Acupuncture for the treatment of hot flashes in breast cancer patients

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1.CONTENTS

2. PREFACE

I wrote the protocol for the study *Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial* in 2004. A pilot study was run the year after, the full-scale study commenced in 2006 after gaining accept from the local ethics committee. The study has been run on a shoe string budget; constant applications for funding resulted in limited resources, consequently eleven years have elapsed since it started.

I have been working as a physiotherapist and acupuncturist in a pain clinic at Vestfold Hospital Trust for the past 20 years. My interest in treating breast cancer patients suffering from hot flashes happened due to coincidence. Good results with a few patients caught the attention of consultants at the hospital Breast Centre, they began to refer more women for acupuncture treatment, and a need to document treatment effect arose. I have had a hand in all aspects of the study, planning, writing the protocol, treating all the patients, analyzing qualitative results, handling data and writing the scientific papers.

I have gained an enormous amount of respect for all women with breast cancer; they have enthusiasm, optimism, willingness, intelligence and beauty unlike any other patient group I have come across. The women included in this project are a testimony to the successful combination of eastern and western medicine. Thankfully there is now some focus on long term side-effects of breast cancer treatments, though much more research is needed, the focus needs to be maintained.

I would like to thank my bosses and colleagues at the pain clinic for their encouragement and the freedom they have given me to complete this study, especially Sissel Hagen Rustad. Thanks to my patient supervisor Odd Mjåland for his generosity, enthusiasm, knowledge, and endless energy; new to research he spoon fed me the first couple of years. To Trine Stub, a great friend, co-author and mentor. Thank you too to Professor Steven Sailor and Milada Cvancarova Småstuen for help with statistical analysis, and to Jacob Myhre for help with design and layout.

3. ABSTRACT

Introduction:

Breast cancer is the most frequent cancer among women, in 2012 it accounted for 12% of all newly diagnosed cancers world-wide and 25% of all cancers in women. Around 60% of women diagnosed with breast cancer have an oestrogen receptor positive tumor, and in accordance with international guidelines are medicated with oestrogen antagonists for a minimum of 5 years. Adjuvant treatment involves the use of drugs that block the effects of oestrogen e.g. tamoxifen, or in post-menopausal patients the synthesis of oestrogen with an aromatase inhibitor e.g. anastrozole or letrozole. Chemotherapy and anti-oestrogen treatments often provoke symptoms usually associated with menopause such as hot flashes, sweating, insomnia, reduced libido, joint and muscle pains and depression. Hormone replacement therapy is not an option for breast cancer patients; adverse effects of anti-oestrogen medication are typically treated in the West with antidepressives, gabapentin, anti-hypertensive drugs or stellate ganglion blocks, potentially producing adverse effects themselves. Women with breast cancer are increasingly looking for alternative treatments that do not have adverse effects.

Previous studies:

Studies examining the effect of acupuncture treatment on healthy menopausal women suffering from hot flashes due to a natural fall in oestrogen levels have shown promising results. Trials investigating acupuncture treatment on breast cancer operated women medicated with anti-oestrogens, complaining of adverse effects, mainly hot flashes, have shown conflicting results, prompting further research.

Aims of this research project:

1. To access the frequency and severity of adverse effects of non-hormonal drugs (NHD) used for treating hot flashes in breast cancer survivors.

Primary outcome measure: Adverse effect risk of NHD's.

2. To investigate short and long-term efficacy of acupuncture in women with breast cancer suffering from hot flashes as a result of anti-oestrogen medication, by conducting a randomized, controlled trial.

Primary outcome measure: Number of hot flashes the women experienced day and night at baseline, end of treatment, and at three months' post-treatment.

Secondary outcome measure: Quantifying health related quality of life, measured using the validated Kupperman index at baseline, end of treatment, and at three and 24 months' post-treatment.

3. To examine quality of life two years after acupuncture treatment by conducting a qualitative study.

Primary outcome measure: Insights into long-term quality of life experienced by the individual participants, as seen from their perspective.

Materials and methods:

1. A systematic review and meta-analysis of non-hormonal pharmacological interventions in breast cancer survivors suffering from hot flashes was carried out.

2. The study *Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial* was a prospective, randomized, controlled trial. Women suffering from hot flashes following breast cancer surgery and adjuvant oestrogen-antagonist treatment were randomized to either 15 treatments with traditional Chinese acupuncture or sham acupuncture (control).

   Mean number of hot flashes were recorded by the women at base-line, then once a week during the 10-week treatment period, and during the following three months after the last treatment. Kupperman index score was also recorded at these time points, and again 2 years later.

3. A statement in answer to an open question was made by the women at the two year follow up point.

Results:

1. The systematic review (12 RCT's) and meta-analysis (10 RCT's) showed that the odds for experiencing adverse effects due to NHD was significantly higher in patients randomized to high dose NHD than those randomized to controls, including placebo, low dose NHD and acupuncture.

2. Results for the study *Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial:* Mean hot flash frequency was significantly reduced by 50 and 60 % day and night respectively in the acupuncture group (AG) during treatment, and further reduced by 30% day and night during the following three months. A significant 25% reduction in mean hot

flash frequency was seen in the sham group (SG) during treatment at night, but this effect was reversed during the following three months. No significant effect was seen during the day.

Kupperman index score was reduced by 44% from baseline to end of treatment in the acupuncture group, and was maintained during the following three months, but was not significant 2 years later. No changes were seen in the sham group either during or after treatment. No serious adverse effects were measured.

3. Qualitative information collected 2 years' post-treatment indicated that adverse effects due to anti-oestrogen treatment seriously affect the quality of life of breast cancer operated patients. Patients who had previously been treated with acupuncture complained less of hot flashes, and seemed to have a more positive outlook on life, than women who had previously been treated with sham acupuncture.

Conclusions:

Adverse effects of oestrogen antagonists, including hot flashes, may affect long-term adherence to these drugs and reduce quality of life in breast cancer survivors. Non-hormonal drugs used to treat hot flashes also have adverse effects, prompting the need for research focusing on non-pharmacological therapies. Acupuncture seems to be an effective treatment for hot flashes due to adjuvant oestrogen antagonist treatment. Qualitative outcomes suggest that women with breast cancer suffer from long-term adverse effects of oestrogen antagonists.

4. LIST OF PAPERS

This thesis is based on the following papers:

1. Hervik J, Stub T. Adverse effects of non-hormonal drugs used to treat hot flashes in breast cancer survivors. A systematic review and meta-analysis. *Breast cancer Research and Treatment* 2016; 160 (2): 223-236. doi:10.1007/s10549-016-4002
2. Hervik J, Mjåland O. Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial. *Breast Cancer Research and Treatment* 2009 Jul;116(2):311-6. doi: 10.1007/s10549-008-0210-3
3. Hervik J, Mjåland O. Quality of life of breast cancer patients medicated with anti-estrogens, two years after acupuncture treatment. *International Journal of Women's Health* 2010 Sep 28;2:319-25. doi: 10.2147/IJWH.S12809
4. Hervik J, Mjåland O. Long term follow up of breast cancer patients treated with acupuncture for hot flashes. *SpringerPlus* 2014 Mar 14;3:141. doi: 10.1186/2193-1801-3-141

5. FIGURES AND TABLES

6. DEFINITIONS AND ABBREVIATIONS

Definitions

Acupuncture: The insertion of needles, through the skin and sub-dermal tissues at specific points, the aim being to promote health and restore body function.

Acupuncture point: A small area (1-5mm^2) along a meridian (channels connecting acupuncture points) where according to traditional Chinese medicine, Qi concentrates. Points are often located at boney points, muscle insertions and in depressions between muscles; usually in highly innervated areas.

Bias: Any influence or action at any stage of a study that systematically distorts the findings.

De Qi: Is a subjective sensation often described as numbness, a spreading, distension, pressure and a radiating pain along the corresponding meridian when the needle is inserted and stimulated at an acupuncture point. In western medicine the sensation is thought to be due to the stimulation of peripheral nerves.

Double-blind experiment: Subjects have no knowledge of whether they are receiving real or placebo treatment. The researchers are unaware of whether they are administering real or placebo treatment or the statistician is blinded as to the allocation of the subjects.

Hot flashes: A subjective sensation of heat that is associated with a subsequent drop in core temperature. Sweating, flushing, palpitations, anxiety and irritability may accompany hot flashes.

Kupperman Index: A validated index comprised of symptoms associated with menopause.

Menopausal symptoms: Symptoms that may occur in women due to suppression of ovarian function, either due to natural, surgical, chemical or radiological induced menopause.

Qi: TCM theory considers Qi to be a vital energy, it is perceived by function, it permeates the whole body and is present in all living things. It influences health physically, psychologically and spiritually.

Quality of life: Is defined by WHO as how an individual perceives his own life, in light of the cultural context and values of his environment, aims, expectations and worries.

Qualitative statements: Statements consisting of subjective information.

Sham acupuncture: Needles are inserted at points away from known acupuncture and trigger points, in areas that have a low concentration of nerve endings. Needles are inserted superficially into the skin.

Single-blind experiment: Trial subjects have no knowledge of whether they are receiving real or placebo treatment, or the researcher gathers data without knowledge of whether subjects are in the real treatment group, or control group.

Traditional Chinese medicine (TCM): Is an ancient holistic system of health and healing, based on harmony and balance. It is a complete system of health care incorporating herbal medicine, acupuncture, massage, exercise and diet.

Trigger point: A point of irritability in body tissue that when directly palpated is tender or painful, compression of such a point can give rise to referred pain.

Validation of measurement: The assessment of whether a measurement reflects what it is intended to measure.

Abbreviations

Acu-Group	Acupuncture Group
AE	Adverse Effects
AI	Aromatase Inhibitor
ARK	Arcuate Nucleus
ASCO	American Society of Clinical Oncology
BC	Breast Cancer
BOLD	Blood Oxygen Level-Dependent
CAM	Complementary and Alternative Medicine
CGRP	Calcitonin Gene Receptors

CONSORT	Consolidated Standards of Reporting Trials
CTCAE	Common Terminology Criteria for Adverse Effects
CTRL	Control
CSF	Cerebrospinal Fluid
EA	Electro-acupuncture
ECG	Electrocardiogram
EEG	Electroencephalogram
ER-	Oestrogen Receptor Negative
ER+	Oestrogen Receptor Positive
HER2	Human Epidermal Growth Factor Receptor
HF	Hot Flashes
HRT	Hormone Replacement Therapy
HRQoL	Health Related Quality of Life
LHRH	Luteinizing Hormone Releasing Hormone
MRI	Magnetic Resonance Imaging
NAFKAM	Nasjonalt Forskningssenter innen Komplementær og Alternativ Medisin
NRM	Nucleus Raphes Magnus
PAG	Periaqueduct Gray
PBN	Parabrachial Nucleus
PGWB	Psychological and General Well Being Index
QoL	Quality of Life

RCT	Randomized Controlled Trial
SNRI	Serotonin and Noradrenalin Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
STRICTA	Standards for Reporting Interventions in Clinical Trials of Acupuncture
TCM	Traditional Chinese Medicine
TAM	Tamoxifen
VAS	Visual Analogue Scale
WHI	Women's Health Initiative
WHO	World Health Organization
WHQ	Women's Health Questionnaire

7. INTRODUCTION AND BACKGROUND

7.1. Breast Cancer

Breast cancer is the most common type of cancer among women, 1.7 million new cancer cases were diagnosed in 2012 worldwide [1]. Three thousand and ninety-four Norwegian women were diagnosed with breast cancer in 2012, compared to 2840 in 2010 [2]. Incidence rates are highest in western Europe. The incidence of breast cancer has for many years been much lower in the East compared to the West. Adoption of western lifestyles and culture seems to provoke a change in disease patterns, including breast cancer. Demographic trends indicate that even more women will face breast cancer in the future. Despite the high incidence rates, in western countries, 89% of women diagnosed with breast cancer are still alive 5 years after their diagnosis, this high rate has been attributed to programs aimed at early detection and treatment [3].

Treatment of breast cancer involves 1. surgery, 2. radiation and 3. drugs (chemotherapy and endocrine). Three types of receptors may or may not be present in breast cancer cells, these are; oestrogen, progesterone and human epidermal growth factor receptor 2 (HER 2). In accordance with European guidelines medication with oestrogen antagonists is recommended for a minimum of five years for women with oestrogen-receptor positive tumours [4]. In Norway, approximately 55% of breast cancers are oestrogen receptor positive (ER+), for which post-operative adjuvant hormonal therapy is routine [5]. For the last 25-30 years' tamoxifen has been used in ER+ breast cancers, it has been shown to reduce the incidence of recurrence and death by 47 and 26% respectively [6]. Premenopausal women produce most of their oestrogen in their ovaries. Tamoxifen works locally by binding itself to oestrogen receptors in the breast, blocking oestrogen and deactivating receptors in breast tissue. It has traditionally been used primarily in both pre-and postmenopausal women, with a switch to an aromatase inhibitor (AI) when the postmenopausal state is confirmed. Post-menopausal women produce most of their oestrogen in the adrenal gland where it is converted from androgens, and in fatty tissue. AI's block the synthesis of testosterone to estradiol by inhibiting the aromatase enzyme.

Neoadjuvant chemotherapy is used before and/or after surgery; pre-surgery it is used to shrink tumours making surgery possible, or less disfiguring. It is always recommended post-surgery when cancer is detected in lymph nodes, and in more aggressive types of cancer e.g. in premenopausal women with invasive breast cancer, in hormone receptor negative cancer and HER 2 cancer. Chemotherapy is also used to prolong life in advanced, metastatic breast cancer. Treatment is often individualized, medications can be used alone or in combination, the treatment period typically varies from 3 to 6 months. Adverse effects depend on the specific treatment regimen, length of treatment and general

health of the patient. They usually disappear after treatment is over, however, long term adverse effects can include: menopausal symptoms, fatigue, cognitive problems, peripheral neuropathy and more rarely osteoporosis and heart problems [7].

Radiotherapy is commonly used to treat breast cancer after surgery. Studies have shown that for women with early breast cancer, the cure rate for breast conserving surgery followed by radiotherapy is equal to mastectomy [8]. Radiotherapy treatment is relatively short term usually from 3 to 5 weeks. Post-operative radiotherapy is primarily used to reduce the risk of local recurrence and to increase the chance of survival. Adverse effects of radiotherapy include soreness of the radiated area during treatment; shrinkage of breast tissue, local swelling and skin discoloration post-treatment. Long-term adverse effects include lymph oedema if the axilla has been radiated. Rarely, radiotherapy causes changes in lung tissue and fibrosis resulting in reduced elasticity and expansion of the lung; symptoms include shortness of breath and cough [7].

7.2. History of Oestrogen-Antagonist Treatment

Although the use of oestrogen antagonists is recent, hormonal manipulation has been recognized as a treatment for breast cancer for more than a century. As far back as 1896, Georg Beaston suggested that premenopausal women with inoperable breast cancer might benefit from removal of the ovaries [9].

Tamoxifen, a non-steroidal antioestrogen was originally identified as a post-coital contraceptive in rats by Dr Arthur L Walpole [10], who headed up a fertility program at *Imperial Chemical Industries* in the early 1960's. However, further trials in humans revealed that the drug induced ovulation rather than reduce fertility [11], it was therefore discarded. By the end of the decade the role of the oestrogen-receptor in breast cancer was clear, provoking Walpole to suggest clinical testing of tamoxifen. The drug was approved in Europe in the early 1970's after the publication of an introductory clinical trial of the anti-oestrogenic agent IC146474 in late or recurrent carcinoma of the breast, was undertaken [12]. Further research establishing effects, adverse-effects, dosage and duration of treatment was carried out by *The Early Breast Cancer Trials Collaborative Group* during the 1980's and 90's. Tamoxifen, the first targeted therapy to be developed for breast cancer, has certainly improved both prognosis and survival rates for women in this category [6,13].

Like tamoxifen, drugs inhibiting aromatase action were also originally developed for another purpose. Aromatase inhibitors were originally designed as an anti-epileptic compound, for which they were unsuccessful. Cancer research in the late 1950's found adrenalectomy to be an effective anti-tumour therapy, this finding lead to the testing of glucocorticoids and adrenal enzyme inhibitors [14,15]. Clinical observation of a single breast cancer patient treated with amino glutethimide [16] prompted trials demonstrating efficacy of this compound in post-menopausal women with breast cancer, paving the way for the implementation of aromatase inhibitores in breast cancer therapy.

During the last 10 years' aromatase inhibitors, have been incorporated into standard care of ER+ breast cancers, in both natural and chemically induced postmenopausal women. Several controlled studies have indicated that aromatase inhibitors should be the initial drug choice in postmenopausal women [17,18]. AI's have demonstrated superiority to tamoxifen reducing early recurrence and improving long term survival, also women demonstrate a greater tolerance for adverse effects for AI's compared to tamoxifen [19]. AI's are categorized into steroidal e.g. exemestane (Aromasin), which forms a permanent bond with the aromatase enzyme complex; and non-steroidal e.g. anastrozole (Arimidex), letrozole (Femara), which inhibits the enzyme.

During the last few years' results from two large RCT's that have tested adjuvant use of tamoxifen for 10 years as opposed to 5; n=12894 and n=6935 respectively [20,21]. A meta-analysis of these two studies was also performed [21]. Results showed that tamoxifen used for 10 years reduced recurrence by 3-4 % and death due to breast cancer by 2-3%. Goss et al. in a placebo controlled study investigated

the extended use of the aromatase inhibitor letrozole after 5 years of tamoxifen. Eight hundred and seventy-seven women were premenopausal at diagnosis and 4289 were postmenopausal. All participants had a post-menopausal status before being randomized to letrozole therapy or placebo, after 5 years of tamoxifen. Extended letrozole after 5 years of tamoxifen was effective in women who were both pre- and postmenopausal at diagnosis, but was significantly better in those who were premenopausal. Outcomes were disease free survival, overall survival, toxicity and QoL. The authors concluded that women who were premenopausal at diagnosis should be considered for extended adjuvant therapy with letrozole after completing tamoxifen [22].

The most recent recommendations for the use of adjuvant hormonal therapy come from *The American Society of Clinical Oncology* (ASCO). Up until now there has been insufficient data to recommend the use of an AI for a duration of greater than 5 years [4]. However, a further randomized controlled study by Goss et al. [23] presented in early June 2106 at *ASCO's Annual Meeting* compared 5 and 10 years' treatment with letrozole for 1,918 postmenopausal women with hormone receptor positive, non-metastatic breast cancer. The primary end point was disease free survival. Results showed that the relative risk for relapse was reduced by 34% for the women taking aromatase inhibitors for 10 rather than 5 years, also a significant lower incidence of contralateral breast cancer was seen, however overall survival was not significantly higher. The authors recommend further analyses to provide a comprehensive picture of toxicities and QOL. Consequently, *ASCO* currently recommends the use of AI's for 10 years for postmenopausal women, and for 5 years for women who have previously used tamoxifen, provided post-menopausal status is confirmed. For women who are premenopausal ten years of tamoxifen use is recommended. Clinical consequences of the study in Norway are not clear at this time.

7.3. Adverse effects of oestrogen antagonists

Hot Flashes and sweating are reported as the most prominent adverse effect of tamoxifen medication [24,25,26]. These episodes may be accompanied by other physical reactions including sweating, redness, chills, palpitations, dizziness, nausea, paresthesia and acute shortness of breath; emotional symptoms include anxiety, panic, and emotional incontinence [27,28]. A combination hot flashes, sleep disturbances and fatigue is often seen, and these symptoms seem to directly affect each other, reducing quality of life. In a literature review that includes studies from 1982 to 2008, quality of life was shown to be an effective predictor of survival duration [29], consequently, these symptoms need to be addressed.

Hormone replacement therapy (HRT) in alleviating hot flashes is apparent in healthy women. Though treatment has waned somewhat after the publication of *the women's health initiative* (WHI) which showed relative risks for invasive breast cancer, coronary heart disease, and stroke were increased when using HRT [30]. Later the WHI study was criticized for not publishing all the data, and for including only elderly women. In Norway sales of hormone replacement drugs containing oestrogen fell by 48% from 2002 to 2007 [31]. Since the hormone oestrogen can promote cancer cell growth in ER+ breast cancer, HRT is not a treatment option for HF's for these women.

Other drugs that have proved effective in the reduction of hot flashes include clonidine hydrochloride, a centrally active agonist that reduces vascular activity and is primarily used in the treatment of hypertension. Transdermal clonidine significantly reduced the frequency, severity and duration of hot flashes in a randomized, controlled trial [32]. However, patients receiving clonidine reported adverse effects such as dry mouth, constipation, skin itching and drowsiness. A similarly designed study evaluating the effect of oral clonidine showed a significant reduction in hot flash frequency (38%) compared to the control group (24%) in post-menopausal women with breast cancer taking tamoxifen. Significant adverse-effects were seen including insomnia [33].
Gabapentin, an anticonvulsant, also indicated in some cases of neuropathic pain, has been used for the last decade to reduce hot flashes. Multiple randomized trials have shown gabapentin to be effective in reducing hot flashes in both healthy women and women with breast cancer [34,35]. Gabapentin was compared to oestrogen and placebo in a study where a total of 60 women received either 625 mg/day of conjugated oestrogens, 2400mg/day of gabapentin, or placebo for 12 weeks. Reduction in hot flash score was reduced by 72%, 71% and 54% respectively. Because at such a high dosage the gabapentin group only had a 20% more reduction in hot flashes than the placebo group, the authors recommended a dose of 900mg/day for the treatment of hot flashes [35].

In the 1990's it became apparent that women taking selective serotonin reuptake inhibitors (SSRI) had a decrease in hot flashes [36]. Several trials were conducted to investigate the hypothesis that antidepressants could effectively be used to reduce hot flashes. One randomized, controlled study investigated the efficacy of venlafaxine for the treatment of hot flashes [37]. One hundred and ninety-one women were included, they were randomized to receive either venlafaxine doses of 37.5 mg per day increasing to 150 mg during a 4-week period, or placebo. Venlafaxine reduced hot flashes significantly better than placebo, a dose of 75 mg per day was more effective than 37.5 mg (61% and 37% respectively), however a dose of 150 mg per day did not reduce hot flashes further (61%). Women taking the higher dose complained of more adverse effects, including dry mouth, reduced appetite, nausea, and constipation.

During the last few years there has been some controversy surrounding the use of SSRI's used in combination with tamoxifen. Nearly all newly diagnosed breast cancer patients experience distress and anxiety, and up to 25% suffer clinically significant depression in the year after diagnosis [38]. The use of antidepressants in this patient group is substantial, with one study reporting that about half of all patients in a breast cancer waiting room sample had received psychotropic drugs during their breast cancer treatment [39]. Since SSRI's are used to treat both hot flashes and depression in women with breast cancer, a substantial number of women will receive anti-depressants and tamoxifen simultaneously. Tamoxifen has been shown to reduce the recurrence of breast cancer by half [6,40]. The clinical effects of tamoxifen with respect to efficacy and toxicity vary widely among individuals, up to 35% of women with advanced ER+ breast cancer do not respond to tamoxifen [41]. Further some SSRI's such as paroxetine and fluoxetine are known to inhibit cytochrome P450 (CYP) 2D6 [42], an enzyme important in the metabolism of tamoxifen and many other drugs [43]. However, firm clinical evidence predicting which SSRI should be used in patients taking tamoxifen is lacking, more research is needed in order to secure optimal effect of tamoxifen in breast cancer patients who also take SSRI's, and therefore reduce recurrence and mortality.

Hot flashes (HF) have been shown to bother women taking aromatase inhibitors slightly less than those medicated with tamoxifen. A study comparing exemestane with tamoxifen treatment of metastatic breast cancer in post-menopausal women demonstrated a HF incidence of 35.1% with exemestane, compared to 38.1% with tamoxifen [43]. Similar results were found in other trials, for example in BIG-1 (the breast international group) where 2459 breast cancer patients were randomly assigned to monotherapy with tamoxifen for 5 years, and 2463 to monotherapy with letrozole for 5 years. Women randomized to tamoxifen reported a 41.7% HF incidence compared to 37.7% in those receiving letrozole [44].

7.4. Hot Flash Mechanisms

HF's are traditionally associated with menopause, and are indeed the most well-known symptom occurring in up to 75% of healthy menopausal women [45]. Menopause is generally defined as the 12-month period occurring after the final menstruation, indicating ovarian follicular depletion and reduction of oestrogen secretion. Symptoms associated with menopause besides hot flashes include sleep problems, mood changes and genitourinary problems [46].

Oestrogen has an important role in maintaining body temperature stability, reduced circulating levels of oestrogen appear to destabilized temperature regulation. However, the precise mechanism by which reduced levels of oestrogen relate to HF's is not known. Oestrogens, and therefore the lack of oestrogens alter the central nervous system. Oestrogen signalling in the hypothalamus has been shown to affect the excitability of hypothalamic neurons and thereby neuroendocrine and autonomic functions [47]. HF's appear to be complex physiological events, in which the physiological changes are different to other flushing conditions. Research has identified hot flashes starting with a chilling feeling, an association with peripheral blood flow, increased heart rate, metabolic rate and sweating [27]. Suggested definitions for HF's are: *recurrent transient periods of flushing, sweating and a sensation of heat, often accompanied by palpitations and a feeling of anxiety, sometimes followed by chills* [48], and *a sensation of heat that is associated with objective signs of cutaneous vasodilatation and a subsequent drop in core temperature, which may be accompanied by sweating, flushing, palpitations, anxiety, irritability and even panic* [49].

Although the exact mechanism of this process is not yet known, the most accepted hypothesis of the HF mechanism is the disturbance of the body thermostat in the hypothalamus, with a narrowing of the thermoregulatory zone. It has been suggested that HF's are trigged by small increases in core body temperature, and that vasomotor instability due to oestrogen withdrawal is accompanied by a narrowing of the hypothalamic thermoregulatory zone [50,51], where the zero zone is a threshold point between sweating and shivering, sensitive to a 0.4-degree centigrade fluctuation in temperature [52]. Thus, a disruption of this centre would potentially provoke exaggerated sweating or shivering at higher or lower temperatures respectively. Central sympathetic activation is also elevated in symptomatic women also potentially narrowing the thermoregulatory zone [50]. The hypothalamus is mainly concerned with maintaining homeostasis and controlling hormones. It acts as a thermostat, initiating sweating and vasodilatation to reduce heat when body temperature increases, and vasoconstriction and shivering when the body needs warmth. Neural processes from the anterior hypothalamus innervate the superior cervical ganglion [53], this explains the head and upper body distribution of the hot flash, and the indication for stellate ganglion blocks as a potential treatment method.

Reduced concentrations of β endorphins and serotonin, and an increased release of noradrenalin are associated with a fall in oestrogen levels affecting the thermoregulatory set point, causing a resetting of this point and thereby vasomotor instability. Norepinephrine and serotonin are thought to be the main neurotransmitters involved in lowering the set thermoregulatory point, leading to vasodilatation and HF's. Norepinephrine has been shown to stimulate luteinizing hormone releasing hormone (LHRH) producing neurons, which are located adjacent to the thermoregulatory centre possibly affecting temperature set points [50,54,55].

According to Freedman, healthy women who do not have HF's have a thermoregulatory zone of several tenths of a degree centigrade [50], he suggests that the thermoregulatory zone of women with HF's is extremely narrow, virtually non-existent. As a result, small variations in core body temperature by as little as one-tenth of a degree centigrade, that do not trouble some women, trigger HF's and chills in others. An increase in body temperature can be triggered by something as simple as an increased room temperature or eating spicy hot food; pushing the upper threshold range further up, causing cooling mechanisms to be stimulated (figure 1).

This theory can be applied to breast cancer patients. HF's due to interventions that lead to the depletion of oestrogen can potentially narrow the thermoregulatory zone. Such treatments include oestrogen antagonist medication, chemical or surgical oophorectomy and certain chemotherapeutic agents. HF's may not only be due to absolute levels of oestrogen, but also to the relative decline in oestrogen levels. Sudden decline, it has been suggested may further mediate changes in norepinephrine and serotonin, causing women medicated with oestrogen antagonists and those who have undergone bilateral oophorectomy to experience a higher frequency of HF's, compared to menopausal women experiencing gradual ovarian failure [56]. Conversely, the drug clonidine, which lowers norepinephrine, widens the zone in women with hot flashes, so do oestrogen and certain antidepressants, though the exact mechanisms are still unknown.

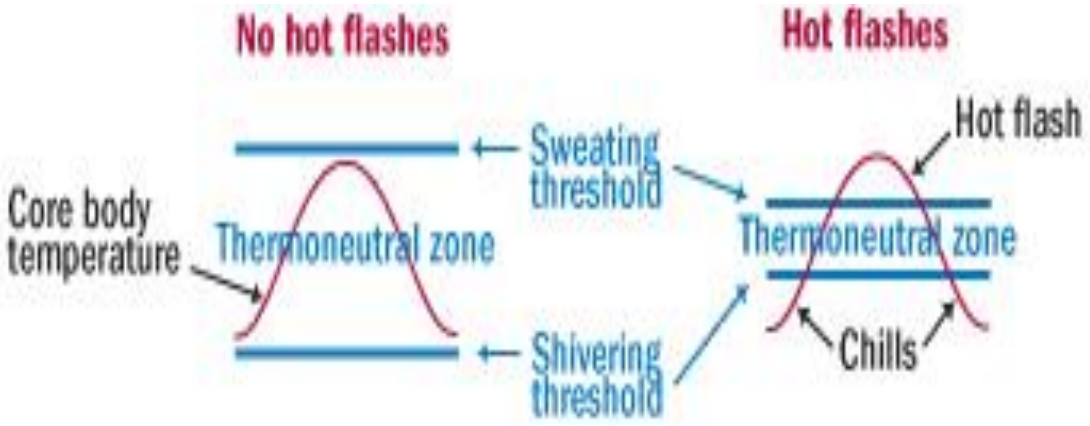

Figure 1. Dysfunctional temperature regulation

Demonstrating the hypothalamic thermoregulatory zone in women with and without HF

Source: Adapted from Freedman, RR. *Seminars in Reproductive Medicine* 2005; 23 (2): 117-125.

7.5. Complementary and Alternative Treatments used to Reduce Vasomotor Symptoms

Black cohosh (cimicifuga racemosa) has been approved in Germany for the treatment of hot flashes. It has been suggested that black cohosh has an oestrogen-like action, suppressing luteinizing hormone, binding itself to oestrogen receptors; studies indicate that the substance is non-toxic with no adverse effects [57,58]. Its efficacy was however not significantly different from that of placebo in a RCT where black cohosh was administered to breast cancer survivors in the USA [59].

Other options that have been investigated include plant-derived prescriptions such as *soy* and *red clover* which contain isoflavones (plant phytoestrogens). Soy consumption to treat menopausal symptoms may be due to comparisons demonstrating that women from countries where substantial amounts of soy are eaten, have lower rates of heart disease, uterine and breast cancer; and also, fewer menopausal symptoms than women who live in countries where soy is a much smaller part of their diet. A recent meta-analysis looked at four different trials comparing soy to placebo in women with breast cancer suffering from HF, no differences in HF frequency and severity scores were apparent [60]. A RCT cross-over trial [61] included 177 breast cancer survivors. After 4 weeks of either soy tablets or placebo no difference in HF frequency was found. Cross-over results were also negative.

Vitamin E has been used as a possible treatment for hot flashes for the last seven decades [62], even though research has not been able to demonstrate any effect. A cross-over trial in which 120 healthy menopausal women received 4 weeks of vitamin E (800IU/day), then 4 weeks of placebo, resulted in a reduction of on average one HF a day; although after the trail ended the women did not prefer vitamin E to the placebo [63]. There has been some recent concern about the carcinogenicity of vitamin E, although these concerns have been proved invalid by one trail [64]; more evidence is needed for vitamin E to be recommended as a safe and effective treatment option for HF.

Relaxation and various *cognitive approaches* [56,65,66] are often used primarily for patients who do not want to take medications, or as a secondary intervention for women who do not achieve full relief through the use of other treatments. Relaxation techniques, methods of reducing anxiety and stress may be related to decreased adrenergic tone. A recent RCT investigated the use of relaxation in 150 breast cancer patients. The women received one session of relaxation training, which they followed up using tapes daily for one month. At the end of the month, frequency and severity of HF was significantly reduced compared to the control group who did not receive any intervention; however, there was no significant difference 3 months later [67]. A review of literature assessing psycho-educational interventions to alleviate HF's concluded that most trials had positive results, but were

designed with small sample sizes; also, intervention and outcome measures varied greatly [68], provoking the need for larger well designed RCT's.

Hypnosis shows promise as a treatment technique for reducing HF's in breast cancer patients. A single arm pilot study reported a 59% reduction in HF's after 4 weekly sessions of hypnosis to reduce hot flashes in 16 breast cancer survivors [69]. A larger RCT assigned 51 subjects to either hypnosis or no treatment. After 5 weekly sessions, HF scores (frequency x average severity) had decreased by 68% from baseline to end point in the hypnosis arm. Significant improvements in self-reported anxiety, depression, sleep and incidence of hot flashes interfering with daily activities, were observed in patients who received hypnosis [70].

A clinical trial carried out at the Henry Ford Hospital Detroit, compared the effect of *venlafaxine* with *acupuncture* for the management of vasomotor symptoms in women with ER+ breast cancer. Fifty patients were randomized to receive 12 weeks of acupuncture or venlafaxine treatment. From pre-to post treatment both groups showed a significant reduction in HF's, and increased quality of life, including improvement in mental health. However, two weeks' post-treatment the venlafaxine group reported an increase in HF levels, whilst in the acupuncture group HF's remained low. Adverse effects were reported by the venlafaxine group, these included nausea, dry mouth, dizziness, and anxiety. The acupuncture group did not experience any negative adverse effects; they reported benefits, including increased sex drive, more energy, clarity of thought, and a sense of well-being [71].

In a recent Cochrane review investigating different CAM modalities for HF's [72], researchers in Chile analyzed 16 studies with a total of 1,461 women, they found that herbal medicine, acupuncture and relaxation can offer women with breast cancer relief from hot flashes equivalent to pharmacological agents, including vitamin E, clonidine, gabapentin and various antidepressants (SSRIs and SNRIs). The authors pointed out that pharmacological adverse effects are often significant, questioning whether the benefits outweighed the adverse effects of the drugs. Due to inconsistencies in the ways the various studies presented data, the relative strength of the studies could not be compared, a recommendation for acupuncture or other natural remedies/herbal medicine could therefore not be made. The review included two RCT's that investigated the effect of homeopathy versus placebo [73,74], neither found a statistically significant improvement in HF frequency for homeopathy over placebo.

7.6. Traditional Chinese Medicine (TCM) from East to West

Western medicine was first introduced into China from the middle of the 17th century. The *Nei Jing* [75] is the source of all Chinese medical theory, the equivalent of the *Hippocratic Corpus*. It is the oldest of the ancient medical texts, and was written by authors from 300 to 100 B.C.
After the Chinese Revolution in 1949, TCM was reviewed. Leaders in China at that time were tempted to do away with their medical heritage and instead copy the medicine of developed industrialized, modern countries. However clinical research was initiated, resulting in the Central Committee demanding equal respect for traditional and modern medicine in 1958.
During the 20th century China has maintained and developed three kinds of medical science, that is; TCM, western medicine, and integrated medicine. Today the trend in China is still integration of eastern and western medicine [76].
In the West, where little was known about Chinese practices, TCM gained attention in the 1970s when alternative therapies were featured in the press and popular media. Politically sanctioned journalistic communication presented descriptions of surgical procedures performed without anaesthesia in China. Acupuncture as a means of inducing analgesia promoted interest primarily in America, where the medical association initially attempted to ban the use of acupuncture due to lack of scientific evidence; it consequently initiated studies investigating the possible physiological changes of acupuncture treatment. Interest for what was considered a mystical treatment method increased greatly in 1971 when an American journalist James Reston published a personal account of acupuncture treatment that eased the pain of an appendectomy in Beijing. His rapport made the front page of *The New York Times* sensationally elevating the acupuncture needle to a healing instrument [77]. The World Health Organisation declared its acceptance for TCM in 2008 stressing at the same time the need to hasten its modernisation. More than 40 disorders have been endorsed by the WHO as conditions that can benefit from acupuncture treatment [1].

The treatment of cancer by acupuncture was prohibited by the 67-year-old "kvakksalverloven" [78] in Norway until 2003 when it was discontinued and replaced by the law for alternative treatments (alternativ behandling av sykdom). The new law opened the door for the treatment of serious disease with alternative medicine, as long as treatment is coordinated with the patient's principal doctor. The law sates**:** *§7. Treatment of serious diseases not including those mentioned in § 6 (infectious diseases) should not be undertaken by other than medical personnel.*
Treatments that aim to reduce pain, as a consequence of serious disease, or that aim to reduce side-effects of various medical treatments; or aim to strengthen the immune system and thereby increase the possibility of recovery may be carried out by non-medical practitioners. The patients doctor must be informed of planned treatments; patients must be over the age of consent and must agree to treatments

as stated in the patient's rights law (pasientrettighetsloven § 4-3). Also, included in this category are cases where the medical system cannot offer curative treatment or relief of symptoms.

As the law stands today it lends itself to acupuncture treatment of symptoms that are a consequence of the adjuvant treatment of breast cancer without ignoring the original diagnosis.

Today most CAM therapies, including acupuncture are generally delivered outside the national health system in Norway. However, a recent survey carried out by researchers from the National Research Centre in Alternative and Complementary Medicine (NAFKAM) of 99 hospitals revealed that 50% offered some type of alternative treatment [79]. Even so, information about efficacy, effectiveness, physiological mechanisms and the safety of treatments is not widely available consequently, NAFKAM has developed a research strategy with focus on patient safety [80], the details of which are discussed later in this thesis in the context of *whole systems research*. Healthcare professionals in Norway practicing alternative treatments are governed by the healthcare law (helsepersonellloven), whilst other therapists have to abide by the law for alternative treatment (lov om alternativ behandling).

A population-based study conducted in 2001 in California showed that 72% of women with breast cancer used at least one form of complementary or alternative medicine (CAM), and one third used two forms. The use of CAM was more common in younger women, those with higher education, and among women with advanced stages of cancer [81].

Few medical oncologists at the present time recommend alternative medicine, they are generally reluctant to integrate their medical treatments with a method foreign to their training. Only half of the women in the previously mentioned study told their doctors that they were also receiving some kind of CAM treatment. Fear of disapproval may be the reason patients keep CAM therapies a secret from their oncologists, leaving their physicians with an incomplete view of their patient's wishes and needs, thereby slowing the progress of integrative therapies.

7.7. Research

The last twenty years has seen a phenomenal interest in acupuncture research both in the East and the West. Studies carried out in the East between 1950 and 1980 were often badly designed, without control groups, and results were frequently based on subjective statements and assumptions. Their conclusions were little more than clinical observations, so called experienced-based medicine. This type of medicine has according to Hugh MacPhersen in his book *Acupuncture Research* [82] three common stages also found in evidence-based medicine: 1. models of theory and practice, 2. process of inquiry and 3. experience of patients and practitioners. Evidence-based medicine adds two more steps, both of which are rigorous and formalized, these steps are: 4. verifiable observations and experiments, and 5. peer review. During the last two decades' Chinese clinicians have published numerous well designed studies in international medical journals, realizing the need for objectivity and unbiased documentation, adding steps 4 and 5, thereby elevating their studies to evidence-based research. Complicating this scientific approach is a philosophical interest in ideas that are *holistic sounding*, by both practitioners of TCM, the public and the media in the West. Hundreds of clinical trials have been conducted in the West since the 1970's, also systematic reviews and meta-analyses of RCT's indicate which medical conditions acupuncture seems to help. Despite such evidence, focus from popular media is still mainly on the exotic aspects of TCM, not on evidence–based research.
The majority of published clinical trials describe the effects of acupuncture relative to TCM theory, there is a distinct lack of published studies examining the physiological effects of acupuncture. Initially most acupuncture studies examined the possible effect of acupuncture in relation to pain. These studies were fueled by reports of acupuncture being substituted for anesthesia during surgery. A review of acupuncture articles published during 2005 revealed that 26 of the 79 studies published that year offered no physiological rationale for acupuncture treatment, 53 studies proposed a physiological basis, 33 of which described neurochemical mechanisms [83].

The CONSORT (Consolidated Standardized Reporting of Trials) has by publishing a statement in 1993, which was updated in 2001 and 2010, attempted to improve the reporting of randomized controlled trials. The 2010 version consists of a statement which recommends that authors present *a plausible explanation for how the intervention under investigation might work* [84]**.** Specific guidelines aimed at improving the reporting of acupuncture trials have been published as an extension to CONSORT non-pharmacological interventions. STRICTA guidelines (The Standards for Reporting Interventions in Clinical Trials of Acupuncture) are intended to ease interpretation and replication, and to raise the quality of the reporting of clinical acupuncture trials [85]. A survey investigating whether authors of acupuncture RCT's and systematic reviews (n=28) used STRICTA in their trial reports, revealed that they believed that STRICTA contributed to the reporting of acupuncture trials, but that the editing process often removed acupuncture intervention information [86]. This might be because

many acupuncture studies are published in journals that do not use STRICTA, or implement strategies to improve author adherence to reporting guidelines.

Two systematic reviews and a meta-analysis have examined papers reporting the effects of acupuncture used in the treatment of hot flashes in breast cancer patients. A systematic review [87] evaluating the evidence related to the use of acupuncture for HF's in cancer patients screened 210 publications. Eight RCT's met the inclusion criteria, all involved women with breast cancer; these studies were published between 2005 and 2014. Only two made an attempt to explain possible biological effects of acupuncture treatment. Both made a short reference to the possibility of hypothalamic β-endorphin affecting thermoregulation. The second systematic review examined acupuncture for treating common adverse effects associated with breast cancer treatment [88]. Twelve RCT's were included. Seven adverse effects were examined including HF's, fatigue, dyspnoea, pain, psychological well-being, lymph oedema and emesis. Five studies of the studies examined acupuncture treatment for HF symptoms. The paper made no attempt at explaining possible effects due to acupuncture for any of the named adverse effects, neither did it refer to studies that offered a hypothesis.

A meta-analysis of RCT's published in 2015, examining the effects of acupuncture on menopause related symptoms in breast cancer survivors included seven of the previously mentioned studies [89] (Chiu 2016). The authors discussed pathophysiological mechanisms underlying vasomotor symptoms experienced by breast cancer survivors, suggesting the involvement of the hypothalamic thermo-regulation centre. The authors referred to studies that hypothesized that the underlying beneficial effects of acupuncture on vasomotor symptoms is that acupuncture causes the release of β-endorphins in the hypothalamus, which in turn exerts inhibitory effects on the vasodilator calcitonin gene-related peptide (CGRP).

7.8. Physiological Mechanisms of Acupuncture

A greater understanding of how acupuncture works and the physiological processes involved could provide a basis for improved needling techniques for control groups in clinical trials, and thereby credibility in clinical practice. Indeed, one of the most problematic elements of clinical research is designing an appropriate placebo that mimics the treatment procedure but does not produce physiological effects attributed to treatment. However, to avoid these physiological effects means having knowledge of what they are, and how they are mediated.

To date no anatomical mapping of the meridians has been established. Peripheral nerves are often located in the same areas as meridians, prompting a closer look at the nervous system as a mediator of acupuncture signals. Also, high densities of sensory nerve endings and nerve-vessel bundles in fascia bellow acupuncture points have been located [90,91]. Further, acupuncture effect has been inhibited at points injected with local anaesthetic [92], and nerve trunk blocks [93] before needling. In the brain, fMRI scans show acupuncture induced changes that are distinctly different from those seen by other types of stimuli, including sharp pain or placebo [94]. These findings suggest involvement of the central and peripheral nervous systems, but do not preclude other types of mediating and monitoring structures.

Examination of the physiological and biochemical processes due to acupuncture, involved in pain reduction, was pioneered by the Scandinavian researches Birger Kaada, Sven Andersson and Lars Teranius in the 1970's. In 1976 Terenius and Wahlstrøm found a morphine-like pain reducing substance in the central nervous system, β-endorphin [95]. During the following years, different groups of neuoropeptides were documented [96]. Such substances and their respective receptors were not exclusively found in the CNS, but over the whole body with the potential to affect numerous systems including the mind. These substances were hailed as the key to understanding how the body and mind affect each other, the so-called *body-mind* concept [97].

Three groups of endorphins are classified as short chained encephalins, dynorphins and longer chained endorphins. The most well-known is the β-endorphin, made up of around 30 amino acids, its large receptor is made up of 20,000 amino acids. Although they are mostly known for their pain modulating effect, together with other neurotransmitters they play a complex role in regulation of numerous physiological systems.

Pain modulation can be controlled by blocking systems at different stages from the first synapse in the spinal cord up to the cerebral cortex. The main ascending pain pathway and the simplest is the spino-thalamic tract (figure 2). Pain signals from pain receptors are mediated to the spinal cords' dorsal horn

by myelinated A-delta (σ) and unmyelinated C-fibres. The first synapse of this pain mediating pathway is located in the dorsal horn, providing a possible location for the blockage of pain. From here the next group of nerve cells cross the mid line, run up the spinal cord via the brain stem to the thalamus. The second synapse is found in the thalamus, from which nerve fibres run to various parts of the cerebral cortex. Other ascending pathways also convey pain to other areas of the brain; the spinothalamic tract however is frequently used to explain pain transmission and reception.

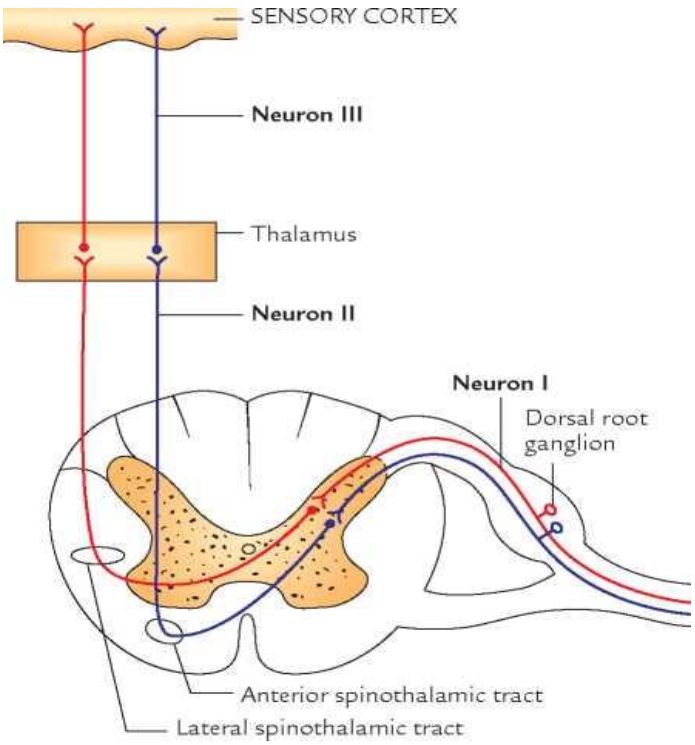

Figure 2. The Spinothalamic tract, demonstrating the main ascending pathway of pain mediation.

(http://www.anatomyzone.com/anatomy-feed/spinothalamic-tract/)

The pain gate theory, discovered by Melzack and Wall in 1965 is an explanation of how thick myelinated Aβ fibres which do not transmit pain stimuli inhibit the effects of firing by Aσ and C-fibres [98]. Aσ-fibres are associated with acute, intense pain, C-fibres are associated with chronic aching or throbbing pain. They also showed that certain types of stimulation including acupuncture and transcutaneous electrical stimulation were shown to "close a gate" at the first synapse in the dorsal horn preventing, or reducing transmission to supra-spinal areas. The pain gate theory however can

only explain local analgesia within the same and neighboring dermatomes; pain gate control cannot facilitate prolonged analgesia.

In the 1970's it became apparent that the arcuate nucleus (ARK) in the hypothalamus and periaqueduct gray (PAG) in the brain stem are the major locations for β-endorphin and encephalin release [99,100]. Both these areas together connect with the nucleus raphe magnus (NRM), they make up the centre of an important descending inhibitory pathway (ARK-PAG-NRM). Clinical trials have produced analgesia by stimulating PAG with electricity and opiates [101]. When stimulated by opiates this area sends efferent connections to NRM. Electrically stimulated analgesia of PAG can be blocked by administering the opiate antagonist naloxone to NRM. Ascending fibres from the spinothalamic tract synapse at PAG, which via its distal connection to NRM can inhibit pain in the dorsal horn. The main function of NRM is pain mediation. It releases serotonin when stimulated, and sends projections to the dorsal horn of the spinal cord connecting with encephalin releasing interneurons to directly inhibit pain. Another descending inhibitory pathway involves the parabrachial nucleus (PBN). The PBN releases dynorphin, the pathway is referred to as PBN/PAG/NRM. Both these pathways have been shown to inhibit or reduce nociceptive signals.

The relationship between the endogenous opioid system and acupuncture analgesia was confirmed by findings by Mayer et al [102] and Pomeranz et al [103]. They found that the opioid receptor antagonist Naloxone, removed the analgesic effect of acupuncture in mice and humans. Further clarifying research revealed that naloxone could only block the analgesic effect of low frequency electro-acupuncture (4Hz,) but not high frequency (200 Hz), suggesting that the release of opioids is initiated by low rather than high frequency stimulation [104]. Studies experimenting with the dosage of naloxone found that dynorphin is the only opioid peptide responsive to high-frequency stimulation [105,106].

Electro-acupuncture (EA)

Electrical frequency specificity was primarily studied by Han et al., they suggested that the frequency of electro-acupuncture stimulation determined the pathway it activated [105,106]. More specifically they found that lower frequency (2 Hz) EA produced analgesia through μ- and δ-opioid receptors stimulating the release of β-endorphin, encephalin and endomorphin. Higher frequency (100 Hz) EA produced analgesia through the κ-opioid receptor releasing dynorphin. It follows then that low frequency stimulates the descending inhibitory ARC-PAG-NRM pathway and higher frequency the PBN-PAG-NRM pathway.

Studies of endogenous substances have been widely studied, closely followed by serotonin. About 10% of the body's serotonin is produced in the CNS, its functions include regulation of mood, sleep and appetite; cognitive functions include memory and learning skills. Han and Pomeranz [107] suggested serotonin as an analgesic transmitter. EA was shown to activate serotoninergic NRM neurons at both high and low frequencies. This analgesic effect of EA was shown to be reduced by a serotonin synthesis inhibitor injection. In 1989 Cheng demonstrated an increase in serotonin level in CSF, the brain stem and the whole cerebral cortex in response to EA [108].
Pomaranz and Stux, pioneers of the physiology of analgesia and acupuncture demonstrated that analgesic effect of EA in rats was correlated to the total level of endorphins and serotonin in the CNS. A reduction of serotonin led to a compensatory increase in endorphins, and visa-versa. This effect proved to vary from individual to individual. The rats that demonstrated a greater compensatory effect had less pain reduction when treated with EA, than those where only a slight or no compensatory increase was measured [109]. In 1974 the *Research Group of Acupuncture Anesthesia PMC* demonstrated that perfusion of CSF from rabbits with acupressure-induced analgesia to non-acupressured rabbits produced analgesia in the recipients [110].

A series of studies to assess whether electrical stimulation of the alternative mode would produce a significantly stronger analgesic effect than that produced by stimulation of fixed frequency was undertaken by scientists at the University of Texas. Assuming that the reduction of the post-operative opiate dosage indicated degree of analgesia, they found that alternative mode stimulation reduced morphine requirement by 53%; whereas a constant low (2 Hz) or constant high (100 Hz) frequency produced only a 32% or 35% decrease, respectively [111]. Studies on diabetic neuropathic pain showed similar results [112]. These studies indicate that neuropeptides in CNS can be mobilized by electrical stimulation of different frequencies applied at peripheral sites, prompting further investigation into further clinical application potential.

Needle stimulation

The use of hypodermic needles in traditional medicine is assumed to be an essential part of diagnostic procedure or as a way of administering treatment. Western medicine does not consider the use of needles alone in any way therapeutic. Acupuncture involves the insertion of very fine gauge needles into body tissue as a way of affecting different body processes. Insertion of acupuncture needles is often combined with intermittent manipulation at the start of and during treatment, and/or in combination with the removal of needles.

Manual needle manipulation consists of rotating or rapid insertion and withdrawal of the needle for a few seconds up to minutes. Manipulation aims at promoting a feeling of heaviness, aching and/or

numbness around the area of the needle, this reaction is traditionally known as *de qi* in Chinese medicine [113]. The concept of the phenomenon *de qi* has not been clearly defined, however the sensation is often considered essential to the effectiveness of acupuncture therapy [114], although this has never been scientifically proven. Even so, most clinical trials investigating the effects of acupuncture describe manipulation of needles. Response to needle manipulation has been shown to stimulate a limited number of sites in the body inducing autonomic, endocrine and systemic hemodynamic responses [115]. Such findings suggest that not only local reflexes are stimulated, but also that the CNS is involved. Several studies have confirmed that changes in various parts of the brain are involved [116-118].

Needle stimulation sensations have been described as burning, hurting, pinching, pricking, sharp, shocking, stinging, tender, dull, tingling, painful, and electrical shock sensations [119]. The sensation of *de qi* seems to vary greatly from individual to individual. Beissner et al. [120] showed that pricking sensation was associated with Aσ fibres, and heavy, dull sensations were related to C fibres, possibly provoking different reactions in the brain.

Studies have described how *de qi* can also be detected by the therapist who may observe a grasping of the needle by the body tissue, causing resistance to further needle manipulation. In 2001 Langevin and colleagues examined *de qi* - needle grasp as a biomechanical component, by quantifying the force needed to pull an acupuncture needle out in 60 participants [121]. A computer controlled needling instrument inserted, manipulated and drew out needles at 8 acupuncture points and 8 control points. Two types of needle manipulation (bidirectional and unidirectional rotation) were compared to no rotation. The authors found unilateral rotation to be more effective. Unilateral manipulation provoked a 67% increase in mean pull-out force, compared to 52% in bidirectional rotation. Since a unilateral winding movement caused a more effective needle grasp the authors suggested that connective tissue may be involved. This suggestion seems to tie in with findings in an electron microscopy study of debris found on acupuncture needles; after manipulation, entwined elastic and collagen fibres were observed [122]. Langevin and colleagues concluded that pull-out force was 18% greater at acupuncture points than control points, making needle grasp a measurable biomechanical phenomenon.

The *de qi* sensation was shown to be of consequence in non-invasive imaging studies where peripheral pain increased limbic activity, acupuncture treatment when a *de qi* sensation was achieved reduced limbic activity [116]. Sakai et al. [117] investigated effects on the sympathetic and parasympathetic nervous systems and EEG changes in response to acupuncture needle manipulation. Manipulative needling of the trapezius muscle reduced sympathetic activity and increased parasympathetic nervous activity, heart rate was reduced, and systolic pressure increased.

Hori and Takamoto's research [123,124] used ECG's, EEG's and near-infrared spectroscopy to investigate the effects of acupuncture on the autonomic nervous system and brain hemodynamics. They showed that changes in parasympathetic nervous activity was correlated with the number of *de qi* sensations during acupuncture and that these autonomic changes were correlated with EEG spectral changes. Their results indicated that autonomic changes provoked by acupuncture needle manipulation might be mediated through the CNS, especially the forebrain; possibly reducing chronic pain by inhibiting the sympathetic nervous system. Near-infrared spectroscopy showed a significant activity reduction in the supplementary motor cortex, an area associated with dystonia and chronic pain, in response to needle manipulation.

Although acupuncture points are often located in areas containing an increased amount of nerve endings, and many points coincide with motor points on peripheral nerves, a connection between stimulation of nerves around acupuncture points and the *de qi* sensation has not been confirmed. Streitberger [125] found no association between the number of nerve endings and *de qi* response, when P6 (located on the palmar aspect of the forearm, proximal to the wrist, between the palmaris longus and flexor carpi radialis tendons) was needled and manipulated in an ultrasound imaging study. Indeed, even though a needle was inserted into the median nerve, the investigators could not provoke the *de qi* sensation in a few cases. Another clinical trial suggested that *de qi* response may be different in healthy individuals compared to those suffering from a medical condition. Liu et al. [126] reported that during acupuncture both hypothalamus response, measured by fMRI and *de qi* score were different in heroin addicts and healthy subjects. The *de qi* score of heroin addicts was significantly higher and the activation of the hypothalamus was more robust.

The action to initiate the needle sensation known as *de qi* in Chinese medicine is without doubt mechanical. Edward Yang et al. [127] in an attempt to give mechanistic evidence related to acupuncture physiology, speculated that the mechanism introduces a separate channel of cellular communications with calcium waves. Two mechanical waves which the authors could measure acoustically were stimulated by the needle manipulation. These waves the authors suggest "appear ideally suited to describe what the ancient Chinese called Qi."

Manual needle manipulation has been considered to be a method of low frequency stimulation. Kong et al. [128] demonstrated that the sensations of manual acupuncture on Large Intestine 4 (LI 4, hégu) a point found on the thenar eminence, were mainly soreness and distension; while those of EA were mainly tingling and numbness; although frequency was not specified. Their research also found that fMRI signal increased in various centres in the brain including the precentral gyrus, postcentral gyrus, and insula during EA; while it decreased in posterior cingulated, superior temporal gyrus and insula in

response to manual needling stimulation. These findings could indicate that different brain mechanisms may be provoked by different methods of stimulation.

Acupuncture points

The concepts of meridians and acupuncture points originated empirically as practitioners attempted to understand and map radiating sensations provoked due to needle stimulation. Points are located centrally on the torso, and also laterally where each point has a reflected location. Each point is labelled with the name of the meridian, the number of the point and the given Chinese name, e.g. Large Intestine 4 (LI4, hégu). Acupuncture points along many meridians are located over major neural pathways, e.g., Pericardium 3 (PC3, quzé) on the anterior of the wrist joint, over the median nerve. The World Health Organization has addressed the need for a standard terminology in order to describe acupuncture points which often have several names due to Chinese origins, dialect challenges and translational problems. Also, other Asian countries have practiced acupuncture, creating their own nomenclature and numbering. In the 1960's both China and Japan established naming and numbering systems by setting up a *Japanese Meridian and Points Committee* and *All China Acupuncture and Moxibustion Society* [129].

A Regional Consultation in Tokyo (1984) and Working Groups in Hong Kong (1985) and Seoul (1987) reached agreement on nomenclature for the 8 extra meridians, the 48 extra points, and scalp acupuncture lines [130]. Acupuncture points described and named in this thesis are referred to according to these guidelines.

Standardization enhancing reliability and reproducibility of acupuncture studies, in turn leading to a better understanding of acupuncture's mechanisms and clinical indications is needed. An increased number of acupuncture-related journals instruct that papers must follow the *WHO Standard Acupuncture Point Locations in the Western Pacific Region* [131].

Acupuncture points are located anatomically, or in the case of trigger points, by palpation. Depth of needle penetration is dictated by the anatomical location of the point. Practitioners commonly subjectively judge needling depth according to the depth of penetration needed to stimulate neural pathways and provoke a needle sensation. There seems to be little consensus as to needle penetration depth, many factors may influence this including gender, age, body size and angle of needling [132], and the therapists own experience. Subjective needle depth insertion and the lack of instruments to measure penetration depth makes comparison and repetition of treatments difficult. Definitions of safe needling depth and standard localization needs to be established internationally. Specific needling depth descriptions and background rational are often lacking in acupuncture studies.

A systematic review investigating scientific information regarding safe needling depth of acupuncture points and the needling depth of clinical efficacy, included 47 studies [133]. The authors concluded that there are great inconsistencies regarding measurement of point depth, also consensus of which type of measuring method should be used is lacking. This prompts the need for a definition of safe needling depth through standardization with a view to safety, optimal efficacy, the reproduction of studies and transfer to clinical practice.

Quantifying needle response

Some investigators have tried to quantify needle response in order to make needle sensation more comparable between treatment participants, different acupuncture points and insertion/stimulatory techniques. Hui et al. investigated a method for creating a single value to represent *de qi* by performing manual acupuncture at 4 points on the extremities during fMRI, in 42 acupuncture naïve participants [134]. As a control, non-invasive tactile stimulation was applied to acupuncture points by gentle tapping. After each procedure participants were asked to characterise sensations and rate the intensity on a numerical scale of 1–10. Frequency of acupuncture stimulation and intensity were calculated, both quantitative and qualitative results provided evidence in support of the *de qi* phenomenon and its association to nervous tissue. The authors attempted to reduce the complex sensation profile of *de qi* to a single value, thereby allowing more straightforward comparisons between subjects, acupuncture points, and stimulation techniques. Kou and colleagues suggested the Visual Analogue Scale (VAS) as an objective way to quantify *de qi* sensation [135].

MacPherson and Asghar attempted to make a *de qi* assessment questionnaire by separating the *de qi* sensation from pain [136]. The Southampton Needle Sensation Questionnaire (SNSQ), [137], also focused on the discrimination between pain and *de qi*. Kong and colleagues created a scale entitled Subjective Acupuncture Sensation Scale (SASS), in 2005 when launching a study on acupuncture analgesia [138].

These questionnaires did not involve face to face interviews with patients, thus the lack of subjective descriptions of sensations perceived during acupuncture stimulation appears to be a design flaw. Currently no international standard questionnaire accurately accesses *de qi* quantitatively and qualitatively. Such questionnaires would need to include physical signs of *de qi*, subjective patient sensations, and the acupuncturists observations. Measurement of *de qi* is of utmost importance in acupuncture trials as a method of standardizing acupuncture treatment, where the stimulation of needles is understood to be related to treatment outcome, and where researchers aim at reproducing treatment results.

MRI

Mapping the effect of acupuncture on regionally specific structures within the brain is a useful tool to measure more objective findings in acupuncture research, in which subjective measurements including the visual analogue scale are often used to test changes in symptoms. MRI can provide specific data indicating a quantifiable basis for evidence of acupuncture, thereby elevating acupuncture to an evidence based treatment.

Numerous studies have investigated human brain response to acupuncture using non-invasive functional MRI (fMRI) [139]. Most of these studies have used a short acupuncture treatment time of up to 15 minutes, even though acupuncture analgesia studies suggest that a longer duration of treatment for at least 20 minutes is needed to stimulate β-endorphin release [140]. There is evidence to suggest that continuous needle stimulation either by manual manipulation or electrical stimulation for at least 20 minutes is necessary for maximum acupuncture-induced analgesia to occur [141,142].

Fang and colleagues [115] found that acupuncture produced extensive deactivation of the limbic-paralimbic-neocortical system, an area which plays an important role in processing the cognitive dimensions of pain signals and acts as the regulatory centre of emotion, cognition, consciousness, autonomic, endocrine, and immunological functions. MRI studies by Hui and colleagues [142], showed amygdale deactivation in response to needle stimulation at acupuncture points LR2 (xíngjian), and ST40 (fenglóng) and hippocampus deactivation when LR2 (xíngjian), LR3 (tàichong), and ST44 (nèitíng) were stimulated. These responses were seen when a needle sensation without sharp pain was experienced by participants. Asghar et al. [143] reported different fMRI blood oxygen level-dependent (BOLD) signals when *de qi* versus acute pain was experienced, when needling LI4 (hégu).

MRI mapping of the brain indicates that rotating the needle in real acupuncture points LR3 (tàichong) and GB40 (qiuxu) activates the sensory cortex bilaterally, the left frontal lobe, the right side of the thalamus, and the left side of cerebellum more significantly than needling without rotation [144]
In a cross-over study 12 participants received three sessions of electro-acupuncture (EA) at LI4 (hégu), the interventions were: 1. EA alone; 2. EA after injection of local anaesthetics into the deltoid muscle; and 3. EA after a brachial plexus block. Brain regions showing change in BOLD signal were identified by MRI scans. Results showed that electro-acupuncture alone and combined with local anaesthetic injection into the deltoid muscle activated the bilateral thalamus, basal ganglia, cerebellum and left putamen. No significant activation was observed during EA + brachial plexus block, indicating that blocking the brachial plexus completely abolishes patterns of brain activation induced by EA at acupuncture point LI4 (hégu). The authors concluded that the results suggest EA activates specific brain regions through stimulation of the local nerves supplying the tissues at LI4 (hégu), which transmit sensory information to the CNS via the brachial plexus [145].

Physiological mechanisms of acupuncture affecting body temperature

How do these different physiological responses to acupuncture discussed above relate to vasomotor symptoms in breast cancer survivors?

Firstly, falling levels of oestrogen in menopausal women are accompanied by reduced amounts of serotonin and norepinephrine provoking noradrenalin release, affecting thermoregulatory signal transmission [146-148]. Acupuncture has been shown to increase β endorphin production, activate serotoninergic neurons, and increased levels of serotonin and norepinephrine in CSF, the brain stem and cortex [96-104] and therefore has the potential to influence the hypothalamic thermoregulatory centre.

Another theory of how acupuncture can affect vasomotor instability involves the calcitonin gene-related peptide (CGRP), produced in both peripheral and central neurons [149]. It is a potent peptide vasodilator and has been associated with peripheral cutaneous vasodilation and sweating during hot flashes [150,151]. Calcitonin gene-related peptide receptors are found throughout the body predominantly in C and Aδ nerve fibres. It has been suggested that the peptide is involved in modulation of physiological functions in all major systems including endocrine and cardiovascular systems [152]. The modulation of calcium channels has been suggested as the primary mechanism for the inhibitory effects of opioids on peripheral neurons [152-154]. Endogenous opioids modulate the release of CGRP at the spinal cord level [155]. CGRP has been found to increase in plasma during hot flashes in post-menopausal women [155] and in the urine of post-menopausal women with hot flashes compared to those without HF [156]. Intracellular investigations have reported that acupuncture stimulates the delivery of Ca^{2+}, thereby potentially influencing peripheral opioid peptide secretion [157]. In a group of post-menopausal women suffering from HF, CGRP in 24-hour urine decreased significantly after 12 weeks of acupuncture treatment [158]. Randomized studies have yet to prove that acupuncture effects the release of CGRP in peripheral nerve endings. If research investigating CGRP antagonists as a treatment for migraine due to vascular instability shows efficacy, a similar intervention may be worth investigating as an alternative treatment for hot flashes.

Any intervention that increases oestrogen, β endorphins, or serotonin concentrations and reduces noradrenalin levels, has the possibility to reduce hot flashes in menopausal women, according to the hypotheses currently agreed upon at this time. The effect of acupuncture is however probably multifactorial; more investigations are needed to demonstrate efficacy and provide precise physiological mechanism explanations.

7.9. Acupuncture Studies for Hot Flashes in Breast Cancer Operated Patients

Systematic reviews designed to determine whether acupuncture is effective and safe for reducing hot flushes and improving the quality of life of healthy menopausal women with vasomotor symptoms, include a review by Dodin et al. in which 16 RCT's, with 1155 women were identified [159]. Acupuncture was compared to sham acupuncture (8 studies), HRT (3 studies), relaxation (1 study) and to waiting list/no intervention (4 studies). The authors found insufficient evidence to determine whether acupuncture is effective for controlling menopausal vasomotor symptoms. Further, they concluded that the evidence was of low, or very low quality and the studies comparing acupuncture versus no treatment, or HT, were not controlled with sham acupuncture or placebo HRT. Data on adverse effects were lacking. Two other systematic reviews concerning healthy women were done by Lee et al. [160] where 6 trials included 309 patients and by Choo who reviewed 5 trials from Chinese literature [161]. Both reviews concluded that there is no evidence that acupuncture is an effective treatment for HF's, again both comment on the low quality of the included studies, specifically small sample sizes.

A Norwegian study of 267 healthy menopausal women complaining of HF's demonstrated a significant hot flash reduction in women receiving acupuncture and self-care, compared to those only receiving self-care [162]. Other studies investigating the effect of acupuncture in the treatment of menopausal hot flashes in healthy women have generally been small and have reported mixed results [163-167].

Five systematic reviews have examined the effects of acupuncture to treat HF in breast cancer patients. Garcia et al. evaluated the evidence related to the use of acupuncture for HF's in cancer patients, 210 publications were screened [87]. Eight RCT's met the inclusion criteria, all involved women with breast cancer. The authors concluded that the current level of evidence is insufficient to either support or refute the benefits of acupuncture for the management of HFs in cancer patients. Dos Santos et al. examined acupuncture for treating common adverse effects associated with breast cancer treatment [88]. Twelve RCT's were included. Five of the studies examined acupuncture treatment for HF symptoms; results indicated that acupuncture alone and EA are useful for treating HF's. Lee et al. [168] failed to demonstrate the effectiveness of acupuncture for HF's when 8 RCT's were reviewed. Chen et al. [169] identified twelve RCTs, only three trials showed a staistically significant difference when acupuncture was compared with the controls. The authors also performed a meta-analysis that indicated a statistically significant difference in the number of HF's from base-line to end of treatment, and during follow-up, compared with the controls. Three of the included trials reported Kupperman Index (KI) scores, and meta-analysis of these showed a significant difference between acupuncture and controls after treatment and during follow-up.

The most recently published systematic review identified a total of 272 studies, five of which were selected and analysed [170]. Slight superiority for acupuncture compared with sham acupuncture was observed; however, the evidence gathered was not sufficient to affirm the efficacy of acupuncture compared with sham acupuncture.

Two further meta-analyses included 7 [89] and 12 RCT's [171]. The first concluded that acupuncture significantly reduced the frequency of HF immediately after the completion of treatment and during the 3 month follow up period. However, there were no statistically significant differences in HF frequency and severity when acupuncture was compared to sham. The second meta-analysis concluded that contradictory results yielded no convincing evidence to suggest that acupuncture was an effective treatment of hot flash in patients with breast cancer. The authors of both papers indicated the need for multi-centre studies and larger sample sizes. Our RCT presented in Paper II was included in all 5 systematic reviews and all 3 meta-analyses presented above.

Individual studies investigating acupuncture as a treatment for hot flashes in breast cancer patients were initially small pilot studies [172-176]. However, the last few years has seen an increase in randomized, controlled studies in this field. Frisk [177] randomized 45 breast cancer women complaining of HF to either electro-acupuncture for 12 weeks or HRT for 24 months. Numbers of hot flashes, hours slept and the number of times patients woke up at night, were recorded. A Psychological and General Well-Being Index (PGWB), and Women's Health Questionnaire (WHQ) were registered before and during treatment and at 6, 9, 12, 18 and 24 months after start of treatment. After 12 weeks of acupuncture the HF score was reduced by 80%, a median decrease in number of HF from 9.6 at baseline to 4.3 after 12 weeks, 4.8 after 12 months, and 2.9 after 24 months was measured. Despite the clear effect of acupuncture, HRT was more effective in HF reduction. However, the HABITS study [178] that Frisk's study was a part of, found slightly higher recurrence rates of breast cancer in the HRT group compared to the non-hormonal group, prompting premature closure of the trial. Frisk et al. concluded that although HF decreased less in the EA group than in the HRT group, EA reduced number of hot flashes significantly and HRQoL improved at least to the same extent as the HRT group. This may have been due to the effects of EA on other symptoms, for example anxiety, vitality and sleep, shown by subscale analyses. Results indicated that EA should be further evaluated as treatment for women with breast cancer, since HRT can no longer be recommended for these women.

Two trials have compared acupuncture to non-hormonal medication for hot flashes. An RCT by Walker randomized 50 women with breast cancer suffering from HF to either 12 weeks of acupuncture or the anti-depressive venlafaxine. Results showed an effective and comparable reduction of HF in both groups; however, the effects of acupuncture lasted for 2 months' post treatment, compared to 2 weeks in the women medicated with venlafaxine [71]. The venlafaxine group experienced 18

incidences of adverse effects (including: nausea, dry mouth, dizziness, anxiety) whereas the acupuncture group experienced no negative adverse effects. Women receiving acupuncture reported increased sex drive, an improvement in their energy, clarity of thought, and sense of well-being. Mao randomized 120 breast cancer survivors to 8 weeks of EA or gabapentin compared to sham acupuncture and placebo pill controls [179]. Hot flash score was lowest in the EA group at the end of treatment and 4 months later, gabapentin showed a similar effect during treatment, but not at the 4-month follow-up point. The drug groups (gabapentin and placebo) had significantly more adverse effects than the acupuncture groups (gabapentin 39.3%, placebo 20.0%, EA 16.7% and SA 3.1%).

In a one arm study De Valois and colleagues demonstrated a reduction of hot flashes at 18 weeks' post treatment in 50 breast cancer operated women, who had received 8 weekly acupuncture treatments [180]. Mean frequency measurements of HF were reduced by 49% at end of treatment compared to baseline. Trends at 4 and 18 weeks' post-treatment indicated long term effects. Also, Women's Health Questionnaire (WHQ) domains showed significant statistical and clinical improvements, including anxiety/fears, memory/concentration, menstrual problems, sexual behaviour, sleep problems, somatic symptoms, and vasomotor symptoms.

In a recent prospective single-arm observational pilot study of 10 Korean patients with breast cancer suffering from HF, receiving anti-oestrogen therapy with tamoxifen or anastrozole, acupuncture significantly alleviated HF severity assessed by a visual analogue scale and HF score. Acupuncture was administered 3 times a week for 4 consecutive weeks, for 20±5 minutes at each session. Four weeks after the final treatment the severity of hot flashes was reduced by 70%-95% in all patients [181].

Two randomized, controlled studies from the USA and Sweden could not demonstrate that acupuncture was more effective than sham in reducing vasomotor symptoms. Seventy-two women with breast cancer experiencing three or more hot flashes per day were randomly assigned to receive either acupuncture or sham acupuncture in a study by Deng et al. [182]. Interventions were given twice weekly for 4 consecutive weeks. Hot flash frequency was evaluated at baseline, at 6 weeks, and at 6 months after initiation of treatment. Patients initially randomly assigned to the sham group were crossed over to acupuncture starting at week 7. Mean number of HF per day was reduced from 8.7 to 6.2 in the acupuncture group and from 10.0 to 7.6 in the sham group. Acupuncture was associated with 0.8 fewer hot flashes per day than sham at 6 weeks, but the difference did not reach statistical significance. When participants in the sham acupuncture group were crossed over to true acupuncture, a further reduction in the frequency of hot flashes was seen. This reduction in HF frequency lasted for up to 6 months after the treatment was completed.

Liljegren [183] randomized eighty-four tamoxifen medicated women to receive either acupuncture or control (non-insertive stimulation at non-acupuncture points) twice a week for 5 weeks. Seventy-four patients were treated. In the acupuncture group 42% (16/38) reported improvements in hot flushes after 6 weeks compared to 47% (17/36) in the control group. Both groups reported improvement regarding severity and frequencies in hot flashes, but no statistically significant difference was found between the groups.

The most recent study examining vasomotor symptoms included 190 women with breast cancer. One hundred and five women were randomly assigned to enhanced self-care and 85 to acupuncture plus enhanced self-care [184]. Acupuncture plus enhanced self-care was associated with a significantly lower HF score than enhanced self-care alone at the end of treatment and at 3 and 6-month post-treatment. Acupuncture was associated with fewer climacteric symptoms and higher QoL. Indicating that acupuncture in association with enhanced self-care is an effective integrative intervention for managing hot flashes and improving quality of life in women with breast cancer.

Several recent randomized controlled trials have demonstrated that acupuncture may be effective for managing HF's in breast cancer patients for up to 3 months' post treatment [173,182,185]. However, there is a distinct absence of randomized studies investigating long term effect. Apart from studies by Frisk and Lesi (177,184) mentioned above, the author of this thesis could only find long-term effects described by Flishie. His retrospective audit of treatment records of 182 women with breast cancer suggests long term HF relief from one month to 6 years (mean 9 months) using acupuncture and self-acupuncture [186].

Hot flashes, night sweats and disturbed sleep have been shown to influence each other; Bokmand and Flyger designed a study to evaluate the effect of acupuncture on HF's and disturbed night sleep in patients treated for breast cancer [185]. Ninety-four women were included, the study had 3 arms: acupuncture (n=31), sham acupuncture (n=29) and a no treatment control group (n=34). Plasma oestradiol was measured to rule out this as cause of effect. Adverse effects of the treatment were registered. In the acupuncture group, 16 patients experienced a significant reduction of HF's, compared with 7 patients in the sham group ($p < 0.05$). The effect was recorded after the second acupuncture treatment, it lasted for at least 12 weeks' post-treatment. Improvement in sleep was statistically significant in the acupuncture group compared with the sham acupuncture, as well as no treatment groups. The effect was not correlated with increased levels of plasma oestradiol, and no adverse effects due to acupuncture were registered.

Adverse effects of acupuncture

Acupuncture is generally considered to be a safe treatment technique with few adverse effects, however robust data to support this assumption is lacking. A prospective acupuncture survey of reports by 78 physicians and physiotherapists, reported 2178 adverse events occurring in 31,822 consultations [187]. The most common adverse effects were minor bleeding (3%), needling pain (1%) and aggravation of symptoms (1%). The authors classed the incidence of adverse effect risk as minimal, further, they concluded that acupuncture in skilled hands seems to be a comparatively safe intervention. No adverse effects were reported in any of the 8 randomized, controlled trials included in a systematic review of acupuncture to control hot flashes in cancer patients [87].

In 1996 AJ Norheim published a paper investigating adverse effects of acupuncture as recorded in the Medline database for the years 1981-1994 [188]. A total of 125 papers were localized, articles without case reports were excluded, leaving 78 reports for inspection. A total of 193 patients were reported with adverse effects of acupuncture during the 14 years. Pneumothorax was the most common mechanical organ injury, while hepatitis dominated among infections. Acupuncture treatment is claimed to be responsible for the death of three patients. One patient died from bilateral pneumothorax, another got endocarditis and died of complications, the third patient died of severe asthma during acupuncture treatment. The author concluded that most adverse effects of acupuncture seem to rely on insufficient basic medical knowledge, low hygienic standard, and inadequate acupuncture education. Further he reported few serious adverse effects, and that acupuncture could generally be considered as a safe treatment. After the publication of his investigation paper the author was excluded from the Norwegian acupuncture association (Akupunctur Foreningen). Today, ten years later the same association has a professional attitude to adverse effects and Norheim is an honorary member.

Limitations

Very few randomized controlled trials have been undertaken concerning breast cancer, oestrogen antagonist therapy and hot flashes; and most are small. The RCT's named above included from 50 to 190 women. Frisk [177] accessed patients' HF symptoms at 24 months, Deng [182] and Lesi [184] at 6 months, long-term follow up is otherwise lacking.

A variation of control groups has been used. Acupuncture has been compared to HRT, non-hormonal medication, sham acupuncture, non-insertive stimulation at non-acupuncture points and self-care. Bokmand and Flyger [185] in the only three-armed study, tested the effect of acupuncture against both sham acupuncture and a non-treatment control group.

Randomized, controlled acupuncture trials are all single blind; double blinding, involving blinding of both the patient and the therapist is not an option, acupuncturists are aware of the treatment they administer. To date no double-blind acupuncture studies concerning blinding of both therapists and patients for this patient category have been published; we found six studies in which patients were blinded [71,179,182,183,184,185]. Blinding is crucial to avoid overestimating treatment effect. Blinding of the administrator assessing outcomes and further blinding of the statistician as to intervention or control allocation increases confidence in outcomes. Other factors influencing the blinding procedure to be considered are the visual impact of needling, including needle manipulation, and the skill of the individual therapist [187,189]. In order to blind patients sham acupuncture has been used in numerous studies, it seems to be the most acceptable control developed so far. Researches started to use this method in the 1990's, Streitberg and Kleinhenz were some of the first researches to use sham as a control group. They demonstrated a significant reduction in chronic pain in athletes treated with real acupuncture compared to sham [190].

Western medicine considers the effects of acupuncture to include stimulation of the central nervous system by activating afferent fibres. It could be assumed therefore that sham acupuncture at points not located in the vicinity of peripheral nerves will not produce the same level of response. Sham acupuncture used as a control method assumes that inserting a needle into a point that is not classified as a traditional acupuncture point will not induce physiological effects. However, this non-specific type of needling has been shown to provoke neurological, circulatory and immune system responses [191], thus sham acupuncture is not inert. Consequently, the use of this method may affect research results by failing to detect an effect that is present (type II error). To further reduce the possibility of physiological responses needles are often superficially inserted at non-acupuncture points, without any type of stimulation. The assumption that this type of modified sham or "minimal acupuncture" reduces physiological responses further, compared to sham where needles are inserted at the same depth as those at traditional acupuncture points seems logical, however investigations have demonstrated physiological responses, dismissing the technique as placebo.

Sham acupuncture often provokes stronger placebo effects than other types of controls. Sham acupuncture provoked a greater placebo response than placebo pills in a RCT comparing these two interventions for the treatment of HF, in breast cancer women [177 Frisk]. Ted Kaptchuk was among the first to try to separate components of the placebo effect, he reported a "dose-dependent response" for a placebo, which related to the amount of care patients received; patients receiving more care, even if it was fake, reported symptom improvement [192]. Deceiving patients is considered unethical, so Kaptchuk investigated effects of a placebo pill for irritable bowel syndrome in patients who were told that they were taking a placebo, but that placebo pills often have beneficial effects. Patients who knew that they were taking the placebo pills reported symptom relief that was 50% higher than a control

group receiving no treatment; this result was comparable to real medications used for IBS [193]. Functional MRI studies [194,195] demonstrated that placebo treatments affect the areas of the brain that modulate pain reception. This introduces the notion that a therapist's clinical manner and apparent skills can potentially affect a patient's central nervous system, producing biochemical changes identical to drugs and other pain reducing treatments. Research continues to focus on investigating treatment effect, but if placebo is so powerful, more studies investigating placebo response are indicated with a view to developing techniques, treatment environments and personnel that stimulate such a response. Every type of therapist should be aware of the strength of placebo in clinical settings.

The use of non-insertive stimulation as a control is plausible; no penetration takes place, producing even less sensory stimulation compared to sham. Non-insertive techniques include pricking blindfolded patients [196] and, mock electrical stimulation of acupuncture points [197], or the use retractable needles in a holder that look as though they pierce the skin [198]. When writing the protocol for the study *Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial* we designed a non-invasive control group. We suggested lying patients in prone lying, their faces resting through a hole in the treatment bench promoting relaxation, allowing them to breathe, hindering them from observing the treatment technique. Their backs were to be pricked with a tooth pick at non-acupuncture points, to represent insertion of a needle. After 30 minutes, they were to be pricked again to represent withdrawal of the needle. The local ethics committee did not allow us to use this technique, preferring sham acupuncture. The perfect control that is indistinguishable from acupuncture and does not provoke physiological effects is still an enigma.

Studies investigating neurophysiological changes due to acupuncture suggest 20 minutes as an average response time to needling [93-96]. If this response is individual, some patients may need longer treatment sessions to respond to acupuncture. Low dose, regarding length of each treatment session and number of treatments is an important limitation in RCT's where acupuncture is an intervention. Only 8 treatments over a 4-week period were used in a study by Deng and colleagues, the difference in the reduction of HF in the acupuncture group and the sham group was not significant [182]. Bokmand and Flyger [185] prescribed only 5 treatments with a frequency of once a week, only 4 points were used, and treatment time was 15 to 20 minutes. Although a significant effect could be measured in the acupuncture group compared to the other two arms, it could be speculated whether an increased number of treatments might have given an increased effect; also, whether 15-20 minutes was a long enough stimulation time to achieve an optimal effect in the CNS.

There is a distinct lack of qualitative studies for this patient group. Women undergo great physical trauma through lumpectomy or mastectomy and possibly breast reconstruction. Anti-oestrogen treatments and chemotherapy have serious adverse-effects including cognitive fogginess and

emotional problems. There is a lack of social and psychological information concerning women with breast cancer. Information and emotional support by health professionals was seen to have a direct effect on quality of life in a Chinese study of 250 breast cancer patients [199]. In a literature review of published articles from 1974 to 2007 Montazeri [29] examined the QoL in breast cancer patients. He found that adjuvant hormonal therapies negatively affected quality of life; symptoms such as arm pain, fatigue, postmenopausal problems, psychological anxiety and depression were common among breast cancer patients, even years after the disease diagnosis and treatment. No qualitative studies concerning acupuncture in anti-oestrogen medicated breast cancer patients, suffering from HF's, have been published. However, a recent study examined qualitative information delivered during interviews by 14 women who received up to 10 individualized acupuncture treatments during chemotherapy. The women were interviewed before, during and after chemotherapy, they reported both broad and specific effects including alleviation of symptoms and an increased well-being [200].

8. AIMS OF THIS THESIS

The aims of this thesis were:

1. To access the frequency and severity of adverse effects of non-hormonal drugs (NHD) used for treating hot flashes in breast cancer survivors.
2. To investigate short and long-term efficacy of acupuncture in women with breast cancer suffering hot flashes as a result of anti-oestrogen medication, by conducting a randomized, controlled trial.
3. To examine quality of life two years after acupuncture treatment by conducting a qualitative study.

Table 1: Aims, Research Questions and Methodology Applied to this Research Project

Aims	Research Questions	Methodology	Publication
To estimate frequency and severity of adverse effects of non-hormonal drugs for HF in breast cancer survivors.	What is the frequency and severity of adverse effects of non-hormonal drugs used to treat hot flashes in breast cancer patients, compared to different controls?	Systematic review and meta-analysis. Application of CTCAE grading system, grading of AE.	1
To investigate the effect of acupuncture treatments for HF, in women with breast cancer, medicated with oestrogen-antagonists.	Can acupuncture reduce number of hot flashes? If so, how long does the reduction last? Does acupuncture improve menopausal symptoms?	Performing a RCT which included 59 breast cancer survivors who received 15 acupuncture or sham treatments. Number of HF was compared at base-line, at the end of treatment and at 3 months' post-treatment. Patients filled out a Kupperman Menopausal Index score at base-line, at the end of 15 treatments and at 3 months' post-treatment.	2
To qualitatively investigate the long-term QoL of breast cancer survivors, medicated with oestrogen antagonists.	How do breast cancer survivors taking oestrogen anatgonists subjectively view their QoL 2 years after receiving acupuncture treatment?	Gathering qualitative data by asking the participants to answer an open, broad and non-specific question concerning their lives 2 years' post-treatment.	3
To investigate long-term severity of menopausal symptoms in breast cancer survivors, 2 years after receiving acupuncture for HF due to oestrogen-antagonists.	To what level are breast cancer survivors affected by long-term menopausal related symptoms?	Accessing Kupperman Menopausal Index score at a point 2 years after receiving acupuncture treatment.	4

9. METHODS AND RESULTS FOR THIS RESEARCH PROJECT

Each individual study will be presented separately in this section, including the following:

1. Specific aims of the study
2. Specific methodology applied to the study
3. Abstract of the publication

9.1. General methodology applied to this research project

Therapies and conventional drugs developed by reductionist systems might demonstrate *efficacy*, but might not be *effective* in a real-world situation of interactions between simultaneous interventions, provided by multiple clinicians, on an individual over time. Adverse effects are an important part of outcomes of complex systems approach in cancer victims, who often receive multiple therapies either in sequence or at the same time. Wider research including with both qualitative and quantitative designs to can provide appropriate outcome measures for individuals, groups and populations.

Mixed method research may combine quantitative and qualitative research techniques, methods and approaches in one research project [201,202], allowing design choices to be made in order to optimally answer research questions. Quantitative methods are indicated where outcome measures of an intervention are investigated, possibly based on a background qualitative study where a hypothesis has been developed [203]. Where quantitative studies "explain," qualitative studies aim to describe and understand. In this project a systematic review was performed to establish the severity of AE's due NHD's, with the intention of establishing whether the investigation of other treatments for HF's is indicated. Quantitative research was used in a RCT to investigate acupuncture treatment where numbers of HF and total numerical KI scores were recorded, while qualitative methods were used to describe women's experiences after breast cancer therapy. This combination of quantitative and qualitative studies goes some way to assessing acupuncture as a whole system, which requires both methods to equally present meanings, processes and outcomes. While the systematic review and meta-analysis demonstrates an indication for such studies, quantitative and qualitative designs can and did provide information concerning different aspects of health and experiences post breast cancer therapy. The combination of well-designed qualitative and quantitative methods constitutes a comprehensive research design, with the possibility of addressing the complexity of a whole system centred around the patient, potentially providing appropriate clinically relevant outcome measures.

9.2. Paper I.

Adverse effects of non-hormonal pharmacological interventions in breast cancer survivors, suffering from hot flashes. A systematic review and meta-analysis.

Aims:

The specific aims were:

1. To systematically investigate how adverse effects of the three most commonly used non-hormonal drugs to treat hot flashes in breast cancer patients, are reported in randomized controlled trials.
2. To classify adverse effects and drug related aggravations according to the Common Terminology Criteria for Adverse Effects (CTCAE) [204].
3. To perform a meta-analysis to evaluate the risk of adverse effects for patients pharmacologically managing their hot flashes with non-hormonal self-administered therapy, compared to different controls

Method

The purpose of a systematic review is to provide health care workers, policy makers and the public with information as to the effectiveness, feasibility, safety of an intervention/therapy. It is considered the best way to summarize available evidence based on research questions. A systematic review is a review in which pre-specified search and assessment criteria are used to address a research question [20]. This method was therefore considered appropriate when adverse effect risk of non-hormonal drugs, used by breast cancer survivors for HF, was to be investigated.

A meta-analysis is defined as is the use of statistical methods to summarize the results of independent studies [206]. Further, it is a quantitative, epidemiological study design, used to systematically assess previous research studies. A meta-analysis aims to provide outcomes with more precise estimates than any individual study contributing to the pooled analysis. Limitations occur where search, publication and selection bias are encountered, potentially misleading results. Our systematic review only included 12 RCT's, this was not due to language or time limits.

The terms harmful effect, adverse reaction and adverse effect are more commonly used to describe adverse drug reactions, whereas adverse reaction indicates a response by a patient [207]. These terms

are not used consequently as they have been defined, common terminology in this area is lacking. Even CONSORT [84] lacks a clear definition of adverse event. This leaves authors of papers in this subject free to choose terms for harmful events, in this paper we chose the term adverse effect.

In Paper I, a set of RCT's were systematically identified, appraised and summarized in response to the research question: *Are the most commonly used non-hormonal drugs for hot flashes in breast cancer patients associated with adverse effects?* Data was extracted to give information on the total number of adverse effects (AE), and number of patients experiencing AE. Severity of AE's was graded using the CTCAE grading system [204].

In this review, we wanted to attain an overview as to whether commonly used self-administered medication for HF's in this patient category, already had access to effective treatment with little or no adverse effects. If not, other types of therapy combining efficacy with low adverse effect frequency and/or severity need to be investigated.

Abstract paper I

Purpose: To access frequency and severity of adverse effects of non-hormonal drugs for hot flashes in breast cancer survivors compared to controls and analyse adverse effect risk, by reviewing published randomized trials.

Methods: Cochrane Central Register for Controlled Trials, Embase, Medline, PsycINFO and PubMed data-bases were searched. Trials were included where participants were survivors of breast cancer suffering from hot flashes, treatment was self-administered venlafaxine, gabapentin or clonidine, and AE were reported. AE frequency and severity was graded. A meta-analysis of ten trials with sub-group analyses was conducted.

Results: Forty-nine studies were identified, 12 were included. A total of 1467 participants experienced 772 adverse effects, 81% (n=627) in the treatment group and 19% (n=145) in the control group. Sixty-seven percent of AE was graded as mild and 33% as moderate. The frequency of AE for NHD was overall significant versus placebo. Sub-group analysis indicated that AE frequency and severity increased at higher doses in venlafaxine and gabapentin compared to placebo.

Conclusion: The odds for experiencing AE was significantly higher in patients randomized to high dose NHD than those randomized to controls, including placebo, low dose medication and acupuncture. These therapies should be considered as a potential treatment alternative.

9.3. Paper II.

Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial.

Aims

1. To investigate whether acupuncture treatment can reduce the number of hot flashes in women operated for breast cancer, medicated with tamoxifen.

2. To investigate whether acupuncture treatment can improve health related QoL.

Method

A randomized controlled trial is a study design that randomly assigns participants into an experimental group or a control group [208]. Randomized controlled trials are the best way of determining whether a cause-effect relation exists between treatment and outcome measures. Features of this design include concealed random allocation to intervention groups, single or double-blinding, an identical approach to all intervention groups (apart from the experimental intervention group). The intention to treat principle is followed, that is that participants are evaluated within their allocated group irrespective of whether they received the intended intervention; and that the size of the difference for the predefined outcomes are reported for the groups [209].

This design was considered appropriate for this study that evaluated the effect of acupuncture treatment by measuring the reduction in number of hot flashes during the 10-week treatment period, and up to 12 weeks' post-treatment; KI scores were measured at these three time points. Patients were randomized to either acupuncture or sham, the latter was used as a control. Patients were blinded to the type of treatment they received, the therapist was not blinded, making this a single-blind study. The design was pragmatic, and close to a clinical setting. Acupuncture points were decided upon based on points used in studies treating HF's in both healthy and breast cancer women [163-165].

Abstract Paper II

Objectives: To investigate the efficacy of acupuncture in women with breast cancer suffering from hot flashes as a result of anti-oestrogen medication.

Methods: Fifty-nine women suffering from hot flashes following breast cancer surgery and adjuvant oestrogen-antagonist treatment (tamoxifen) were randomized to either 10 weeks of traditional Chinese acupuncture or sham acupuncture. Number of hot flashes during the day and night were recorded prior to treatment, during the treatment period, and during the 12 weeks following treatment, once a week. A validated health score (Kupperman index) was conducted at baseline, at the end of the treatment period, and at 12 weeks following treatment.

Results: Mean number of HF was significantly reduced by 50% during the day and almost 60% at night in the TCM group, and further reduced by 30% both at day and night during the next 12 weeks. In the sham acupuncture group HF's were significantly reduced by 25% at night during treatment, the effect was reversed during the following 12 weeks. No HF reduction was seen during the day in the sham group. KI was reduced by 44% from baseline to the end of treatment in the TCM group, and largely maintained 12 weeks later, no corresponding changes were seen in the sham group.

Conclusions: Acupuncture seems to provide effective relief from hot flashes both day and night in women operated for breast cancer, treated with tamoxifen. This treatment effect seems to coincide with an improvement in general health.

9.4. Paper III

Quality of life of breast cancer patients medicated with anti-estrogens, two years after acupuncture treatment. A qualitative study.

Aims

To qualitatively investigate long-term, health-related QoL, in breast cancer survivors, medicated with oestrogen antagonists.

Methods

Qualitative methods are research strategies for the description and analysis of characteristics, properties, and/or qualities of the phenomenon to be studied [210]. The material to be analysed is usually text, but sometimes includes recordings representing conversations and/or observations. Whole systems research considers nesting qualitative studies within rigorous adaptations of the RCT, an integration of approaches, where each approach is equal [211]. A qualitative research method was considered appropriate for this study. The women in the study wrote a statement in answer to an open question, the intention was to gain subjective information about the lives of breast cancer survivors.

Abstract Paper III

Objective: To qualitatively examine the quality of life of breast cancer patients medicated with oestrogen antagonists, two years after having acupuncture treatment for hot flashes.

Methods: Eighty-two women who had 2 years previously participated in a randomized, controlled trial investigating the effects of acupuncture on hot flashes, an adverse effect of oestrogen-antagonist treatment, were asked to answer an open question. The question, "would you like to share your thoughts and experiences related to your breast cancer diagnosis, treatments or anything else?" was by being open, broad and non-specific, intended to stimulate subjective information. Qualitative data were analyzed using systematic text condensation.

Results: Most women were troubled by two or more adverse effects due to anti-oestrogen medication, negatively affecting their life quality. Women previously treated with sham acupuncture complained that hot flashes were still problematic, whilst those previously treated with traditional Chinese acupuncture found them less of a problem and generally had a more positive outlook on life.

Conclusion: Adverse effects due to anti-oestrogen treatment seriously affect the quality of life of breast cancer operated patients.

9.5. Paper IV.

Long term follow-up of breast cancer patients treated with acupuncture for hot flashes

Aims

To investigate health-related QoL in breast cancer survivors, two years after receiving acupuncture treatment for HF.

Method

This study is a follow up of the original RCT (Paper II), it investigates long term effects of acupuncture for HF's in women with breast cancer. The validated KI, originally called the Blatt-Kupperman menopausal index has been used widely in studies of climacteric symptoms, it was originally derived from clinical experience in New York in the 1950s [212]. KI is considered a reliable method of estimating the severity of symptoms related to natural, surgical and chemically induced menopause. The index is quick to fill out, comprising of 11 symptoms, it is simple and easily understood, possibly increasing response rate. These data measurements were considered adequate to estimate a total score regarding menopausal symptoms.

Abstract

Objective: To investigate QoL and longer term effects of acupuncture treatment in breast cancer patients, two years after receiving treatment for hot flashes.

Methods and materials: Eighty patients, who had 2 years previously been randomized to either a course of 15 acupuncture treatments or sham acupuncture (control) over a period of 10 weeks, were asked to fill out a Kupperman index, indicating health related quality of life.

Results: Sixty-one women returned KI questionnaires. A mixed models procedure with diagonal covariance matrix was used for statistical analyses. Baseline values between the sham-group and acupuncture group were not significantly different. However, scores at the end of treatment and after 3 months showed a statistically significant difference between the groups, this difference lost its significance when scores were analyzed after 2 years.

Conclusion: Acupuncture seems to have a positive effect on health-related quality of life for up three months' post-treatment, this study suggests that these effects may be longer-term; however, there was no significant effect 2 years later.

9. DISCUSSION

This research project demonstrated that the risk of experiencing AE's was significantly higher in breast cancer survivors suffering from HF's, randomized to high dose NHD's, than those randomized to controls. Control groups included placebo, low dose medication and acupuncture, these therapies are potential treatment alternatives. When acupuncture versus sham was investigated as a treatment for HF's in a RCT, acupuncture significantly reduced HF's both day and night in breast cancer women on tamoxifen therapy. A reduction in menopausal symptoms was also statistically significant for acupuncture versus sham, these effects lasted at least three months and may be longer-term. Qualitative information provided by the women in this project suggested that AE's due to anti-oestrogen treatment have a serious impact on quality of life, women described different coping mechanisms.

10.1. The Standards for Reporting Interventions in Clinical Trials of Acupuncture

STRICTA [85] has published guidelines that aim to improve reporting of acupuncture trials, especially interventions. These guidelines aim to increase interpretation, ease the task of replication and to raise the quality of the reporting of clinical acupuncture trials. The latest STRICTA Statement has been developed as an extension to a CONSORT statement regarding non-pharmacological interventions.

Guidelines include:

1. Explanation. A reason for choosing the intervention, information about the diagnosis, acupuncture point selection and treatment procedures.
2. Number of needles used per treatment, an explanation of what this number was based on, and the technique used.
3. How many treatments were planned, frequency of treatments. The actual number of treatments undertaken should be reported under *results*, and variations with explanations should be reported.
4. Other interventions should be reported e.g. medications, lifestyle advice, simultaneous treatments.
5. The background, experience and training of the therapist should be stated.
6. Information as to why a certain control method or a comparative method has been chosen, in context of the research question and methodology.

These guidelines were not yet published when the RCT (Paper II) was initiated. However, retrospective inspection of the study design indicates that all of the six STRICTA guidelines were addressed in paper II, although very briefly, due to publishing restrictions.

10.2. Body mass index (BMI)

BMI is often lacking as a measurement at base-line in studies investigating HF's in breast cancer patients, and was not considered in our RCT. A high BMI, or increase in BMI may increase the risk of HF's, although there is conflicting evidence. A meta-analysis of 7 studies (n=4,219) concerning healthy menopausal women with HF's, demonstrated that obesity does increase the risk of HF's, though not to a great extent [213]. An observational 5-year study of 631 midlife (age 45-54) healthy women monitored BMI and BMI change at annual clinic visits. No statistically significant associations between BMI or BMI change and HF outcomes were found. The authors suggested that other factors, such as smoking habits may be more important in determining hot flash risk during midlife in healthy women [214].

Weight gain however, does appear to be an adverse effect of adjuvant breast cancer therapy. A cross-sectional study of breast cancer survivors (n=300) on aromatase inhibitor therapy investigated a possible association between body size and HF's [215]. The authors found that current body size was not associated with hot flash occurrence, severity or change in AI therapy, however, weight gain was independently associated with HF occurrence and HF severity. Further, women who gained at least 4.5 kg since breast cancer diagnosis were twice as likely to have HF's than women who maintained or lost weight. Present literature indicates that weight gain is related to chemotherapy rather than oestrogen-antagonist therapy [216-219]. In the Women's Healthy Eating and Living (WHEL) study the association between chemotherapy or tamoxifen and weight gain was assessed in 2972 participants [219]. Chemotherapy was significantly associated with weight gain while tamoxifen was not. Weight gain peaked at year 2, and then plateaued; only 10% had returned to pre-diagnosis weight after 6 years. An observational, longitudinal study of weight gain after breast cancer diagnosis over three years (n=185), concluded that treatment with radiation does not appear to contribute to weight gain [220]. When taking into consideration all breast cancer treatments, weight gain seems to be most strongly correlated with use of cytotoxic therapies.

The recording of BMI is a simple measure that can be taken at baseline and at follow-up points. It should be considered as an essential measurement contributing to the demonstration of the degree of homogeneity between treatment groups like smoking and drinking habits, at base-line in future studies. Further, the possible influence of BMI values regarding HF's, including group distribution of women treated with chemotherapy should be considered when discussing results.

10.3. Whole systems research (WSR)

WSR developed by CAM researchers uses qualitative and quantitative methods in order to comprehensively study the effectiveness, process, context, outcomes, and philosophy of the intervention. CAM systems such as TCM, naturopathic medicine, homeopathy or integrative medicine are suitable for WSR, although it can also be used in conventional medicine, for example pain management and palliative care [211,221]. Randomised controlled trials traditionally answer questions related to efficacy, however limitations can arise when applied to the study of CAM systems. RCT's can have poor external validity, since they have limited ability to assess complex approaches, unique healing systems, therapeutic intervention context and holistic outcomes. For complex systems, a mixed method approach is often more suitable.

WSR regards quantitative and qualitative approaches as equal, the system requires both methods to equally present meanings, processes and outcomes [221]. Qualitative studies often provide valuable information that can be utilized in the design of RCT's. Individualized treatments for whole systems do not fit in with RCT standard design. Motivation to participate, outcome expectations and relationship to the therapist are often considered as part of a healing process in CAM research, challenging RCT methodology including diagnostic processes, randomization, standardization and bias.

WSR suggests that the complicated interplay between the patient, therapist and needle should be considered as a unit rather than independently in acupuncture studies [211]. This approach further complicates acupuncture research design, evaluation and outcomes, making the reduction of acupuncture to component parts e.g. as a simple intervention, complex. Acupuncture as part of a package of therapist attention, rest on a treatment bench and relaxation, almost certainly affects placebo response, the exotic aspect of acupuncture may also be a consideration. As with any other type of intervention, response can be affected by numerous factors including expectations, confidence in the therapist, treatment location and previous treatment experience. Expectation not only affects reporting as to treatment effect; it can also modify physiological responses associated with pain perception in the CNS [222]. Considering the possible physiological effects of sham acupuncture and powerful responses due to placebo, it is possible that the outcomes of acupuncture RCTs can be undervalued [223].

NAFKAM researchers have discussed "the gap" between published CAM research that shows little or no effect of alternative treatments and clinical cases that report positive results. They suggest that the gap may be due to investigations mainly being placebo controlled, randomized trials. The authors suggest that RCT's are designed to answer questions related to the effect and safety of medicines, not

complex treatment systems that are found in both alternative and some types of traditional medicine. Whereas control systems and effectiveness/efficacy of medicines are investigated before such treatments become available to the public, CAM therapies are often established and widely used by the public before effectiveness and safety are established. Such safety issues have been identified by NAFKAM and a five-phase research strategy has consequently been suggested, the order of which illustrates different research priorities to those traditionaly associated with RCT's. These five phases include 1. context, paradigms, philosophical understanding and use; 2. treatment safety; 3. treatment package effect; 4. effect of the treatment components in a treatment package; and 5. biological mechanisms [80].

In Paper II we included a KI score indicating health related QoL regarding menopausal symptoms in isolation in the RCT, the very nature of this is reductionist, it does not have the potential to capture holistic and often changing patterns of an individual, as do qualitative approaches, hence the use of qualitative design in Paper III. Acupuncture researchers using mixed qualitative and quantitative methods have demonstrated the phenomenon of emergence, where patients have reported both global and multidimensional changes over time [224]. Participants can even forget to mention the original chief complaint because of their enthusiastic description of multiple other changes that they had not originally anticipated. Statements from the women in Paper III demonstrated elements of emergence, for example where relationships, work or appearance were in focus, as opposed to their illness. More qualitative studies are needed to increase understanding and knowledge of issues of well-being, especially given a situation in which we have previous limited knowledge [224].

The statements below were not included in the publication (Paper III) due to publishing restrictions. Here are some examples of what the women wrote in response to the research question: *would you like to share your thoughts and experiences related to your breast cancer diagnosis, treatments, or anything else?*

A 38-year-old, previously treated with acupuncture wrote: When I was diagnosed 14th August 2006, I decided that I was going to be the boss in the fight against cancer. Not the other way around. I have always been psychologically strong, and that hasn't changed. I am back at work full time, one year later - my main goal. But I pay a price every day, exhaustion! The solution – working part time, I don't like it but I have to work to live, not live to work. I can't take stress anymore, I still have problems sleeping at night, I think that that is also a lot to do with my stress levels. Hope things improve when I go part time.
I got to know lots of fantastic women because of my illness. Last year at the rehab centre I got to know seven other women, who were around my age, we have become great friends, and have been on 3 weekend trips abroad already!

Because of the medications I take (Zolvadex and Femar) my body doesn't function like it used to. I have always been strong and fit. Now I have constant pains in my whole body, all my joints ache. My fingers are stiff. The hot flashes come back if I am stressed and if I eat spicy food or chocolate and red wine. I never have 30 hot flashes a day like I did when I first started with acupuncture!
Acupuncture gave me my life back when I was low, fewer hot flashes meant that I got some much needed rest and energy. I have recommended acupuncture to lots of women suffering from hot flashes.

Patient 58 years old (acu-group): I felt a lump when I scratched my breast one day. Four weeks later I was operated. The operation and radiation treatments went OK. I didn't feel like a sick person. Apart from hot flashes I haven't had any problems.

Patient 65 years old (acu-group): Acupuncture helped me a lot. I still have a few hot flashes at night, but they are not so strong. I regularly attend an exercise group in the swimming pool, which I feel is good for me. Otherwise no complains apart from aching joints, whether this is down to the medicine I take or old age, I don't know!

Patient 55 (acu-group): What illness? I have put it all behind me! Hot flashes now and again, but thanks to Jill they are few and far between!

Patient 52 (sham group): The hot flashes are horrid, I might try acupuncture again, it helped a bit but I am not sure that it is worth the long drive to the hospital every week. I work full time and have loads of hot flashes, I wish there was a medicine that could help. I get really hot and nauseous, my heart beats really fast and sometimes I get dizzy. Stress affects these symptoms.

I am stressed, and exhausted, I don't get much sleep and I work full time. My husband and I own a restaurant and our economy is tight. I am constantly anxious at work when I am serving; although I do not have any swelling, my arm on the operated side aches when I carry heavy serving plates, the pain seems to provoke the hot flashes and dizziness. I must seem rude sometimes as I hurry away from customers, but I often feel faint and have to rush to the back door to cool down and pull myself together.

Patient 68 (sham group): In hospital, I felt looked after, and was confident that the hospital staff were well trained.
Losing my hair was traumatic for me, I have always had longish thick hair, and without it I lost my identity. I ended up with a short wig, I tried a long one, but it just looked so wig-like and ridiculous. Hot flashes and a wig that did not breathe were a tough combination, little streams of sweat ran down my scalp down behind my ears and into the creases in my neck. Unfortunately, acupuncture didn't help me!

Patient 54 (sham group): The cancer has spread to my back, pelvis, lungs and liver. I have Zometa treatment once a month, I take Femara 2.5mg, medrol 4mg, Somac 40mg every day. Fentanyl plaster is changed every 3rd day. Then I take OxyNorm if I have a lot of pain. Calcium and Omega 3 daily!!!!!!!

Every evening and night hot flashes soak my clothes. Mornings are best, I usually try to take a walk, but I feel absolutely exhausted all the time. I get a headache every evening.

Patient 60 (sham group): The hot flashes are stronger in periods, if I am especially tired they increase.
It's difficult to know whether the treatments for cancer got me down or whether life itself beat me up. I am disappointed with my family and friends; my husband did not support me during chemotherapy. He came with me to the hospital; he was there physically but mentally he was somewhere else; he was constantly on the phone or his lap top sending e-mails. I felt really lonely. We split up last year.
I have almost lost contact with two of my closest friends. I got fed up of hearing them preaching. Somehow even though they have never been seriously ill themselves they had all the answers. They wouldn't listen to me, to how I wanted to tackle my situation, they knew best – there was no sensitivity or consideration from them. I don't miss them now; I don't have any affection for them anymore. Aren't friends supposed to be there for you in times of difficulty?

Patient 58 (acu-group): My sex life is over; I bleed when I have sex. My vagina is so dry that I sometimes have trouble walking. My husband and I aren't so close now, I put it down to lack of intimacy. I use oestrogen cream occasionally, but am worried about using the suppositories, I am not supposed to use hormones. There doesn't seem to be any treatment, anyway my male doctor doesn't seem interested.

Patient 47 (Sham group): I feel like an old lady, my body aches and I am stiff when I get up in the mornings or sit for a long time. I am only 47, it makes me wonder what state I will be in, in 20 years' time. I am hoping that things get better when I stop taking tamoxifen. I have put weight on, it seems stupid to complain but 6kg is quite a lot, I don't feel like myself anymore. I look and feel washed out, it is due to lack of sleep, hot flushes kick in at around 4am. I work but do not have any energy left at the end of the day, I have practically no social life now.

Patient 53 (acu-group): I have been diagnosed with rheumatism, but thanks to a daily low dose of cortisone I am almost pain free. The last couple of years have been hard, I still take tamoxifen. Acupuncture was effective; a few months after I finished treatment at the pain clinic I had a slight increase in symptoms, but I am sure stress and the rheumatism provoked them.

I have spent a lot of time thinking. I only work part-time now in a library, but I love it. My life is different but in a lot of ways better than it was before I was struck down by the big C. I don't miss my banking job, or the daily commute, or my business suits and high heels, or hours spent running and lifting weights. The stressed out me is a thing of the past, my children like me better now, I have time for them. What's more, I like myself now; I have discovered a feminine, softer, relaxed side of myself that I am certain goes a long way to controlling the symptoms I have, and keeping me healthy.

10.4. Perspective for future research and practice

Safety data reporting both numbers and severity of AE's in research is often lacking. This could be due to lack of common terminology and definitions. Reporting efficacy of a therapy that may, or may not outweigh AE's, does not provide enough information needed for clinical practice. Reporting and grading systems for AE's, facilitating comparison of therapies, needs to be included in study design and be a prerequisite of ethics committee and publication approval.

Clinical information provided by the systematic review as to severity of AE's of the most commonly used NHD's and AE risk related to dosage, is relevant for any clinician assessing therapy for HF's. This information is particularly valuable as the time period of oestrogen antagonist use increases and women need help to manage long-term HF problems. Clinical options include the administration of NHD's alone, where dose is adjusted to minimalize AE's; or using low dose NHD in combination with other therapies that have no or few adverse effects, e.g. acupuncture. Inadequate management of AE's can lead to oestrogen-antagonist noncompliance [225], a potentially life threatening consequence.

Hot flashes appear to be a long-term problem for breast cancer survivors. According to data from the RCT and follow up, acupuncture reduces the number of HF's and appears to have long-term effect. Research has indicated that AE's due to acupuncture are negligible or few, if a qualified therapist performs the treatment, indicating that acupuncture is a low risk therapy [187]. Larger studies need to be carried out to confirm our results, in which WSR design can be implemented. Suggestions for design improvements include larger sample sizes, recording values and changes in AE's and BMI, follow-up at 3,6 and 12 months' post-treatment. Also, the use of surveys to access higher numbers of women regarding long-term qualitative information, where open ended questions allow participants to relay subjective information.

Acupuncture treatment based on our results can easily be included in clinical practice either as an individual treatment or in combination with low-dose NHD's. Treatment is cheap, quick and relatively short-term, it can be administered in an out-patient setting and patients appear to be highly motivated. Since new guidelines for the use of oestrogen antagonists in ER+ breast cancer suggests the extension of such therapy for up to 10 years, effective treatment strategies to treat HT and other menopausal-type symptoms need to be confirmed and/or developed.

10.5. The following methodological approaches are discussed in the individual papers:

1.**Bias** is a consideration in any type of research, and some degree of bias is nearly always present in a research study. Bias is defined as any tendency preventing unprejudiced consideration of a question [226]. In research, bias occurs when a systematic error is introduced into sampling or testing, by selecting or encouraging one outcome or answer over others [227]. Bias can occur at any phase of research, including study design, data collection, data analysis and publication.
2.**Reliability** is defined as: a measure of the consistency of measurement when repeated over time to produce equivalent or highly similar results on repeated administrations [227]. In other words, an investigation must be repeatable under the same conditions and generate the same results. Reliability is a necessary ingredient for determining overall validity, enhancing the strength of the results.
3.**Validity** is an estimate of the accuracy of measurement methods or study results [205]. To be internally valid the design and conduct of an RCT must eliminate the possibility of bias. Internal validity is defined as the extent to which study methods are consistent, providing results that are unbiased and give an accurate estimate of the effects associated with the intervention [228]. Types of internal validity include face, content, criterion and construct validity. External validity is defined as the extent to which the results from a study is representative of actual practice [205].
4.**Generalizability** indicates whether results for one population are applicable for other populations. [205].

10.6. Methodological aspects Paper I

Research Project: A systematic review with a clear objective and defined eligibility criteria was added to this research plan after the other studies (Paper II-IV). The PICO format (see search string figure) was used to perform a systematic search in order to identify studies that met the eligibility criteria. Both authors performed searches and assessed the studies. To assess the validity of the RCT's included, a methodological quality assessment table was created. The results of the review confirm the need to investigate the efficacy of other types of therapies where AE's are less problematic than those related to NHD's, for HF symptoms in breast cancer survivors. Investigations concerning acupuncture therapy for this patient category suffering from HF's are presented in Papers II-IV.

Terminology: Finding terms for harmful effects of drugs or therapies provides some problems. In everyday language an adverse effect to a drug is often called a side-effect, indeed this term is regularly used in published medical research articles when unwanted or harmful events are reported. WHO defines a side-effect as being *related to the pharmacological properties of the drug* [229], a definition which includes both beneficial and harmful effects, which may or may not occur through the pharmacological action for which the drug is being used. A toxic effect is often incorrectly used instead of adverse effect. It describes an exaggeration of the desired therapeutic effect, which is not common at normal doses; a toxic effect is always dose related. A term for a negative harmful effect which is not an exaggeration of a therapeutic effects is an adverse drug reaction, that indicates a response by a patient that WHO defines as *a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function* [229]. This definition eliminates the beneficial effects included in the term side-effects, the term adverse effect or reaction specifically targets negative responses.

Lack of common terminology and definitions for AE's creates problems in reporting both numbers and severity of AE's. Also, if the reporting of AE's does not fall within guidelines for reporting clinical trials, AE information may be lacking, making the comparison between studies difficult.

Most RCT's investigate efficacy, however efficacy of a therapy may not outweigh AE's, possibly affecting compliance. Reporting systems should record symptom patterns at baseline before intervention implementation, report AE's separately for intervention and control groups, report number of AE's and the number of patients experiencing them, and lastly apply a grading system that categorize AE according to severity.

Internal validity: *Face validity* is the extent to which a method measures according to the intentions [205]. Face validity was secured by the following methods: 1. performing a systematic search for

relevant RCT's using the PICO system 2. the use of the Cochrane Handbook of Systematic Reviews and Interventions [230] for methodological assessment, 3. the use of the CTCAE grading system [231] to grade severity of adverse effects, and 4. by performing a meta-analysis. These methods were used with the intention of answering a research question *What is the frequency and severity of adverse effects (AE) of non-hormonal drugs (NHD) for hot flashes in breast cancer survivors compared to controls?*

Content validity is the extent to which the questionnaire items cover the area of interest, or the extent to which a measure adequately and comprehensively measures what it claims to be measuring [205]. The CTCAE grading system provided standardization and consistency of AE risk related to treatment.

Construct validity expresses an agreement with other tests available [205]. To our knowledge this is the first systematic review examining AE's due to NHD's as a primary outcome. Guidelines from Cochrane Handbook for Systematic Reviews of Interventions were followed regarding the search for studies, selection and collection of data, assessing risk bias, analysing data, performing the meta-analysis, presenting a summary of results in a table, interpreting results and drawing conclusions. Review Manager 5 (RevMan 5) software was used to perform the meta-analysis. This validated data program has been developed to enable Cochrane contributors to meet the demands of producing high quality systematic reviews for publication.

External Validity: Outcomes of Paper I are externally valid providing information as to severity of adverse effects attributed to the three different drugs reviewed and degree of severity related to dose. This information is a valuable clinical tool for clinicians helping women manage HF problems, where adequate management may contribute to increased oestrogen antagonist compliance. Clinical implications of the findings presented in the systematic review provide information relevant to clinicians about the use of 3 NHD's, including which AE's are common and the severity of AE's relative to drug dosage.

Reliability: Recommendations from the Cochrane handbook were diligently followed when methodologically assessing the RCT's. Both authors were involved in this process, any disagreements were settled by discussion. Authors of the included studies were contacted when information in the publications was unclear. The Reviewman five computer program, a reliable measuring instrument was used to perform meta-analysis. An example of the search string is included, showing key words and mesh terms, facilitating the repetition of this systematic review.

Supplementary data: String search example. Table 2

History

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Search	Add to builder	Query	Items found	Time
#13	Add	Search **#10 AND #11** Filters: **published in the last 5 years**	6	14:51:42
#12	Add	Search **#10 AND #11**	20	14:50:51
#11	Add	Search **#6 AND #9**	2699	14:48:52
#10	Add	Search **#3 AND #6**	74	14:48:05
#9	Add	Search **#7 OR #8**	579601	14:40:57
#8	Add	Search **assessment, risk[MeSH Terms]**	195361	14:38:05
#7	Add	Search **(adverse effect*[Title/Abstract] OR adverse event*[Title/Abstract] OR side effect* [Title/Abstract])**	391767	14:34:29
#6	Add	Search **#4 OR #5**	21670	14:28:07
#5	Add	Search **clonidine[MeSH Terms]**	12703	14:27:30
#4	Add	Search **(clonidine[Title/Abstract] OR Gabapentin[Title/Abstract])**	18316	14:26:46
#3	Add	Search **#1 OR #2**	23488	14:25:09
#2	Add	Search **acupuncture therapy[MeSH Terms]**	18823	14:23:00
#1	Add	Search **(acupuncture[Title/Abstract] OR electroacupuncture[Title/Abstract])**	18610	14:21:10

10.7. Methodological aspects Paper II

Sample: Women were recruited for the study from the hospital breast centre, where women operated for breast cancer attended for post-operative controls. Information leaflets concerning the study were available in the waiting room. Women complaining of hot flashes were given both verbal and written information about the study by a hospital oncology nurse or doctor.
Patients were not eligible to participate in the study if they presently or previously had received any type of acupuncture treatment. Women who had previously, or were presently treated for hot flashes either with medication or CAM therapies were excluded. All medication and treatment for unrelated health issues was allowed.
Women with serious systemic or psychological conditions were excluded, the consultant at the breast centre was responsible for medically assessing patients regarding endocrine, vascular and psychological disorders. Regarding blood pressure, a limit of diastolic pressure over 95mg Hg was implemented. The oncology consultant at the breast centre was responsible for assessing eligibility criteria and referring potential interested participants to the study coordinator, who double-checked for eligibility. Sixty potential participants received an invitation to the study, detailed study information and a consent form. Of these, 59 subjects were randomized to acupuncture and sham acupuncture (control group).

Internal Validity: *Face validity* was secured by using weekly HF diaries to measure number of HF's, and KI to measure menopausal symptoms. These methods were chosen in order to answer to the main research questions: *can acupuncture treatment reduce the number of hot flashes and improve health-related QoL in women operated for breast cancer, medicated with tamoxifen?* These methods were considered highly relevant for the purpose of the study.
Content validity: In this study a validated KI was used to record the severity of menopausal-related symptoms. The concept of content validity was not totally fulfilled using this method, apart from depression there are no psychometric parameters, also recordings for sexual difficulties are lacking.
Criterion validity expresses an agreement with a gold standard [205]. There is a lack of questionnaires recording menopausal symptoms specifically aimed at breast cancer patients. Validated questionnaires used for women in this category are based on menopausal symptoms for healthy women. Alternatives for recording symptoms related to menopause are discussed further in Paper III.
Construct validity: KI is a validated index that has been used extensively in studies investigating HF's in menopause and in 2 other RCT's investigating acupuncture for HF in breast cancer survivors. Strict inclusion and exclusion criteria also strengthened internal validity.

Bias: A random sample, based on the belief that the sample represents the background population was used [227]. Patients were physician referred, some women having seen study information posters in the waiting room at the hospital breast centre expressed a wish to participate, and others when complaining about HF's were referred by a consultant. Both approaches to referral are possible sources of selection bias, and are therefore a threat to validity. Patients expressing interest in the study may have a favourable attitude to acupuncture and the consultant may have referred patients that he felt were motivated for such treatment. This may have resulted in an overestimation of treatment results in both the acupuncture and the sham groups.

Serious bias during group allocation was avoided by a careful randomization process. A *sealed envelope technique* was employed, whereby patients chose an envelope containing treatment allocation numbers from a black plastic bin bag. The numbers in the sealed envelopes randomly allocated patients to intervention groups, where 1 represented the sham group and 2 represented the acupuncture group. The randomization process was managed by a secretary with no knowledge of what the numbers inside the envelopes represented, the sealed envelopes were made of dense brown paper. The participants were instructed to give their chosen envelope to the therapist, who, depending on the number inside the envelope delegated the study participant to either acupuncture if the envelope contained a number 2, or sham if the envelope contained a number 1. Participants were not made aware as to their delegated group, or what the numbers represented. Treatment was initiated within 14 days after referral for all patients. All the participants met with the study coordinator/secretary at baseline, at the end of the 10-week treatment period and after a further 12 weeks.

Further, bias was minimalized by patient blinding as to the type of treatment they received, and use of a secretary in the blinding process who collected HF diaries and KI questionnaires at base-line, end of treatment and after 3 months.

Inclusion criteria demanded that patients were finished with chemo and radiation therapy, but did not relate these treatments to group distribution or outcomes. If chemotherapy influences weight gain, and weight gain in turn influences HF frequency, an uneven distribution of post chemotherapy patients to acupuncture or sham groups could have influenced results. This point should be considered in future studies.

Bias connected to different treatment techniques used on the two groups is an issue. Patients in the acupuncture group experienced a manually stimulated needle sensation at all acupuncture points twice during each treatment, slightly increasing the amount of treatment time and therapist-patient contact, possibly increasing placebo effects. Gently holding the needle shaft for a comparable amount of time

in the sham group at the start and end of each treatment may have gone some way to compensate for this problem. The risk of bias may have been increased by the use of the main researcher also administering treatment. However, the candidate's supervisor and co-author, a surgeon with no knowledge of acupuncture acted as a coordinator, relaying results accumulated by the study secretary to the statistician. He also assisted in the interpreting of statistics possibly providing a more objective assessment, thereby reducing bias tendencies.

Information bias may occur when the recall time is long (recall bias). This was not considered an issue in this study where follow-up assessment was undertaken three months' post-treatment.

Reliability: Reliability of the quantitative data acquired by the use of HF diaries in the RCT (Paper I) was totally dependent on the participants remembering to record HF data on the same day each week, how precise they were at counting HF's day and night on that particular day, and weather they recorded their HF number for 3 months' post-treatment, or in fact just made an estimation before delivering HF diaries for inspection. Recording data once a week is less intrusive to everyday life and may be a more reliable method than doing so every day, although repeating the task every day would have created a routine and may have been more reliable for some patients. These methods of collecting data can easily be reproduced and a high response rate made the collection of data simple.

Placebo: Treatment effect in alternative medical studies is rightly or wrongly often considered to be due largely to placebo. Patient interviews in popular media focuses on patient-therapist contact and attention, possibly increasing placebo. In this study women in both groups were allocated approximately equal amounts of therapist contact, which was kept to a minimum; a business-like attitude was adopted by the therapist in an effort to reduce placebo, however other factors possibly influenced treatment outcome. The primary placebo effect explained by Streitberger and Vickers [232] is the patient's belief that the treatment will be effective, that is, patient expectation. Just the knowledge of being treated can be a powerful placebo. Both true and sham acupuncture certainly stimulate patient's expectations and beliefs towards a potentially beneficial treatment, provoking activity in the reward system of the CNS [233]. Such reactions in the CNS indicate that the use of sham used as a control group is imperfect, the use of which possibly fogged the difference between the effects of true acupuncture and control described in this study.

Response rate: The response rate was 100%. There were no drop outs, all patients completed treatment and noted number of hot flashes weekly for up to three months after treatment. This indicates that patients were highly motivated.

External Validity: To be clinically relevant a study must be externally valid; it must be possible to repeat the intervention/s in a specific group, in a defined clinical setting and be applicable to larger populations. Results from this RCT are clinically applicable and highly repeatable. The study took place in a hospital clinical setting, treatment is relatively cheap, takes only 30 minutes, no expensive equipment is needed, and the acupuncture treatment can easily be repeated by any qualified therapist. Also since breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012, of which around 60% are ER+, it follows that a large proportion of women suffer from adverse-effects of oestrogen antagonist therapy, indicating a large patient group and therefore few recruitment difficulties. The outcomes of the RCT demonstrating increasing HF reduction up to 3 months' post-treatment contribute to treatment planning, follow up and relevant information for patients.

Generalizability: Generalization as to whether this type of treatment would be applicable for women of other ethnicities is impossible to predict based on our studies, it however appears to be a valid treatment method for Norwegian women suffering from HF's due to breast cancer treatment. Women included in this trial were medicated with tamoxifen, whether this method of treatment and results are applicable for healthy women suffering from HF's, or indeed breast cancer survivors with HF's due to chemotherapy, oophorectomy or other types of ovarian failure, cannot be answered by this study.

Statistics: No power calculation was performed to determine sample size. When the protocol for this study was written only a few pilot studies had been undertaken concerning the treatment of acupuncture in breast cancer survivors. These studies included 22 [174], and 38 [173] women. RCT's investigating acupuncture for HF in healthy menopausal women included sample sizes of 24, [163], 105, [165] and 29 [166]. Based on these figures we invited 60 women to participate in the study, 59 agreed. In retrospect, it is clear that a sample calculation would have increased precision and minimized possible systematic errors, ensuring that the conclusion about the treatment effect was valid. Statistical analysis was undertaken by an experienced statistician.

Stricta: Adverse effects were not recorded in this study, although they could easily and simply have been reported when patients filled out KI's at the end of treatment, this is a flaw in the design of this project. Reporting systems for AE's need to be systematically implemented also in CAM research. STRICTA guidelines need to include parameters specifically regarding AE's, in line with CONSORT, where a set of 10 specific and comprehensive guidelines regarding AE reporting RCT's is included.

Supplementary data: CI values were not included in the published article. Tables demonstrating 95% CI for HF during the day and night, and for KI scores are shown in the tables below.

Table 3: shows CI comparisons between the two groups at time intervals for HF during the day				
Treatment/time	Mean	Std.Deviation	95% CI Interval Lower Bound	95% CI Interval Upper Bound
Acupuncture 1	9.5	4.9	7.75	11.25
Acu 2	4.7	3.7	3.38	6.02
Acu 3	3.2	2.2	2.41	3.99
Sham 1	12.3	7.3	9.64	14.96
Sham 2	11.7	8.5	8.61	14.79
Sham 3	12.1	8.3	9.08	15.12

Groups: Acupuncture n= 30, Sham n=29

Time 1 = baseline

Time 2 = end of treatment

Time 3 = 3 months' post-treatment

A statistically significant difference between the groups was seen after treatment (time 2) and 3 months later (time 3). Acupuncture vs sham was statistically significant (P <0.001) for both these time points, but not at baseline (time 1), although 95% confidence intervals for the 2 groups overlap slightly at baseline, indicating a trend towards statistical significance.

Table 4: shows CI comparisons between the two groups at time intervals for HF during the night				
Group/Time	Mean	Std Deviation	95% CI Intervals Lower Bound	95% CI Intervals Upper Bound
Acu 1	6.0	4.2	4.5	7.5
Acu 2	2.6	2.0	1.88	3.32
Acu 3	1.7	1.6	1.3	2.27
Sham 1	7.2	5.7	5.13	9.27
Sham 2	5.4	4.4	3.8	7.0
Sham 3	6.1	5.1	4.24	7.96

When the two groups were compared at the different time points a statistically significant difference between the groups was seen after treatment (time 2) acupuncture vs sham P = 0.009 and at 3 months' post-treatment (acupuncture vs sham P < 0.001) but not at baseline (time 1), although as for HF during the day, CI are seen to overlap slightly.

10.8. Methodological Aspects Paper III

A qualitative approach was employed in paper III with the intention of receiving information that could enhance, compliment or even contradict the quantitative data described in Paper II. Information possibly including complex behavioral patterns, attitudes and interactions, useful for clinical decision making and further research [234]. A means of providing wider views of patient outcomes. Physicians and clinical researchers are often unfamiliar with qualitative research and unsure how it relates to their interests in evidence-based medicine. Gilchrist and Engel wrote "qualitative research answers questions for clinicians that quantitative research cannot. These are questions about individuals' motivations, perceptions, expectations, and meaning" [235].

Women provided qualitative information by writing a statement, other methods of gathering qualitative information may have included individual or group interviews. However, gathering qualitative data from women's statement, was the approach feasible within the time and financial frames that we had. Individual interviews would have proved too time consuming with such a large population, we had no experience in interviewing groups. Alternatively, more than one method of gathering information could have been used, as in *methodological triangulation* which involves the use of multiple qualitative and/or quantitative methods of study; e.g. in this study a combination of written statements, individual and group interviews could have been compared, similar results providing an increase in validity. According to *Thurmond* the benefits of triangulation include increasing confidence in research data, creating innovative ways of understanding a phenomenon, revealing unique findings, challenging or integrating theories, and providing a clearer understanding of the problem [236]. These benefits largely result from the diversity and quantity of data that can be used for analysis. Attaining qualitative information by more than one method is more suited to larger studies with an extensive research team, where greater planning and organization is essential.

Role of the researcher: Modern research dismisses the concept of the neutral researcher that does not influence the development of findings and knowledge [237]. This concept is demonstrated by Latour and Woolgar who examined how the daily activity and behaviour of scientists can influence scientific findings and facts even in a laboratory situation [238]. The concept introduces numerous possibilities of bias in this research project considering that the main researcher was involved in design, is an acupuncturist, was responsible for administering treatment and analysing qualitative data. The fact that the main researcher is an acupuncturist indicates a strong sense of engagement in the area of study, obviously believing in the treatment method as an effective tool for reducing HF symptoms, based on experience. This human element cannot be ignored or totally eliminated, however it can be reduced by involving other researchers, supervisors and advisors offering objectivity. The research team in this

project involved a project secretary, a supervisor (surgeon), an oncology nurse, a breast cancer consultant, 2 different statisticians, and 2 co-authors.

The main motivation for the initiation of this project was positive responses from patients and oncology consultants regarding the effect of acupuncture, creating the possibility of bias at this early phase. Malterud suggests identifying and noting initial views and attitudes to a future research project, also reviewing these notes during the research process, as a way of maintaining awareness [210]. Although the protocol for this project was written by the main researcher, a surgeon (supervisor) experienced in research methods, with no knowledge of acupuncture, provided constant feedback and correction. He also acted as a mediator between the study secretary and an experienced statistician.

The main researcher interpreted qualitative but not quantitative results. Qualitative data was also interpreted by an oncology nurse who was blinded to participant identity and previous treatment group. Interpretation of qualitative material includes identifying patterns, finding meanings, themes and categories; elements that are undoubtedly affected by researcher's attitudes and experiences. Also, since patients were aware that the qualitative statement was a follow-up to the RCT they had previously taken part in, and that the main researcher might read the statements, they could have included more positive information than intended. Bias here was reduced by the invitation to write a statement being signed by the project secretary, it could have been further reduced by informing participants that their identification would not be revealed to researchers assessing the statements.

Writing the articles for publication based on the research project also provided elements of possible bias. It is possible that the main researcher used phrases and descriptions that can be considered positive for acupuncture. Despite the input and supervision of the co-author there is also a risk that the conclusions were weighted too heavily towards acupuncture treatment.

Sample: Our sample was taken from 59 women originally included in the RCT, and a further 31 patients included at a later date. The consultant or oncology nurse at the hospital breast centre recruited these 31-breast cancer operated women who complained of HF problems due to tamoxifen use for the study, after assessing inclusion/exclusion eligibility. The women were comparable to the participants originally included in baseline values of mean numbers of hot flashes day and night, and total KI score; the values of which were not significantly different for the original 59 women. The newly included 31 women had been randomized to receive acupuncture or sham treatment and had received treatment and follow up according to the protocol from the original RCT. Eight patients had died 2 years' post-treatment, 82 women who were still blind as to their acupuncture treatment in the RCT received an invitation to take part and a qualitative research question by post. A total of 61 women responded. The length of the different statements varied from 0-364 words. One woman

returned a statement with only a smiley face, but no words. We counted this as response, facial expressions are after all used in texting, in online chat conversation and in e-mails, and are a part of current popular culture. The smiley face was regarded as a positive, though general response. Patients were invited to fill out a KI index as part of the long-term RCT (Paper IV) follow-up 6 to 8 weeks after returning statements. The intention behind this delay was an attempt at receiving as much information as possible, for example some participants may have considered it unnecessary to give information about HF symptoms as part of their qualitative statement if they had already indicated a HF severity score in the KI.

Internal Validity: Validity can be regarded as trustworthiness, rigor and quality in qualitative research. These concepts are not as easily defined or implemented in qualitative research as they are in quantitative studies. However, in order to achieve validity and reliability in qualitative research study design has to reduce bias. Rigorous systems were implemented during study administration, including the use of a secretary who implemented patient coding and blinding of the assessors.
Face validity: The qualitative question was designed to stimulate diverse subjective information from the participants, as opposed to influencing them as to statement content, with the intention of gaining insights into QoL and experiences after breast cancer treatment.
Content validity: The area of interest was purposely only loosely defined by the qualitative research question, with the specific intention of not influencing the women as to what they wrote and the length of their statements.
Construct validity: Statements provided information about symptoms commonly included in menopausal indexes including HF, insomnia, cognitive fogginess, sexual and emotional problems. However, they also unexpectedly wrote about other issues such as their families, work and situation acceptance.

Reliability: The design for this qualitative research is highly repeatable: The women wrote statements in the comfort of their own home. A research question was sent in the post and a statement returned the same way, and only two researchers were needed to assess content.

Response rate: A response rate of 75%, can be considered high considering that this was a long-term follow up, 2 years' post-treatment. This high response rate may have been due to the motivation of participants who considered being part of a research study as important. Or, that the content and length of the statement was not predetermined and therefore up to each participant. Or, the fact that the research question was accompanied by a self-stamped addressed envelope, making it easy and cheap for respondents return answers. Another motivational element may have been a need to commit thoughts and feelings to paper, the feeling that someone was interested in their well-being.

Data analysis: Validity of qualitative methodology has been identified as fundamental to understand and describe the philosophical basis, key treatment components and contextual frameworks of CAM modalities [80,211,221].

We would have liked to issue a qualitative question at 6 and 12 months' post-treatment, but due to capacity problems this was only done 2 years' post-treatment. Information bias may have occurred due to a long recall time (*recall bias*). Earlier follow-up could have provided more accurate information on individual symptom changes and broader subjective information, which may be clinically relevant and would have strengthened *face validity*. Also, earlier and more frequent follow-up points would have increased *content validity* by more substantially covering the research area and period of interest.

Content analysis was performed by 2 analysts who carefully read and re-read the women's statements five times (at least once out loud). The order of statement reading was random, neither patient identity or previous type of treatment was revealed to the analysts, patients were coded. Codes were not related to any information about the individual and therefore could not be used for identification. The alphabet was used to code patients, patients were coded consequently according to the time taken to return statements; for example, the first statement to be returned was coded as A, the second B etc. When all the letters of the alphabet had been used the project secretary coded consecutive women AA, BB, then AAA etc. Initially the statement material was organized into three main areas chosen by the assessors, these were diagnosis, treatments and daily life. Each assessor further refined these areas individually, then developed suggestions for categories after reading and re-reading the statements. These categories were not defined beforehand, they were based on repetition of terms, phrases and themes. Each statement was then discussed to ensure that the *meaning* of the statement was understood and any ambiguity resolved, categories were agreed, increasing *content validity.* Seven categories were developed and are presented under *supplementary data* below. Examples of statements from the women were limited in the published paper due to editorial limitations.

Limitations: According to the number of favorable or negative statements concerning the different categories, the authors attempted to compare the two groups of women; that is, those previously treated with acupuncture and those previously treated with sham. A more favorable outcome was perceived for the acupuncture group in relation to HF's 2 years after finishing treatment. However, this study brings attention to the problems, challenges and coping mechanisms facing women after breast cancer treatments. In retrospect, however, the authors consider that comparison of the two groups related to previous acupuncture concerning subjective information is unreliable, and should have been presented only as a description of life experiences after breast cancer. Interesting elements concerning illness, everyday life and coping mechanisms were presented by the women in the study. A more appropriate title for this study may have been *Life after breast cancer therapy, women's experiences. A qualitative study.*

External Validity and Generalizability: Emotions and perspectives from both participants and researchers are considered undesirable biases in quantitative research, the same elements are considered essential and inevitable, in qualitative research. Statements gave information that is important for therapists, patients and their families, providing a platform for understanding the issues breast cancer women face, regarding both physical and emotional issues. The simple method of obtaining statements chosen for this study is highly applicable for other groups suffering from menopausal symptoms. Qualitative information obtained from this study may provide knowledge for the planning of future studies, both quantitative and qualitative. However, generalizability, indicating whether results for the population in this study is applicable for other populations, for example healthy women suffering from HF's and women with other types of cancer diagnoses is impossible to answer from data obtained in this study.

Supplementary data not included in the published paper:

Categories were developed from groups making similar statements. Categories included:

1. Hot flashes, similar statements described the development of HF, factors affecting HF, accompanying symptoms and management of HF. Also, whether acupuncture had been effective.

2. Adverse effects due to oestrogen antagonist medication. Apart from HF symptoms, tiredness, sleep deprivation and muscle/joint pain were frequently mentioned. The word exhausted featured in many of the women's statements.

3. How their breast cancer tumour was discovered. Their immediate reaction.

4. Hospitalization and adjuvant treatments. Nearly all were pleased.

5. Vaginal dryness. Loss of sexual activity was often mentioned.

6. Work and social activity**.** Topics included whether and how they tackled work and social life.

7. Acceptance. Women wrote about coming to terms with breast cancer, adjusting their lives according to physical and mental symptoms, and optimism for the future.

10.9. Methodological aspects Paper IV

Sample: This study is a follow up of the original RCT (Paper 2), it investigates long term effects of acupuncture for HF in women with breast cancer. Our sample was taken from 59 women originally included in the RCT, and a further 29 patients included at a later date, as described in Paper III. Sixty-one women returned a KI by post.

Measurements: Previously called the Blatt-Kupperman menopausal index, the KI has been used widely in studies of climacteric symptoms. The original index was derived from clinical experience in New York in the 1950s, and was a simple list of a physicians' summary of menopausal symptoms, assessed by an index.

QoL outcomes usually focus on health-related aspects, the KI used in this study uses a set number of outcomes that may or may not represent values important to individual patients. The Kupperman Menopausal Index has been modelled on health-related issues suffered by healthy menopausal women, and therefore may not be ideal for measuring menopausal symptoms in breast cancer survivors. Menopausal symptoms in healthy women often present gradually over time, menopausal-type symptoms suffered by breast cancer patients often have a sudden onset. Symptoms may be due to dysfunction of the ovaries in pre-and peri menopausal women receiving chemotherapy, a sudden withdrawal of hormone replacement medication in post- menopausal women, and/or chemically induced by oestrogen antagonist medication.

A variety of emotional factors possibly affect QoL in these women including shock, fear, stress and sadness associated with the contracture of a serious disease. Stress and uncertainty of primary and adjuvant treatments, and an uncertain future almost certainly play a role in QoL and well-being, possibly affecting KI score. Some or all of the afore named symptoms and elements may or may not be present in women with breast cancer complaining of HF's.

Of the 11 symptoms presented in the KI, ten are predetermined, only one gives these women an opportunity to record a symptom that is subjectively personally distressing. All symptoms are given equal weight in the score system, patients score 0,1,2 or 3, according to severity. Over 50% of the women included in our study mentioned sleep problems in their statements in the qualitative study (Paper III), if this and possibly other symptoms are considered so bothersome, they could have been accredited with a higher score. This point should be a consideration in the development of future Qol indexes related to menopausal symptoms in breast cancer patients.

Apart from depression, KI does not consider psychological, emotional, or practical problems. KI does little to assess and record the gravity of such problems and their development, progress, or remittance. Emotional problems often influence sleep, potentially indirectly affecting other symptoms and their scores featured on the KI. The addition of an index such as the Psychological General Well-Being Index (PGWB) would have provided increased insight into patient's psychological well-being. The PGWB index includes 22 items, it measures components of psychological well-being such as anxiety, positive well-being, self-control, depression, general health and vitality; and in its short version only takes 5 minutes to fill out, and therefore could have been used as well as the KI.

Other ways of measuring QoL related to menopausal symptoms in this patient category include the Menopause Rating Scale (MRS) and the short form-36 (SF-36). These scales were compared to KI and evaluated as to applicability and reliability in a study of 306 healthy menopausal women. Results showed that the MRS correlates best with dimensions of the SF-36. Further, that MRS is a valuable modern tool for the assessment of menopausal complaints, combining excellent applicability and good reliability, thereby providing an adequate diagnostic instrument for menopausal quality of life that is highly relevant for women in the menopausal transition [239]. Another suitable alternative to the KI index that includes psychological parameters, with optional subscales for menstrual problems and sexual difficulties is the Women's Health Questionnaire (WHQ). However, the inclusion of 30 items makes it considerably longer than KI, also its subsections are more complex, possibly reducing compliance.

Internal Validity: *Face validity* was secured by using KI to measure menopausal symptoms at a long-term time point, in order to gain quantitative information regarding health-related QoL in breast cancer survivors, two years after receiving acupuncture treatment for HF. The validated KI was used to record the severity of menopausal-related symptoms by providing a total score. Index scores were compared to 3 earlier time point scores reported in paper II. In order to gain information regarding psychological and sexual problems an appropriate addition, e.g. MRS or WHQ would have increased *content validity*.

Different types of menopausal indexes have been used in studies regarding both healthy menopausal and breast cancer women, including KI. More individual studies need to be initiated in order for systematic reviews to be able to conclude which type of index is most suited to assessing menopausal symptoms in breast cancer women, indicating a gold standard that can be used to secure *criterion validity.* However, the extensive use of the KI index in investigations of menopausal symptoms regarding healthy women goes some way to securing *construct validity*, even though in this study it is used for breast cancer survivors.

Response rate: A response rate of 76% was achieved, this rate can be considered high considering that this was a long-term follow up, 2 years' post treatment. As discussed in Paper III this may be due to motivation of participants, and the easy and cheap facilitation of KI return by including a self-stamped addressed envelope. The KI is quick to fill out, also, the participants had previously filled out a KI at base-line, end of treatment and at 3 months' post-treatment, making the task of filling the index out familiar, easy and simple.

Bias: When this study was conducted, international guidelines dictated that post-menopausal women switch from tamoxifen to an aromatase antagonist after 2 years. Twenty-eight women (12 in the acupuncture group and 15 in the control group) had, during the 2-year gap between the time they finished treatment and the time they filled out the KI, switched to an aromatase antagonist. Adverse effects of the oestrogen antagonist tamoxifen and aromatase inhibitors are similar, however several studies have reported that hot flashes are more bothersome for patients taking tamoxifen, and joint aches are more prevalent in AI patients [16,17,18]. This invites speculation that HF's may have been reduced just by switching from tamoxifen to AI, similarly joint pains due to AI medications may have increased during the 24-month period. Both values would affect the total KI in both groups. We did not investigate changes in individual symptoms recorded in KI, only total scores at 24 months' post-treatment. Further research into the severity of individual symptoms may have given a more precise picture of which symptoms increased or decreased during the follow up periods, providing more detailed information.

Patients filled the KI out alone to avoid the possibility of them responding in a manner they might have considered as positive to the investigator, reducing possible response bias. KI's were returned by post, bias was further reduced by patient identity being coded, a nurse unaware of patient identity was responsible for adding total KI scores.

Statistics: Sample-size calculations were not performed, such calculations could have been based on the RCT, statistical software such as NCSS (PASS 14) could have been used, this is a serious limitation in this study. The number of participants included was based on the sample number in the RCT. Two sets of data with a different number of time points were analysed, for the original 59 women included in the RCT and for the final 61 women. Confidence intervals show a slight overlap at time one for both groups considering all the 61 patients, indicating variations at base-line. These variations were not statistically significant, however with so few points statistical significance is hard to achieve. This is also true when data for the original 59 women was analysed. Mixed models was used to compensate for these variations at baseline. KI scores measuring menopausal related health for

all 61 participants did not demonstrate at statistically significant difference between the groups after 2 years. However, if the trajectories of the 2 groups for all 61 patients are considered, and base-line values are compared to time 4, a border-line trend towards statistical significance between the groups can be seen. This result was omitted in the published paper.

External validity and generalizability: this long-term investigation as a follow up to a RCT is clinically applicable and highly repeatable. Since new guidelines for the use of oestrogen antagonists in ER+ breast cancer suggests the extension of oestrogen antagonist therapy for up to 10 years, long-term investigations like this are needed to provide information regarding health and QoL issues, with a view to developing treatment strategies. Future research regarding long term follow up should consider surveys as a method of increasing sample sizes.

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PAPER I

ADVERSE EFFECTS OF NON-HORMONAL DRUGS USED TO TREAT HOT FLASHES IN BREAST CANCER SURVIVORS. A SYSTEMATIC REVIEW

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REVIEW

Adverse effects of non-hormonal pharmacological interventions in breast cancer survivors, suffering from hot flashes: A systematic review and meta-analysis

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Abstract
Purpose To access frequency and severity of adverse effects (AE) of non-hormonal drugs (NHD) for hot flashes in breast cancer survivors compared to controls and analyze adverse-effect risk by reviewing published randomized trials.
Methods Cochrane Central Register for Controlled Trials, Embase, Medline, PsycINFO and PubMed databases were searched. Trials were included where participants were survivors of breast cancer suffering from hot flashes, treatment included self-administered venlafaxine, gabapentin or clonidine, and AE were reported. AE frequency and severity were graded. A meta-analysis of ten trials with sub-group analyses was conducted.
Results Forty-nine studies were identified, and 12 were included. A total of 1467 participants experienced 772 adverse effects, 81 % ($n = 627$) in the treatment group and 19 % ($n = 145$) in the control group. Sixty-seven percent of AE was graded as mild and 33 % as moderate. The frequency of AE for NHD was overall significant compared to placebo. Sub-group analysis indicated that AE frequency and severity increased at higher doses of venlafaxine and gabapentin compared to placebo.
Conclusion The odds for experiencing AE was significantly higher in patients randomized to high-dose NHD than those randomized to controls, including placebo, low-dose medication and acupuncture. These therapies should be considered as a potential treatment alternative.

Keywords Adverse effects · Non-hormonal drugs · Breast cancer · Hot flashes

Introduction

Breast cancer is the second most common cancer in the world and the most frequent cancer among women. 1.67 million new cases were diagnosed in 2012 [1].

Treatment of breast cancer includes surgery, chemotherapy, radiation and endocrine therapy. Fifty percent of women diagnosed with breast cancer have a tumour that is oestrogen receptor positive, and consequently, they are offered hormone-suppression treatment lasting for at least five years [2]. Tamoxifen is an oestrogen receptor modulator which blocks the effect of oestrogen in breast tissue. It is indicated for use in premenopausal women and, as an initial treatment, in post-menopausal women. Aromatase inhibitors are recommended only for post-menopausal women, in whom the main source of oestrogen comes from the conversion of testosterone to estradiol, facilitated by the aromatase enzyme.

A common adverse effect of oestrogen-antagonist therapy is hot flashes. Up to 80 % of women medicated with tamoxifen suffer from hot flashes, 30 % of which rate them as severe [3, 4]. Severe hot flash problems can result in women stopping potentially lifesaving oestrogen-antagonist treatments; up to 25 % of women with breast cancer do not adhere to adjuvant oestrogen-antagonist therapy [5]. Consequently, better management of adverse effects

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including hot flashes is important for increasing compliance and achieving optimal results.

Self-administered treatments for hot flash problems such as drugs, creams or patches are the easiest and most practical therapy for most women. The most effective treatment is oestrogen therapy, but it is not recommended in women with breast cancer, and no safe conclusions regarding the use of progesterone are available [6]. Sixty percent of breast cancer tumours are oestrogen and/or progesterone receptor positive and therefore responsive to hormonal influence [7]. Contraindications surrounding hormonal therapies for the treatment of menopausal symptoms in breast cancer survivors have provoked increased use of non-hormonal drugs. Non-hormonal treatment includes therapies that do not affect oestrogen or progesterone production or action [8]. Self-administered therapies including anti-hypertensive medications, selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), and anticonvulsant medicines have been studied for hot flash symptoms and increasingly used during the last decade. The most commonly used drugs in this category include venlafaxine, a selective serotonin reuptake inhibitor; the anticonvulsant gabapentin; and clonidine a centrally acting antiadrenergic agent, commonly used to control hypertension.

Randomized controlled trials (RCT) of drugs in these categories are limited; however, two systematic reviews have reported on the efficacy of these three drugs as a treatment for hot flashes in both breast cancer survivors and healthy menopausal women [8, 9]. Paroxetine and Fluoxetine, both being SSRIs, have also shown efficacy in the reduction of hot flashes [10–13]; however, these drugs interfere with the metabolization of tamoxifen to endoxifen [10, 14] and are therefore contraindicated in women using tamoxifen.

Various complementary and alternative therapies have been studied as a treatment for HF in breast cancer patients. Vitamin E has not demonstrated efficacy [8], while phytoestrogens possibly involve oestrogenic influence and are therefore not recommended for women with breast cancer [15]. Controversy around the safety of Cimicifuga Racemosa (Black Cohosh) as a treatment for menopausal symptoms exists because of its purported oestrogenic activity. A systematic review of 26 articles concluded that current evidence does not support an association between black cohosh and increased risk of breast cancer, and those conflicting but promising results for the reduction of HF in breast cancer patients warrant the need for further research [16]. Cognitive behavioural therapy trials [17, 18] and relaxation [19] have shown modest, short-term effect. Two trials investigating the effect of homoeopathy versus placebo [8], neither were RCT, found a statistically significant improvement in HF frequency for homoeopathy over placebo. Acupuncture was as effective as venlafaxine in a trial comparing these two interventions. However, 18 incidences of adverse effects were recorded in the venlafaxine group, whereas the acupuncture group experienced no adverse effects [20]. A systematic review of acupuncture to control hot flashes, which included 8 breast cancer studies ($n = 474$), concluded that the current level of evidence is insufficient to support the treatment of hot flashes [21].

The importance of this review

The efficacy and adverse-effect profiles of hot flash treatment vary in non-hormonal pharmacological interventions. Comparing studies of interventions in this category may provide an indication as to whether treatment effect outweighs adverse effects in breast cancer survivors. Potential information regarding the tolerability of each drug has direct clinical implications, affecting decision making and compliance.

Aims

The aims of this review are to

1. systematically investigate how adverse effects of the three most commonly used non-hormonal drugs, to treat hot flashes in breast cancer patients, are reported in randomized controlled trials;
2. classify adverse effects and drug-related aggravations according to the Common Terminology Criteria for Adverse Effects (CTCAE) [22] and
3. perform a meta-analysis to evaluate the risk of adverse effects for patients pharmacologically managing their hot flashes with non-hormonal self-administered therapy, compared to different controls.

Terminology

If a substance is capable of producing a therapeutic effect, it can also produce harmful or unwanted effects. Terms used to describe such unwanted effects include side effect, adverse effect, adverse event, adverse reaction and toxic effect [23]. The term *adverse effect* used in this paper is defined by *The European Medicines Agency* [24] as *any untoward medical occurrence in a patient or clinical trial subject administered a medical product.* This term encompasses all unwanted effects, without making assumptions about their mechanism [25].

Methods

Search methods for identification of studies

The focus question was: *Are the most commonly used non-hormonal drugs for hot flashes in breast cancer patients associated with adverse effects?* The four elements from PICO were used when searching for relevant articles:

1. Population: Patients with breast cancer, suffering from hot flashes.
2. Intervention: Non-hormonal self-administered pharmacological therapies, including venlafaxine, gabapentin and clonidine.
3. Comparison: Placebo, other non-hormonal drugs, conventional medical therapies, CAM, waiting list and usual care.
4. Outcome: Adverse effects, adverse events, adverse reactions, tolerability, side effects and toxicity.

The following electronic databases were searched with no language, publication, or time restrictions: Cochrane Central Register for Controlled Trials (Central) in the Cochrane library, Embase, Medline, PsycINFO and PubMed.

Titles and abstracts were identified through the search strategy. If no abstract was available, the full text paper was obtained for inspection. Both authors did the searches, read the articles and extracted the data (search strings are attached in the appendix). Grey literature was searched in order to find possibly missed articles through electronic searches. References of all retrieved articles and systematic reviews were searched [8, 9, 26–28]. Depending on the database, various combinations of MESH terms and keywords were used. MESH terms included *breast neoplasms, breast cancer, hot flashes, clonidine, adverse effect, adverse drug reaction reporting systems*. The following keywords were applied: *breast cancer, hot flash, hot flush, vasomotor symptom, clonidine, venlafaxine, gabapentin, adverse effect, adverse event and side-effect.*

Inclusion comprised randomized controlled trials that reported adverse effects of treatment. Both parallel group design and cross-over studies were included. Data from cross-over studies were included from both treatment periods, since all cross-over studies specified that there was no cross-over effect.

Data were extracted to give information on the total number of adverse effects and number of patients experiencing the adverse effects. Severity of adverse effects was assessed using the CTCAE grading system and was entirely dependent on the information provided in the articles. The system grades adverse effects from 1 to 5, where 1 indicates mild symptoms, 2 moderate symptoms, 3 severe symptoms, 4 life threatening and 5 fatal symptoms. When summarizing the data, the total number of adverse effects was counted, regardless of the number of participants experiencing them. Both authors categorized and graded the data. Lack of consensus was settled by discussion.

A methodological assessment including risk of bias was made by both authors using criteria from the Cochrane Handbook of Systematic Reviews and Interventions [29]. The trials were rated as follows:

A grading of "A" indicates a RCT of high quality with low risk of bias with adequate measures to conceal allocation, detailed randomization description and implementation of the intention to treat principle.

Grade "B" was used when method of allocation concealment was not described, or was unclear, creating a moderate risk of bias.

A grade "C" was used when the method of allocation was not concealed; such trials were excluded because of high risk of bias.

Extracted data included number of patients randomized to each group, number of dropouts, use of power calculation, whether the intention to treat principle was followed, intervention (including dose), duration of intervention, main findings and funding. The authors of retrieved articles were contacted when in doubt of or there is a lack of information in the publications (Table 1).

Meta-analysis

Study populations were divided into groups experiencing adverse effects versus those with no adverse effects in both treatment and control groups. Homogenous study designs including participants, interventions, control groups and outcome measures were combined and a meta-analysis performed; $P < 0.10$ defined significant heterogeneity. Odds ratios and 95 % confidence intervals were calculated from the number of patients experiencing adverse effects in each group based on the total number of patients randomized to either treatment or control group. Studies with no adverse effects either in one or both groups were given an added continuity correction of 0.5 in order to estimate a valid approximation of odds ratio [30]. Data regarding the adverse effect in a trial carried out by Boekhout, which compared venlafaxine and clonidine to placebo, were found to be identical for both the venlafaxine and clonidine groups [31]. These data were included only once in the meta-analysis to avoid overrepresentation of adverse effects in the intervention group. Three studies comparing different drug dosages to placebo were divided according to high and low dosage in the meta-analysis [32–34]. Based on the total number of participants randomized to the treatment or control group, odds ratios and 95 % confidence intervals were calculated from the number of

Table 1 Assessment of the methodological quality of the randomized controlled trials

Study ID	Indication	Participants		Dropout		PC/ITT analyses	Methodological assessment	Intervention	Duration of treatment	Main findings	Funding
		Treatment	*Control*	*Treatment*	*Control*		*Cochrane Handbook*	*Treatment vs Control*			
Buijs [36]	Venlafaxine versus clonidine for hot flashes in women with breast cancer	Venlafaxine/ clonidine $n = 30$	Clonidine/ venlafaxine $n = 30$	Venlafaxine period $n = 15$	Clonidine period	Yes/Yes	A-clear	Venlafaxine (75 mg × 1) Clonidine (0 05 mg x 2) Cross-over design Randomized Double blind	18 weeks - 2 × 8 weeks with 2 week wash out period	Venlafaxine and clonidine were equally effective in hot flash reduction Main reasons for discontinuation were adverse effects, which were worse with venlafaxine	NR
Biglia [39]	Gabapentin versus vitamin E for hot flashes and sleep quality in breast cancer patients	Gabapentin $n = 60$	Vitamin E $n = 55$	29	25	Yes/Yes	B-unclear. No allocation concealment or blinding	Gabapentin 900 mg/day vs Vitamin E 800 IU/day. Parallel group design, randomized but not blinded	12 weeks + 12 week obs.	Gabapentin (900 mg) significantly reduced hot flash frequency and score, a non-significant reduction was seen in the vitamin E group	Not funded
Boekhout [31]	Management of hot flashes in breast cancer patients with venlafaxine and clonidine	Venlafaxine $n = 41$ Clonidine $n = 41$	Placebo $n = 20$	Venlafaxine $n = 6$ Clonidine $n = 13$		Yes/Yes	A-clear	Venlafaxine 75 mg/day vs Clonidine 0.1 mg/day vs placebo Parallel group design. Stratified randomization. Double blind	12 weeks	Venlafaxine and clonidine are effective treatments for hot flashes in breast cancer patients. A more immediate reduction was seen with venlafaxine, however hot flash scores were lower with clonidine at week 12	NR

Table 1 continued

Study ID	Indication	Participants		Dropout		PC/ITT analyses	Methodological assessment *Cochrane Handbook*	Intervention *Treatment vs Control*	Duration of treatment	Main findings	Funding
		Treatment	*Control*	*Treatment*	*Control*						
Carpenter [32]	Dose-related efficacy of venlafaxine in the treatment of hot flashes in breast cancer patients	Venlafaxine 37.5/placebo $n = 64$.	Venlafaxine 75 mg/placebo $n = 20$	21	3	Yes/Yes	A-clear	Venlafaxine low and high-dose groups randomized to 2 sequences each, 6 weeks treatment then 6 weeks placebo or visa versa. Cross-over design, randomized, double blind	12 weeks	Venlafaxine resulted in modest decreases in hot flashes, only hot flash interference improved at the higher dose. Although adverse effects were mild most women discontinued venlafaxine long-term possibly due to treatments not outweighing benefits	National Institute of Nursing Research. USA
Goldberg [38]	Transdermal clonidine for tamoxifen-induced hot flashes	Clonidine/placebo $n = 55$	Placebo/clonidine $n = 55$	13	8	No/Yes	A-clear	4 weeks of transdermal clonidine (equivalent to 0.1 mg oral dose), the 4 weeks placebo or visa versa. Cross-over, randomized, double-blind design	8 weeks	Clonidine significantly reduced hot flash frequency and severity, 4 different adverse effects were recorded	Public Health Service Grants. USA
Liobl [42]	Venlafaxine versus clonidine for hot flashes in breast cancer patients	Venlafaxine $n = 40$	Clonidine $n = 40$	9	7	Yes/Yes	A-clear	Venlafaxine (37.5 mg x 2) Clonidine (0.075 mg x 2) Double-blind, randomized, cross-over design, only 39 patients were crossed over at week 4.	Part A = 4 weeks Part B (cross-over) = 8 weeks. No wash out period	Venlafaxine is significantly more effective in reducing the frequency of hot flashes in breast cancer patients than clonidine	NR

Table 1 continued

Study ID	Indication	Participants		Dropout		PC/ITT analyses	Methodological assessment *Cochrane Handbook*	Intervention *Treatment vs Control*	Duration of treatment	Main findings	Funding
		Treatment	*Control*	*Treatment*	*Control*						
Loprinzi [33]	Venlafaxine in management of hot flashes in survivors of breast cancer	1.Venlafaxine 37.5 mg/day $n = 56$ 2.Venlafaxine 75 mg/day $n = 55$ 3.Venlafaxine 150 mg/day	Placebo $n = 56$	1. V(37.5 mg) $n = 7$ 2.V(75 mg) $n = 12$ 3. V(150 mg) $n = 5$	6	Yes/Yes	A-clear	Venlafaxine, 3 doses, 37.5 mg, 75 mg and 150 mg vs placebo. Parallel group design, randomized, double blind	4 weeks	Decrease in hot flash frequency was significant in all three venlafaxine doses compared to placebo. Four different adverse effects were significantly higher in 75 mg and 150 mg groups vs placebo	Public Health Service Grants. USA
Maclaughlan [40]	Hypnotherapy versus gabapentin for the treatment of hot flashes in breast cancer survivors	Hypnoth. $n = 13$	Gabapentin $n = 14$	4	6	Yes/Yes	B- unclear (no blinding, small sample size)	Gabapentin 900 mg/day vs 3 x 1 hour hypnotic inductions, 1 week apart, instruction in self-hypnosis and home CD use. Parallel group design, randomized, non-blinded	8 weeks	Hypnotherapy and gabapentin demonstrate efficacy in improving hot flashes, there were no significant differences between the 2 arms	Not funded
Mao [41]	El.acupuncture versus gabapentin for hot flashes in breast cancer survivors	El.acup. $n = 62$ (real $n = 30$, sham $n = 32$)	Gabapentin 900 mg/day $n = 58$ (real $n = 28$, placebo $n = 30$)	El.acup $n = 10$ (real $n = 6$, sham $n = 4$)	Gaba $n = 5$ (real $n = 1$, placebo $n = 4$)	Yes/Yes	A-clear	Electroacupuncture (real and sham) versus gabapentin (real and placebo). Parallel group design, 4 arms, randomized, double-blind	8 weeks, obs. at week 24	Acupuncture produced larger placebo and smaller nocebo effects than the pills El.acup reduced HF by 47.8%, gabapentin by 39.4%, sham acup by 45% and placbo pills by 22.3%	1. Pfizer 2. Genetech 3. Incyte 4. Millenium Pharmaceut 5. Bayer 6. Veridex 7. Calithera Biosciences 8. Glaxo.S.K. 9. Wyeth
Pandya [37]	Clonidine for tamoxifen-induced hot flashes in breast cancer patients	Clonidine $n = 99$	Placebo $n = 99$	26	23	No/Yes	A-clear	Clonidine 0.1 mg before bed vs placebo. Parallel group design, randomized, double-blind	8 weeks + 4 week obs	Clonidine significantly reduced frequency and severity of hot flashes	National Cancer Institute, Maryland, USA
Pandya [34]	Gabapentin for hot flashes in women with breast cancer. Dose related efficacy and adverse effect profile was assessed	Gabapentin (300 mg) $n = 139$ Gabapentin (900 mg) $n = 144$	Placebo $n = 137$	Gaba 300 mg $n = 25$ Gaba 900 mg $n = 24$	24	Yes/Yes	A-clear	Gabapentin 300 mg/day vs 900 mg/day vs placebo. Parallel group design, randomized, double-blind	8 weeks	Gabapentin is effective in the control of hot flashes at 900 mg/day, but not at 300 mg, measured at 8 weeks	US National Cancer Institute

Table 1 continued

Study ID	Indication	Participants		Dropout		PC/ITT analyses	Methodological assessment *Cochrane Handbook*	Intervention *Treatment vs Control*	Duration of treatment	Main findings	Funding
		Treatment	*Control*	*Treatment*	*Control*						
Walker [20]	Acupuncture versus venlafaxine for vasomotor symptoms in patients with hormone receptor positive breast cancer	Acupuncture *n* = 25	Venlafaxine *n* = 25	1	5	No/Yes	B-unclear (not possible to blind providers and participants, possibly affecting bias)	Acupuncture (16 treatments) vs venlafaxine (37.5 mg/day for 1 week, then 75 mg for 11 weeks) Parallel group design, randomized, not blinded	12 weeks, observed for 1 year	Acupuncture and venlafaxine significantly and equally reduced hot flash symptoms. Eighteen incidents of adverse effects were seen in the venlafaxine group, there were none in the acupuncture group	Susan Komen Foundation

The column "Participants" refers to the number of participants randomized to either treatment or control group. "Dropout" refers to participants who left the study in either the treatment or the control group, respectively

patients experiencing adverse effects in each group. To perform a meta-analysis, data were entered directly from the datasheets into Review Manager 5 computer program [35].

Results

Outcome of the literature searches

A total of 49 articles were identified. They were initially examined on the basis of titles and abstracts; 37 were excluded from further examination due to the following: 30 did not meet inclusion criteria and seven were multiple article registrations in databases. A total of 12 articles were included in this review (Fig. 1).

The control intervention was clonidine in three studies [31, 37, 39] and placebo in five studies. These five studies compared venlafaxine, or clonidine, or gabapentin to placebo [32–34, 37, 38]. Two of these studies examined venlafaxine at two [32] and three [33] different doses and one study examined gabapentin at two different doses [34]. Three studies compared gabapentin to other therapies: vitamin E [39], hypnotherapy [40] and electro-acupuncture [41], and one compared venlafaxine to acupuncture [20].

Methodological assessment as described in the Cochrane handbook was used to rate the included trials: All were classified as high quality (A), apart from three RCTs in which risk of bias was increased by providers and participants not being blinded [20, 39] and one where no blinding was used and the sample size was small [40].

Five studies included more than one active treatment arm [31–34, 41]. Four studies had a cross-over design [32, 36, 38, 42]. Number of participants ranged from a minimum of 27 to a maximum of 420. The duration of the studies ranged from 4 to 24 weeks.

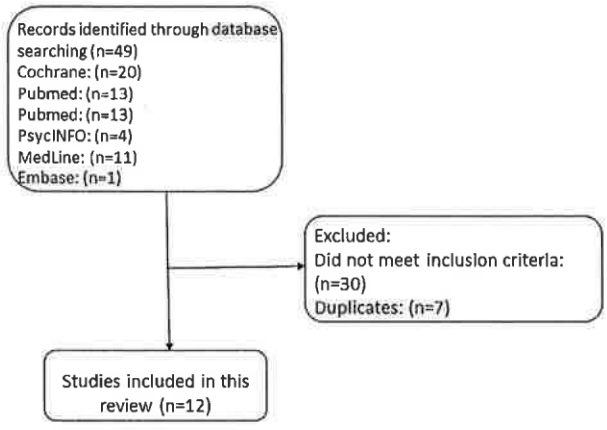

Fig. 1 Flow chart for included RCTs

Table 2 Adverse effects reported in the randomized controlled trials

Study ID	Number of participants		Total no. of AE (no. of participants with AE)		Type of AE
	Treatment	Control	Treatment	Control	
Biglia [39]	Gabap. $n = 60$	Vit E 55	17 (60)	0 (55)	Somnolence, dizziness, dry mouth, nervousness, weight gain
Boekhout [31]	Venl 41. Clon 41.	Placebo $n = 20$	Venl 206 (41) Clon163 (41)	82 (20)	Reduced appetite, nausea, sleepiness, dizziness, fatigue, dry mouth, sweating, constipation
Buijs [36]	Venlafaxine $n = 30$	Clonidine $n = 30$	27 (30)	5 (30)	Headache, dizziness, dry mouth, mood disorder
Carpenter [32] (high dose)*	Venlafaxine $n = 9$	Placebo $n = 9$	Dry mouth p = 0.002 vs placebo **	NR	Dry mouth
Carpenter [32] (low dose)*	Venlafaxine $n = 26$	Placebo $n = 26$	Constipation $p = 0.001$ headaches $p = 0.007$ dry mouth $p = 0.001$ vs placebo **	NR	Constipation, headache, dry mouth
Goldberg [38]	Clonidine $n = 55$	Placebo $n = 55$	dry mouth ($p < .001$) constipation (.02) itchiness (.01)	NR	Drowsiness, dry mouth, constipation, itching
Loibl [42]	Venlafaxine $n = 33$	Clonidine $n = 31$	38 (27)	14 (27)	Loss of appetite, sleeplessness, nausea, drowsiness, tiredness, sweating, constipation, restless sleep, nervousness, moodiness, dry mouth
Loprinzi [33] (High dose)*	Venlafaxine 150 mg $n = 54$	Placebo $n = 56$	43(54)	2 (56)	Decreased appetite, nausea, dry mouth, constipation
Loprinzi [33] (Low dose) *	Venlafaxine 37.5 mg $n = 56$.	Placebo $n = 56$	14 (56)	2 (56)	Decreased appetite, nausea, dry mouth, constipation
Loprinzi [33](Medium dose)*	Venlafaxine 75 mg $n = 55$.	Placebo $n = 56$	18 (55)	2 (56)	Decreased appetite, nausea, dry mouth, constipation
Maclaughlan [40]	Gabapentine. $n = 14$	Hypnotherapy $n = 13$	3 (24)	0 (13)	Fatigue, vertigo
Mao [41]	Gabapentin 900 mg/day = 28	El.acupuncture = 30	Gabapentin 13 (28)	5 (30)	Bruising, constipation, dizziness, dry mouth, fatigue, headache, increased pain, drowsiness
Pandya [37]	Clonidine $n = 99$	Placebo 99	41 (99)	21 (99)	Difficulty sleeping
Pandya [34] (high dose) *	Gabapentine 900 mg $n = 116$	Placebo $n = 113$	10 (120)	6 (113)	Appetite, distress, drowsiness, fatigue, nausea, pain, memory, shortness of breath, sleep, vomiting
Pandya [34] (low-dose study)*	Gabapentine 300 mg $n = 114$	Placebo $n = 119$	6 (114)	6 (113)	Appetite, distress, drowsiness, fatigue, nausea, pain, memory, shortness of breath, sleep, vomiting
Walker [20]	Venlafaxine n= 25	Acupuncture n=25	28 (25)	0 (25)	Nausea, dry mouth, headache, difficulty sleeping, double vision, increased blood pressure, constipation, anxiety, lightheaded, jittery
SUM			627 (774)		

Table 2 continued

Study ID	Grade 1-5 (CTCAE)				
	Treatment				
	G1	G2	G3	G4	G5
Biglia [39]	5	12			
Boekhout [31]	V 104. Cl 93	V. 102, Cl 70			
Buijs [36]	16	11			
Carpenter [32] (high dose)*					
Carpenter [32] (low dose)*					
Goldberg [38]					
Loibl [42]	38				
Loprinzi [33] (High dose)*	40	3			
Loprinzi [33] (Low dose) *	13	1			
Loprinzi [33](Medium dose)*	17	1			
Maclaughlan [40]	3				
Mao [41]	13				
Pandya [37]	41				
Pandya [34] (high dose) *		10			
Pandya [34] (low-dose study)*	6				
Walker [20]	28				
SUM	417	210	0	0	0

Study ID	Grade 1-5 (CTCAE)				
	Control				
	G1	G2	G3	G4	G5
Biglia [39]	0				
Boekhout [31]	40	42			
Buijs [36]		5			
Carpenter [32] (high dose)*					
Carpenter [32] (low dose)*					
Goldberg [38]					
Loibl [42]	14				
Loprinzi [33] (High dose)*	2				
Loprinzi [33] (Low dose) *	2				
Loprinzi [33](Medium dose)*	2				
Maclaughlan [40]					
Mao [41]	5				
Pandya [37]	21				
Pandya [34] (high dose) *	6				
Pandya [34] (low-dose study)*	6				
Walker [20]	0				
SUM	98	47	0	0	0

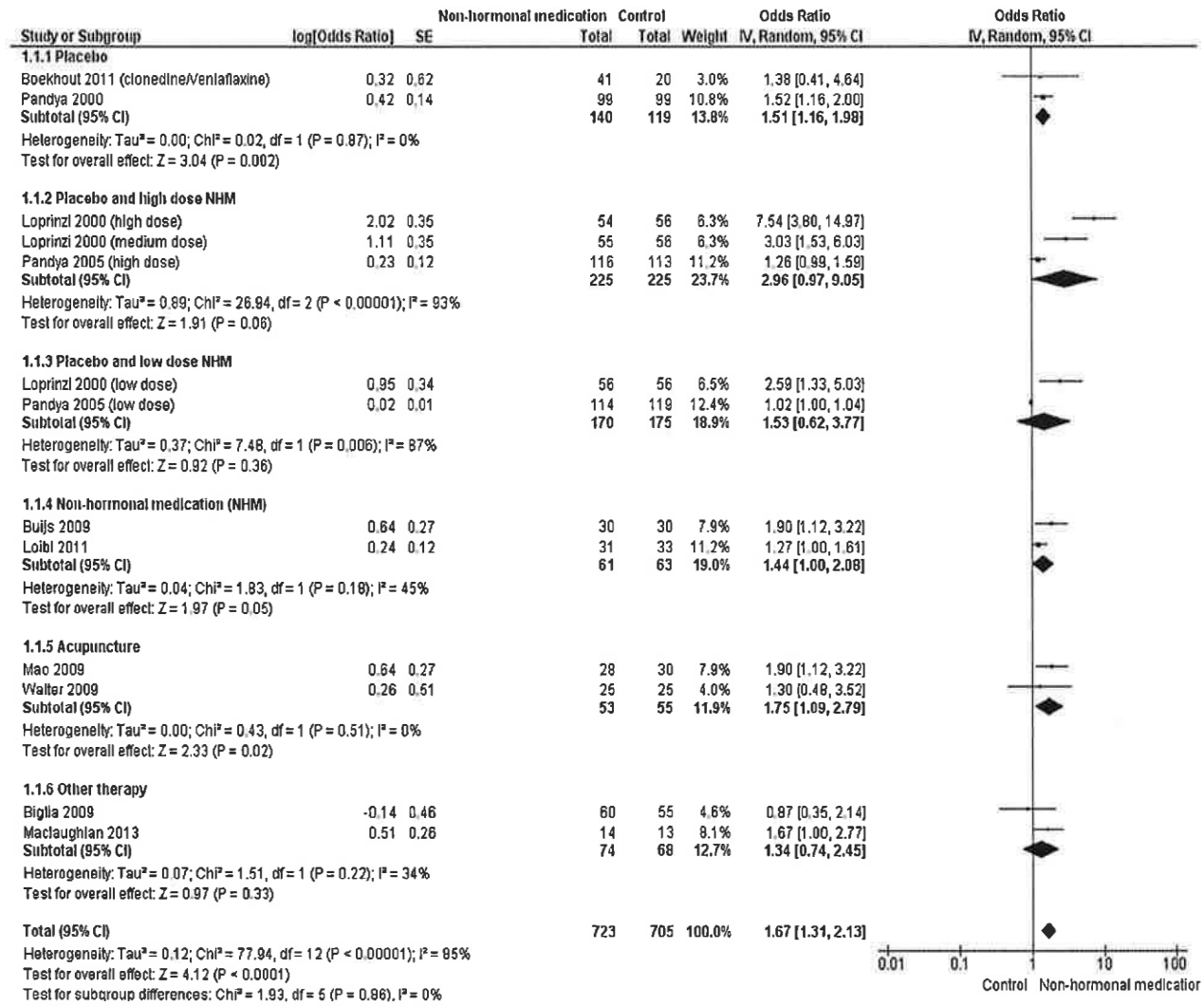

Fig. 2 Forest Plot

Types of adverse effects were reported in all the included studies. Number of patients suffering from adverse effects and number of adverse effects were reported in all but two studies [32, 38] where specific adverse effects were compared to placebo and reported as p values. We tried to contact the authors of these two studies in order to gain access to more comparable data. We were not able to get in touch with Goldberg; Carpenter kindly provided more data, but the actual numbers concerning adverse effects were not available. These two studies were consequently excluded from the meta-analysis. One study presented data on adverse effects only if these were the reason for dropping out, possibly causing an underestimation of the number of adverse effects [34]. A total of 1467 participants experienced 772 adverse effects. Of these, 81 % ($n = 627$) were in the treatment group and 19 % ($n = 145$) were in the control group. Adverse effects included appetite disorder, nausea, dry mouth, fatigue, dizziness, headache, difficulty sleeping, anxiety, memory problems, sweating, constipation, double vision and increased blood pressure.

Sixty-seven percent of the adverse effects were graded as CTCAE I ($n = 515$) and 33 % were graded as CTCAE II ($n = 257$) (Table 2). Adverse effects causing participants to dropout were classified as CTCAE grade II.

Whether dropping-out in the included studies was due to adverse effects was reported in all but four studies [33, 34, 38, 41]. In the three studies comparing venlafaxine and clonidine, the number of dropouts due to adverse effects were fourteen and five [36], six and four [42] and six and two [31], respectively, totalling 26 in the venlafaxine groups versus 11 in the clonidine groups. Gabapentin was compared to placebo [34], hypnotherapy [40] and vitamin E [39], where sixteen, three and seventeen women, respectively, dropped out of the gabapentin groups due to adverse effects; there were no dropouts in the second arms. Venlafaxine was compared to placebo [32], where the number of dropouts were 3 versus 1, and acupuncture [20], where the only dropouts due to adverse effects were 3 women in the venlafaxine group.

Meta-analyses

Adverse effects' data from 10 RCTs were included in the meta-analysis with a total of 1,428 subjects.

Non-hormonal medication versus overall control

An overall comparison was made between non-hormonal medication and control. Ten trials had 13 different outcomes due to low and high drug doses in the same trials. A significant difference was found between non-hormonal medication and control, with OR of 1.67, 95 % CI of 1.31–2.13 and I^2 of 85 % ($P < 0.0001$).

Different sub-group meta-analyses according to the categories of controls were performed, and are presented below.

Non-hormonal medication versus placebo

A comparison was made between non-hormonal medication and placebo. Two trials (259 participants) made this comparison, and a statistically significant difference was found between non-hormonal medication and placebo, with OR of 1.51, 95 % CI of 1.16–1.98 and I^2 of 0 % ($P = 0.002$).

High-dose non-hormonal medication versus placebo

There was no statistically significant difference between high-dose non-hormonal medication and placebo in a meta-analysis of two trials ($n = 450$) for three different combined outcomes, with OR of 2.96, 95 % CI of 0.97–9.05 I^2 and 93 % ($P = 0.06$).

Low-dose non-hormonal medication versus placebo

A comparison was made between low-dose non-hormonal medication and placebo. Two trials (345 participants) made this comparison, and no statistically significant difference was found between the groups (OR 1.53, 95 % CI 0.62–3.77, $I^2 = 87$ %, $P = 0.36$).

Non-hormonal medication versus non-hormonal medication

There was a significant difference between non-hormonal medication (venlafaxine) and non-hormonal medication (clonidine) in a meta-analysis of two trials, with OR of 1.44, 95 % CI of 1.00–2.08 and I^2 of 45 % ($P = 0.05$).

Non-hormonal medication versus acupuncture

A comparison was made between non-hormonal medication and acupuncture. Two trials (108 participants) made this comparison; a significant difference was found between the groups in favour of acupuncture, with OR of 1.75, 95 % CI of 01.09–2.75 and I^2 of 0 % ($P = 0.02$).

Non-hormonal medication versus other therapy

There was no statistically significant difference between non-hormonal medication and other therapies in a meta-analysis of two trials, with OR of 1.34, 95 % CI of 0.74–2.45 and I^2 of 34 % ($P = 0.33$).

Discussion

This meta-analysis demonstrated that the odds for experiencing adverse effects was significantly higher in patients randomized to non-hormonal medication than for patients randomized to controls, such as placebo and acupuncture. High-dose non-hormonal medication (venlafaxine and gabapentin) provoked an increased number of adverse effects compared to low-dose medication. This may suggest that low-dose non-hormonal medication is a good alternative for breast cancer survivors with hot flashes, providing sufficient reduction in frequency and intensity of hot flashes. Rada et al. [8] in their systematic review report that non-hormonal therapies have a mild to moderate effect in reducing frequency and intensity of hot flashes in women with a history of breast cancer. This result was based on nine different studies evaluating the effect of SSRIs ($n = 6$), clonidine ($n = 2$) and gabapentin ($n = 1$).

Acupuncture has few adverse effects compared to non-hormonal medication and should be considered as a potential treatment alternative if efficacy can be confirmed in future studies. Four systematic reviews evaluating acupuncture for hot flashes in breast cancer survivors included six [44], seven [43], eight [21] and twelve [45] RCT's respectively. Overall, authors concluded that acupuncture effectively reduced hot flashes, but was not statistically significant compared to sham; and that there is currently insufficient evidence to either support or refute acupuncture for this patient category.

Twelve trials were identified for this systematic review, and ten of these were included in the meta-analysis. We pooled results in an attempt to give an overall comparison of non-hormonal medication versus control; six different sub-group analyses were done. However, only two trials made up each group, thereby only demonstrating tendencies.

Study strengths and limitations

As far as we know, this is the first systematic review and meta-analysis to examine adverse effects of non-hormonal medications for hot flashes in breast cancer survivors, as the primary outcome measure. The included studies were of high methodological quality and with reduced risk of bias, thereby providing reliable results. Heterogeneity is always an important consideration when compared to RCTs, and the forest plot showed strong study similarities.

Two-thirds of adverse effects reported in this review were classified as grade I and a third as grade II. The CTCAE grading of adverse effects was solely based on information provided by the articles included in this review, and should be considered as an approximation of adverse effect severity. Inconsistent use of safety terminology made it difficult to categorize and evaluate the data; the CTCAE grading system was not consistently used.

Three different non-hormonal medications were assessed and compared to different control groups. This was a limiting factor in the meta-analysis. To reduce the risk of inflating the size of the pooled treatment effect, zero-cell counts were included [46]. A continuity correction of 0.5 was used for studies with zero-cell counts, in order to provide a conservative approximation of adverse event risk [47].

Six studies included in the meta-analysis had active controls, including other non-hormonal medicines, acupuncture and other therapies, possibly inflating adverse-effect frequency outcomes; however, the forest plot (Fig. 2) does not indicate such influence when studies with active controls are compared to those with passive controls.

Other elements of conceivable bias include possible under-reporting of adverse effects by participants motivated to experience treatment effect, simply due to being included in a clinical trial. Publication bias is also a consideration; clinical trials demonstrating a statistically significant treatment effect compared to control are more likely to be published [48].

Search strategy for this review included five search engines, and more RCTs may have been identified if more search engines had been added. However, we also identified a systematic review focusing on active interventions for hot flash symptoms in breast cancer patients [8] and 4 reviews focusing on a combination of post-menopausal women and breast cancer survivors [9, 26–28]. Examination of the full texts and reference lists of these reviews did not provide any additional RCTs for this meta-analysis.

Other studies

To our knowledge, only one systematic review evaluating non-hormonal therapies for hot flashes in women with a history of breast cancer has been published, and the focus was on treatment efficacy [8]. We could not find any systematic reviews that examined adverse effects due to non-hormonal drugs as a primary outcome in this patient category. Rada and colleagues reported evidence supporting the use of clonidine, gabapentin and SSRIs/SNRIs for hot flash symptoms in breast cancer survivors. The authors commented that adverse effects were inconsistently reported. 16 studies were included, of which 10 were pharmacological studies and 6 non-pharmacological studies. They confirmed our findings that adverse effects increase when higher doses of gabapentin and venlafaxine were used. They also suggested that adverse effects may outweigh benefit in clonidine.

Another systematic review of 13 randomized trials comparing active interventions for hot flash problems in women with and without breast cancer [26] did not agree with our findings of dose-related increased frequency of adverse effects. The authors reported that high doses of venlafaxine (75 mg/day) and gabapentin (900 mg/day) appeared to improve hot flash symptoms to a greater extent compared to lower doses, without incurring more adverse effects. Since the population did not only include breast cancer patients, the results make comparison with our study difficult.

Implications

Despite these limitations, the sub-group analyses provided information relevant for clinical practice, including the relationship between drug dosage and adverse effects, drug comparisons in relation to adverse effects and the possible role of acupuncture as a treatment for hot flashes if efficacy can be confirmed. Further research is indicated to investigate these findings with focus on efficacy versus adverse effects; also the effect of combined therapies should be considered with a view to increasing the compliancy of oestrogen-antagonist medication.

Conclusion

The odds for experiencing adverse effects was statistically significantly higher in patients randomized to high-dose non-hormonal medication than for patients randomized to controls, such as placebo, low-dose medication and acupuncture. Consequently, these therapies should be considered as a potential treatment alternative if efficacy for hot flushes can be confirmed.

Compliance with ethical Standards

Conflict of interest The authors Jill Hervik and Trine Stub declare no conflict of interest.

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PAPER II

ACUPUNCTURE FOR THE TREATMENT OF HOT FLASHES IN BREAST CANCER PATIENTS, A RAMDOMIZED, CONTROLLED TRIAL

PAPER III

QUALITY OF LIFE OF BREAST CANCER PATIENTS MEDICATED WITH ANTI-ESTROGENS, TWO YEARS AFTER ACUPUNCTURE TREATMENT. A QUALITATIVE STUDY

International Journal of Women's Health

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ORIGINAL RESEARCH

Quality of life of breast cancer patients medicated with anti-estrogens, 2 years after acupuncture treatment: a qualitative study

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Odd Mjåland[2]

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Objective: The aim of this study was to examine the quality of life of breast cancer patients medicated with estrogen antagonists, 2 years after having acupuncture treatment for hot flashes.

Methods and materials: Our sample was taken from women who had recently participated in a randomized controlled trial investigating the effects of acupuncture on hot flashes, a side effect of estrogen-antagonist treatment. Forty-one women from the true acupuncture treatment group and 41 women from the control group (sham acupuncture), who had 2 years previously received a course of 15 acupuncture treatments over a period of 10 weeks, were asked to answer an open question. The question, "Would you like to share your thoughts and experiences related to your breast cancer diagnosis, treatments or anything else?" was by being open, broad, and nonspecific, intended to stimulate subjective information, which was not included in the original, or future quantitative studies. Qualitative data were analyzed using systematic text condensation.

Results: Most women were troubled by two or more side effects due to anti-estrogen medication, negatively affecting their life quality. Symptoms included hot flashes, sleep problems, muscle and joint pain, arm edema, fatigue, weight gain, depression, and lack of sexual desire. Women previously treated with sham acupuncture complained that hot flashes were still problematic, whilst those previously treated with traditional Chinese acupuncture found them less of a problem and generally had a more positive outlook on life. These results compare favorably with the findings from our original study that measured quantitatively health related quality of life.

Conclusion: Side effects due to anti-estrogen treatment seriously affect the quality of life of breast cancer operated patients. Patients who had previously been treated with traditional Chinese acupuncture complained less of hot flashes, and had a more positive outlook on life, than women who had previously been treated with sham acupuncture.

Keywords: breast cancer, anti-estrogen medication, quality of life

Introduction

The aim of our study was to examine the quality of life of breast cancer operated patients, treated with estrogen antagonists, 2 years after acupuncture treatment. By posing an open, broad, and nonspecific question about experiences related to breast cancer diagnosis and treatment, we hoped to gather subjective information from this patient group, not normally included in quantitative outcome measures.

There were around 430,000 new cases of breast cancer in Europe in 2008; 55% of these were estrogen-receptor positive.[1] Conventional medical treatment involves the use of hormone therapy for those diagnosed with estrogen-sensitive tumors, for a minimum of 5 years. Drugs include the estrogen antagonist tamoxifen and aromatase inhibitors

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such as anastrozole, exemestane, and letrozole. Many women suffer from side effects, the most common being hot flashes, affecting around 80% of women taking tamoxifen.[2] The severity of hot flashes has been shown to be more severe and intense than those experienced by healthy menopausal women.[3,4] The use of hormone replacement therapy, an option for healthy women, is contraindicated in estrogen-sensitive breast cancer patients. Pharmacological agents used to treat hot flashes, eg, antihypertensive clonidin, steroids, and antidepressants, often have adverse effects, such as hypotension, weight gain, and nausea respectively.[5] A study from Henry Ford Hospital, Detroit randomized 50 women with breast cancer to either acupuncture or venlafaxine treatment over a period of 12 weeks; patients were followed up for 1 year. Results showed that acupuncture appeared to be as effective in reducing hot flashes as venlafaxine, an antidepressive medication.[6]

The authors of this study have previously carried out a randomized, controlled trial, investigating the effects of acupuncture treatment in breast cancer operated patients complaining of hot flashes.[7] Results from the trial showed a significant reduction in number of hot flashes both day and night, coupled with a significant improvement in health-related life quality that lasted for a further 3 months post treatment in patients receiving traditional Chinese medicine (TCM) acupuncture. The only significant effect, experienced by patients in the sham acupuncture group, was a reduction in hot flashes at night during treatment; however, the effect did not last throughout the following 3 months. We concluded that acupuncture was a valuable option for this patient group suffering from side effects due to long-term anti-estrogen medication. However, the effect of acupuncture treatment beyond 3 months was not investigated.

In an attempt to accumulate qualitative information related to health and life quality from women who had been diagnosed and treated for breast cancer, the authors devised an open question: "Would you like to share your thoughts and experiences related to your breast cancer diagnosis, treatments, or anything else?" Although all patients had received acupuncture 2 years previously, the question put to them did not specifically mention acupuncture treatment. This deliberate emission was an attempt to avoid leading them in a specific direction regarding their statements, allowing them to give information important to them, whether it was centered around their breast cancer diagnosis, various treatments, social issues, or indeed other aspects of life. Acupuncture studies investigating hot flashes, in both women with breast cancer, and healthy women, have recorded changes in health outside expected outcome measures.[8] We hoped that accumulation of subjective information would provide us with a broader understanding of the quality of life, including physiological, psychological, emotional, and social elements for these women. An Iranian literature review from 1982 to 2008, examined the relationship between quality of life and survival time in cancer patients. Quality of life data were shown to be significant predictors of survival duration.[9] Quality of life is a term which only became a medical issue in the 1960s, and is defined by WHO as "how an individual perceives his own life, in light of the cultural context and values of his environment, aims, expectations and worries".[10] Indeed, TCM embraces these interactions. All the women included in our study had been primarily treated with traditional Western medicine; Chinese medicine was used to reduce side effects of western medication.

Design, materials and methods

Patients

To gain subjective information from this patient group, a qualitative design was considered applicable. Data were gathered from participants' written answers to an open question, sent in the post, accompanied by an explanatory letter. Our sample was taken from a previous randomized controlled trial which included 59 Norwegian female patients. All patients had been recruited from The Breast Centre at Vestfold Central Hospital. Because a third of these were not reachable, a further 31 women were included; these women were comparable to the women originally included in the study, in age and in social and drinking habits. Baseline values of mean numbers of hot flashes at day and night, and total Kupperman index score, measuring health-related quality of life, were not significantly different, and they were treated and followed up in an identical manner to those included originally. All patients were randomized by a closed envelope technique to 15 standard treatments with TCM acupuncture or sham (minimal) acupuncture, and monitored for a further 12 weeks after completing treatment. All participants had been medicated with tamoxifen for at least 3 months, and were postmenopausal, defined as no menstruation for at least 3 months before treatment start. Patients taking medication for hot flashes either prior to or during the study were excluded. Further exclusion criteria included: previous acupuncture, simultaneous treatment with other complementary or alternative therapies, and serious systemic or psychological disorders. No hot flash severity limits were implemented.

Methods

A total of 82 patients received an invitation to take part, and a questionnaire in the post, 2 years (±2 months) after finishing the acupuncture course of treatments. Forty-one patients had previously received TCM acupuncture, and 41 patients had received sham acupuncture (control group). Patients had been blinded to the type of treatment they had received in the original study, and had not at any point in time received any information indicating what type of treatment they had received prior to writing their statements. The study was approved by the regional committee for medical research ethics.

Analysis of data

Content analysis was done by reading and rereading the material to gain an overall impression. Simple counting of the number of women who referred to different aspects of their diagnosis, treatment, and daily life was undertaken. Groups making similar statements were indexed to develop analytical categories and were derived inductively to produce a grounded theory, developing a hypothesis from the collected data rather than defining it beforehand. To develop categories, interesting or unfamiliar terms were noted. All relevant data from each category were identified and examined using constant comparison; categories were added to reflect as many nuances in the data as possible. Categories were further refined and grouped together by using spreadsheets and the split-screen function of word-processing, creating key themes and categories for further investigation. Although researcher bias was not considered a problem, two analysts were used; neither patient identity nor previous type of treatment was revealed to the analysts. Categories were charted with entries from several respondents, and charts were mapped to define concepts and find associations between themes, with a view to providing explanations for the findings.

Results

Eight women from the original study had died during the 2 years since completing their acupuncture treatment. Twenty-one women did not return written statements. A total of 61 statements were received; 33 of these women had previously been treated with TCM acupuncture, and the other 28 had received sham acupuncture. The mean age of the participants was 51.3 (52.5 in the TCM group and 50.2 in the control group). The women provided their answers by mail. These were anonymously assessed by the first author and an oncology nurse, both experienced in research methods. The women also completed a validated Kupperman menopausal index, examining the severity of any symptoms often associated with menopause, and a questionnaire aimed at gathering information about symptom development. Patients answered five questions about: treatments in connection with their diagnosis, hot flash severity, whether they had had more acupuncture or other treatments (including medication) for their hot flash problems, and whether they still used the same estrogen-antagonist medication, had changed to another, or stopped. This data will be published at a later date in a quantitative article.

The women returned statements about their experiences relating to their breast cancer diagnosis, acupuncture treatment for hot flashes, related symptoms, and side effects of estrogen-antagonist treatment, and their daily life. There was great variation in style, and the length of their statements ranged from 0 to 364 words; the number of words in both groups was comparable. Statements were analyzed by systematic text condensation.

Although the question posed to the participants did not specifically mention hot flashes or acupuncture, 28 of the 61 participants commented on one or both. Fifteen patients, previously treated with traditional acupuncture for their hot flashes, commented on the positive effects they had experienced during and after treatment. Most went on to describe the quality and quantity of their hot flashes; 10 mentioned that they were still fewer and milder than they had been before they received treatment. Comments included: "The hot flashes have returned but only slightly at night, but they are over quickly and I have got used to them". "My family saw a change in me when the hot flashes started to lessen during acupuncture treatment, I went back to work again, my colleagues are important to me. During the last 2 years I have had some top up treatments, and will in the future if I start to get warm again". "Acupuncture helped a lot, my hot flashes were reduced to a level that I felt that I could manage, and have stayed like that". A majority of these women went on to describe how they approached, or managed their hot flashes; techniques included avoiding situations facilitating their hot flashes, such as stress, certain foods and alcohol. Five women mentioned simple relaxation techniques as a means of stopping, controlling, or shortening hot flashes. Thirteen patients from the control group commented on acupuncture and level of hot flashes, though less favorably than the TCM group. Nine women complained of severe hot flashes, only one said that acupuncture had reduced her hot flashes, four said that acupuncture had not worked, and one commented that it was painful. A typical comment was: "I have strong and frequent hot flashes, about once an hour, I wake up 4–5

times at night, even so, the hot flashes are worse during the day". Another participant wrote: "I sweat a lot and have lots of hot flashes every day, but have learnt to tackle them, they don't bother me as much, acupuncture did not work for me". One lady related her hot flashes to stress at work, she wrote: "I work full time as a restaurant manager, I have lots of hot flashes, especially when I am stressed, I start to get warm, sweat and feel sick". Four women mentioned that food and drink affects them: "I get instant hot flashes from fatty foods, caffeine and red wine". Another woman wrote, "I found out that strong, spicy food, red wine, and chocolate provokes hot flashes". One lady commented, "If I lead a regulated life and do not eat chocolate, I feel better, and my hot flashes are not as bothersome, but it is not easy, I have not got much will power".

Only a total of five women mentioned their social and family lives, but only to demonstrate the strength of their symptoms; all but one were from the control group. One lady told how she disturbed her husband at night when she could not sleep; another described how shocked her friends were when she had a hot flash and sweat dripped down her face. One lady described how pleased she was to meet and bond with other young breast cancer patients; she felt that they understood each other's problems when she attended a rehabilitation centre.

A total of 20 women, equally divided between the two groups, described how they discovered their breast tumor and their experiences with the health service. A young woman of 30 wrote: "When I was diagnosed, I decided that I would be in control of the disease, not the other way around. I have always been mentally strong and that has not changed". Another wrote: "When I was diagnosed, I was not afraid, I felt safe at the hospital. The whole process has enriched my life. Although tamoxifen took all my strength and gave me enormous aches and pains, these disappeared when I changed to Arimidex [letrozole]. I can't complain, I have a few aches here and there, just like other women of my age". Another said: "I scratched my breast one day and felt a lump. Four weeks later I was operated, I tolerated the post-operative treatment well. I tell my friends that I am not sick, I just have a few problems". Most women who mentioned the health service seemed pleased with the service and personnel. Only two complained, both about their general practitioners; they both said that their doctors did not understand their complaints of side effects due to anti-estrogen medication and did not have time to listen to them. Another wrote that she was comforted when the surgeon said pre-operatively that she would be totally healthy again, she also said that she had confidence in all the hospital personnel. One participant wrote: "Being diagnosed with breast cancer was a shock, but much worse were the side effects of tamoxifen, hot flashes 3–4 times an hour, day and night, I was tired out, my quality of life was zero. Thanks to my doctor at the breast centre I was referred to acupuncture treatment, my hot flashes gradually reduced and I got some sleep".

A lot of women, more than 50% from both groups, wrote about side effects of their estrogen-antagonist medication. Apart from hot flashes and sweating, sleep problems and tiredness were a big problem, followed by arm edema, muscle and joint pain, body weight increase, headaches, and dry vaginal mucus membranes. One young lady wrote: "I have always been strong and in good shape, but not anymore. My body aches, in a way I cannot describe, my joints ache. My fingers are stiff, it takes time for them to warm up and they stiffen quickly when I use them". Many women used the word exhausted, a total of 16 patients either complained of sleep problems or of being tired. "I am weary and tired all the time, even though I sleep for a few hours after work". Another stated: "Hot flashes, edema in my arm, sleep problems and tiredness has reduced my quality of life and ability to work". One tired lady wrote: "I am exhausted, I did not receive any information on how the side-effects of the chemotherapy and medicines would affect me, I have had a hard time explaining these problems to the social services and my work place. As far as I know, these side-effects have not been documented, they need to be. I am a single mother and have had to tackle periods of depression, lack of sleep, hot flashes and fatigue alone, it has been really hard". Vaginal dryness, a side effect of estrogen reduction was mentioned by several women. One wrote: "It is very uncomfortable, my vagina is dry, I have had numerous urine infections, and I bleed when I have sex". Another lady wrote, "my sex life is over!" A third lady commented: "I have lost my sex drive, my husband and I are not as close now as we used to be, I put this down to lack of intimacy". A total of 20 women mentioned more than two side effects in their statements, indicating that these problems are of great importance to them.

On a positive note, many women had come to terms with their situation; many commented that despite their health problems, they were happy and content. A total of 18 patients (13 from the traditional acupuncture group and five from the control group) ended their statements on a happy note. Comments included: "I am OK. I am certain that I have received the best treatment in the world", "Despite my breast cancer diagnosis, my life is positive, I am fine", "I am healthy, the only thing I cannot do is go topless on the beach". "I have

learnt to live with my problems. I cannot complain, it could be much worse. I am good". "Ok, so I have lost my sex drive, got gum disease and tendinitis, but I am alive and happy".

Discussion

Our results present information describing quality of life, coping mechanisms, and experiences in women operated for breast cancer. Women made statements about their situation in response to an open question 2 years after finishing acupuncture treatment (TCM or sham) for hot flashes, a side effect of anti-estrogen medicines. The variety of the written statements made by the women, although unstructured, included similar consistent themes, indicating that the question had been understood adequately. By posing such an open question, and consequently receiving unstructured statements, categorizing proved problematic. However, themes were established by repeated statements about the same subjects, but with some variation. In the original acupuncture trial 2 years previously, participants were randomized to treatment with TCM acupuncture and sham acupuncture (control). Those originally included in the TCM group who mentioned hot flashes and/or acupuncture in their statements, did so favorably, reporting fewer hot flashes, better hot flash management, and a positive attitude to acupuncture. Those who had originally been included in the control group complained more of the severity and frequency of their hot flashes; their attitude to acupuncture was generally less positive than the other group. Since acupuncture intervention reduced the amount of hot flashes significantly in the TCM group, and showed only minimal effect in the control group 2 years earlier, it is not surprising that participants from the TCM group view acupuncture more favorably than those from the control group. But what of their hot flash complaints and problems? The women from the control group reported either more frequent and/or more intense hot flashes than the other group, or at least they experienced and understood their symptoms as severe. Could it be possible that attitude to a treatment and previous experience can affect symptoms and how we tackle them at a later date? Is it feasible to expect that a series of acupuncture treatments still has effect 2 years later? Long-term follow up studies are few and inconclusive. A study from Tromsø University examining the effect of acupuncture 6 and 12 months after treatment in healthy menopausal women could not demonstrate any long-term effect.[11] Frisk et al, however, could demonstrate a reduction in number of hot flashes up to 24 months after electro-acupuncture treatment in breast cancer operated women.[12] An explanation for the difference between the two groups in our study could be that the significant effects of acupuncture in the TCM group gave the women a better start, by reducing hot flashes and bettering sleep quality during the first few months of anti-estrogen treatment.

Despite access to various cancer groups and societies, some women felt the need to talk about their diagnosis and time in hospital. We would not immediately have expected so many women to describe these experiences. Could there be a need for these women to get it off their chests? Might they have considered the questionnaire as someone to talk to or a good listener? Is it possible that some of these women have not talked to anyone about their experience in hospital before? Or do these women have an insatiable need to talk about their situation? Busy oncology departments in Norway do not have the luxury of a psychologist or even appointments meant solely for talking or discussion, general practitioners offer 15-minute appointments, an inadequate amount of time for an in-depth conversation. However, nearly all were positive to the health service; they communicated that they had confidence in and trusted the healthcare professionals that they came into contact with. General emotional and informational support by health professionals was shown to have a direct effect on quality of life in a study of 250 Chinese breast cancer patients.[13]

Nearly half of the women in our study commented on symptoms they consider to be side effects of anti-estrogen medication. The recommended duration of hormonal therapy is 5 years. With such a long course of therapy, adverse effects can cause a major decrease in the quality of life. In a bibliographic review of literature covering all publications that appeared in English language in biomedical journals between 1974 and 2007, Montazeri examined the quality of life in breast cancer patients. The literature indicated that adjuvant hormonal therapies negatively affected quality of life; symptoms included arm pain, fatigue, and postmenopausal problems. Psychological anxiety and depression were common among breast cancer patients, even years after the disease diagnosis and treatment.[14] The statements written by the women in our study confirm these findings and range of symptoms. Our original study showed a clear relationship between hot flashes, sleep problems, and depression. Acupuncture had a significant effect on all these symptoms. Only patients medicated with tamoxifen were included in the original study. In line with international guidelines, postmenopausal women switch to an aromatase antagonist after 2 years. Forty-two percent of the women (19% in the TCM group and 23% in the control group) had, during the 2-year gap between the time they finished treatment and the time they made their statements, switched to an aromatase

antagonist. A study from the University of Sussex examined the quality of life of women with breast cancer, medicated with either tamoxifen, anastrozole (aromatase antagonist), or a combination of the two. A gradual improvement in quality of life during a 2-year period was reported by over 800 women. Endocrine symptoms increased between baseline and 3 months for all groups, and stabilized thereafter. Patients taking anastrozole only, reported significantly fewer cold sweats and vaginal discharge, but more vaginal dryness, painful intercourse, and loss of sexual interest, than those taking only tamoxifen.[15] Garreau et al found, by questioning over 300 women, that those taking an aromatase inhibitor suffered more from musculoskeletal problems and were more likely to switch therapy than those taking tamoxifen.[16] Side effects of estrogen-antagonist treatment affect many aspects of these women's lives. These problems need to be addressed. Many women complain of not being able to move forward in their lives, being constantly reminded of their cancer diagnosis by irritating symptoms. A comfort to some will be evidence from the University Hospital, Groningen, The Netherlands, indicating that symptoms decreased significantly after discontinuation of tamoxifen, although hot flashes, sleep disturbances, and vaginal dryness persisted in those treated with high-dose chemotherapy.[17]

The findings in this study represent life experiences associated with breast cancer diagnosis and treatment, in a selected group of Norwegian women. Norway is one of the world's richest countries; it provides heavily subsidized healthcare, and women's rights are strong. These findings are therefore probably not transferable to other cultures and parts of the world. In hindsight we regret not obtaining data about psychological variables, since personality traits may affect approach, expectations, and reactions to diagnosis, treatments, and coping mechanisms. Interviews, discussions, and focus group data may have provided more depth; however, this study provided us with subjective information about quality of life, as experienced by women who have undergone treatment for breast cancer. These findings reinforce our belief that the side effects of anti-estrogen therapy should receive more attention in medical worlds of both East and West. For many years, medicine in the West has focused largely on prevention, operative, and conventional postoperative treatment of breast cancer, and women have put up with adverse effects of long-term anti-estrogen medication. This study highlights the need for more quantitative and qualitative studies examining problems facing women diagnosed with breast cancer, providing solutions for evidence-based treatments, psychosocial interventions, and allocation of resources.

Conclusion

This study suggests that side effects of estrogen-antagonist treatment are a significant problem for women diagnosed with breast cancer, affecting their quality of life. Although patients who had 2 years earlier been treated with TCM acupuncture complained less of hot flashes, and generally seemed to have a more positive outlook on life, they were as troubled by other side effects as the women in the control group.

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Disclosure

The authors report no conflict of interest in this work.

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PAPER IV

LONG TERM FOLLOW UP OF BREAST CANCER PATIENTS TREATED WITH ACUPUNCTURE FOR HOT FLASHES

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Long term follow up of breast cancer patients treated with acupuncture for hot flashes

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Abstract

Objective: Short term effects of acupuncture treatment for hot flashes (HF) in breast cancer patients have been demonstrated in several studies, including a randomized controlled trial, by the present authors. Results for the first 59 Tamoxifen medicated women receiving a 10 week course of acupuncture treatment have already been published. A significant reduction in the number of hot flashes was demonstrated both day and night, for up to three months following treatment in the women receiving traditional Chinese acupuncture. The control group receiving sham (minimal acupuncture) demonstrated a HF reduction only at night during treatment, however the effect did not remain significant during the following 12 weeks. The study was continued in order to investigate longer term effects of acupuncture treatment, and patient's quality of life two years after treatment.

Methods and materials: Eighty patients, who had 2 years previously been randomized to either a course of 15 acupuncture treatments or sham acupuncture (control) over a period of 10 weeks, were asked to fill out a Kupperman index (KI) indicating health related quality of life.

Results: Sixty one women returned KI questionnaires. A mixed models procedure with diagonal covariance matrix was used for statistical analyses. Baseline values between the sham-group and acupuncture group were not significantly different. However scores at the end of treatment and after 3 months showed a statistically significant difference between the groups, this difference lost its significance when scores were analyzed after 2 years.

Conclusion: Acupuncture seems to have a positive effect on health related quality of life for up three months post-treatment, this study suggests that these effects may be longer-term, however there was no significant effect 2 years later.

Keywords: Acupuncture; Breast cancer; Hot flashes; Quality of life; Long-term follow up

Introduction

As treatment of breast cancer becomes increasingly effective, more women are living with side effects due to postoperative interventions affecting their quality of life (Kronenberg 1994; Hervik and Mjåland 2010; Carpenter et al. 2002). Women with breast cancer may undergo years of post-operative treatments including endocrine therapy, affecting their daily lives.

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, with over 1 million new diagnoses of breast cancer annually worldwide, 55% of these are estrogen-receptor positive (ER+) (Boyle and Levin 2008). In accordance with European guidelines medication with estrogen antagonists is recommended for a minimum of five years for women with ER+ tumors (Perry et al. 2008).

Hormone therapy medication includes the estrogen antagonist Tamoxifen, and aromatsase inhibitors such as Arimidex, Aromasin and Femara. Seventy-eight percent of women taking Tamoxifen reported hot flashes as a side effect, and 52% reported night sweats in a survey investigating the prevalence of menopausal symptoms in women with breast cancer (Walker et al. 2010). Hot flashes (HF) are considered to be the most bothersome side-effect of estrogen antagonist treatment, and are often accompanied by sweating, palpitations, dizziness, nausea and chills. Women treated with estrogen antagonists often

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report that HF at night disturb sleep patterns leading to insomnia and irritability.

Hot flashes are associated with peripheral blood vessel dilation causing an increased skin temperature and sweating. It has been suggested that HF are trigged by small increases in core body temperature. Freedman and Subramanian have demonstrated that vasomotor instability, encountered by women with estrogen withdrawal is due to a reduced hypothalamic thermoregulatory zone, compared to women without HF (Freedman and Subramanian 2005). Sweating and heat symptoms present if the upper threshold is crossed, and chills if the core temperature falls below the lower threshold. Reduced concentrations of β endorphins and serotonin, and an increased release of noradrenalin are associated with a fall in estrogen levels affecting the thermoregulatory set point, thereby causing vasomotor instability. Based on this theory, any intervention increasing levels of β endorphins and serotonin, and reducing noradrenalin could be expected to reduce HF. Although the physiological effects of acupuncture are still being investigated, research has indicated that the autonomic nervous system is affected, influencing neuropeptides such as β endorphins, serotonin, and cytokines (Spetz Holm et al. 2012); thereby indicating that acupuncture has the potential to influence the thermoregulatory centre.

Several recent randomized controlled trials have demonstrated that acupuncture may be effective for managing HF in breast cancer patients for up to 3 months post treatment (Hervik and Mjaland 2009; Deng et al. 2007; Nedstrand et al. 2005; Bokmand and Flyger 2013). However there is a distinct absence of randomized studies investigating long term effect. Frisk compared electroacupuncture with HRT in a study including 45 women, demonstrating long-term reduction in HF 24 months after the start of treatment (Frisk et al. 2008). Flishie's retrospective audit of treatment records of 182 women with breast cancer suggests long term relief of HF from one month to 6 years (mean 9 months) using acupuncture and self acupuncture (Filshie et al. 2006). Recently de Valois conducted a single arm study demonstrating a reduction in HF for up to 18 weeks after the last of 8 treatments in 50 patients (Valois et al. 2010). The authors of this paper have in a qualitative study demonstrated that women with breast cancer were less bothered by hot flashes, and had a more optimistic outlook on life, 2 years after acupuncture treatment compared to those treated with sham acupuncture (Hervik and Mjåland 2010). Quantitative studies investigating long-term effect of acupuncture for the relief of HF in this patient category are lacking.

The purpose of this study was to measure the long term effects of acupuncture two years after a 10 week course of treatment, in women with breast cancer included in a randomized controlled trial.

Materials and methods

Background

The authors of this study have previously carried out a randomized, controlled trial, investigating the effects of acupuncture treatment in 88 breast cancer operated patients, medicated with the estrogen antagonist Tamoxifen, complaining of hot flashes. Preliminary results for the first 59 women initially included have been published (Hervik and Mjaland 2009). All participants had been medicated with Tamoxifen for at least 3 months before starting treatment, and were postmenopausal. Exclusion criteria included: those taking medication for hot flashes, previous acupuncture, simultaneous treatment with other complementary or alternative therapies, and serious systemic or psychological disorders. No hot flash severity limits were implemented. Patients were randomized to either traditional Chinese acupuncture (n = 43) or sham acupuncture (n = 45), 15 treatments were administered over a 10 week period. Patients were monitored during the treatment period and for a further 12 weeks post-treatment.

The qualitative effect of acupuncture treatment beyond 3 months was later investigated. Qualitative information was collected from patients included in the study two years post treatment (Hervik and Mjåland 2010). Written statements in response to the question, "would you like to share your thoughts and experiences related to your breast cancer diagnosis, treatments or anything else?" were analyzed using systematic text condensation. Most women reported being troubled by two or more side-effects due to anti-estrogen medication, negatively affecting their life quality. Symptoms included hot flashes, sleep problems, muscle and joint pain, arm edema, fatigue, weight gain, depression, and lack of sexual desire. Women previously treated with sham acupuncture complained that hot flashes were still problematic, whilst those previously treated with traditional Chinese acupuncture found them less of a problem and generally had a more positive outlook on life.

Patients

Our sample when investigating long-term follow up at 24 months was taken from the initial 59 women originally included in the trial, and a further 29 patients included at a later date. These 29 women were comparable to the women originally included, in all aspects. Baseline values of mean numbers of hot flashes at day and night, and total KI score, measuring health related quality of life, were not significantly different. Patients were treated and followed up in an identical manner to those included originally.

Eight patients had died two years post treatment, a total of 80 patients therefore received an invitation to take part and a Kupperman index questionnaire in the post, 2 years (+/− 2 months) after finishing the course of acupuncture treatments. Thirty-nine patients had previously received

TCM, and 41 patients had received sham acupuncture (control group). Patients had been blinded to the type of treatment they had received in the original study, and had not at any point in time, received any information indicating what type of treatment they had received prior to answering the long term follow- up KI questionnaire. The study was approved by the regional committee for medical research ethics.

The validated KI that had in the original RCT been established at baseline, at the end of treatment, and 12 weeks post-treatment, was filled out by patients 24 (+/−2) months later. The KI incorporates 11 types of symptoms usually associated with menopause; these include hot flashes, sweating, sleep problems, depression, tiredness, dizziness, palpitations, joint pain, headache, vaginal dryness and other problems (patients must specify). Symptoms are given a score depending on their severity, where 0 = no symptoms and 3 = unbearable symptoms, with a maximum score of 51. The index indicates a health related quality of life score for those suffering from menopausal symptoms either due to natural or chemically induced causes.

Results

No significant difference in KI scores were seen at baseline for the two groups of women. A significant improvement in health-related quality of life (measured with KI) was observed during treatment that lasted for a further 3 months post treatment in patients receiving traditional Chinese medical (TCM) acupuncture. There was no significant improvement in KI values in the sham group.

Nineteen participants did not return written statements. A total of 61 statements were received, 33 of these women had previously been treated with traditional Chinese acupuncture, and the other 28 had received sham acupuncture. The mean age of the participants was 51.3 (52.5 the TCM group and 50.2 in the control group). The women provided their answers by mail.

In line with international guidelines, post menopausal women switch to an aromatase antagonist after 2 years. Twenty-eight women (12 in the TCM group and 15 in the control group) had, during the 2 year gap between the time they finished treatment and the time they made their statements, switched to an aromatase antagonist.

Statistics

A mixed models procedure with diagonal covariance matrix was used for statistical analysis. Comparison of baseline score (time 1) between the sham group (n = 45), mean KI 15.8 and acupuncture group (n = 43), mean KI 13.4 showed no statistically significant difference. When analyzing differences following treatment time (time 2) (mean KI 8.4 versus mean 11.7) and after 3 months (time 3) (mean KI 10.0 versus mean 13.7), a statistically significant difference was found. However, no such difference was found on analyzing time 4, after 2 years (Table 1).

Pairwise comparisons at time intervals for all patients.

Group 1 - Acupuncture.

Group 2 – Sham/control (Figure 1).

At baseline: no statistically significant difference between the groups is observed (95% CI overlap for time 1- baseline).

Time 2 (end of treatment): a statistically significant difference between the groups.

Time 3 (12 weeks post treatment): a statistically significant difference between the groups.

Time 4 (2 years post treatment): there is no statistically significant difference between the groups.

Discussion

Our study showed lasting effect of a 10 week acupuncture treatment course, measured by the KI up to 2 years after initial treatment. To our knowledge this is the first randomized, controlled long-term study measuring quality of life of breast cancer patients, after a series of acupuncture treatments. Although this study is of limited size it supports previous RCT's that demonstrate that acupuncture is a safe and effective alternative to HT for relieving vasomotor problems, and other symptoms usually associated with menopause. All patients completed acupuncture treatment, and 76% returned questionnaires 24 months later, indicating a positive attitude to acupuncture in this patient group.

Wider long term effects of acupuncture were demonstrated by using KI, extending focus beyond the main complaint of HF, closely followed by sweating and insomnia; these three symptoms have been shown to affect each other, and similarly improve simultaneously (Hervik and Mjaland 2009; Savard and Morin 2001). The Kupperman menopausal index has been used widely in studies of climacteric symptoms, both in natural and chemically induced menopause, evaluating symptom severity and

Table 1 Mean KI scores for groups 1 and 2 at time intervals (a)

Group F	Time	Mean	Std. error	df	95% confidence interval	
					Lower bound	Upper bound
1	1	15,767	.688	88	14.399	17,136
	2	8,372	.649	88.000	7.081	9.663
	3	10,023	.656	88.000	8.719	11,327
	4	11.742	.925	59	9.890	13.594
2	1	13.422	.673	86	12.084	14.760
	2	11,711	.635	88,000	10.449	12,973
	3	13,689	.641	88.000	12.414	14.963
	4	12,300	.941	59	10,418	14,182

a. Dependent Variable: Measure.

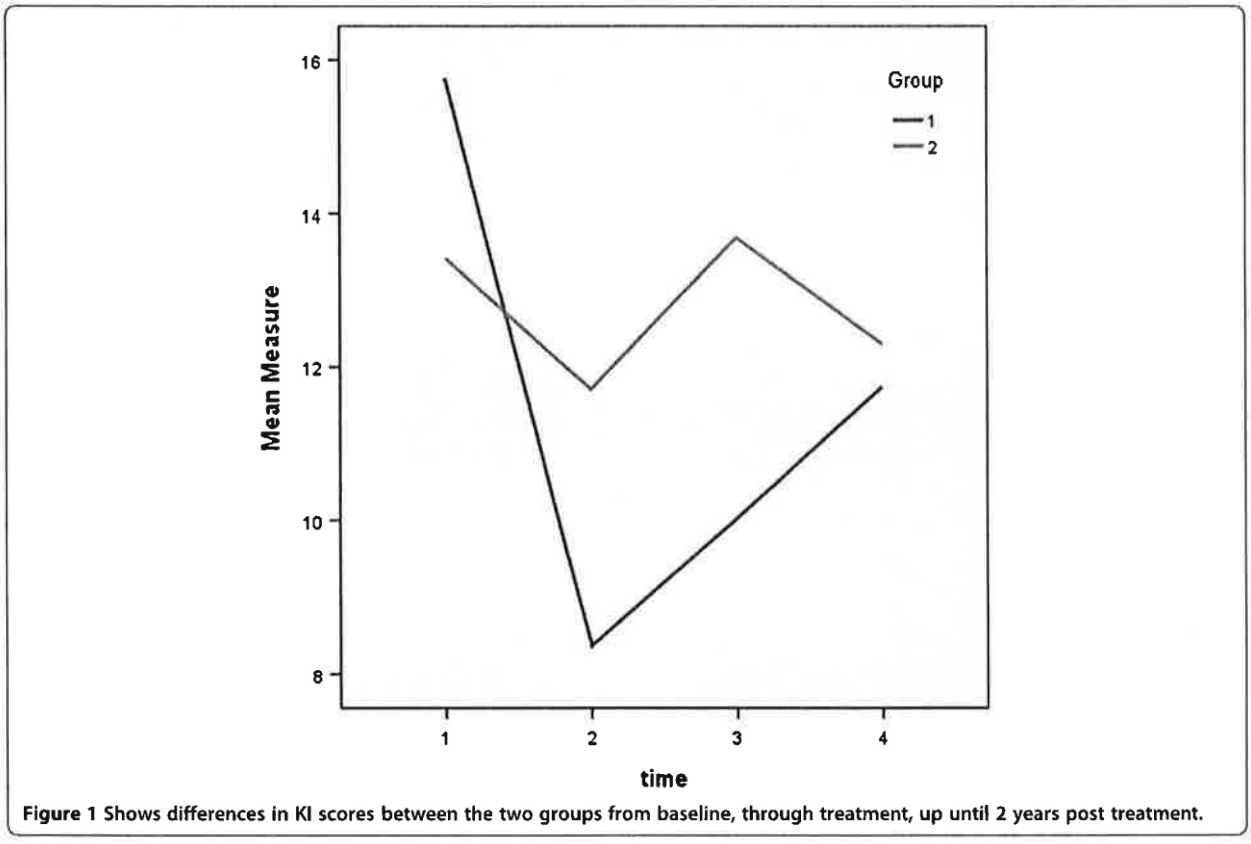

Figure 1 Shows differences in KI scores between the two groups from baseline, through treatment, up until 2 years post treatment.

measuring the effect of intervention. It contains the most common symptoms associated with menopause, but has some limitations; although vaginal dryness is measured, loss of libido, a symptom around 70% of women taking estrogen antagonists complain of (Garreau et al. 2006) is not. Also, unlike the menopausal rating scale (MRS) KI is not validated according to psychometric standards, though depression is included as one of the parameters. Reduced cognitive function is a worrying symptom associated with estrogen-antagonist therapy, with as many as 46% of the 1,199 women included in a survey conducted by Breast Cancer Action reported experiencing mental fuzziness (Zivian et al. 2008). Other indexes, such as MRS or SF36, might have provided a more comprehensive demonstration of health related physiological and psychological quality of life, however KI is quick and easy to fill out possibly increasing compliance.

Although hormonal replacement therapy (HT) appears to be the most effective treatment for HF with a rate of around 80% efficacy in healthy women (Albertazzi 2007), the use of HT is contraindicated in women with breast cancer. Non hormonal treatments available for the management of vasomotor symptoms associated with menopause include clonidin, gabapetin and selective serotonin reuptake inhibitors; adverse effects to these drugs are not uncommon, they include hypotension, cognitive disruption, headache, weight gain, nausea etc. (Hickey et al. 2008). The use of selected serotonin reuptake inhibitors (SSRI's), anti-depressives used to treat both hot flashes and depression in women with breast cancer, has recently been the focus of controversy. It has been suggested that SSRI's can inhibit the conversion of Tamoxifen to the anti-estrogen endoxifen, and therefore reduce the effectiveness of Tamoxifen in patients taking both drugs (Stearns et al. 2003; Goetz et al. 2007).

During menopause low levels of estrogen and high levels of follicular stimulating hormone (FSH) are related to vasomotor symptoms in healthy women. To be a safe treatment acupuncture should not increase levels of estrogen in women with ER+ breast cancer. A study by Dong demonstrated that there was no increase in estrogen in patients treated with acupuncture (Dong et al. 2001). This finding was confirmed by Liljegren who found no significant differences in hormone levels in blood, including FSH and estradiol, in a study comparing the effect of true acupuncture to sham in 84 Tamoxifen medicated breast cancer patients with HF (Liljegren et al. 2012). Hormone levels were tested at baseline and one week after the end of five weeks of treatment.

The HABITS study (Holmberg et al. 2004) randomized 434 women with previous breast cancer to either HRT or best treatment without hormones; the study was stopped

after 26 women in the HRT group suffered a new breast cancer event compared to 7 women in the non HRT-group, when 345 of the participants were followed up after 2 years. Treatment in the non-HRT group included electro-acupuncture which proved to be less effective that hormonal therapy in the reduction of HF, though more effective than placebo long-term. Since a higher recurrence rate of breast cancer in the HRT group was observed acupuncture appears to be a safer treatment option.

If acupuncture has the potential to influence thermoregulation via the stimulation of neurotransmitters, providing not only short-term, but also a long-term reduction in the amount of HF, it provides a viable alternative to hormone therapy and other non-hormonal drugs that are not without side-effects. Acupuncture is a cheap alternative, and is relatively safe when carried out by a qualified practitioner. Furthermore since HF have been shown to have a profound influence on sleep patterns, treatments that indirectly affect sleep may provide a better quality of life; possibly an explanation as to why acupuncture treatment was effective for up to two years. The resulting reduction of HF and establishment of better sleep patterns after acupuncture may have provided patients with a higher quality rehabilitation period, less tired and more able to contribute to work and family commitments. Psychological anxiety and depression are common symptoms among breast cancer patients for years after diagnosis and treatment, often these psychological symptoms are accompanied by sleep problems (Montazeri 2008). This invites speculation that less fatigued patients may possibly experience a reduced amount of psychological symptoms, and have enough energy to deal with other side-effects associated with estrogen-antagonist therapy.

Symptoms that often accompany HF such as sweating, dizziness, palpitations and nausea, leave women feeling less confident about their appearance in public, and anxious about the possibility of stressful situations that often provoke HF. Treatments such as acupuncture, designed to reduce HF and thereby the likelihood of running make-up, sweat soaked hair and clothes, and the fear of body odor, can interrupt a vicious cycle of anxiety and stress which in turn provoking even more vasomotor symptoms.

Side-effects of estrogen-antagonists can lead to discontinuation of anti-estrogen medication; an action which could have serious consequences. Non hormonal treatments are needed to effectively reduce at least some of these symptoms; acupuncture is a viable treatment method. This study has demonstrated that the long term effect of acupuncture decreases with time, from around 12 weeks post-treatment, it is not significant two years post-treatment. Although differences between the group receiving TCM acupuncture and those receiving sham after two years are not significant, the effect of treatment may still be present, but can have lost statistical significance due to limited sample size.

Conclusion

Previous RCT's have indicated that acupuncture reduces hot flashes, and betters life quality for up to three months post-treatment in women with breast cancer. This study suggests that these effects may be longer-term, however they were not significant 24 months after treatment.

Competing interest

The authors have no conflict of interest.

Authors' contributions

Study concept and design –JH and OM. Acquisition of data – JH. Analysis and interpretation of data JH and OM. Drafting of manuscript – JH. Critical revision – OM. Both authors have read and approved the final version of the manuscript.

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APPENDIX

STUDY INFORMATION

Sykehuset i Vestfold
HF Tønsberg

We would like to invite you to take part in a research study: CAN ACUPUNCTURE REDUCE HOT FLASHES IN BREAST CANCER OPERATED WOMEN MEDICATED WITH ANTI-OESTROGENS?

The intention of the study is to compare two methods of acupuncture; the aim is to reduce hot flashes (a side-effect of anti-oestrogen treatment). Thin acupuncture needles are inserted into particular areas on the body, each treatment takes 30 minutes. Treatment methods are predetermined, and set according to the study plan, they cannot be chosen by either you or your doctor/therapist.

Fifteen treatments will be given twice weekly for the first 5 weeks, thereafter once a week for the following 5 weeks.

There will be no charge for acupuncture treatments associated with the study. If you would like to take part you will be asked to note the total number of hot flashes day and night, one day each week. Hot flash recording starts one month before treatment is initiated, during 10 weeks of treatments, and throughout the following 12 weeks. We will also ask you to fill out a simple questionnaire concerning your health before the first treatment, after the last treatment, three, and 24 months later.

Data including diagnosis, medical treatments and study results will be stored in the hospital data system, personnel authorized to access this information are bound by patient confidentiality. Results of the study will be published as statistics and tables; patient identity will be kept secret.

The study team includes: Dr Hans Aas (medical responsibility), oncology nurse Mette Amundsen (information and registration) and acupuncturist/physiotherapist Jill Hervik (project leader, responsible for patient treatment).

In order to qualify for the study chemotherapy and/or radiation treatments must be completed, and you should have used the anti-oestrogen medicine Tamoxifen for at least three months. You should have

had no acupuncture treatment previously, and are not currently undergoing any other type of treatment aimed at reducing hot flashes, including medication or any type of alternative treatment.

Whether you choose to take part in the study or not, you will be offered acupuncture treatments and other medical treatments appropriate for your diagnosis. Study participation is optional, there is no obligation to complete treatments or record statistics; you are free to stop participation without giving a reason, this will not affect your medical treatment in any way.

If you qualify for this study, are bothered by hot flashes, and wish to take part, talk to your doctor about a referral or contact Mette Amundsen at The Breast Centre, Sykehuset i Vestfold.

CONSENT FORM

I would like to take part in the study CAN ACUPUNCTURE REDUCE HOT FLASHES IN BREAST CANCER OPERATED WOMEN MEDICATED WITH ANTI-OESTROGENS?

I have received information about the purpose of the study. I understand that my involvement means that I am expected to note the number of hot flashes affecting me one day a week from 4 weeks prior to treatment, during 10 weeks of treatments and for a further 12 weeks. I am also aware that I will be asked to fill out a questionnaire at 4 time points, the last time point being 24 months after the last acupuncture treatment.

I have been informed about any possible discomfort due to acupuncture treatment.

I understand that I am free to withdraw from the study at any point in time and that withdrawal will not affect my medical care.

I have read the patient information sheet and have received a copy of this consent form.

Name…….

Date…….

REGISTRATION

REGISTRERED BY..... DATE.....

PATIENT D.O.B.....

NAME.....ADDRESS.....

TELEPHONE NO.....

1. POSTMENOPAUSAL. YES ..... NO.....

IF YES, LAST MENSTRUATION.....

2. PREVIOUS USE OF HRT YES..... NO.....

IF YES FROM..... UNTIL.....

3. OPR. DATE .....

4. TYPE OPERASION: MASTECTOMY .....

LUMPECTOMY .....

AXILLA RESECTION .....

OTHER.....

5. POSTOP. RADIATION YES..... NO.....

6. POSTOP. CHAEMOTHERAPY YES..... NO.....

7. PLANNED USE OF ANTI-OESTROGEN TREATMENT

FROM..... TO..... (YEAR)

8. ALL PRIMERY POSTOP. TREATMENT IS FINISHED INC. RADIATION AND CHAEMOTHERAPY YES..... NO.....
9. THE PATIENT HAS SIGNED A CONSENT FORM IN ORDER TO TAKE PART IN THE RESEARCH PROJECT YES..... NO.....

IF THE ANSWERS TO QUESTIONS 1,8 AND 9 ARE NO, THE PATIENT MAY NOT TAKE PART IN THE STUDY.

HOT FLASH DIARY

Please record the approximate number of hot flashes you experience during the day and night, on the same day each week. Begin recording hot flashes 4 weeks before you commence treatment. We ask you to continue noting the numbers of hot flashes you experience during 10 weeks of treatments, and for 12 weeks after the last acupuncture treatment. Completed hot flash tables can be returned to Wenche Hansen, secretary for the research study, in the stamped addressed envelope enclosed.

Name ..... D.o.B.....

KUPPERMAN INDEX

Name.....

Date of birth.....

Date.....

	No symptoms	Mild symptoms	Moderate symptoms	Severe symptoms
HOT FLASHES				
SWEATING				
SLEEP DISRUPTION				
DEPRESSION				
DIZZYNESS				
TIREDNESS				
JOINT PAINS				
HEADACHE				
PALPITATIONS				
DRY VAGINA				
EXTRA SYMPTOM *				

*Feel free to note a symptom that you consider a side-effect of anti-oestrogen medication (tamoxifen, arimidex, aromasin, femar)

Do you smoke? Yes..... No.....

If so, how many cigarettes each day? .....

Do you drink beer, wine or spirits? Yes..... No.....

If yes, how many drinks have you consumed on average each week during the last year?

Beer..... Wine.....Sprits.....

LETTER TO PATIENTS AT 2 YEAR FOLLOW-UP

Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial

Hello again!

The above study is drawing to a close; we would like to thank you for your participation and would like to invite you to provide some information about your present health situation.

We would be grateful if you could fill out the enclosed form and return it in the stamped addressed envelope enclosed.

All information will be treated confidentially.

On behalf of the study team

Wenche Hansen
Pain Clinic, Vestfold Hospital.

LONG TERM FOLLOW UP QUESTIONNAIRE

Name.....D.o.b.....

Since finishing acupuncture treatments at the pain clinic have you:

1. Had anymore treatments related to your breast cancer diagnosis, e.g chemotherapy/radiation?

   If so, when?

   What type(s) of treatment?

2. Had more hot flashes?

   If so when did these symptoms start to increase?

   3 Received any more acupuncture treatments for hot flashes since your last treatment at the pain clinic?

   If so, how many?

   When?

4. Received any other type of treatments or medications aimed at reducing hot flashes?

   If so, what?

5. Do you still use an anti-oestrogen medicine, e.g. tamoxifen, arimidex or femara?

   If yes, which medicine?

   If no, when did you stop taking the medication?

6. Would you like to share your thoughts/experiences related to your breast cancer diagnosis, treatments or anything else? If so, please write a statement below, the length of which is up to you.