



Scalp Cooling in the US: Clinical Trials and Toxicity

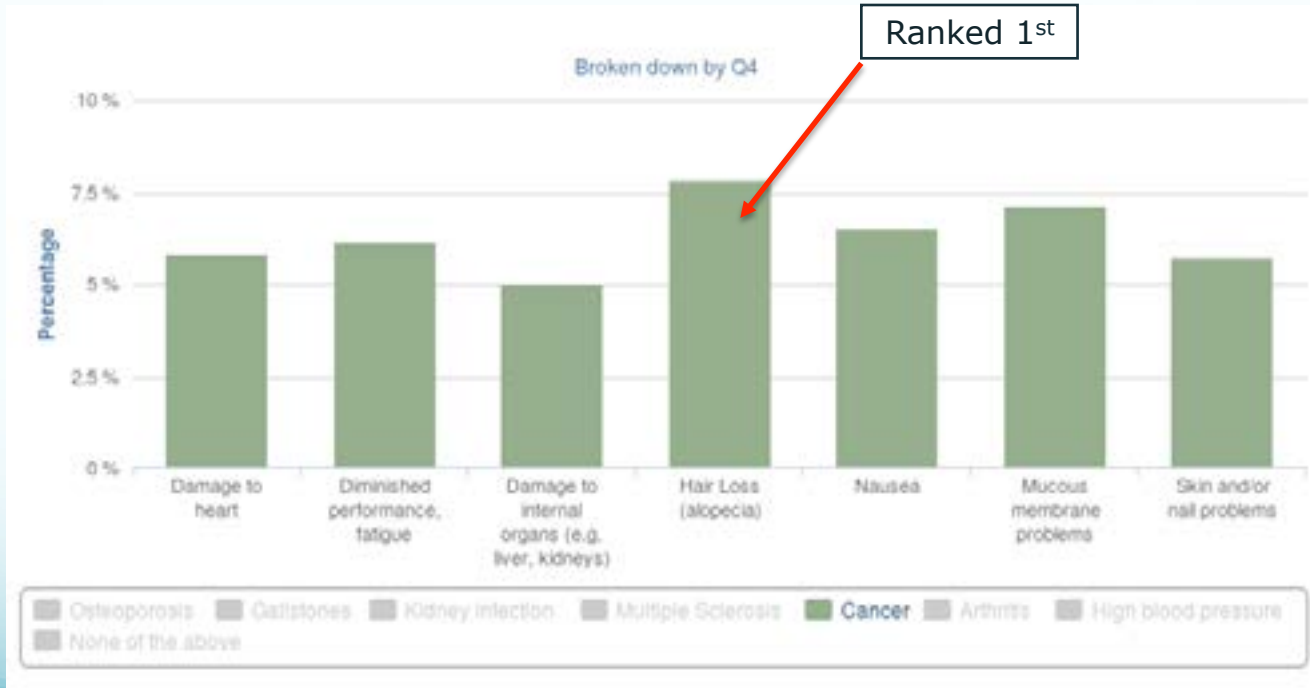
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Chemotherapy Induced Hair Loss

- Temporary hair loss is one of the most distressing and traumatic side effects of chemotherapy
- Women with chemotherapy induced alopecia compared to those without report:
 - lower self-esteem
 - poorer body image
 - lower quality of life
- May impact patients' decision to accept or decline chemotherapy

Ranking of Chemotherapy Side-Effects



Source: Consumer online survey of 400 females ages 40-75 from all ethnicities, all states and a wide range of household income without pre-knowledge of previous diagnosed diseases.

Frequency and severity of alopecia for selected chemotherapy agents and combinations

	Severe	Moderate	Mild
Frequent	<ul style="list-style-type: none"> ■ Doxorubicin (>40 mg/m²) ■ Epirubicin (>30 mg/m²) ■ Daunorubicin ■ Paclitaxel (every 2 to 3 weeks) ■ Docetaxel ■ Cyclophosphamide (IV at doses >300 mg/m²) ■ Ifosfamide ■ Etoposide (IV) ■ Ixabepilone ■ Eribulin ■ Combination chemotherapy with doxorubicin, docetaxel, paclitaxel, etoposide 	<ul style="list-style-type: none"> ■ Mechlorethamine ■ Methotrexate ■ Carboplatin (AUC 5 to 6) ■ Paclitaxel (weekly) 	<ul style="list-style-type: none"> ■ Bleomycin
Infrequent	<ul style="list-style-type: none"> ■ Vincristine ■ Vinblastine ■ Etoposide (oral) 	<ul style="list-style-type: none"> ■ Oxaliplatin ■ Cyclophosphamide (oral) 	<ul style="list-style-type: none"> ■ Fluorouracil ■ Capecitabine ■ Hydroxyurea ■ Thiotepa ■ Carboplatin (weekly) ■ Cisplatin

Permanent Alopecia

- Delayed recovery or permanent alopecia has been reported with docetaxel
- Incidence related to dose, duration of therapy
 - Variable reports of 8-10%
 - Less frequent at 75 mg/m² than 100 mg/m²
 - Can be prevented with scalp cooling?

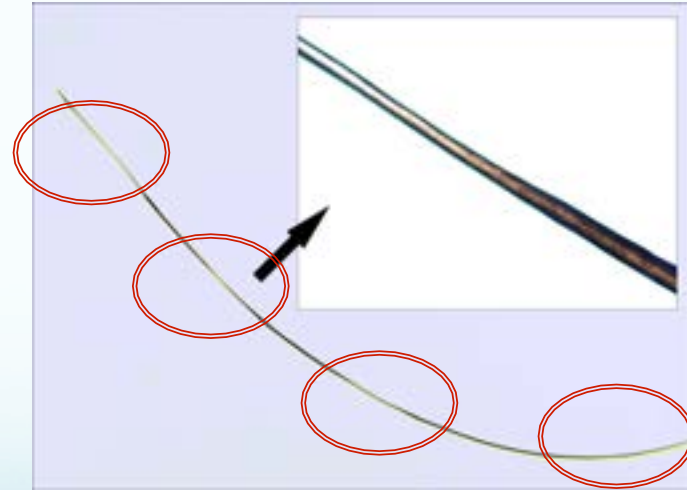


Preventing Chemotherapy Induced Alopecia: Past to Present

- Scalp cooling
 - Automated systems that circulate coolant through cooling caps
 - Manual cooling with frozen cold caps that must be replaced with a new frozen cap as the cap warms

Scalp Cooling: Potential Mechanisms of Action

- Vasoconstriction
 - Reduces the blood flow to hair follicles during peak plasma concentrations of chemotherapy
 - Reduces cellular uptake of chemotherapy
- Reduced biochemical activity
 - Makes hair follicles less susceptible to damage from chemotherapeutic agents



Courtesy of Corina van den Hurk

Available Scalp Cooling Devices for the Prevention of Chemotherapy Induced Alopecia

Device	Details
Free-standing with circulating coolant (automated)	
Dignicap	US FDA cleared
Paxman caps	
Frozen cold caps (manual)	
Penguin caps	Cap must be frozen and changed every 30 minutes as it begins to thaw. The Penguin cap can be molded to the shape of the head
Elastogel caps	
Polar cold caps	
Artic cold caps	
Chemo cold caps	

Scalp Cooling to Prevent Chemotherapy Induced Alopecia

- Widely used internationally
- Newly introduced in the U.S.
 - Not covered by insurance (yet!)
 - Delay in US related to concerns about increased risk of scalp mets and poor efficacy
- Most older studies included multiple chemotherapy regimens, diseases, and variable assessment of hair preservation (use of wig, many retrospective)
- Recent increase in prospective, well-designed trials



Scales Used to Measure Hair Loss

Modified Dean scale for quantification of chemotherapy-induced alopecia

Dean score	Percentage of hair loss
Grade 0	No hair loss
Grade 1	>0 to ≤25% hair loss
Grade 2	>25 to ≤50% hair loss
Grade 3	>50 to ≤75% hair loss
Grade 4	>75% hair loss

NCI CTCAE version 4.0 alopecia

Adverse event	Grade 1	Grade 2
Alopecia	Hair loss of <50 percent normal for that individual that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage	Hair loss of ≥50 percent normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact

Two Prospective Multi-Center Trials in the US

- Dignicap
 - Prospective trial in stage I-II breast cancer patients
 - TAC and AC/T excluded
 - Non-randomized concurrent matched controls (capped at 15 if total hair loss)
 - Used Dean Scale assessed by patients compared to baseline
- Paxman SCALP trial
 - Prospective randomized trial in stage I-II breast cancer patients
 - Control vs scalp cooling
 - Any chemotherapy allowed
 - Used NCI CTCAE scale assessed by providers

DigniCap Study: Chemotherapy Regimens in Treatment and Control Groups

Chemotherapy Regimen & Dose	Number of patients N(%)	Number of controls N(%)
Docetaxel 75 mg/m ² & cyclophosphamide 600 mg/m ² every 3 weeks or 4 - 6 cycles	76 (75%)	10 (62.5%)
Paclitaxel 80 mg/m ² weekly for 12 cycles	12 (12%)	2 (12.5%)
Docetaxel 75mg/m ² , carboplatin AUC 6 for 6 cycles every 3 weeks, trastuzumab weekly or every 3 weeks, with or without pertuzumab every 3 weeks	12 (12%)	3 (19%)
Docetaxel 75 mg/m ² , trastuzumab·pertuzumab, every 3 weeks for 6 cycles	1 (1%)	0
Doxorubicin 60 mg/m ² & cyclophosphamide 600 mg/m ² every 3 weeks for 4 cycles	0	1 (6%)
Totals	101	16

Alopecia Self-Report: Maximum Dean Score and Success Rate (Dean score <3)

	DigniCap N = 101		Control N = 16	
Dean Score	Score N(%)	% Success	Score N(%)	% Success
0 (no hair loss)	5 (5.0%)	67 (66.3%)* 95% CI, 56.2-75.4 %	0 (0.0%)	0 (0.0%)
1 (>0 and up to 25% hair loss)	31 (30.7%)		0 (0.0%)	
2 (>25% and up to 50% hair loss)	31 (30.7%)		0 (0.0%)	
3 (>50% and up to 75% hair loss)	19 (18.8%)	34 (33.7%)	1 (6.3%)	16 (100.0%)
4 (> 75% hair loss)	15 (14.9%)		15 (93.8%)	

- *p-value for comparing DigniCap to control P<0.001 from a Fisher's exact test
- Maximum Dean score: Dean score 4 weeks after the last chemotherapy or the highest numerical score documented before discontinuing study evaluations

Success by Chemotherapy Regimen in Treatment and Control Groups

Chemotherapy regimen	DigniCap	Control
	Treatment success ⁴	Treatment success ⁴
TC ¹	46/76 (60.5%)	0/10
TCarbo ²	10/12 (83.3%)	0/3
Paclitaxel ³	10/12 (83.3%)	0/2

1. TC: Docetaxel/cyclophosphamide x 4-6 cycle 2.TCarbo: Docetaxel/carboplatin + HER2 targeted therapy x 4-6 cycles. 3. Paclitaxel: Paclitaxel weekly x 12 4.Treatment success: Dean score < 3

Scalp cooling with the Dignicap System versus control

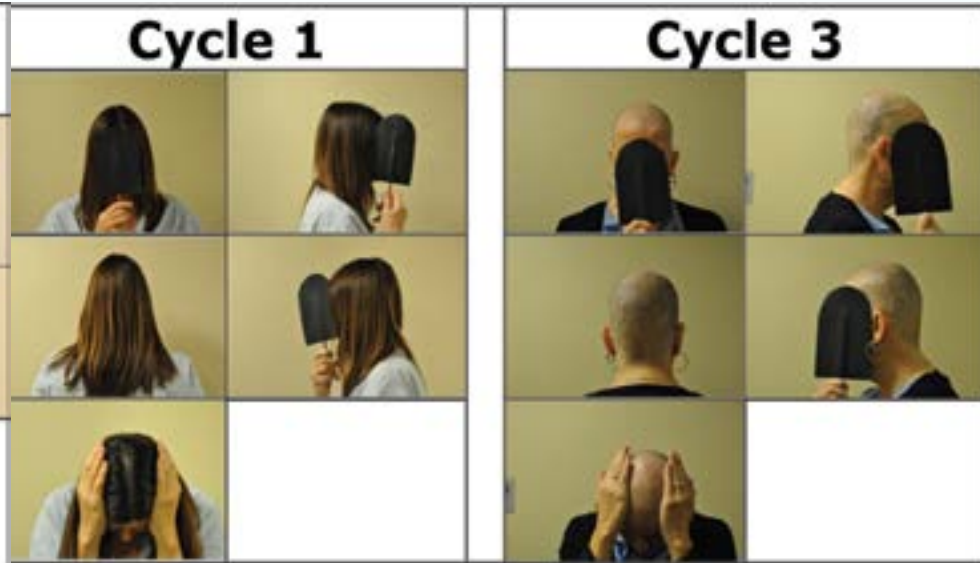
Scalp Cooled Patient

Planned chemotherapy: TC x 4



Control Patient

Planned chemotherapy: TC x 4



TC: docetaxel 75 mg/m² & cyclophosphamide 600 mg/m² IV every 3 weeks x 4 cycles

Quality of Life Measurements: Scores of Quite a Bit/ Very Much One Month After the End of Chemotherapy

EORTC Breast Cancer-Specific Quality of Life Questionnaire Item	Response of "Quite a Bit" or "Very Much" ^a					P Value ^c
	Scalp Cooling Group		Control Group ^b		Absolute Difference, % (95% CI)	
	Analytic Sample Size	Response Rate, % (95% CI)	Analytic Sample Size	Response Rate, % (95% CI)		
Have you lost any hair?	88	33.0 (23.1 to 42.8)	16	68.8 (46.0 to 91.5)	-35.8 (-60.5 to -11.1)	.007
Were you upset about your loss of hair?	74	32.4 (21.8 to 43.1)	15	60.0 (35.2 to 84.8)	-27.6 (-54.6 to -0.58)	.04
Have you felt physically less attractive as a result of your disease or treatment?	88	27.3 (18.0 to 36.6)	16	56.3 (31.9 to 80.6)	-29.0 (-55.0 to -3.0)	.02
Have you been feeling less feminine as a result of your disease or treatment?	88	21.6 (13.0 to 30.2)	16	31.3 (8.5 to 54.0)	-9.7 (-33.9 to -14.6)	.40
Did you find it difficult to look at yourself naked?	88	15.9 (8.3 to 23.6)	16	18.8 (0 to 37.9)	-2.8 (-23.4 to -17.8)	.78
Have you been dissatisfied with your body?	88	15.9 (8.3 to 23.6)	16	37.5 (13.8 to 61.2)	-21.6 (-46.5 to -3.3)	.04

Abbreviation: EORTC, European Organization for Research and Treatment of Cancer.

^b The last observation carried forward was used.

^c Calculated using the χ^2 test.

^a Responses collected 1 month after the end of chemotherapy.

Penguin Cold Cap: UCSF Registry Study

Chemotherapy regimen	Pts enrolled in registry	Discontinued scalp cooling			Lost to follow-up (%)
		Due to device-related side effects (%)	Due to hair loss (%)	Discontinued chemotherapy for toxicity unrelated to scalp cooling (%)	
TC × 4	40	0	2 (5)	3 (7.5)	0
TC × 5-6	10	1 (10)	0	0	0
P/AC	23	1 (4.3)	2 (8.7)	0	0
AC/P	10	2 (20)	2 (20)	0	0
T/Carboplatin × 4-6 (±Herceptin)	4	0	0	0	2 (50)
Other	16	2 (12.5)	3 (18.75)	0	1 (6.25)
Overall	103	6 (5.8)	9 (8.7)	3 (2.9)	3 (2.9)

TC docetaxel/cyclophosphamide, P paclitaxel, AC doxorubicin/cyclophosphamide

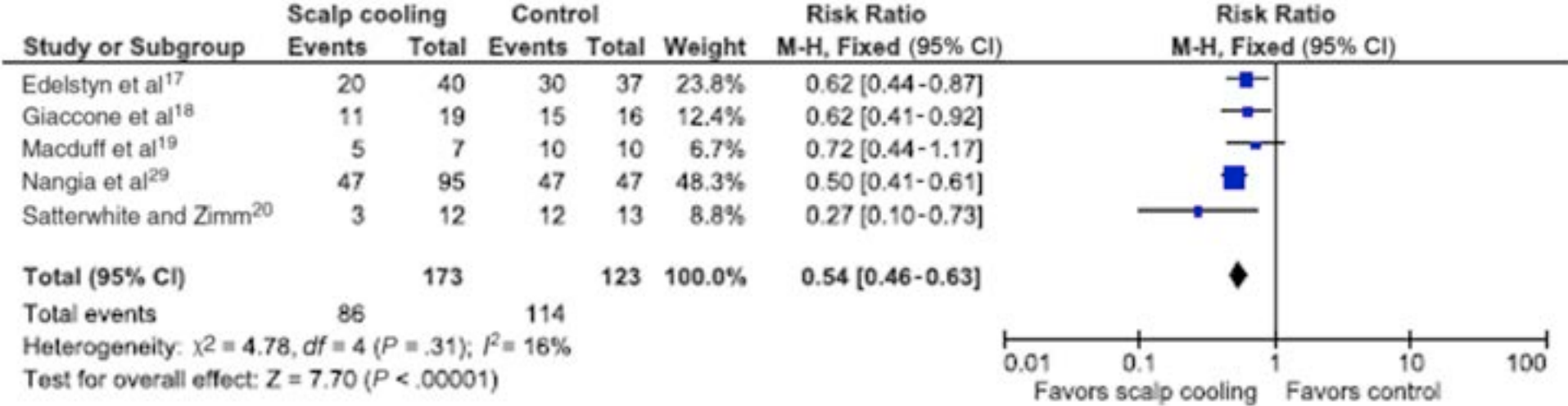
Chemotherapy regimen	Evaluable pts	Successful alopecia prevention		Mean maximum VAS by pt report
		% success by patient self-assessment (≤50% hair loss)	% success by physician report (Dean's score ≤2)	
TC × 4	37	83.8% (31)	80% (28/35 ^a)	38.6
TC × 5-6	10	50% (5)	75% (6/8 ^a)	44.4
P/AC	23	43.4% (10)	55.5% (10/18 ^a)	58.9
AC/P	10	20% (2)	20% (2/10)	62.5
T/Carboplatin × 4-6 (±Herceptin)	2	100% (2/2)	100 (1/1 ^a)	20
Other	15	60% (9)	61.5% (8/13 ^a)	46.9
Overall	97	60.8% (59)	64.7% (55/85 ^a)	47

^aData unavailable for remaining patients

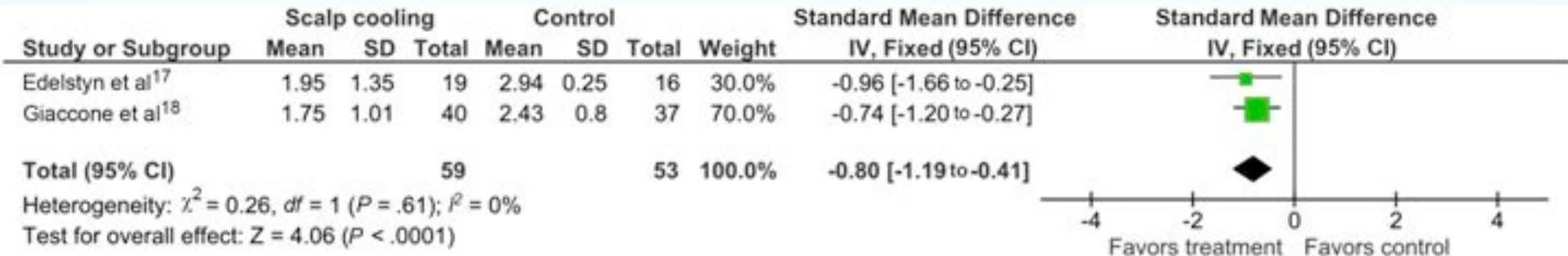
Meta-Analysis of Randomized Trials

Scalp hypothermia to prevent alopecia during chemotherapy

- 10 studies included with 654 patients
 - 80% had breast cancer, most chemo included anthracyclines
 - 6 studies compared cooling with no cooling
 - 3 compared one system with another
 - 1 evaluated post-cooling time (20 vs 45 min)



Significant impact on alopecia defined as patients generally requiring a wig



Using an ordinal scale for alopecia (grade 1: 0-25%, grade 2: 26-50%, grade 3: >50%), scalp cooling significantly reduced the grade of alopecia

Safety: DigniCap Study

- Toxicity included grade 1/2 headache.
- Three discontinued cooling, primarily from feeling cold.
- No patient has developed scalp metastases with a mean follow up from last chemotherapy administration of 12.9 months (range of 6.7 to 18 months).
- Follow-up continues annually
 - No scalp metastases at a median FU of over 3.5 years

Risk of Thermal Injury?

- 4 cases from MSKCC reported with grade 1-2 thermal injury to scalp
 - Penguin:
 - Case 1: Used alternative scalp covering (paper towel)
 - Blistering at upper mid forehead
 - Case 2: used appropriate protection
 - Blistering in forehead area
 - Case 3: crusting and desquamation of scalp
 - Elastogel: used after alopecia from AC, during paclitaxel
 - Large bulla on scalp



Table 1 Characteristics of patients with frostbite on the scalp following the use of cold caps

Case no.	Age/ Sex	Cancer	Chemo regimen	Cold cap usage details				Onset	Follow-up ^b	Potential contributory factors
				Make	Pre-infusion	During infusion	Post-infusion			
1	49/F	Breast	TCHP	Penguin™	60'	2.5 h.	5 h.	Cycle 3	Mild persistent alopecia (at 5 months)	Lack of adequate padding between the cold cap and skin; duration of post-infusion cooling
2	55/F	Breast	AC → T	Elasto-Gel™	15'	60'	50 min.	Cycle 3	Mild persistent alopecia (at 4 months)	Pre-existing alopecia; lack of padding; duration of post-infusion cooling?
3	58/F	Breast	PH	Penguin™	50'	30'	2.5 h.	Cycle 4 ^a	Alopecia resolved (at 2 months)	Pre-existing diffuse alopecia; duration of post-infusion cooling
4	50/F	Breast	CMF	Penguin™	50'	60'	4.5 h.	Cycle 1	Mild persistent alopecia, skin sensitivity (at 6 months)	Lack of adequate padding; duration of post-infusion cooling

Meta-Analysis: Risk of Scalp Metastases with Scalp Cooling

- 23 full text articles
 - 10 quantified the incidence of scalp metastasis with scalp cooling over time
- Results
 - Scalp cooling: 1,959 pts evaluated over ~ 43.1 mo.
 - Incidence rate of scalp mets: 0.61% (95% CI: 0.32% to 1.1%)
 - Non-scalp cooling: 1,238 pts evaluated over ~ 87.4 mo.
 - Incidence rate of scalp mets: 0.41% (95% CI: 0.13% to 0.94%)
 - P = 0.43 for the comparison

Table 1 Included Studies

Study	Scalp cooling		No scalp cooling		Length of follow-up (months) scalp cooling median	Weighted length of follow-up scalp cooling	Length of follow-up (months) no scalp cooling median	Weighted length of follow-up no scalp cooling	Characteristics
	Scalp mets	Total pts	Scalp mets	Total pts					
Lemieux et al. [11]	6	553	1	87	69	19.478	64	4.498	First time breast cancer patients. Study undertaken in Canada. Mainly T1 and T2 tumor size; stage 1 & 2, treated with mainly cyclophosphamides and doxorubicin
Parker [14]	0	6			12	0.037			Stage 4 recurrent disease. Treated with IV CMF (2 cycles)
Profiere et al. [18]	0	77	0	109	44	1.729			First time breast cancer patients. 4 cycles of adjuvant IV chemotherapy with mitoxantone + cyclophosphamide. Antiemetics also administered. Study undertaken in France
Ridderheim [15]	0	3			15	0.023			Adjuvant treatment breast cancer
Ron et al. [19]	0	19	0	16	14	0.136	14	0.181	Breast cancer patients treated with cyclophosphamide, methotrexate, and 5-fluorouracil [CMF]; unclear as to stage of breast cancer
Rago [17]	0	101			29.5	1.521			Early-stage breast cancer patients
Spaith et al. [20]	3	770	0	141	36	14.150	36	4.100	93% breast cancer patients. Treated with IV chemo mainly anthracyclines and/or taxotere. Unclear as to stage of breast cancer
Tollenaar et al. [35]	0	35			46	0.822			Patients treated with cyclophosphamide + doxorubicin + 5-fluorouracil on first operative day (one course of treatment). Unclear as to stage of cancer
van de Sande [12]			4	885			110	78.635	Stage 4 + lymph nodes
van den Hurk et al. [13]	3	395			26	5.242			treated with CMF; unclear as to stage of breast cancer
Totals	12	1959	5	1238					
Averages					32.39	43.14	56	87.41	

Additional Safety Data

- Scalp mets
 - Overview from Munich cancer registry
 - >33,771 breast cancer patients
 - 77% treated adjuvantly, mainly with taxanes/anthracyclines
 - Incidence not higher with scalp cooling
 - Scalp cooling 0.04-1%
 - No scalp cooling 0.03-3%
- Overall survival
 - Retrospective study
 - 1370 women with stage 1-3 breast cancer from Quebec; median f/u 6.3 years
 - No difference in OS in scalp cooled vs no scalp cooling groups

Scalp-Cooling Caps Help Prevent Hair Loss in Chemo

By RACHEL RABKIN PEACHMAN

New York Times

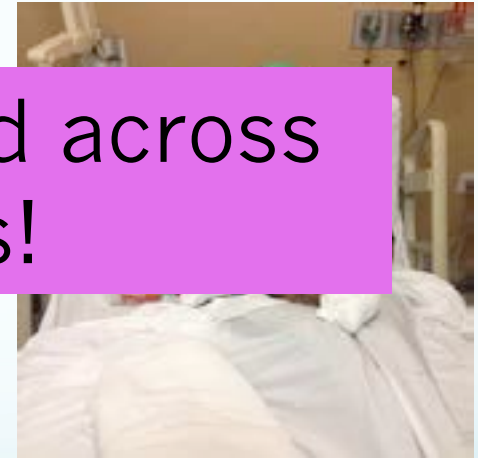
FEB. 14, 2017

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Both devices now approved across multiple indications!

least some of their hair throughout chemotherapy.

“We have a huge growing population of breast cancer survivors, and many of them are very traumatized by their treatment,” said Dr. Hope S. Rugo, the director of breast oncology and clinical trials education at the U.C.S.F. Helen Diller Family Comprehensive Cancer Center and lead investigator of one of the studies. “We’re working on all sorts of areas to try to limit that impact, and one is scalp cooling.”



Scalp Cooling Prevents CIA

Success is Regimen Dependent

- Considerations for practices and patients
 - ‘Chair time’ and post-cooling time
 - Move to another room difficult due to two patient per device design
 - Paxman has 2 models, allowing either one or two patients to be treated
 - Cost to patient and infusion center
 - Cap fitting: precise fit is critical to success
 - Paxman: single patient use cap with the ability to pay per use of the system
 - Dignicap: digniTherm click cap, custom fit kit allows patients to place cap themselves, single patient model coming soon
 - For manual devices
 - Space considerations for center
 - Need for assistance for patients
- Other issues
 - Failure rate with anthracyclines
 - Better caps?
 - Impact of sequence?
 - Optimal post-cooling time
 - An area in need of further study

International Registry



Patient support in the US
<http://www.hairtostay.org/>





I was diagnosed with breast cancer in 2013. I was thrilled to have the opportunity to participate in a clinical trial at UCSF for DigniCap, an experimental treatment that cools the head during chemotherapy to reduce hair loss. I had no side effects and retained most of my hair. I never needed a wig during treatment and even went on national TV 3 weeks after my final round of chemo.

It was a powerful experience to look healthy throughout chemotherapy and be treated as a healthy person by others. Those who knew I was undergoing chemotherapy were perplexed at how vibrant I appeared and that influenced how they treated me. That, in turn, influenced how I identified as someone who was healing instead of someone who was sick. **Having hair also allowed my children (then 9 and 6) to see me as just their mommy, not a sick woman.**