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REVIEW

The effect of scalp cooling on CIA-related quality of life in breast cancer patients: a systematic review

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Abstract

Purpose Chemotherapy-induced alopecia (CIA) remains a distressing adverse event of cancer treatment but may be prevented by scalp cooling. The effectiveness of scalp cooling, however, is dependent on the chemotherapy regimen with successful hair preservation (i.e., < 50% hair loss) in 41–59% of women on taxane-based therapies in comparison to 16–36% on anthracycline-based therapies. Despite the potential utility, use of scalp cooling has shown a more equivocal impact on quality of life (QoL). In this review, we aim to evaluate the use of scalp cooling for CIA and quantitative QoL measures.

Methods A systematic review of PubMed, Embase, Web of Science, and Cochrane databases for clinical studies on scalp cooling to prevent CIA published before October 29, 2018 was performed. Clinical studies with 5 or more patients that reported on a quantitative QoL measure were included and graded according to a modified five-point scale from the Oxford Centre for Evidence-Based Medicine.

Results Studies meeting inclusion criteria included 4 randomized clinical trials (RCT), 8 cohort studies, and 1 cross-sectional study with 1282 unique patients. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30: 46%) and Breast Cancer Module (QLQ-BR23: 46%) represented the most commonly used QoL assessments. Overall, 4 (31%) of the 13 studies concluded that scalp cooling was associated with significant improvements in QoL measures; 8 (62%) determined that there was either non-significant or no improvements; and 1 (7.7%) provided a mixed conclusion. Although 2 (50%) RCT demonstrated that scalp cooling can effectively prevent CIA depending on the chemotherapy regimen, these studies did not show that successful hair preservation was associated with improved QoL measures.

Conclusions This review demonstrates that scalp cooling is not consistently associated with significant QoL improvements as assessed by EORTC QLQ-C30 and -BR23. Representing a critical limitation, more than one-third of the studies did not subcategorize QoL outcomes for successfully or unsuccessfully scalp-cooled patients but rather reported on QoL measures for all scalp-cooled patients in general. Failure to prevent hair loss in patients undergoing an expensive and potentially uncomfortable treatment likely contributes to decreased well-being, impacting the overall distribution of QoL measures in scalp cooling patients compared to controls. Future studies should incorporate validated QoL instruments specific to hair disease and classify QoL outcomes for scalp-cooled patients based on the degree of hair preservation.

Keywords Scalp cooling · Scalp hypothermia · Chemotherapy-induced alopecia · Quality of life · QLQ-C30, QLQ-BR23

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Introduction

Chemotherapy-induced alopecia (CIA) represents one of the most common and distressing adverse events resulting from cancer treatment. For many patients, hair loss is associated with impaired body image, diminished psychosocial well-being, and increased depression, resulting in a substantial negative impact on quality of life (QoL) [1]. To reduce the incidence of CIA and mitigate its unfavorable effects on patients, scalp hypothermia via cold caps and scalp cooling systems has emerged as an effective prevention intervention. Thought to have a dual mechanism of action by (1) reducing follicular metabolism and (2) promoting vasoconstriction to ultimately decrease chemotherapeutic drug delivery to the hair follicular unit, scalp cooling significantly reduced rates of alopecia in patients with solid tumors undergoing chemotherapy according to a recent systematic review and meta-analysis of randomized control trials [2, 3]. The ultimate success of hair preservation with scalp hypothermia, however, depends on the chemotherapy regimen with rates of successful hair preservation ranging significantly from as low as 16% on anthracycline-based therapies to 59% on taxane-based therapies [2, 4]. Other potential factors that may influence the utility of scalp cooling include the infusion time, patient age, scalp cooling device, scalp temperature, and the study-specific definition of successful alopecia prevention [2].

Irrespective of these variables, scalp cooling devices are typically well tolerated with limited adverse events such as chills, dizziness, headache, nausea, paresthesia, scalp pain, sinus pain, and local skin reactions including pruritus and ulceration [4]. The theoretical risk of increased scalp metastases has been consistently refuted in the literature [3, 5–7]. Despite the demonstrated utility and limited adverse event profile of scalp cooling, recent studies have published conflicting quantitative QoL data associated with scalp hypothermia [4, 5, 7, 8]. This discrepancy in QoL outcomes is particularly relevant as the main health-related concern with CIA remains the impact on QoL [3]. Accordingly, the ultimate therapeutic benefit of scalp hypothermia may thus be best measured by QoL assessments. Herein, we provide a comprehensive systematic review of the literature to assess the impact of scalp cooling for CIA on QoL.

Methods

We performed a librarian-assisted systematic review of the PubMed, Embase, Web of Science, and Cochrane databases for all clinical studies published before October

Table 1 Search strategy implemented for all databases

Database	Search	Results
PubMed	(Orbis Paxman[tiab] OR Orbis-system[tiab] OR DigniCap[tiab] OR Dignitana[tiab] OR Penguin[tiab] OR cold-cap*[tiab] OR cooling device[tiab] OR scalp-cooling[tiab] OR cooling-system[tiab] OR (sensor-controlled[tiab] AND scalp-cooling[tiab] OR scalp hypothermia[tiab]) OR "SCSC"[tiab]) AND (chemotherapy-related[tiab] OR chemotherapy-induced[tiab] OR "CIA"[tiab] OR hair preservation[tiab] OR hair-loss[tiab] OR "Hair Mass index"[tiab] OR Hair Check[tiab] OR "Alopecia"[Mesh] OR "Alopecia/chemically induced"[Mesh] OR "Alopecia/prevention and control"[Mesh])	131
Embase	('chemotherapy related':ab,ti OR 'chemotherapy induced':ab,ti OR 'chemotherapy induced alopecia'/exp OR 'cia':ab,ti OR 'hair preservation':ab,ti OR 'hair loss':ab,ti OR 'hair mass index':ab,ti OR 'hair check':ab,ti OR 'alopecia'/exp OR 'hair loss'/exp OR 'induced hypothermia'/exp OR 'temperature related phenomena'/exp) AND ('orbis paxmanab':ab,ti OR 'orbis system':ab,ti OR dignicap:ab,ti OR dignitana:ab,ti OR penguin:ab,ti OR 'cold cap*':ab,ti OR 'cooling device':ab,ti OR 'scalp cooling':ab,ti OR 'scalp cooling'/exp OR 'cooling system':ab,ti OR ('sensor controlled':ab,ti AND ('scalp cooling':ab,ti OR 'scalp hypothermia':ab,ti OR 'scsc':ab,ti)))	720
Web of Science	TS = (chemo* AND (alopecia OR hair-loss)) AND TS = (cold* OR cooling)	158
Cochrane	chemo* AND alopecia AND hair AND (cool* OR cold*)	19

29, 2018 on scalp cooling interventions to prevent CIA. Using the search strategy shown in Table 1, we found a total of 787 unique studies, which were screened according to the scheme presented in Fig. 1. Specific search terms included but were not limited to cold cap, scalp cooling, scalp hypothermia, chemotherapy-related, chemotherapy-induced, alopecia, hair loss, hair preservation, and prevention. Subsequently, two authors independently screened abstracts for relevant studies. Bibliographies of relevant publications were searched for additional studies. Only primary clinical studies that reported on a quantitative QoL measure were included. Case reports and cases series with less than five patients, literature reviews and/or meta-analyses, commentaries and opinion pieces were excluded from this review. Publications by identical authors investigating the same patient population were also excluded to avoid selection bias. The included reports were then assessed for quality evidence by a graded scale of 1 to 5, modified from the Oxford Centre for Evidence-based Medicine: (1) properly powered and conducted randomized clinical trial (RCT), (2) prospective comparative cohort study, (3) non-comparative cohort study, (4) case series or cross-sectional study, and (5) case report or opinion of respected authorities [9]. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist is presented in eTable 1 [10].

Results

The 13 studies meeting inclusion and exclusion criteria included 4 randomized clinical trials, 8 cohort studies, and 1 cross-sectional study and involved a total of 1282 unique patients as summarized in Table 2 [2, 4–8, 11–17]. Most studies were published from Europe ($n=7$, 54%) or the United States ($n=4$, 31%). All studies investigated use of scalp cooling to prevent CIA in breast cancer patients, and the majority ($n=8$, 62%) included a control group of non-scalp-cooled patients. Every study included at least 1 quantitative assessment of QoL. Reported QoL measures included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30: $n=6$, 46%) and Breast Cancer Module (EORTC QLQ-BR23: $n=6$, 46%), Body Image Scale (BIS: $n=3$, 23%), Generalized Anxiety Disorder 7-item scale (GAD-7: $n=1$, 7.7%), Measure of Body Apperception Questionnaire (MBA: $n=1$, 7.7%), Patient Health Questionnaire-9 (PHQ-9: $n=1$, 7.7%), a study-specific Visual Analog Scale for well-being (VAS: $n=1$, 7.7%), a study-specific questionnaire on distress (and $n=1$, 7.7), and WHO Well-being Index (WHO-5: $n=1$, 7.7%). A large minority ($n=6$, 46%) of studies included 2 or more QoL measures. The timing of QoL assessment also varied among the studies with questionnaires most commonly administered on a specific chemotherapy cycle (range 2–6 cycles) in 5 (38%) investigations or sometime after chemotherapy completion (range 0 to 6 months) in 4 (31%) investigations.

While the majority ($n=9$, 69%) of studies provided numerical results for quantitative QoL measures, there was substantial variability in the particular categories reported (e.g., total QoL score vs domain score vs question score) as shown in Table 3. Almost two-thirds ($n=8$, 62%) of studies classified QoL outcomes in scalp cooling patients based on the degree of hair preservation, while the remaining ($n=5$, 38%) described QoL outcomes among all patients undergoing scalp cooling (Fig. 2). For example, Nangia et al [4]

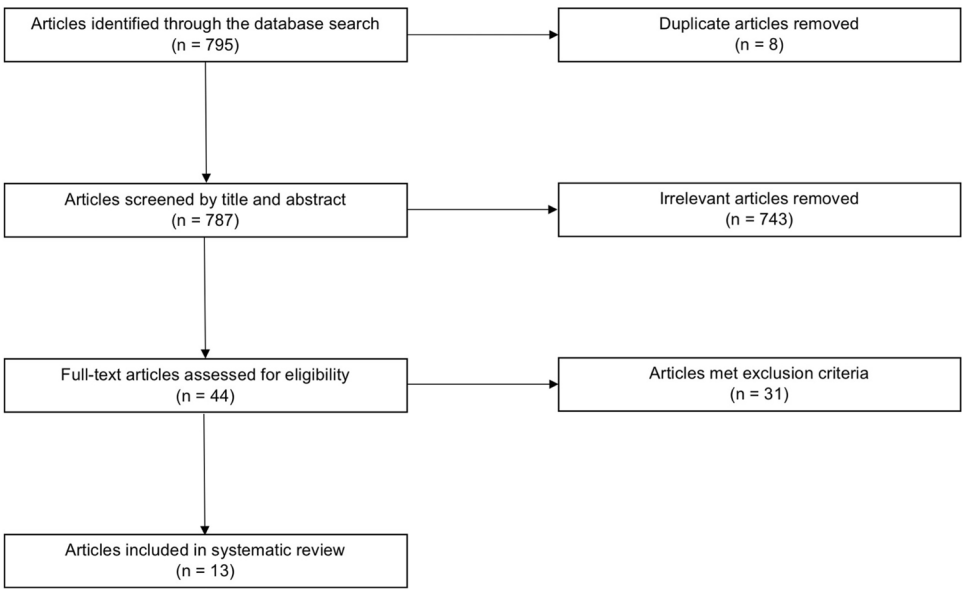

Fig. 1 Comprehensive search and selection strategy of eligible articles

Table 2 Summary of studies investigating scalp cooling for chemotherapy-induced alopecia with quality of life measures

Scalp cooling method	Country	Study design, no. of Pts	Control group	CT regimen	QoL assessment scale	Outcome	QOE
SCS, Bitto et al [11]	Germany	Cross-sectional study, 70	No control group	Anthracycline and taxane-based regimens	WHO-5	After an unspecified time course, successfully scalp-cooled pts reported significantly higher QoL scores (mean = 70) compared to pts who stopped SC due to hair loss or AE (mean = 48)	4
SCS, Carla et al [12]	Italy	Prospective cohort, 49	No control group	Not specified	EORTC QLQ-C30 Self-reported VAS for anxiety, mood, well-being, activity	After 2 CT cycles, no significant difference between QLQ-C30 mean value at baseline and after CT or between pts w/ and w/o alopecia	3
SCS, Chan et al [13]	Australia	Prospective cohort, 60	No control group	DC; DCTr; AC, ACT; FEC	PHQ-9 GAD-7 BIS	After adjustment for treatment group and baseline scores, no significant change in anxiety, depression, or body image scores post tx	3
SCS, Cigler et al [14]	United States	Prospective cohort, 101	No control group	Not specified	EORCT QLQ-BR23	After 1 month of CT, pts who did not have hair preservation were more likely to report feeling less physically attractive, less feminine, and dissatisfied with their body than those w/ hair preservation*	3
CC, El-saka et al [15]	Egypt	Randomized control trial, 120	No scalp cooling	AFC	EORTC QLQ-C30 and BR23	After 6 CT cycles, pts in the hair loss group were more likely to have had severe emotional functioning and moderate body image disturbance, respectively*	1
CC, Macduff et al [5]	United Kingdom	Randomized control trial, 30	No scalp cooling	ED	Modified EORCT QLQ-BR23	Throughout and following 6 CT cycles, no significant difference in reported level of upset or negative feelings about appearance	1

Table 2 (continued)

Scalp cooling method	Country	Study design, no. of Pts	Control group	CT regimen	QoL assessment scale	Outcome	QOE
CC, Nangia et al [4]	United States	Randomized control trial, 182	No scalp cooling	AC; AFC; T; TCarbo; D; DPTr; DC; DCrTr	EORTC QLQ-C30 HADS BIS	After 4 CT cycles, no significant difference in emotional or social functioning, anxiety or depression scores, or BIS between scalp cooling pts w/ and w/o hair preservation and non-scalp cooling pts	1
Unspecified scalp cooling, Prochilo et al [16]	Italy	Prospective cohort, 27	No control group	TTr; DC; AC	HADS	After completing CT, there was a statistically significant reduction in anxiety and significant increase in depression based on Wilcoxon signed-rank test	3
SCS, Protiere et al [6]	France	Prospective cohort, 136	No scalp cooling	MiC	Study-specific questionnaire on distress	During each of 4 CT cycles, scalp cooling patients self-reported lower levels of distress compared to non-scalp cooling patients; however, there was no significant difference	2
SCS, Rugo et al [7]	United States	Prospective cohort, 122	No scalp cooling	DC; AC; DCarboTr ± P; DTrP; T	EORTC QLQ-BR23	After 1 month of CT, there were statistically significant differences in 3 of 5 QoL measures between scalp cooling and control patients, respectively: "Were you upset about your hair loss?" (32.4% vs 60%, $p=0.04$); "Have you felt physically less attractive?" (27.3% vs 56.3%, $p=0.02$); and "Have you been dissatisfied with your body?" (15.9% vs 37.5%, $p=0.04$)	2
Unspecified scalp cooling, Schaffrin-Nabe et al [17]	Germany	Prospective cohort, 40	No scalp cooling	EC	EORTC QLQ-C30	After an unspecified time course, scalp cooling pts demonstrated significantly higher QoL and positive emotional status scores than control ($P<0.001$)	2

Table 2 (continued)

Scalp cooling method	Country	Study design, no. of Pts	Control group	CT regimen	QoL assessment scale	Outcome	QOE
SCS, Smetanay et al [2]	Germany	Randomized control trial, 79	No scalp cooling	EC; T; DCarboTrP; DC	Modified EORTC QLQ-C30 and BR23	After completing CT, there was no significant difference in QoL measures between scalp cooling and control pts	1
SCS, van den Hurk et al [8]	The Netherlands	Prospective cohort, 266	No scalp cooling	AdC; FEC; FAdC; DAdC	EORTC QLQ-C30 and BR23 BIS MBA HADS	After 3 weeks following CT completion, successfully scalp-cooled pts were significantly more likely to report more appetite than scalp cooling pts who required wig Scalp cooling pts who required a wig were significantly ($p < 0.05$) more likely to report concern with hair loss (44%) than no scalp cooling pts (25%) No significant difference in the total BIS, anxiety and depression score of scalp cooling vs non-scalp cooling pts	2

A doxorubicin hydrochloride, *Ad* adriamycin, *AE* adverse event, *BIS* Body Image Scale, *C* cyclophosphamide, *Carbo* carboplatin, *CC* cold caps, *CIA* chemotherapy-induced alopecia, *Cis* cisplatin, *CT* chemotherapy, *D* docetaxel, *E* epirubicin, *EORTC QLQ-BR23* European Organization for Research and Treatment of Cancer Quality of Life Breast Cancer Module, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, *F* 5-fluorouracil, *GAD-7* Generalized Anxiety Disorder 7-item scale, *H* Herceptin, *HADS* Hospital Anxiety and Depression 6 Scale, *hr* hour, *MBA* Measure of Body Apperception questionnaire, *Mi* mitoxantrone, *P* pertuzumab, *PHQ-9* Patient 9 Health Questionnarie-9, *Pt* patient, *QoL* quality of life, *SCS* scalp cooling systems, *T* paclitaxel, *Top* topotecan hydrochloride, *Tr*, trastuzumab, *VAS* visual analog scale, *WHO* World Health Organization, *WHO-5*, WHO (Five) Well-being Index

*Did not report on statistical significance of QoL measures

Table 3 Summary of comparative scalp cooling studies with quantitative quality of life results

QoL scale, citation	Scale interpretation	No scalp cooling	Scalp cooling: hair preservation*	Scalp cooling: no hair preservation*	Statistical significance
Study-specific questionnaire on distress [6]	Higher score indicates more distress	*At cycle 4 of CT* Distress scores 1–2: 43.1% Distress scores 3–4: 56.9%	*At cycle 4 of CT* Distress scores 1–2: 61.5% Distress scores 3–4: 38.5%		No
Modified EORTC QLQ-C30 and -BR23 [2]	Positive value indicates improvement	*Change from baseline to 6 months post CT* Emotional functioning: 20 Social functioning: 20	*Change from baseline to 6 months post CT* Emotional functioning: 4 Social functioning: 10		No
EORTC QLQ-C30 HADS BIS [4]	Higher score indicates more symptoms or distress	*After 4 cycles of CT* Anxiety: 3 Depression: 2 BIS: 5	*After 4 cycles of CT* Anxiety: 4 Depression: 3 BIS: 5	*After 4 cycles of CT* Anxiety: 4 Depression: 3 BIS: 7	No
EORTC QLQ-C30 and BR23 BIS MBA HADS [8]	Higher score indicates less appetite	*3 weeks after CT completion* Appetite: 27	*3 weeks after CT completion* Appetite: 17	*3 weeks after CT completion* Appetite: 39	Yes
EORTC QLQ-BR23 [7]	Higher percentage indicates more distress	*1 month after CT completion, reported "quite a bit" or "very much"* Upset about hair loss: 60% Felt physically less attractive: 56%	*1 month after CT completion, reported "quite a bit" or "very much"* Upset about hair loss: 32% Felt physically less attractive: 27%		Yes

BIS Body Image Scale, *CT* chemotherapy, *EORTC QLQ-BR23* European Organization for Research and Treatment of Cancer Quality of Life Breast Cancer Module, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, *HADS* Hospital Anxiety and Depression 6 Scale, *MBA* Measure of Body Apperception questionnaire, *QoL* quality of life

*Mean scores of all scalp cooling patients given when further subdivision not provided from original article

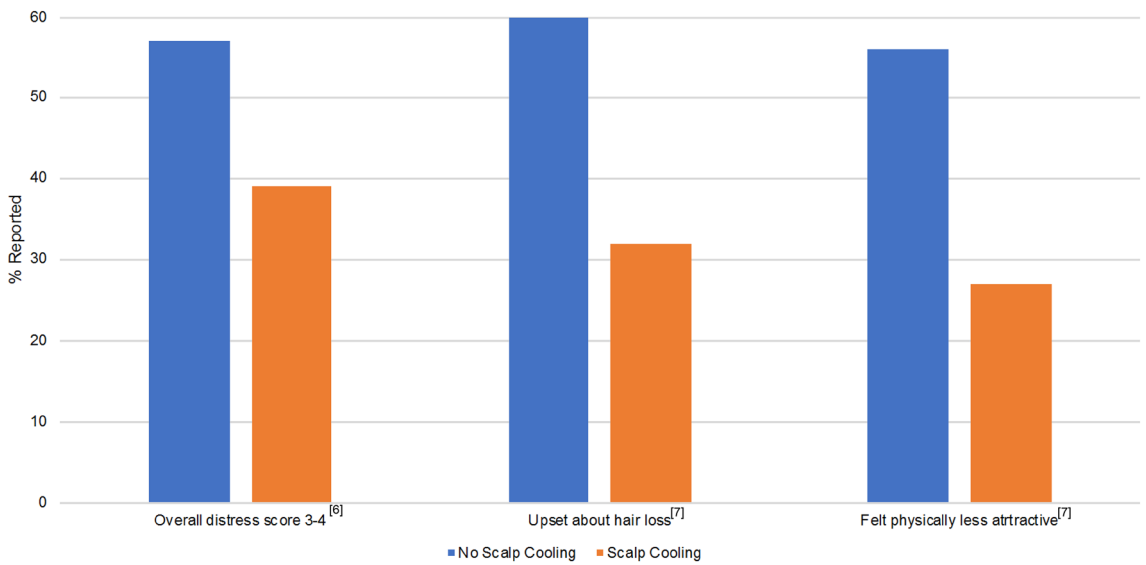

Fig. 2 Select comparative scalp cooling studies with quantitative quality of life results

used the EORTC QLQ-C30, reporting on emotional and social functioning of scalp-cooled patients with and without hair preservation in comparison to non-cooled patients. After 4 cycles of chemotherapy, there was 0% change from baseline in emotional and social functioning in all groups of patients ($p > 0.05$) [4]. In comparison, Rugo et al [7] used the EORTC QLQ-BR23 and provided response rates to individual QoL questions for all scalp-cooled patients (regardless of hair preservation) versus non-cooled patients. One month after the end of chemotherapy, 27.3% of scalp-cooled patients answered "have you felt physically less attractive as a result of your disease or treatment?" as "quite a bit" or "very much" in contrast to 56.3% of control patients ($p = 0.02$) [7].

Ultimately, 4 (31%) of the 13 studies concluded that scalp cooling was associated with significant improvements in QoL measures; 8 (62%) determined that there was either non-significant or no improvements in QoL measures; and 1 (7.7%) provided a mixed conclusion (i.e., QoL improving in some domains and worsening in others). Significant QoL improvements were identified by the EORTC QLQ-C30 in 2 (33%) of 6 studies; the EORTC QLQ-BR23 in 1 (17%) of 6 studies; and the WHO-5 in 1 (100%) of 1 relevant studies. The other included scales did not show statistically significant QoL improvements related to scalp cooling.

Using the EORTC QLQ-C30 and -BR23, none of the 4 (0%) randomized control trials determined that scalp cooling was associated with significant improvements in QoL measures, although 2 of 4 (50%) RCT concluded that scalp cooling can effectively prevent CIA depending on the chemotherapy regimen [2, 4, 5, 15]. More specifically, successful hair preservation (i.e., < 50% hair loss) was seen in 41–59% of women on taxane-based therapies and 16–36% on anthracycline-based therapies, which did not correlate with improved QoL measures as reported by these RCT [2, 4].

Discussion

The impact of a breast cancer diagnosis and its ensuing treatments on a woman's physical, psychological, emotional, financial, and social well-being is undeniably substantial and exceedingly complex. CIA, furthermore, has consistently represented one of the most dreaded adverse events of cancer treatment and considered by many women to be even worse than loss of a breast [18]. To accordingly combat CIA, scalp cooling has demonstrated significant efficacy in hair preservation [3]. This systematic review, however, shows that scalp cooling is not consistently associated with significant QoL improvements as assessed by EORTC QLQ-C30 and -BR23, BIS, GAD-7, MBA, PHQ-9, VAS for well-being, and WHO-5, as only one-third of relevant studies found significant results. Among the 2 RCT which demonstrated that scalp cooling can effectively prevent CIA depending on the chemotherapy regimen, hair preservation was not associated with improved QoL measures [2, 4, 5, 15].

These QoL assessments capture a number of different domains including global health status; physical symptoms; cognitive, emotional, social, and role functioning; sexual functioning and enjoyment; body image; anxiety; depression; and self-worth. Furthermore, the EORTC QLQ-C30 and -BR23 represented the most commonly used QoL assessments in this review. The former is a general QoL measure that covers a variety of domains relevant to cancer patients, while the latter is meant to supplement with more focused questions for breast cancer patients [19]. While the -BR23 does include 2 direct questions about hair loss (e.g., "Have you lost any hair?" and "Were you upset by the loss of your hair?), neither the -C30, -BR23, nor any of the other QoL scales used in these studies are validated measures to capture patient well-being associated with dermatologic disease or alopecia. Given these non-specific QoL assessments, other dimensions of the breast cancer diagnosis and treatment potentially mitigated the ability to determine the QoL specific to hair preservation, contributing to a probable Type II error [5, 20]. Future studies should consider use of the Chemotherapy-induced Alopecia Distress Scale (CADS), a validated QoL of instrument specific to CIA, to further assess scalp cooling on alopecia-specific quality of life [21]. The CADS consists of 17 questions and assesses physical, emotional, activity, and relationship domains. This scale is more strongly associated with body image than general QoL, which may be appropriate as distress related to alopecia may closely relate to body image (i.e., CIA may worsen body image and individuals with lower baseline body image may experience increased distress related to CIA) [1, 21, 22]. However, scalp cooling was not associated with significant improvements in BIS in 3 relevant studies within this systematic review.

In addition to the variable QoL scales, differences in methods and outcome reporting may also have impacted the inconsistent conclusions among studies. More specifically, more than one-third of the studies did not subcategorize QoL outcomes for successfully or unsuccessfully scalp-cooled patients but rather reported on QoL measures for all scalp-cooled patients in general. Representing one investigation that did sub-classify results, van den Hurk et al [8] found that scalp-cooled patients with alopecia had significantly worse QoL outcomes than non-scalp-cooled patients with alopecia. The uncertainty of hair loss and overall disappointment in unsuccessfully scalp-cooled patients compared to control patients may have contributed to their decreased well-being. It is also possible that women who self-selected to undergo scalp cooling (in non-randomized studies) placed a higher importance on hair preservation than women who did not pursue scalp cooling. Therefore, failure to prevent

hair loss in this population of self-selected women may have had more devastating consequences compared to controls. In accordance, women who have unsuccessfully undergone scalp hypothermia may be most impacted by their hair loss and thus benefit from further resources to address their well-being [8].

As well as discrepancies in reporting and methods, overall cost and financial burden of scalp cooling may have impacted QoL outcomes. Depending on the specific cooling device and geographic location, scalp hypothermia costs roughly $1500 to $3000 per patient with additional administrative and overhead costs that are not routinely covered or reimbursed by health insurance [4]. While the EORTC QLQ-C30 includes one question on financial difficulties, none of the included studies reported on average household income or adjusted QoL outcomes based on income or financial burden.

Conclusion

CIA remains a critical concern in many women with breast cancer undergoing treatment. While scalp cooling may prevent hair loss in up to 59% of breast cancer patients on a taxane-based regimen and 36% on an anthracycline-based regimen, the evidence to show its impact on QoL is less robust. In designing future studies on scalp cooling for CIA, it is essential that clinicians use a validated instrument to measure the effects of skin and hair disease on QoL, consider the financial impact of scalp cooling on QoL measures, and further discriminate QoL outcomes for scalp-cooled patients based on the degree of hair preservation.

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Compliance with ethical standards

Conflict of interest Dr. Lacouture has a consultant/speaking role with Legacy Healthcare Services, Adgero Bio Pharmaceuticals, Amryt Pharmaceuticals, Celldex Therapeutics, Debiopharm, Galderma Research and Development, Johnson and Johnson, Novocure Inc, Lindi, Merck Sharp and Dohme Corporation, Helsinn Healthcare SA, Janssen Research & Development LLC, Menlo Therapeutics, Novartis Pharmaceuticals Corporation, F. Hoffmann-La Roche AG, AbbVie Inc, Boehringer Ingelheim Pharma Gmbh & Co. KG, Allergan Inc, Amgen Inc, E.R. Squibb & Sons LLC, EMD Serono Inc, Astrazeneca Pharmaceuticals LP, Genentech Inc, Leo Pharma Inc, Seattle Genetics, Bayer, Manner SAS, Lutris, Pierre Fabre, Paxman Coolers, Adjucare, Dignitana, Biotechspert, Teva Mexico, Parexel, OnQuality Pharmaceuticals Ltd, Novartis, Harborside, Wiley, and Takeda Millenium. Dr. Lacouture also receives research funding from Berg, Bristol-Myers Squibb, Lutris, Paxman, Novocure, US Biotest, and Veloce, and is funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748. Mr. Marks declares that he has no conflict of interest. Dr. Okhovat declares that he has no conflict of interest. Ms. Hagigeorges declares that she has no conflict of interest. Ms. Manatis-Lornell declares that she has no conflict of interest. Dr. Isakoff declares that he has no conflict of interest. Dr. Senna declares that she has no conflict of interest.

Informed consent As this study was a systematic review and did not involve contact with patients or patient information, it was not applicable for Informed consent to be obtained.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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