing side effects of chemotherapy, most especially in women.[55] This distress is cross-cultural in nature[56] and might affect patient activity levels and discomfort on QoL instruments such as the EQ-5D (Euro-QoL 5 dimension).[51] Thus, a therapy that can reduce the incidence of hair loss such as scalp cooling might likely help to improve patient QoL, particularly when considering the other issues associated with the diagnosis and treatment of cancer. Further, interventions (ie, scalp cooling) that can reduce or eliminate treatment-associated toxic effects might help ease the distress associated with chemotherapy, and could as a result, improve recovery time for patients with breast cancer.[55] Last, with the growing acceptance of "patient centered" care and the recent US Food and Drug Administration clearance for one scalp cooling system, medicine is reaching an inflection point that justifies far more

Figure 3 Risk of Bias Graph

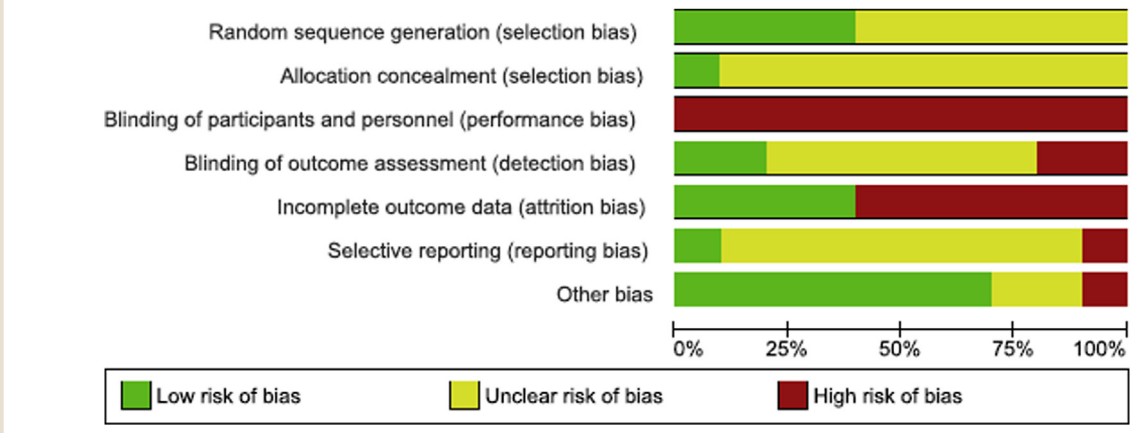
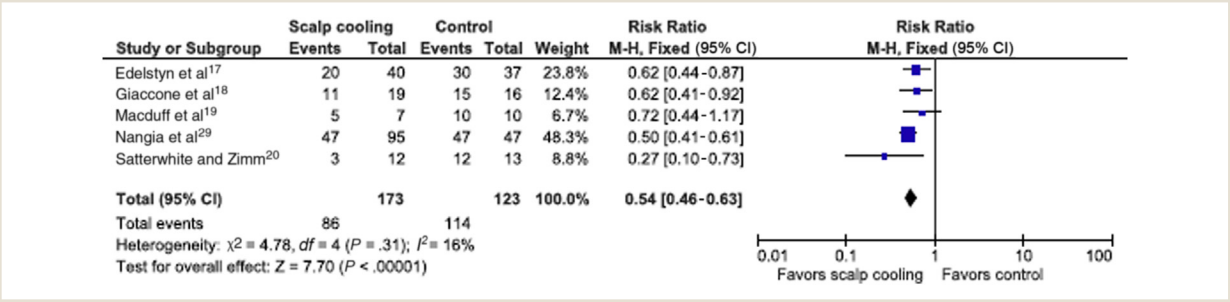


Figure 4 Forest Plot: Significant Alopecia (Risk of Requiring a Wig)



Abbreviation: M-H = Mantel-Haenszel.

widespread adoption of scalp cooling.[56] This systematic review and meta-analysis adds additional support to the finding of statistically significant higher rates of hair preservation (thus supporting patient-centered care) with scalp cooling compared with chemotherapy administered without cooling.

As noted previously, adverse events as an outcome were reported minimally in the RCTs identified. This is not to say that there are not any adverse events associated with scalp cooling. Recent published reports have identified cold thermal injury from the use of older scalp cooling technologies which included Penguin cold caps and Elasto-Gel hypothermia caps.[57] These infrequent adverse events as noted in the report were mild to moderate in severity, infrequent, preventable, and, likely resulted from improper device application procedures.[53]

A more severe adverse event, scalp metastasis, due to scalp cooling in patients with primary breast cancer, has recently been evaluated on in the literature.[53] It was found in this systematic review and meta-analysis that the incidence of scalp metastasis in scalp cooled versus non—scalp-cooled primary breast cancer patients was not statistically different in a pooled and large series of patients followed over 43 to 87 months.[58]

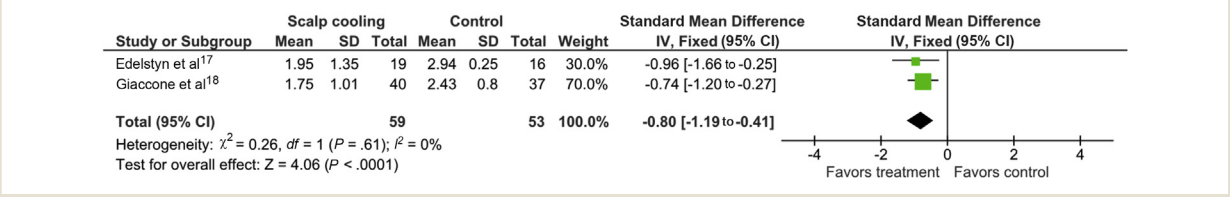
Although cost effectiveness was not an end point evaluated in any of the identified studies, it has been studied in nonrandomized prospective trials.[49] In an incremental cost effectiveness ratio analysis, incremental costs (scalp cooling [machine and nursing time] vs. standard of care consisting of hair dressers, wigs, head covers) versus incremental benefit (measured according to quality adjusted life years or QALY) ratio was 269 Euros per QALY, making it cost effective in a Dutch population—where the willingness to pay for a QALY is between 20,000 and 30,000 Euros. Although these results are promising and might indicate cost effectiveness, they need to be confirmed in a prospective trial.

Interestingly, older (older than 13 years old) scalp cooling technologies that are less form-fitting to the head (Spenco Hypothermia Cap, Spenco Medical Corp; Chemocap, Satterwhite Therapeutic Products, Inc; Cryogel bag [no mention of manufacturer]; Gel cooling cap [no mention of manufacturer]) showed a statistically significant 43% relative risk reduction in alopecia. Newer technologies such as the Paxman system have also shown a 50% relative risk reduction in alopecia in an RCT and in non-RCTs (Dignitana) compared with historical or current controls.[51] This diversity of technologies shows that scalp cooling has a positive effect on reducing alopecia.

The overall GRADE assessment was regarded as moderate, namely, that the confidence in the estimate of the effect might change but that there is likely an effect of scalp cooling in reducing alopecia from chemotherapy. Note as well, that the findings of scalp cooling having a positive effect in reducing alopecia have been repeated numerous times in NRTs and because of this they should be viewed in total (RCTs and non-RCTs) in a positive light.

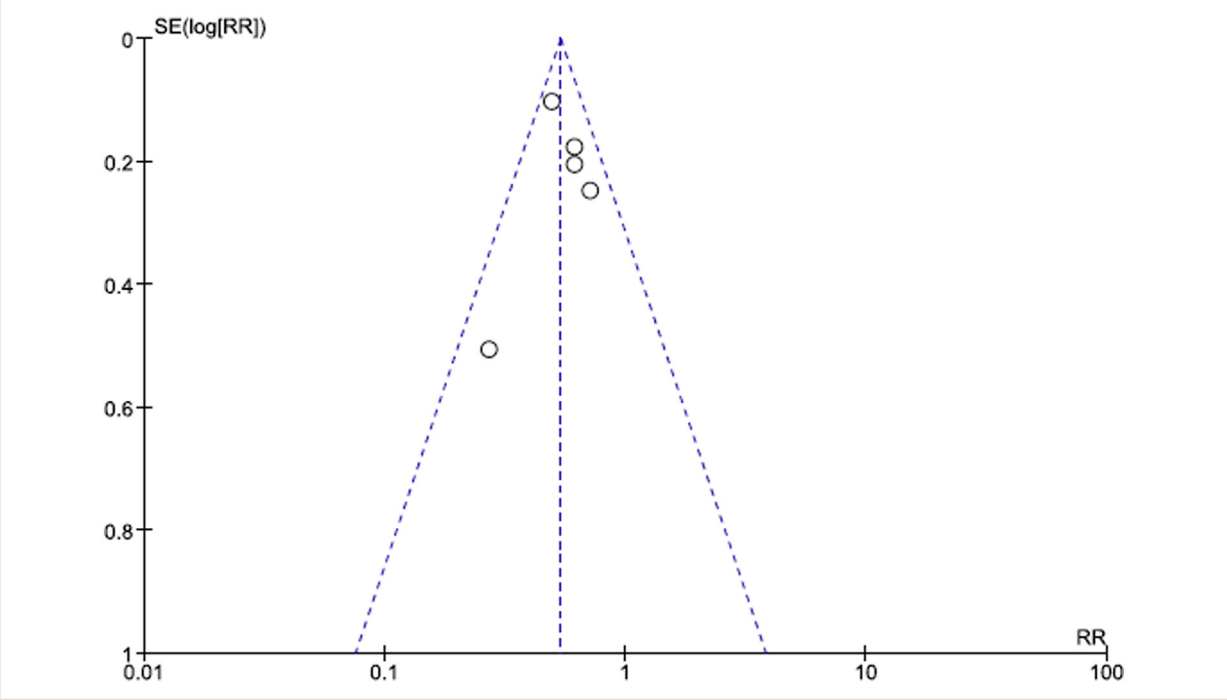
As it relates to agreements and disagreements with other systematic reviews, the Shin et al[12] systematic review and meta-analysis of controlled trials on the effect of scalp cooling estimated the effect of preventing alopecia at a 62% relative reduction in alopecia versus no scalp cooling (evaluating a total of

Figure 5 Forest Plot: Grading of Alopecia, 0 to 3



Abbreviation: IV = inverse variance.

Figure 6 Funnel Plot



Abbreviations: RR = risk ratio; SE = standard error.

Table 2 Grading of Recommendations, Assessment, Development, and Evaluation Assessment of Scalp Cooling Versus No Scalp Cooling for Prevention of Alopecia With Chemotherapy[a]

Outcomes	Illustrative Comparative Risks (95% CI)[b]		Relative Effect (95% CI)	Number of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk	Corresponding Risk			
		Scalp Cooling vs. No Scalp Cooling With Chemotherapy			
Significant Alopecia (>50% of Alopecia; Generally Requiring a Wig)	Study population		RR, 0.54 (0.46-0.63)	295 (5)	⊕⊕⊕⊖ Moderate[c,d,e,f,g,h]
	927 per 1000	500 per 1000 (426-584)			
	Moderate				
	930 per 1000	502 per 1000 (428-586)			

The GRADE Working Group grades of evidence are: 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 influence on our confidence in the estimate of effect and might change the estimate; low quality = further research is very likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate; and very low quality = we are very uncertain about the estimate.
Abbreviations: GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; RR = risk ratio.
[a]Patient or population: patients with preventing alopecia in chemotherapy. Setting: hospital outpatient or physician office. Intervention: scalp cooling versus no scalp cooling with chemotherapy. Comparison: scalp cooling versus no scalp cooling.
[b]The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes.[c-h] The corresponding risk (and its 95% CI) is on the basis of the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[c]Blinding of the participants and clinicians administering the therapy in each arm was not possible. Blinding of the clinical assessor was not clear in 6 of 9 studies. In 5 of 9 of the trials there was attrition of patients.
[d]All randomized trials comparing scalp cooling with no scalp cooling show a positive effect of scalp cooling versus none with low heterogeneity; $I^2 = 11\%$.
[e]Direct comparisons are made of scalp cooling with no scalp cooling in all of the studies included in the meta-analysis.
[f]Four of 5 CIs in the meta-analysis are narrow.
[g]On the basis of the funnel plot (Figure 5), there does not appear to be publication bias.
[h]The risk ratio is > 0.50 and therefore on the basis of the grading of this using GRADE is regarded as not having a large effect.

10 scalp cooling studies; with only 3 of the 10 studies using randomization for assignment of participants and comprising only 16% of the overall weighting of the effect). However, the heterogeneity of studies in this meta-analysis was very high at $I^2 = 74\%$ versus the current analysis with a heterogeneity at $I^2 = 11\%$. One of the reasons for this high heterogeneity in Shin et al[12] might have been because NRTs were included and overweighted the risk reduction. One nonrandomized study[53] included in Shin et al,[12] contributed 44% to overall weighting in the risk reduction at a RR of 0.35 (95% CI, 0.26-0.48). As well, another nonrandomized study[31] (in Shin et al[12]), contributed 14% to overall weighting in the risk reduction at a RR of 0.28 (95% CI, 0.19-0.45). Lastly, patients with other cancers (lung, prostate) and male patients[31] were also included in the Shin et al[12] analysis. A danger with incorporating large NRTs of poor methodological quality is that they might dominate the findings of studies at less risk of bias. It has been noted that CIs for effect estimates from large NRTs should be interpreted with caution because they are less likely to represent the true uncertainty of the observed effect.[23]

Other systematic reviews and overviews[6,9,10] affirm the findings of this systemic review and meta-analysis supporting the evidence found herein.

Conclusion

In patients who receive chemotherapy (eg, anthracylines and cyclophosphamides, and taxanes) mainly for breast cancer but also for patients with other solid tumors, the use of scalp cooling appears to have a positive effect on reducing the amount of alopecia and should be considered as a therapy for reducing alopecia.

Study Limitations

One of the limitations of this analysis is the small number of RCTs identified—10. This might be because of the issue of blinding the clinician as well as patient to the treatment group—on the basis of how scalp cooling works/is administered.

A second limitation is the number of patients who were evaluated. This might be, however, because of the large difference in the positive effect of scalp cooling—thus not requiring large numbers to show an effect.

Clinical Practice Points

- Alopecia is a common side effect of chemotherapy in patients with breast cancer or other solid tumors, and presents significant psychosocial issues for patients.
- Although previous studies have shown that scalp cooling might have an effect on alopecia, these studies were of poor quality—with inherent biases, which made their findings suspect.
- To our knowledge, to date no one has examined the highest quality evidence (ie, RCTs), using rigorous review methods (ie, Cochrane Review), to determine the effect of scalp cooling on alopecia.
- This systematic review and meta-analysis showed that scalp cooling does reduce the incidence of alopecia in a meaningful way.
- These findings should provide clinicians with confidence in offering this therapy to patients and it having a positive effect on reducing alopecia and potentially in how they might feel about themselves.

Disclosure

Jeff Voigt works in evidence assessments using Cochrane methodology. Jeff Voigt was provided an unrestricted grant by Dignicap USA to research, analyze, and write the report.

Supplemental Data

Supplemental appendixes accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clbc.2017.07.012.

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