

**RESEARCH ON THE EFFECTIVENESS, AND SAFETY OF SCALP COOLING:
SUMMARIES AND BIBLIOGRAPHY**

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Table of Contents

Why be concerned about hair loss?	3
Quality of life	3
Persistent alopecia (permanent hair loss).....	5
How does scalp cooling work?	7
The science of scalp cooling	7
Is scalp cooling effective?	8
Review articles on the efficacy of cold caps	8
Prospective multicenter trials.....	11
Randomized clinical trials on the efficacy of cold caps.....	13
Research literature (individual studies)	15
Is scalp cooling safe?	22
Concern about scalp metastases (breast cancer spreading to the scalp)	22
Concern about impact of scalp cooling on survival	26
Editorial endorsement from the American Medical Association	27
Cold cap use and availability in the U.S.	28

A BIBLIOGRAPHY OF THE RESEARCH, EFFECTIVENESS, AND SAFETY ON SCALP COOLING

Why be concerned about hair loss?

Quality of life

Research summary: Review of many studies finds that hair loss is consistently ranked among the most troublesome side effects of chemotherapy. Hair loss has been described as distressing and may affect one's body image. Studies have shown that concern over hair loss can lead some women -up to 8% in one study (Tierney, 1992) - to refuse recommended chemotherapy.

A 2017 editorial in JAMA titled, "Scalp cooling to prevent chemotherapy-induced alopecia: The time has come" concluded that, "identifying interventions, such as scalp cooling for the prevention of chemotherapy-induced alopecia, that reduce or eliminate treatment-associated toxic effects will help ease the distress associated with chemotherapy and may, as a result, improve outcomes for patients with breast cancer" (Hershman, 2017).

- Hershman DL. Scalp cooling to prevent chemotherapy-induced alopecia: The time has come. *JAMA* 2017;317(6):587-8.
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- van den Hurk CJG, Mols G, Vingerhoets JJM, Breed WPM. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psycho-Oncology* 2010;19:701-9.
- Lemieux J, Maunsell E, Provencher L. Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: A literature review. *Psycho-Oncology* 2008;17:317-28.
- Rosman S. Cancer and stigma: experience of patients with chemotherapy-induced alopecia. *Patient Educ Couns* 2004;52:333-9.
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- Tierney AJ, Taylor J, Closs SJ. Knowledge, expectations and experiences of patients receiving chemotherapy for breast cancer. *Scand J Caring Sci* 1992;6:75-80.
- Baxley KO, Erdman LK, Henry EB, Roof BJ. Alopecia: Effect on cancer patients' body image. *Cancer Nurs* 1984;7:499-503.

Persistent alopecia (permanent hair loss)

Research summary: Persistent chemotherapy-related hair loss is defined as the “absence or incomplete regrowth of hair six months following the completion of chemotherapy” (Tallon, 2010). Taxanes – especially docetaxel (taxotere) - commonly used to treat breast cancer, have been found to be associated with persistent chemotherapy-related hair loss. While such loss is rare, reports of it are increasing. Studies have found 3.5%-6.3% of patients treated with docetaxel experienced persistent significant hair loss (Sedlacek, 2006; Bourgeois, 2012).

- Bourgeois H, Jamet A, Grudé F, et al. ERALOP study: Post adjuvant FEC-docetaxel chemotherapy for early breast cancer: Hair regrowth in the real life. In: Proceedings of the Thirty-Seventh Annual CTSC-AACR San Antonio Breast Cancer Symposium: 2014 Dec 9-13; San Antonio, TX. Philadelphia (PA): AACR; *Cancer Res* 2015;75(9 Suppl):Abstract nr P5-21-05.
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- Jamet A, Bourgeois H, Grudé F, et al. Study of risk of persistent alopecia induced by adjuvant chemotherapy for breast cancer: Results of the ERALOP study. *Fund Clin Pharmacol* 2014;28(Suppl 1):67.
- Bourgeois H, Soulié P, Lucas B, et al. ALOPREV: First cooling scalp trial for prevention of persisting alopecia after docetaxel for early breast cancer patients. *Cancer Res* 2012;72(24 Suppl):Abstract nr OT3-3-04.
- Kluger N, Jacot W, Frouin E, et al. Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: A prospective study of 20 patients. *Ann Oncol* 2012;23:2879-84.

- Miteva M, Misciali C, Fanti PA, et al. Permanent alopecia after systemic chemotherapy: a clinicopathological study of 10 cases. *Am J Dermatopathol* 2011;33:345-50.
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- Tallon B, Blanchard E, Goldberg LJ. Permanent chemotherapy-induced alopecia: Case report and review of the literature. *J Am Acad Dermatol* 2010;63:333-6
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- Masidonski P, Mahon SM. Permanent alopecia on women being treated for breast cancer. *Clin J Oncol Nurs* 2009;13:13-4.
- Prevezas C, Matard B, Piquier L, Reygagne P. Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 2009;160:883-5.
- Sedlacek SM. Persistent significant alopecia (PSA) from adjuvant docetaxel after doxorubicin/cyclophosphamide chemotherapy in women with breast cancer. Presented at the 29th Annual San Antonio Breast Cancer Symposium, San Antonio, TX. December 14-17, 2006.
- Park J, Choi Y, Lee W, et al. Five cases of permanent alopecia following chemotherapy. *Korean J Dermatol* 2005;43:1365-70

How does scalp cooling work?

The science of scalp cooling

Research summary: Scalp cooling is believed to prevent chemotherapy-induced hair loss by two mechanisms: 1) decreasing blood flow to the scalp, and 2) preserving the hair follicles by reducing biochemical activity.

There has been a small amount of research done on the optimal temperature for scalp cooling to prevent or minimize hair loss and on the amount of time patients should continue scalp cooling at the end of each chemotherapy session (Van Den Hurk, 2012; Komen, 2016). Further research is needed to clarify these questions.

- Komen MMC, Breed VPM, Smorenburg CH et al. Results of 20- versus 45-minute post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Support Care Cancer* 2016;24(6):2735-41.
- Pliskow B, Mitra K, Kaya M. Simulation of scalp cooling by external devices for prevention of chemotherapy-induced alopecia. *J Therm Biol* 2016;56:31-8.
- Collett A, Al-Tameemi W, Dunnill C, et al. The role of scalp cooling in the prevention of chemotherapy induced alopecia. *Eur J Clin Med Oncol Special Edition* 2014;65-9.
- Breed WPM. Why scalp cooling in breast cancer? *Breast Cancer Manage* 2014;3(3):219.
- Van Den Hurk CJG, Breed VPM, Nortier JWR. Short post-infusion scalp cooling time in the prevention of decetaxel-induced alopecia. *Support Care Cancer* 2012;20(12):3255-60.
- Janssen FE, Van Leeuwen GM, Van Steenhoven AA. Modelling of temperature and perfusion during scalp cooling. *Phys Med Biol* 2005;50:4065-73.
- Bulow J, Friberg L, Gaardsting O, Hansen M. Frontal subcutaneous blood flow, and epi- and subcutaneous temperatures during scalp cooling in normal man. *Scand J Clin Lab Invest* 1985;45:505-8.

Is scalp cooling effective?

Review articles on the efficacy of cold caps

According to the University of Texas Libraries: “Review articles are an attempt by one or more writers to sum up the current state of the research on a particular topic. Ideally, the writer searches for *everything* relevant to the topic, and then sorts it all out into a coherent view of the “state of the art” as it now stands. Review Articles will teach you about:

- the main people working in a field
- recent major advances and discoveries
- significant gaps in the research
- current debates
- ideas of where research might go next”

Research summary: Since 2005, a number of review articles have been written on the use of scalp cooling to prevent chemotherapy-induced hair loss. The earliest review considers 53 publications on the topic while a later review written by the same research team considers 58 publications focused on ‘working mechanism, determinants of success rates, side effects and controversies’ (Breed, 2011). The Komen review (2013) considers 32 studies, the Poder review (2011) reports on 62 studies, and a review by Rugo presented at a poster session (2011) notes that “published results are available on the efficacy of scalp cooling in more than 4000 patients and 83 publications from 1973-2009.”

Three additional reviews (Dabrowski, 2011; Villasante, 2014; Shin, 2015) consider the evidence on a wide array of methods, including scalp cooling, of chemotherapy-induced hair loss prevention. Another perspective is provided in Kadakia’s 2014 review in which he and his colleagues appraise the role of cold therapy in the treatment of a number of symptoms related to chemotherapy, including hair loss.

An addition to the literature on safety and efficacy of scalp cooling is a book (van den Hurk, 2013) that chronicles and compiles the evidence.

Breed and his colleagues conclude that, scalp cooling is effective and “by far the best method to reduce chemotherapy-induced hair loss” but “not for all chemotherapy patients”. In particular they note that results are excellent for those being treated with taxanes (docetaxel [taxotere] and paclitaxel [taxol]), and anthracyclines (doxorubicin [adriamycin]) but poor for those being treated with the two types of drugs simultaneously in combination with cyclophosphamide (cytoxan). Results are somewhat better when the drugs are given sequentially – doxorubicin and cyclophosphamide followed by docetaxel (Breed, 2011). Komen and colleagues (2013) go on to suggest, “Scalp cooling should...be available in every hospital and health care professionals should offer the possibility of scalp cooling to all eligible patients.”

- Shah VV, Wikramanayake TC, DelCanto GM, et al. Scalp hypothermia as a preventative measure for chemotherapy-induced alopecia: A review of controlled clinical trials. *JEADV* 2017 published online doi: 10.1111/jdv.14612
- Shin H, Jo S, Dim D, Swon O, Myung S. Efficacy of interventions for prevention of chemotherapy-induced alopecia: A systematic review and meta-analysis. *Int J Cancer* 2015;136:E442-54.
- Kadakia KC, Rozell SA, Butala AA, Loprinzi CL. Supportive cryotherapy: A review from head to toe. *J Pain Symptom Manage*. 2014;47(6):1100-15.
- Komen MMC, Smorenburg CH, van den Hurk CJF, Nortier JWR. Factors influencing the effectiveness of scalp cooling in the prevention of chemotherapy-induced alopecia. *The Oncologist*. 2013;18:885-91.
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- Breed W, van den Hurk C, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss. *Expert Rev Dermatol* 2011;6:109-25.
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- Rugo HS, Melisko M. P331 Efficacy and safety of scalp cooling to prevent chemotherapy (CTX) induced alopecia: A review of available data. *The Breast*, 2011;20:S80.
- Dabrowski T. Hair loss as a consequence of cancer chemotherapy – Physical methods of prevention. A review of the literature. *Contemp Oncol* 2011;15(2):95-101.
- Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol* 2005;16:352-8.

Prospective multicenter trials

While review articles provide a summary of all the research on a topic, you may want to read some individual studies. Prospective treatment trials define the question of interest first and design the study ‘looking forward’ to capture data that will help answer the question. Prospective studies are considered to be more definitive at drawing conclusions about the impact of interventions than retrospective studies that use information collected for another purpose to ‘look backwards’ to answer the question.

Trials conducted at multiple centers allow for the enrollment of greater numbers of participants, as well as the potential to study a more diverse population.

Research summary:

• The 2012 article by van den Hurk describes a prospective trial that enrolled 1411 patients in the Dutch Scalp Cooling Registry at 28 hospitals. This is the largest observational study on scalp cooling reported to date. The researchers found that overall, 50% of women who used scalp cooling while receiving chemotherapy reported success in preventing hair loss. The best results were found for women treated with taxanes (docetaxel [taxotere]) with 94% reporting success and paclitaxel [taxol]) with 81% reporting success, and worst results for those treated with a combination of taxane, anthracycline (doxorubicin [adriamycin]) and cyclophosphamide (cytoxan) with 8% reporting success.

- Rugo HS, Klein P, Melin SA, et al. Association between use of a scalp cooling device and alopecia after chemotherapy for breast cancer. *JAMA* 2017;317(6):606-14.
- Betticher DC, Delmore G, Breitenstein U, et al. Efficacy and tolerability of two scalp cooling systems for the prevention of alopecia associated with docetaxel treatment. *Support Care Cancer* 2013;21:2565-73.

- van den Hurk CJ, Peerbooms M, van de Poll-Franse LV, et al. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol* 2012;51:497-504.
- van den Hurk CJ, Mols F, Vingerhoets AdJJM, Breed WPM. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psycho-Oncol* 2010;19:701-9.
- Mols F, van den Hurk CJ, Vingerhoets AJ, Breed WP. Scalp cooling to prevent chemotherapy-induced hair loss: practical and clinical considerations. *Support Care Cancer* 2009;17:181-9.
- Spaeth D, Luporsi E, Weber B, et al. Efficacy and safety of cooling helmets (CH) for the prevention of chemotherapy-induced alopecia (CIA): A prospective study of 911 patients (pts). *J Clin Oncol* 2008;26:9564.

Randomized clinical trials on the efficacy of cold caps

Randomized clinical trials are considered to be the ‘gold standard’ of clinical trials. They are unique in that participants are randomly assigned to receive the treatment or intervention being studied or not. In some studies the choice is between the experimental treatment and no treatment; in others it is between the experimental treatment and a treatment that has been previously tested.

Research summary: Scalp cooling was found to be effective in seven of the eight studies. Earlier studies (those conducted prior to 1995) involved 1500+ participants. In these studies scalp cooling was considered successful 56% of the time. Later studies (those conducted between 1995-2003) involved 1000+ patients. In these studies the success rate for scalp cooling was 73%. The latest randomized clinical trial (Nangia, 2017) studied 182 women at seven clinical sites. Nangia and her colleagues found that 63% of participants who used scalp cooling kept more than half of their hair.

- Nangia J, Wang T, Osborne C, et al. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: The SCALP randomized clinical trial. *JAMA* 2017;317(6):596-605.
- Macduff C, Mackenzie T, Hutcheon A, et al. The effectiveness of scalp cooling in preventing alopecia for patients receiving epirubicin and decetaxel. *Eur J Cancer Care (Engl)* 2003;12(2):154-61.
- Ron IG, Kalmus Y, Kalmus M, et al. Scalp cooling in the prevention of alopecia in patients receiving depilating chemotherapy. *Support Care Cancer* 1997;5(2):136-8.
- Giaccone G, Di Giulio F, Morandini MP, Calciati A. Scalp hypothermia in the prevention of doxorubicin-induced hair loss. *Cancer Nurs* 1988;11(3):170-3.
- Parker R. The effectiveness of scalp hypothermia in preventing cyclophosphamide-induced alopecia. *Oncol Nurs Forum* 1987;14(6):49-53.

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- Kennedy M, Packard R, Grant M, et al. The effects of using Chemocap on occurrence of chemotherapy-induced alopecia. *Oncol Nurs Forum* 1983;10(1):19-24.
- Edelstyn GA, MacDonald M, MacRae KD. Doxorubicin-induced hair loss and possible modification by scalp cooling. *Lancet* 1977;2(8031):253-4.

Research literature (individual studies)

Many studies have been conducted looking at the effectiveness of scalp cooling in preventing chemotherapy-related hair loss. Most of these individual studies were included in the review articles described on pages 8-10. Studies are grouped here by year of publication (most recent first) and then alphabetically by author's last name.

Rice BA, Ver Hoeve ES, DeLuca AN, et al. Registry to assess hair loss prevention with the Penguin Cold Cap in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat* 2017, published online DOI 10.1007/s10549-017-4506-z.

Ibrahim T, Kattan J, Assi T, et al. Efficacy of a silicon based continuous scalp cooling system with thermostat on chemotherapy induced alopecia. *J Palliat Care Med* 2015;5(2).

- Rugo HS, Klein P, Melin SA, et al. Clinical performance of the DigniCap system, a scalp hypothermia system, in preventing chemotherapy-induced alopecia. *J Clin Oncol* 2015;33(15 suppl):9518.

- Schaffrin-Nabe D, Schmitz I, Josten-Nabe A, et al. The influence of various parameters on the success of sensor-controlled scalp cooling in preventing chemotherapy-induced alopecia. *Oncol Res Treat* 2015;38(10):489-95.

- Andrews K, Boyle F, Gurton J, O'Reilly A. Crowning Glory: Is that the whole story? Implementing scalp cooling in an Australian setting. Poster presented at Cancer Nurses Society of Australia, 17th Winter Congress; July 24-26, 2014, Melbourne, Australia.

- Friedrichs K, Carstensen MH. Successful reduction of alopecia induced by anthracycline and taxane containing adjuvant chemotherapy in breast cancer – Clinical evaluation of sensor-controlled scalp cooling. *Springerplus* 2014;3,500.

- Cigler T, Fiederlein B, Schneider S, et al. Efficacy of scalp cryotherapy in preventing alopecia among breast cancer patients receiving adjuvant docetaxel and cyclophosphamide. *J Clin Oncol* 2013;31(suppl);abstr e20641.

- van den Hurk CJ, Peerbooms M, van de Poll-Franse LV et al. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol* 2012;51:497-504.
- Abramov M, Semenova I. Cooling of the scalp to prevent anticancer chemotherapy-induced alopecia. (poster). *Eur J Cancer* 2011;47(Suppl.1): S321.
- Kargar M, Sarvestani RS, Khojasteh HN, Heidari MT. Efficacy of penguin cap as scalp cooling system for prevention of alopecia in patients undergoing chemotherapy. *J Adv Nurs* 2011;67:2473-7.
- Kato M, Sakuyama A, Imai R, Kobayashi T. Evaluation of DigniCap system for the prevention of chemotherapy-induced hair loss in breast cancer patient. *Breast* 2011;20 Suppl. 1:S80.
- Yeager CE, Olsen EA. Treatment of chemotherapy-induced alopecia. *Dermatol Ther* 2011;24:432-42.
- Auvinen PK, Mahonen UA, Soininen KM, et al. The effectiveness of a scalp cooling cap in preventing chemotherapy-induced alopecia. *Tumori* 2010;96:271-5.
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- Bourgeois H, Denis F, Kerbrat P, et al. Long Term Persistent Alopecia and Suboptimal Hair Regrowth after Adjuvant Chemotherapy for Breast Cancer: Alert for an Emerging Side Effect: ALOPERS Observatory. In: Thirty-Second Annual CTRC-AACR San Antonio Breast Cancer Symposium. San Antonio, TX; 2009:Abstract nr 3174.
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- Wills S, Ravipati A, Nguyen M, et al. Scalp hypothermia minimizes alopecia in breast cancer patients receiving non-anthracycline adjuvant chemotherapy. *Cancer Res* 2009;69:5040.
- Wang J, Lu Z, Au JL. Protection against chemotherapy-induced alopecia. *Pharm Res* 2006;23:2505-14.
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- Macduff C, Mackenzie T, Hutcheon A, et al. The effectiveness of scalp cooling in preventing alopecia for patients receiving epirubicin and docetaxel. *Eur J Cancer Care (Engl)* 2003;12:154-61.
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- Christodoulou C, Klouvas G, Efstathiou E, et al. Effectiveness of the MSC cold cap system in the prevention of chemotherapy-induced alopecia. *Oncology* 2002;62:97-102.
- Protiere C, Evans K, Camerlo J, et al. Efficacy and tolerance of a scalp-cooling system for prevention of hair loss and the experience of breast cancer patients treated by adjuvant chemotherapy. *Support Care Cancer* 2002;10:529-37.
- El Genidi M. Prevention of chemotherapy-induced alopecia by the new digital scalp cooler device. *Eur J Cancer* 2001;37(Suppl. 6):357.
- Forsberg SA. Scalp cooling therapy and cytotoxic treatment. *Lancet* 2001;357:1134.

- Lenaerts E, Meyen M, Maes T, et al. Scalp cooling in the prevention of anthracycline-induced alopecia. *Eur J Cancer* 2001;37:S360-1.
- Katsimbri P, Bamias A, Pavlidis N. Prevention of chemotherapy-induced alopecia using an effective scalp cooling system. *Eur J Cancer* 2000;36:766-71.
- Peck HJ, Mitchell H, Stewart AL. Evaluating the efficacy of scalp cooling using the Penguin cold cap system to reduce alopecia in patients undergoing chemotherapy for breast cancer. *Eur J Oncol Nurs* 2000;4:246-8.
- Semsek D. Scalp hypothermia for 3 hours reduces alopecia after anthracycline based chemotherapy. *Ann Oncol* 2000;11(Suppl. 4):154.
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- Dorr VJ. A practitioner's guide to cancer-related alopecia. *Semin Oncol* 1998;25:562-70.
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Is scalp cooling safe?

Concern about scalp metastases (breast cancer spreading to the scalp)

Research summary: These articles address a concern that use of cold caps will be associated with breast cancer metastasizing (spreading) to the scalp. The mechanism of this concern is that such spread could occur because of decreased exposure to chemotherapy drugs due to the reduced scalp blood flow caused by cooling. Studies show: 1) spread of breast cancer to the scalp is extremely rare, 2) the likelihood of such spread remains extremely low whether women used scalp cooling or not, and 3) the incidence of scalp metastasis as the site of first recurrence is exceedingly small.

The 2017 systematic review by Rugo and colleagues reviewed the existing studies on scalp metastases. They concluded that, "...scalp cooling is highly unlikely to increase the incidence of scalp metastases in patients with early-stage breast cancer receiving adjuvant chemotherapy" (Rugo et al 2017).

Van den Hurk's 2013 paper presents data from the Munich Cancer Registry. They found that in over 2000 patients, there was no difference in the incidence of scalp metastases in patients who used scalp cooling (0.04 – 1%) and patients who did not use scalp cooling (0.03-3%).

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Concern about impact of scalp cooling on survival

Research summary: It could be hypothesized, “a negative impact of scalp cooling on survival...(which) could occur if scalp cooling, in which less chemotherapy reaches the scalp, resulted in secondary seeding to other organs from dormant cells in the scalp not killed by chemotherapy” (Lemieux et al, 2015). The study conducted by Lemieux and his colleagues (2015) is believed to be the first comparing survival of those who used scalp cooling with that of patients who did not. This retrospective study of 1300+ patients showed no negative impact of scalp cooling on survival.

- Lemieux J, Provencher L, Perron L, Brisson J, Amireault C, Blanchette C, Maunsell E. No effect of scalp cooling on survival among women with breast cancer. *Breast Cancer Res Treat* 2015;149:263-8.

Editorial endorsement from the American Medical Association

Editorial conclusion: “Chemotherapy has been a mainstay of adjuvant therapy for breast cancer and has contributed to a reduction in breast cancer-related mortality. However, with the introduction of targeted therapies, it is appealing to imagine a future in which chemotherapy is no longer necessary and some of the distressing adverse effects of cancer treatments can be avoided. Until that time, identifying interventions, such as scalp cooling for the prevention of chemotherapy-induced alopecia, that reduce or eliminate treatment-associated toxic effects will help ease the distress associated with chemotherapy and may, as a result, improve outcomes for patients with breast cancer” (Hershman, 2017).

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Cold cap use and availability in the U.S.

Many users of cold caps in the U.S. use caps that rely on dry ice or biomedical freezers to achieve and maintain the temperature required for scalp cooling. Recently, scalp cooling systems – in which a cap is connected to a cooling unit that cools the cap to the appropriate temperature – have been clinically tested. In December 2015 the first of these systems, the DigniCap cooling system, was approved by the FDA for use in the US to reduce hair loss that often occurs with chemotherapy for breast cancer. A second system, the Paxman Scalp Cooling System received FDA clearance in April, 2017.

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm476216.htm>

<https://paxmanscalpcooling.com/perch/resources/press-release-fda-clearance-1.pdf>

At the present time, 225+ hospitals and cancer centers in the US either have biomedical freezers and/or offer the DigniCap or Paxman systems for cold cap users.

<http://www.rapunzelproject.org/ColdCaps/Locations.aspx>

Penguin Cold Caps (<http://penguincoldcaps.com/>) and ChemoColdCaps (<http://www.chemocoldcaps.com/index.html>) may be rented while Elastogel caps have previously been available for purchase but are currently not available.

User information, reviews, and support are available through the “Cold cap users – past and present” discussion board on <http://www.BreastCancer.org>.