

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

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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.

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- Rosman S. Cancer and stigma: experience of patients with chemotherapy-induced alopecia. *Patient Educ Couns* 2004;52:333-9.
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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. One study (Sedlacek, 2006) found that 6.3% of patients treated with docetaxel experienced persistent significant hair loss.

- 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.
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- Palamaras I. Permanent chemotherapy-induced alopecia: A review. *J Am Acad Dermatol* 2011;64(3):604-6.
- Prevezas C, Matard B, Pinquier 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, Lee S, Na G, Kim D, 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.

- Collett A, Al-Tameemi W, Dunnill C, Hussain O, Georgopoulos N. The role of scalp cooling in the prevention of chemotherapy induced alopecia. *European Journal of Clinical & Medical Oncology* Special Edition 2014;
- 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: Four reviews have been written on the use of scalp cooling to prevent chemotherapy-induced hair loss, the first in 2005, two in 2011 (one in French), and the most recent in 2013. The earliest review considers 53 publications on the topic while the updated 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 considers 32 studies and the Poder review reports on 62 studies.

Three additional reviews (Dabrowski, 2011; Shin, 2015; Villasante, 2014) consider the evidence on a wide array of methods of chemotherapy-induced hair loss prevention.

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.”

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- 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. *International Journal of Cancer* 2015;136:E442-54.
- Dabrowski T. Hair loss as a consequence of cancer chemotherapy – Physical methods of prevention. A review of the literature. *Contemporary Oncology* 2011;15(2):95-101.
- van den Hurk C. Safety and Effectiveness of Scale Cooling in Cancer Patients Undergoing Cytotoxic Treatment. Department of Clinical Oncology, Faculty of Medicine/Leiden University Medical Center (LUMC), Leiden University, 2013.

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. They found the best results for women treated with taxanes (docetaxel [taxotere] and paclitaxel [taxol]) and worst results for those treated with a combination of taxane, anthracycline (doxorubicin [adriamycin]) and cyclophosphamide (cytoxan).
- The 2008 article written by Mols and the 2010 article by van den Hurk describe a prospective trial that was conducted in 13 hospitals with 98 breast cancer patients treated with scalp cooling and 168 without scalp cooling. Scalp cooling was found to be effective in 52% of the cases.
- The 2008 abstract written by Spaeth described findings on 911 patients (770 using scalp cooling and 141 without scalp cooling) at 8 hospitals. They concluded that cooling was effective for intermediate doses of anthracyclines and/or docetaxel.

- van den Hurk CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. 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.

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- 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). *Journal of Clinical Oncology* 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 six of the seven 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 after 1995) involved 1000+ patients. In these studies the success rate for scalp cooling was 73%. Note that the newest of these studies is 10 years old. This may reflect a number of issues. One possibility is that agreeing to randomization (cooling or not cooling) becomes more difficult as women are aware of the fact that cooling has been shown to be effective.

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- Edelstyn GA, MacDonald M, et al. 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 two review articles described on pages 6-7. Studies are grouped here by year of publication (most recent first) and then alphabetically by author's last name.

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- Kargar M, Sarvestani RS, Khojasteh HN, Heidari MT. Efficacy of penguin cap as scalp cooling system for prevention of alopecia in patients undergoing chemotherapy. *Journal of Advanced Nursing* 2011;67:2473-7.
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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 2010 expert opinion review paper by Rugo reviewed the existing studies on scalp metastases. They concluded that, “Scalp cooling has not been shown to increase the incidence of scalp metastases in patients with both early and late stage breast cancer...It is our expert opinion that scalp cooling can and should be offered to breast cancer patients who will be treated with adjuvant chemotherapy, and also those who are offered palliative chemotherapy associated with a significant risk of alopecia. The risks involved appear to be extremely small and the potential gain for the large number of women receiving adjuvant chemotherapy for breast cancer in the United States is substantial” (Rugo, 2010).

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.

Cold cap use and availability in the U.S.

Most 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. At the present time, 90+ hospitals and cancer centers in the U.S. have such biomedical freezers

(<http://www.rapunzelproject.org/ColdCaps.aspx>).

Penguin Cold Caps (<http://penguincoldcaps.com/>) and ChemoColdCaps (<http://www.chemocoldcaps.com/index.html>) may be rented while Elastogel caps may be purchased. (<http://www.elastogel.com/product-catalog/cancer-care/hypothermia-products>). User information, reviews, and support are available through the “Cold cap users – past and present” discussion board on <http://www.BreastCancer.org>.

At the present time, caps that provide hypothermia through a cooling system are available to the general public only outside the U.S. through Paxman (<http://www.paxman-coolers.co.uk/news/>) and Dignitana (http://www.dignitana.com/product/the_dignicap_scalp_cooling_system.php).

Some use is available in the U.S. through clinical trials, as noted below.

Currently, use of cold caps in the U.S. is not FDA (U.S. Food and Drug Administration) approved. However, in July 2015 Dignitana announced completion of an FDA approved clinical trial with ‘FDA marketing clearance ...currently pending.’

(<http://www.dignitana.se/eng/dignitana-announces-private-placement-offering/>)

Current clinical trials and other studies

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