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Efficacy of scalp cooling for prevention of chemotherapy induced alopecia: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The aim of the study was to compare the risk of chemotherapy induced alopecia among patients with scalp cooling therapy, compared to those that did not receive scalp cooling.

MATERIALS AND METHODS: A systematic search was conducted in the PubMed, Scopus, Cochrane Database of Systematic Reviews and Google scholar databases. Studies, preferably randomized controlled trials, that compared scalp cooling with no scalp cooling (control) for risk of alopecia or hair loss in patients undergoing chemotherapy were considered for inclusion. The strength of association was presented in the form of pooled adjusted relative risk (RR) for categorical outcomes and weighted mean difference (WMD) for continuous outcomes. Statistical analysis was done using STATA version 16.0.

RESULTS: A total of 14 articles were identified, of which 9 were included in the meta-analysis and for the remaining 5 articles, the findings were synthesized descriptively. Compared to control group patients, those that received scalp cooling had 41% lower risk of alopecia [RR 0.59, 95% CI: 0.53, 0.66]. The overall quality of pooled evidence for the risk of alopecia was judged "moderate". There were no differences in the anxiety score [WMD 0.57, 95% CI: -0.55, 1.69], depression score [WMD 0.31, 95% CI: -1.19, 1.80], score reflecting emotional functioning [WMD 0.06, 95% CI: -1.37, 1.49] and social functioning [WMD -8.37, 95% CI: -25.7, 8.93] among the two groups of patients. The pooled evidence suggests that around 66% (95% CI: 37-95%) of the subjects reported some discomfort with use of scalp cooling system. The commonly reported complaints included headache, scalp and neck pain, discomfort due to chill, nausea/vomiting and dizziness.

CONCLUSIONS: Findings suggest that the use of scalp cooling, compared to no scalp cooling, reduces the risk of significant hair loss. The acceptability of this cooling system might be limited by a high incidence of reported complaints.

Key Words:
Scalp cooling, Chemotherapy induced alopecia, Randomized controlled trials, Meta-analysis.

Introduction

Alopecia is one of the most common cutaneous side effects of chemotherapy and affects the quality of life tremendously[1,2]. Patients with chemotherapy inducted alopecia (CIA) usually tend to suffer from low self-esteem, negative body image and in extreme instances, depression and other psychological problems[2,3]. The underlying rationale of alopecia is that these chemotherapeutic drugs act of rapidly dividing cells within the human body and fail to differentiate between malignant cells and normal body cells. Hair follicles are usually in the anagen state, i.e., a state of rapid proliferation and, therefore, become targets for the chemotherapeutic drugs[4,5]. Furthermore, these hair follicles are rich in blood supply and consequently, these drugs tend to accumulate. In the usual course, CIA starts to appear 2-4 weeks after the start of chemotherapy. The alopecia is rarely permanent and hair regrowth tends to start 3 to 6 months after the end of chemotherapy[6,7]. However, the quality, colour and consistency of the hair has been shown to be affected[5-7].

Several approaches[6,8] have been attempted to reduce CIA but none of them have met with considerable success. These approaches could be broadly categorized as physical and pharmacological. One of such physical techniques was use of scalp torniquet that involved use of head bands to diminish superficial blood supply to the scalp and hair follicles[9]. This method was not widely practiced due to high incidence of headache and discomfort. One widely used pharmacological approach is the use of minoxidil. Minoxidil im-

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proves hair growth by stimulating resting hair follicles into anagen phase[10,11]. This drug has proliferative and anti-apoptotic effects on hair follicles. Other pharmacological molecules used for prevention of CIA include cytokines, growth factors such as insulin like growth factor, epidermal growth factor or fibroblast growth factor, antioxidants and Vitamin D3[6,8].

Scalp cooling leads to vasoconstriction and this reduces the blood flow to the hair follicles[12,13]. Due to this reduced flow, the amount of chemotherapeutic drug deposited around the hair follicles also gets reduced. Furthermore, cooling, particularly to a temperature of -20°C, also reduces the cellular activity of the hair follicles and makes them less susceptible to the effect of chemotherapy[12,13]. The effect of scalp cooling on hair fall reduction also depends on the drug regimen used and the duration for which the cooling was done[14]. There have been advances in the scalp cooling techniques over the period of time. Earlier, the use of caps that were frozen to very low temperatures was prevalent. However, the problem with these caps was that they needed to be changed and refrigerated frequently as they used to thaw. With advancement in technologies, the new caps have a mechanism wherein a glycol-based fluid is circulated through the cap, and it helps to maintain the required temperature throughout the course of the treatment[15,16].

There have been two previous attempts to summarize the evidence on the efficacy of scalp cooling techniques in reducing CIA. A similar meta-analysis was conducted by Shin et al[17] in 2015 and intended to compare different interventions for their efficacy to reduce chemotherapy induced alopecia. They found a 62% reduction in the risk of alopecia with scalp cooling. Another recent review by Rugo et al[18] in 2017 documented a 43% lower risk of significant alopecia in those receiving scalp cooling compared to those that did not receive it. Since the publication of the meta-analysis by Rugo et al[18] in 2017, new randomized trials have been published and therefore, there is a need to update the evidence. The current meta-analysis aimed to include the recently published studies and update the evidence on the efficacy of scalp cooling in prevention of chemotherapy induced alopecia. Such an evidence is especially important for oncology nurses. The supportive care for oncology patients is rapidly changing and incorporates evidence-based practice. The role of oncology nurses in adoption and practice of new clinical therapies is pivotal and access to recent studies and emerging data would be critical to enhance understanding of merits and side effects of these new therapies.

Materials and Methods

Search Strategy

Through use of electronic search engines-PubMed, Scopus, Cochrane Database of Systematic Reviews and Google academic databases, a thorough systematic search of English language papers published until 30th April 2021 was carried out. **Supplementary Table I** has the specific details of the search strategy used to identify relevant literature for this meta-analysis. The literature search aimed at identifying studies done in patients undergoing chemotherapy that compared scalp cooling with no scalp cooling (control) for risk of alopecia or hair loss. The primary outcome of interest was significant alopecia, i.e., hair loss of 50% or more. Secondary outcomes were emotional and social function score, anxiety and depression scores and rates of complication due to scalp cooling. The study processes were in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

Selection Criteria and Methods

The search strategy was executed in the various databases mentioned above. The studies identified by these databases were compared, and duplicates were removed. Subject experts (Name 1, Name 2) from the study team screened the titles and abstracts as an initial step. After removing the articles that were considered not useful for inclusion in the review, the full texts of the remaining articles were reviewed in detail. In case of any disagreements between the two study authors with respect to the inclusion or exclusion of studies, a third senior experienced author was consulted, and consensus was made through discussions. Only those studies were included in the meta-analysis that fulfilled the inclusion criteria. In order to identify additional literature, the reference list of the included studies was also reviewed.

Inclusion Criteria

Studies that were randomized controlled trials (preferably) or adopted a cohort approach or retrospective data-based studies were considered for inclusion. For a study to be included, it should

have been done in patients undergoing chemotherapy and should have compared the outcomes of interest (i.e., hair loss, complications, anxiety or depression score and emotional or social functioning) by the two approaches i.e., scalp cooling and no scalp cooling (control).

Exclusion Criteria

Studies with other designs, such as cross-sectional or case-reports or review articles were excluded. Also, those studies that did not provide data on the outcomes of interest or compared one technique of scalp cooling with another technique were excluded.

Data Extraction and Quality Assessment

Through use of a pretested data extraction sheet, two authors separately extracted data from the included studies. The methodological assessment was done independently by two authors using the assessment tool by Cochrane for randomized controlled trials[19]. For one study that was prospective non-randomized in nature, Newcastle-Ottawa Quality Assessment Scale was used[20].

Statistical Analysis

This meta-analysis, using STATA version 16.0, reported effect sizes as pooled relative risk (RR) with 95% CI (confidence intervals) for categorical outcomes and weighted mean difference (WMD) for continuous outcomes. I^2 was used as a measure to denote heterogeneity and in instances where the value of I^2 exceeded 40%, random effects model was used[21]. Sub-group analysis was done based on the type of scalp cooling system used. Another sub-group analysis by type of carcinoma was also planned but as all the included studies had patients with breast cancer, such an analysis was considered not worthwhile. For reporting statistical significance, a *p*-value of less than 0.05 was considered. Egger's test was employed to assess for presence or absence of publication bias. The quality of evidence generated for the primary outcome was assessed through GRADE criteria using GRADEpro software[22,23].

Results

Selection of Articles, Study Characteristics and Quality of Included Studies

Using the search strategy and after removal of the duplicates, overall, 152 citations were obtained (Figure 1). Screening of the titles led to removal of 97 studies. Out of the remaining 55 citations, 37 were omitted after reading of the abstract. The remaining 18 papers were reviewed in detail and finally, 14 articles were considered for the inclusion. There were 9 studies[24-32] that

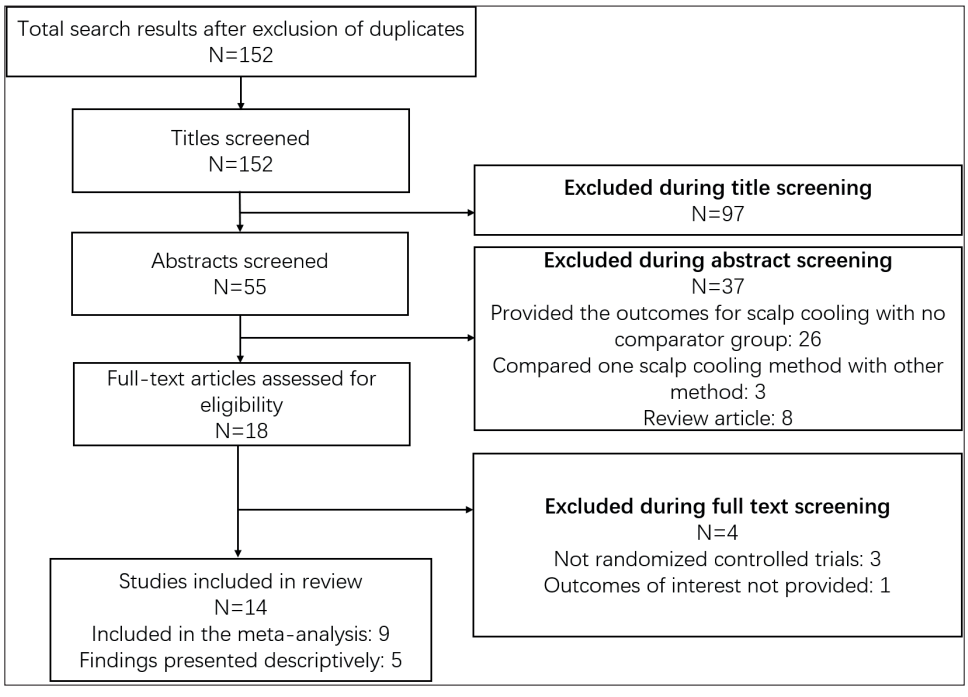

Figure 1. Selection process of the studies included in the review.

were included for the meta-analysis. Other 5 studies[33-37] provided data in a way that could not be pooled along with other studies and were not directly relevant for this meta-analysis. However, as the current effort is to update the previous meta-analysis, the findings of these 5 studies have been synthesized in a descriptive manner.

Table I presents the details of the studies included in the review. All the studies, except one, were randomized controlled trials[25]. One study was prospective non-randomized in design[25]. Four studies[27,28,36,37] were done in USA and three studies[29,33,35] in United Kingdom. One study each was done in Japan, Malaysia, Germany, Netherlands, Italy, Ireland and India[24,25,26,30,31,32,34]. All the studies had majority of patients with breast cancer and the outcomes were assessed in all studies at or within 6 months of chemotherapy. Four studies[24,27,32,34] used Paxman cooling system, three used chemocap[28,33,36] and two studies each used DigniCap system[25,26], gel cooling cap[29,35] and Spenco hypothermia cap[30,37]. One study[31] used cryogel bag. The results of the quality evaluation of the included studies are provided in **Supplementary Tables II** and **III**. The included studies were of modest quality. A total of 7 out of 13 trials reported random sequence generation and 5 trials reported allocation concealment and blinding of outcome assessment team. Due to the nature of the approaches being tested in the study, blinding of the study personnel and study subjects could not be ensured. The quality of one study that was prospective non-randomized was modest.

Primary Outcome

Risk of Alopecia

Compared to control group patients, those that received scalp cooling had 41% lower risk of alopecia (i.e., hair loss of ≥50%) [RR 0.59, 95% CI: 0.53, 0.66; I^2=30.4%, N=9] (Figure 2). Egger's test did not indicate the presence of publication bias (p=0.27). After removing one study by Saad et al[25] which was a prospective non-randomized study, the pooled risk for alopecia remained the same [RR 0.59, 95% CI: 0.53, 0.66; I^2=39.1%, N=8]. Upon subgroup analysis, the risk of hair loss was lower, compared to control group, in different types of cooling systems used [*Paxman cooling system*: RR 0.56, 95% CI: 0.41, 0.75; I^2=75.6%, N=3; DigniCap system: RR 0.60, 95% CI: 0.47, 0.78; I^2=0.0%, N=2; *Others*: RR 0.61, 95% CI: 0.49, 0.77; I^2=1.2%, N=4] (Figure 3). "Others" included chemocap, gel cooling cap, Spenco hypothermia cap and cryogel bag. The overall quality of pooled evidence for the risk of alopecia was judged "moderate" thereby indicating that further research is likely to impact our confidence in the pooled estimate; however, there is likely a protective effect of scalp cooling for hair loss in patients undergoing chemotherapy **(Supplementary Table IV)**.

Secondary Outcomes

There were no differences in the anxiety score [WMD 0.57, 95% CI: -0.55, 1.69; I^2=68.4%, N=2], depression score [WMD 0.31, 95% CI: -1.19, 1.80; I^2=89.7%, N=2], score reflecting emotional functioning [WMD 0.06, 95% CI: -1.37, 1.49; I^2=0.0%, N=2] and social functioning [WMD -8.37, 95% CI: -25.7, 8.93; I^2=93.5%, N=2] among the two groups of patients (Figure 4). Egger's test did not indicate the presence of publication bias (p=0.32 for anxiety score; p=0.86 for depression score; p=0.24 for emotional functioning and p=0.66 for social functioning).

Out of the 9 studies included in the meta-analysis, 5 studies[24,25,26,27,32] provided data on the proportion of patients receiving scalp cooling that developed discomfort/complaints. The pooled evidence of these 5 studies suggests that around 66% of the subjects reported some discomfort (95% CI: 37-95%; I^2=90.46%) (Figure 5). Egger's test did not indicate the presence of publication bias (p=0.21). The commonly reported complaints included headache, scalp and neck pain, discomfort due to chill, nausea/vomiting, dizziness, skin ulceration and pruritis.

Descriptive Findings

Dougherty et al[33] in their randomized controlled trial included female patients with a median age of 50 years. These women were treated for their breast or ovarian cancer using anthracycline along with cyclophosphamides. One group of patients received scalp cooling using "Chemocap" while the second group of patients received "gel pack". In both the group of patients, the cooling system was applied 15 minutes prior to chemotherapy and continued till 45 minutes post chemotherapy administration. The authors found no statistical difference between the effectiveness of the two cooling methods[33]. Van den Hurk et al[34] conducted a study with 53 patients that received scalp cooling and compared the outcomes with 15 patients that did not receive scalp cooling, post chemotherapy with docetaxel. The

Table I. Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics and scalp cooling method used	Sample size	Key outcome (scalp cooling *vs.* no treatment)
Kinoshita et al[24] (2019)	Randomized con-trolled trial	Japan	Female patients with stage 2 breast cancer (> 50%); mean age of around 50 yrs; > 90% received adjuvant chemo-therapy; > 60% treated with docet-axel/cyclophosphamide regimen **Scalp cooling method:** Paxman Hair Loss Prevention System, UK	46 (32 with scalp cooling; 14 with no treatment i.e., control)	Outcomes assessed at 3 months after completion of chemotherapy. **Risk of alopecia (hair loss of ≥ 50%):** RR 0.73 (95% CI: 0.59, 0.91) **Anxiety score** (using Hospital Anxiety and Depression scale; HADS) (Mean, SD): 7.89 (2.02) *vs.* 8.08 (2.02) **Depression score** (using HADS) (Mean, SD): 8.64 (1.68) *vs.* 9.17 (1.40) **Global health status** (using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30)) (Mean, SD): 65.77 (26.77) *vs.* 65.28 (22.14) **Emotional functioning** (using EORTC QLQ-C30) (Mean, SD): 86.90 (16.58) *vs.* 84.03 (15.27) Social functioning (using EORTC QLQ-C30) (Mean, SD): 85.71 (14.85) *vs.* 84.72 (13.22) **Risk of serious adverse events:** RR 0.14 (95% CI: 0.02, 1.26) • (Serious adverse events in scalp cooling group was fever; in control group was acute gastro-enteritis, wound infection, skin rash, cellulitis) • 94% (n = 30/32) of the patients in scalp cooling group reported some complaints such as jaw pain due to strap, headache, discomfort due to chill, nausea, forehead pain and dizziness
Saad et al[25] (2018)	Prospective non-randomized study	Malaysia	Female patients with stage 1 or 2 (in majority) breast cancer; majority re-ceived a combination of 5-fluorouracil, epirubicin, cyclophos-phamide and docetaxel **Scalp cooling method:** DigniCap™ system (Dignitana AB, Sweden).	25 (12 with scalp cooling; 13 with no treatment i.e., control)	Outcomes assessed at 3 months after completion of chemotherapy. **Risk of alopecia (hair loss of ≥ 50%)**: RR 0.58 (95% CI: 0.36, 0.94) **Complications:** Around 50% (n= 6/12) of the patients in scalp cooling group reported some complaints such as headache, discom-fort due to cold sensation and vomiting.

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Table I *(Continued)*. Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics and scalp cooling method used	Sample size	Key outcome (scalp cooling *vs.* no treatment)
Smetanay et al[26] (2018)	Randomized con-trolled trial	Germany	Female patients with stage 1 to 3 breast cancer; median age of 54 yrs; 65% received neoadjuvant chemo-therapy; Most received anthracycline and/or taxane based chemotherapy. **Scalp cooling method:** DigniCap™ system (Dignitana AB, Sweden).	63 (36 with scalp cooling; 27 with no treatment i.e., control)	Outcomes assessed at 6 months after completion of chemotherapy. **Risk of alopecia (hair loss of ≥ 50%):** RR 0.61 (95% CI: 0.45, 0.82) **Complications:** Around 86.0% (n= 31/36) of the patients in scalp cooling group complained of device related adverse events such as headache, chills, feeling of heaviness in head, scalp pain and neck pain.
Nangia et al[27] (2017)	Randomized controlled trial	USA	Female patients with stage 1 or 2 breast cancer; median age of 52 yrs; Majority received Taxane based chemotherapy (65%); Most received doxorubicin and cyclophosphamide (32.8%) and docetaxel and cyclophosphamide (33.6%) **Scalp cooling method** : Paxman scalp cooling system	141 (94 with scalp cooling; 47 with no treatment i.e., control)	Outcomes assessed at end of 4 cycles of chemotherapy; each cycle lasting for 2-3 weeks. **Risk of alopecia (hair loss of ≥ 50%):** RR 0.50 (95% CI: 0.40, 0.61) **Anxiety score** (using HADS) (Mean, SD): 4.00 (0.83) *vs.* 3.0 (1.0) **Depression score** (using HADS) (Mean, SD): 3.0 (0.58) *vs.* 2.0 (0.67) **Emotional functioning** (using EORTC QLQ-C30) (Mean, SD): 83.3 (4.2) *vs.* 83.3 (4.1) **Social functioning** (using EORTC QLQ-C30) (Mean, SD): 83.3 (5.6) *vs.* 100 (5.5) **Complications**: Around 30% (n= 28/94) of the patients in scalp cooling group reported some device related complaints such as chills, dizziness, headache, nausea, paresthesia, pruritis and skin ulceration.
Satterwhite et al[28] (1984)	Randomized controlled trial	USA	Median age of patients was 52 yrs; majority were females (72%); all received doxorubicin-based chemotherapy; majority had breast cancer (36%) followed by stomach cancer (16%), lung cancer (12%), liver cancer (8%) and non-hodgkins lymphoma (8%) **Scalp cooling method:** Chemocap	25 (12 with scalp cooling; 13 with no treatment i.e., control)	Outcomes assessed at end of average of 2 cycles of chemotherapy. **Risk of alopecia (hair loss of ≥ 50%):** RR 0.27 (95% CI: 0.10, 0.73) **Complications:** patients in scalp cooling group reported complaints such as chills, headache, heaviness in the head due to cap. Proportion complaining of these symptoms not mentioned.

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Table I *(Continued)*. Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics and scalp cooling method used	Sample size	Key outcome (scalp cooling *vs.* no treatment)
Macduff et al[29] (2003)	Randomized controlled trial	UK	Females with breast cancer; all received epirubicin with docetaxel Scalp cooling method: gel cooling cap	17 (7 with scalp cooling; 10 with no treatment i.e., control)	Outcomes assessed at end of average of 6 cycles of chemotherapy. **Risk of alopecia (hair loss of ≥ 50%)**: RR 0.72 (95% CI: 0.44, 1.17) **Complications:** patients in scalp cooling group reported complaints such as feeling cold, headache, dizziness and transient chest pain. Proportion complaining of these symptoms not mentioned.
Giaccone et al[30] (1988)	Randomized controlled trial	Italy	Patients with advanced or metastatic cancer: majority with breast cancer (91%) followed by ovarian cancer (9%); patients received chemotherapy consisting of cyclophosphamide, 5-fluoroouracil, vincristine, cisplatin, carboplatin, mitomycin **Scalp cooling method:** Spenco Hypothermia Cap	35 (19 with scalp cooling; 16 with no treatment i.e., control)	Outcomes assessed at end of average of 2 cycles of chemotherapy. **Risk of alopecia (hair loss of ≥ 50%):** RR 0.62 (95% CI: 0.41, 0.92)
Edelstyn et al[31] (1977)	Randomized controlled trial	Ireland	Patients with breast cancer; received doxorubicin, vincristine, 5-fluorouracil, chlorambucil, methotrexate **Scalp cooling method**: Cryogel bag	77 (40 with scalp cooling; 37 with no treatment i.e., control)	Outcomes assessed at end of average of 1 cycles of chemotherapy. **Risk of alopecia (hair loss of ≥ 50%):** RR 0.62 (95% CI: 0.44, 0.87)
Bajpai et al[32] (2019)	Randomized controlled trial	India	Patients with breast cancer; received taxane+anthracycline based chemotherapy; Median age around 40 yrs; majority (60%) with early breast cancer. Scalp cooling method: Paxman scalp cooling system	49 (32 with scalp cooling; 17 with no treatment i.e., control)	Outcomes assessed at end of at least 1 cycle of chemotherapy; mostly around 3 months after completion of chemotherapy. **Risk of alopecia (hair loss of ≥ 50%):** RR 0.44 (95% CI: 0.30, 0.65) **Complications:** There were no grade 3 or 4 adverse events reported. Patients (n=22/32; ~69%) in scalp cooling group reported complaints such as headache, chills and coldness.

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Table I *(Continued)*. Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics and scalp cooling method used	Sample size	Key outcome (scalp cooling *vs.* no treatment)
Dougherty[33] (2006)	Randomized controlled trial	UK	Patients with breast cancer; received epirubicin or doxorubicin, fluorouracil, Cyclophosphamide; median age of 50 years **Scalp cooling method:** Chemocap and Gel cap	170 (86 with Chemocap; 84 with gel pack)	Unclear when the outcomes were assessed. No statistical difference between the effectiveness of the two cooling methods in reducing the risk of alopecia. However, it should be noted that only 72 out of 170 patients were evaluated on this endpoint.
van den Hurk et al[34] (2013)	Randomized controlled trial	Netherlands	Patients received docetaxel, type of cancer unclear. **Scalp cooling method:** Paxman scalp cooling system	68 (53 with scalp cooling; 15 with no treatment i.e., control)	Unclear when the outcomes were assessed. around four-fifth of the patients that received scalp cooling did not require head cover as against only around one-fourth in the non-scalp cooling group. Scalp cooling was well tolerated.
Dougherty[35] (1996)	Randomized controlled trial	UK	Patients receiving intravenous cancer chemotherapy that included either doxorubicin or epirubicin as a single agent or in combination; age range of 40-69 years; patients with breast cancer. **Scalp cooling method:** two intervention groups – one using gel pack and the other using a thermocirculator machine.	48 entered into the trial and 30 completed the final interview (15 each in gel pack and thermocirculator group)	Primary outcome was to ascertain how patients felt about hair loss and scalp cooling. Asked at end (final interview) if scalp cooling was worthwhile (N=30): 15 said "yes" (50%), 11 responded "unsure" (36%), 4 said "no" (14%). Researcher's assessment with use of gel pack was that majority had minimal hair loss and with use of thermocirculator, majority had moderate to severe hair loss
Kennedy et al[36] (1982)	Randomized controlled trial	USA	Patients receiving doxorubicin (anthracycline antibiotic) alone or doxorubicin plus cyclophosphamide (nitrogen mustard alkylating agent) for breast, gastric, lymphoma, sarcoma, pancreatic and mesothelioma; average age 43.7 years and age range of 31-59 years. **Scalp cooling method:** Chemocap	19 (10 with scalp cooling; 9 with no treatment i.e., control)	Outcomes assessed at end of average of 6 cycles of chemotherapy. Subjects assessed for comfort of using scalp cooling: 0-3 scale rated by patient: 0 not at all uncomfortable to 3 very uncomfortable. The study reported tolerance and acceptability to scalp cooling except for some minor side effects such as headache and nausea.
Parker[37] (1987)	Randomized controlled trial	USA	Patients with recurrent Stage IV breast cancer being treated with cyclophoshamide 600 mg/m^2; methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2. Mean age of 53 years (range 35-69). Scalp cooling method: SPENCO hypothermia cap	14 (6 with scalp cooling; 8 with no treatment i.e., control)	Outcomes assessed at end of minimum of 7 cycles of chemotherapy. Two patients in the control group chose to withdraw from the study after the first chemotherapy treatment due to the psychological distress associated with hair loss. Commonly reported side effect of scalp cooling was transient headache. Scalp metastases were also evaluated: Patients receiving hypothermia cap were followed for 12 months after study. No scalp metastases were noted.

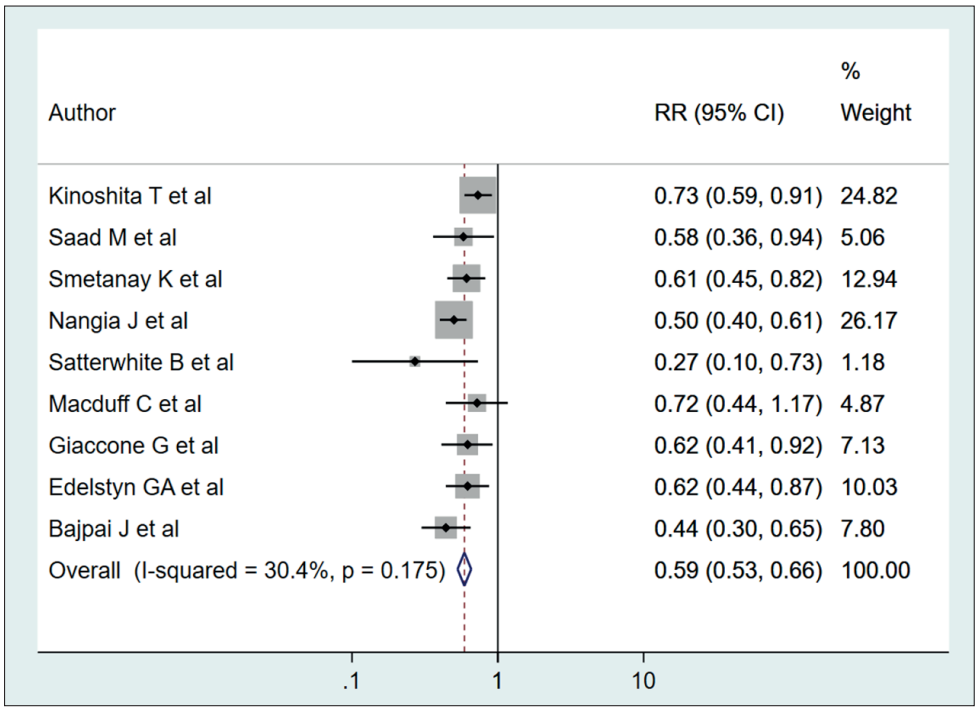

Figure 2. Pooled findings for the risk of alopecia (hair loss ≥50%).

study noted that around four-fifth of the patients that received scalp cooling did not require head cover as against only around one-fourth in the non-scalp cooling group[34]. Further, scalp cooling was well tolerated. Based on these findings, the authors concluded that patients who are planned to receive docetaxel-based chemotherapy should be informed about scalp cooling for prevention of alopecia[34]. In another RCT by Dougherty et al[35], patients received either doxorubicin or epirubicin as a single agent or in combination. These were randomized into two groups- one using

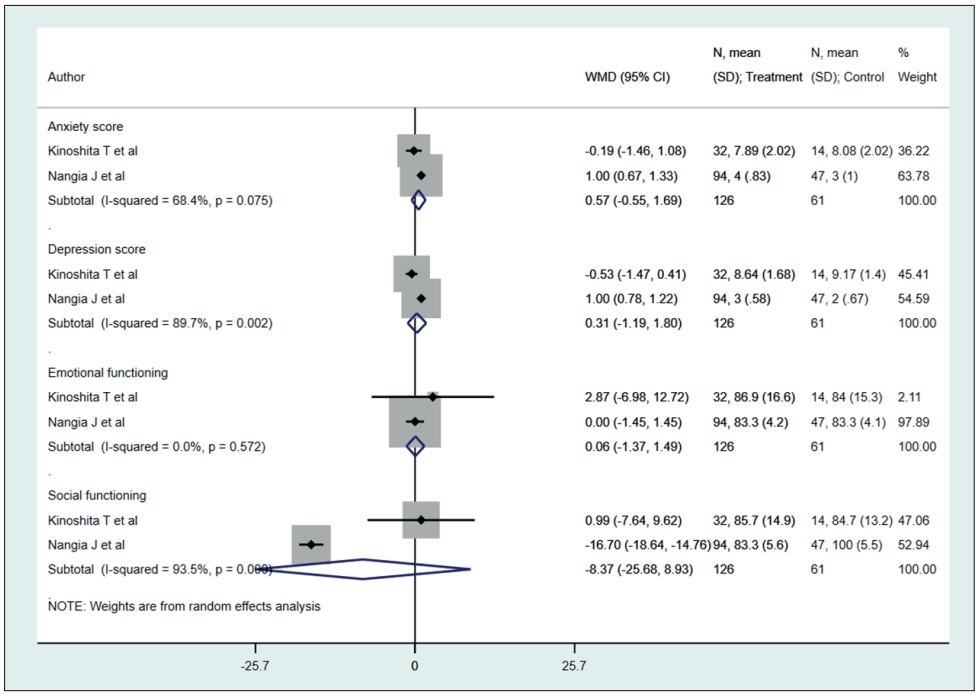

Figure 4. Pooled findings for the anxiety and depression score, emotional functioning and social functioning.

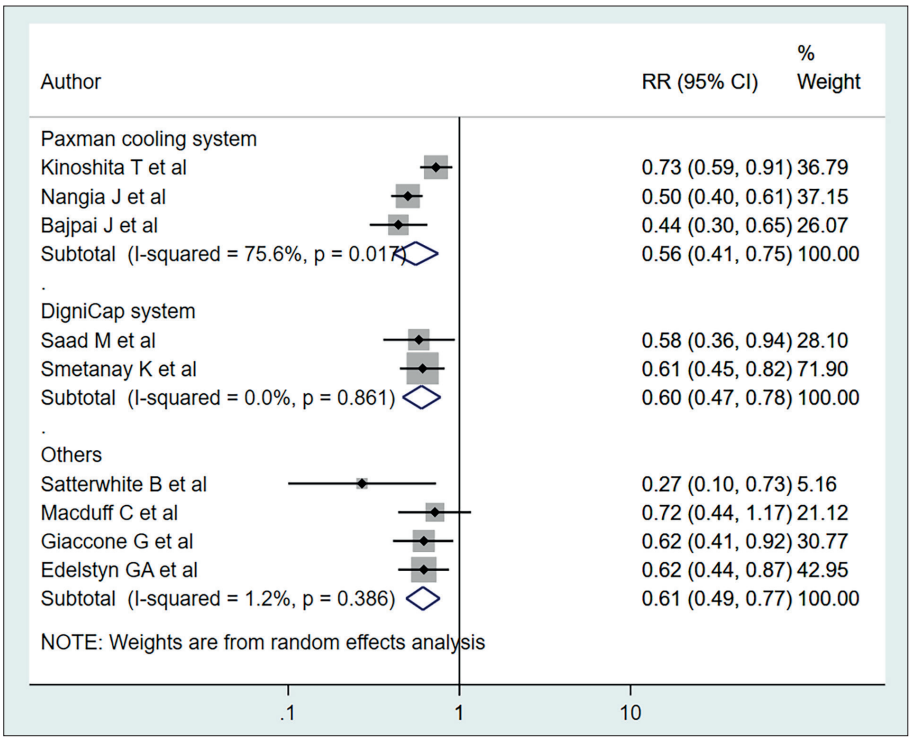

Figure 3. Subgroup analysis for the risk of alopecia (hair loss ≥50%), by scalp cooling systems.

gel pack and the other using a thermocirculator machine. At the end of the chemotherapy, when asked if scalp cooling was worthwhile, around 50% responded as "yes" and only 14% responded as "no". Researcher's assessment with use of gel pack was that majority had minimal hair loss and with use of thermocirculator, majority had moderate to severe hair loss[35]. Kennedy et al[36] conducted a randomized controlled trial wherein patients receiving doxorubicin alone or doxorubicin plus cyclophosphamide for malignancy were included. The intervention group patients received Chemocap, a specialized cap to be placed on patient's head and maintained a temperature between 0-to-20-degree Fahrenheit. The control group patients received no scalp cooling.

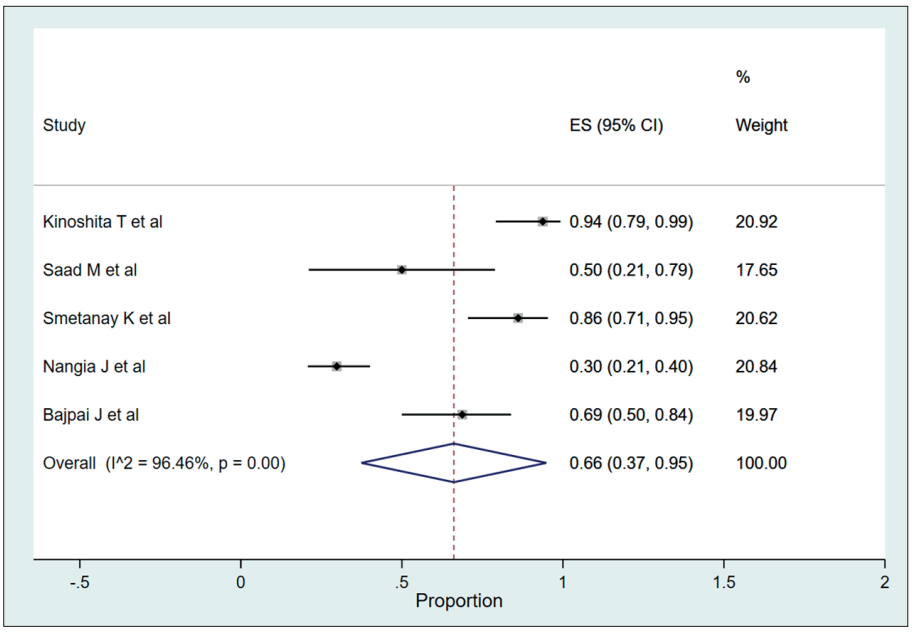

Figure 5. Pooled proportion for subjects reporting discomfort with scalp cooling system.

The study reported tolerance and acceptability to scalp cooling except for some minor side effects such as headache and nausea. Similar side effects were reported by Parker et al[37].

Discussion

Chemotherapeutic drugs act on rapidly dividing cells within the body and are not able to differentiate between normal and malignant cells[38]. Other normal body cells with high mitotic activity gets affected by these chemotherapy drugs. A high proportion of cells (around 90%) in the hair matrix are usually in the anagen phase and therefore very susceptible[39]. The negative effect of these drugs on the mitotic activity of the hair follicles often results in alopecia along with the increase fragility of hair shaft and changes in the texture, thickness and colour of the hairs. Patients undergoing chemotherapy are at a high risk of hair loss and this has immense psychological impact. Patients with chemotherapy induced alopecia tend to have negative body image, suffer from low self-esteem and their quality of life is deeply impacted[1-3].

There have been efforts, such as scalp compression, use of 2% minoxidil and vitamin D3 to prevent this chemotherapy induced hair loss, but the results have not been very exciting[8,9]. However, one promising technique that has gained attraction recently is the cooling of the scalp. Scalp cooling induces vasoconstriction which probably reduces the reach of chemotherapeutic drugs to the hair follicles, thereby reducing the risk of significant hair loss[12,13]. The meta-analysis aimed to update a previous review by Rugo et al[18] who showed, through pooling of 5 studies, a 43% lower risk of significant alopecia in those receiving scalp cooling compared to those that did not receive it. Further to this review, quite a few more trials were published and therefore, it was imperative that the findings needed to be updated. In the current meta-analysis, we noted findings similar to the review by Rugo et al[18]. We found 41% lower risk of alopecia (i.e., hair loss of ≥50%) in those that received scalp cooling. The quality of evidence was considered "moderate". We found no differences in the anxiety score, depression score, score reflecting emotional functioning and social functioning among the two groups of patients. Around 2/3rd of the patients receiving scalp cooling reported some minor discomfort.

The findings of the current meta-analysis also support the findings of a systematic review by Shin et al published in 2015[17]. This review aimed to compare different interventions for their efficacy to reduce chemotherapy induced alopecia. The review found a 62% reduction in the risk of alopecia with scalp cooling. All other interventions such as minoxidil, scalp compression, scalp cooling combined with scalp compression did not reduce the risk of alopecia significantly. These findings taken together support the use of scalp cooling in patients with breast cancer undergoing chemotherapy, with the aim to reduce hair loss. However, the associated discomforts with use of the cooling system needs to be considered and effectively communicated with the patients. In our review, four studies used Paxman cooling system[24,27,32,34]and two studies used DigniCap system[25,26]. Both Paxman and DigniCap are considered to be recent advanced additions to the earlier used cooling systems such as chemocap, gel cooling cap and cryogel bag. Studies using old scalp cooling methods have shown a significant 43% risk reduction in alopecia and with newer technologies, such as the Paxman system, this reduction in risk has been to the extent of 50%[18,40]. These findings underscore that irrespective of the technique used, scalp cooling is effective in reducing risk of alopecia.

There is an emerging role of oncology nurses in advancing supportive care for patients. The data on efficacy of scalp cooling and its tolerability should be readily available to oncology nurses and they must understand the available data with respect to the relevance to clinical practice. In general, by virtue of their direct involvement in patient care and as part of the multidisciplinary oncology team, the nurses have the opportunity to marshal the implementation of transformative clinical practice and thereby, positively affect patient experience and quality of life. Empowered with latest scientific information, the nurses could be strong and informed proponents and advocates incorporating scalp cooling techniques for prevention of alopecia and thereby, improving quality of their patient's life.

Limitations

There are some limitations of this meta-analysis. First, the number of studies were less, and their sample sizes were also small. This could mean that the generalizability of the findings could be limited. Second, the included studies had patients with breast cancer. The efficacy of

scalp cooling in reducing the risk of hair loss in patients with other types of cancers is still unknown and not established. Third, the outcomes were assessed within 6 months of chemotherapy and therefore, the long-term effects of scalp cooling in prevention of hair loss or on rate of hair growth and quality of hair growth is not known. Studies with longer follow-up periods is therefore required. Fourth, there are other factors that could influence the results, such as the study design, adjustment of variables/confounders, population characteristics, grade and type of cancer, chemotherapy regimen used, type of cooling system used and the duration as well as the frequency of cooling provided. Ensuring harmonization of these factors across all the studies is a major challenge and that leads to inconsistency of findings. Finally, the quality of included studies was modest, at best and this calls for large studies with robust methodology to conclusively establish the efficacy of scalp cooling.

Conclusions

The current meta-analysis suggests that in female patients with breast cancer, the use of scalp cooling, compared to no scalp cooling, reduces the risk of significant hair loss. The quality of evidence was judged to be "moderate". Further, the acceptability of this cooling system is limited by a high incidence (around two-thirds of the patients) of reported complaints such as headache, scalp and neck pain, discomfort due to chill, nausea/vomiting and dizziness. Data is limited on the long-term effects of this intervention and its use in patients with other types of cancers. More studies with larger sample size and longer periods of follow up are required.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution
XS conceived and designed the study. LR and XY collected the data and performed the literature search. XS was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethical Approval
Not applicable.

Patients Consent
Not applicable.

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