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Acupuncture treatment for hot flushes in women with breast cancer and men with prostate cancer.

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Det är stoltare, våga sitt tärningskast,
än att tyna med slocknande låge.
Det är skönare lyss till en sträng, som brast,
än att aldrig spänna en båge

Verner von Heidenstam, Åkallan och löftet 1902

To Janne, Emelie and Casper

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Summary in Swedish- svensk sammanfattning

Behandling av vegetativa besvär med akupunktur hos män med prostatacancer och kvinnor med bröstcancer.

Vegetativa besvär, i form av värmevallningar och/eller svettningar, är vanliga problem hos kvinnor i klimakteriet. Besvären kvarstår i genomsnitt under 5 år, men kan bestå livslångt hos en del kvinnor. De vegetativa besvären påverkar livskvalitet och sömn negativt, och är för många kvinnor det mest besvärande symptomet under klimakteriet. Dessa besvär uppträder också hos friska äldre män, även om de är betydligt mindre vanliga än hos kvinnor.

Kvinnor med bröstcancer kan uppleva samma besvär, men ofta ännu starkare och mer långvariga, troligen beroende på den cellgiftsbehandling och den anti-hormonella behandling de får mot bröstcancer, som också kan orsaka ett för tidigt klimakterium.

Hos män med prostatacancer som inte går att operera bort av olika skäl, är en vanlig cancerbehandling medicinsk eller kirurgisk kastrationsbehandling, som tar bort testosteron effekten och därmed bromsar cancer. Behandlingen förorsakar hos uppemot 75 % av männen vegetativa besvär, med negativ påverkan på livskvalitet och sömn. Dessa besvär är mångåriga, och av många män beskrivs de som den mest besvärande biverkan av cancerbehandlingen.

Många försök har gjorts för att förstå uppkomstmekanismerna för de vegetativa besvären. Signalsubstanser som endorfiner, nor-adrenalin och serotonin tros vara involverade på central nivå. Perifert är det tidigare visat att urinutsöndringen av Calcitonin Gene Related Peptide (CGRP), en kraftigt kärlvidgande neuropeptid, minskar hos kvinnor under effektiv behandling av flusherna. CGRP stiger även momentant i plasma under en flush, hos kvinnor med flusher och också hos män med flusher pga kastrationsbehandlad prostatacancer. Man kan därför överväga om U-CGRP kan användas som en biokemisk markör för effekten av behandling av vegetativa besvär.

Den mest effektiva behandlingen mot dessa vegetativa besvär hos kvinnor är hormonbehandling, med östrogen. Det var tidigare oklart om bröstcancer påverkades negativt av hormonbehandling, men idag visar data att hormonbehandling ökar risken för att utveckla, eller få tillbaka bröstcancer, varför hormonbehandling inte längre kan rekommenderas hos kvinnor som haft bröstcancer. Hormonbehandling hos män med kastrationsbehandlad prostatacancer är behäftad med risker för allvarliga biverkningar, och risk att cancer aktiveras, och således inte ett lämpligt alternativ för denna patient-

grupp. Andra behandlingar som studerats är SSRI/SNRI, gabapentin, clonidin, belladonna ergotamin, fytoöstrogener, tillämpad avslappning, motion och akupunktur.

SSRI och SNRI har måttliga effekter på de vegetativa besvären, men är behäftade med biverkningar och inga långtidsuppföljningar finns publicerade. Dessutom kan denna behandling försämra effekten av en viss typ av cancerbehandling (med tamoxifen). Övriga preparat har tveksam effekt, och inte heller de är utvärderade någon längre tid. Tillämpad avslappning och motion har måttliga effekter på de vegetativa besvären, och behöver studeras ytterligare.

Akupunktur har hos kvinnor i klimakteriet visat sig vara effektiv mot de vegetativa besvären, men har i endast begränsad utsträckning studerats på kvinnor med bröstcancer. Hos män med prostatacancer var problemet med värmevallningar och svettningar inte så uppmärksammat och innan vår pilotstudie (delarbete I) som publicerades 1999, fanns det inga studier som visade effekt av akupunktur på värmevallningar och svettningar hos män med kastrationsbehandlad prostata cancer. Behovet av alternativa behandlingar av vegetativa besvär hos kvinnor med biverkningar av eller kontraindikationer för östrogenbehandling, och fr.a. för kvinnor och män med bröst- respektive prostatacancer och vegetativa besvär samt de tidigare lovande resultaten med akupunkturbehandling är bakgrunden till detta avhandlingsarbete.

Delarbete I utgörs av en så kallad ”pilotstudie” där sju män med prostatacancer och kastrationsbehandling erbjöds akupunktur för sina besvär av vallningar och svettningar. Sex män fick minst 10 veckors behandling, och de följdes även upp tre månader efter att behandlingen var avslutad. Antalet värmevallningar och svettningar/24 h redovisades innan behandling, vid 2, 6 och 10 veckors pågående behandling, samt 12-14 veckor efter att behandlingen hade avslutats. Detta är den första studien som gjorts av akupunkturbehandling på män med prostatacancer och värmevallningar.

I *delarbete II* inkluderades 45 kvinnor i en delstudie till den redan pågående internationella HABITS-studien (Hormones After Breast Cancer – Is It Safe?). HABITS-studiens syfte var att undersöka om kvinnor med tidigare bröstcancer och vegetativa besvär, har en ökad risk att återfå sin bröstcancer om de behandlades med hormoner för sina besvär, jämfört med annan behandling. I vår delstudie, Acu-HABITS, inkluderades kvinnor i den Sydöstra sjukvårdsregionen, med vegetativa besvär och tidigare bröstcancer. De randomiserades till antingen hormonbehandling i två år, eller elektrostimulerad akupunktur i 12 veckor. Totala uppföljningstiden var två år. *Delarbete II* analyserade förändringar i antalet värmevallningar och svettningar, besvär av dessa, samt utvärdering av klimakteriebesvär med ett specifikt instrument (Kuppermann’s Index) under behandlingsperioden och efterföljande uppföljningstid.

I *delarbete III* analyserades livskvalitet data från Aku-HABITS studien. Dagböcker, ett generellt livskvalitetsformulär samt ett livskvalitetsformulär inriktat på klimakteriebesvär analyserades för att utvärdera om akupunktur eller hormonbehandling på-

verkade livskvalitet och sömn hos kvinnor med bröstcancer och värmevallningar. Vi utvärderade också om livskvalitet och sömn var associerat till de vegetativa besvären.

I *delarbete IV*, kallad ”Randomized Acupuncture study of Men with Prostate cancer”, RAMP, randomiserades 31 män med kastrationsbehandlad prostatacancer och vegetativa besvär mellan elektrostimulerad eller traditionell akupunktur under 12 veckor, och följdes sammanlagt under 1 år. Delarbete IV analyserade förändringar i antalet värmevallningar och svettningar, samt besvär av dessa, under behandling och efterföljande uppföljningstid. U-CGRP analyserades för att se om förändringar i vegetativa besvär korrelerade till förändringar i urinutsöndringen av CGRP per dygn, och således om CGRP kan betraktas som en markör för de vegetativa besvären.

I *delarbete V* analyserades dagböcker och generella livskvalitet data från samma patienter som studerats i delarbete IV. Vi gjorde analyser för att mäta om akupunktur påverkar livskvalitet och sömn hos män med kastrationsbehandlad prostatacancer och vegetativa besvär liksom om livskvalitet och sömn var associerade till vegetativa besvär.

Delarbete I, II och IV visade att akupunktur under 12 veckor minskade antalet svettningar och värmevallningar, samt besvär av dessa med mer än 50 % hos majoriteten av kvinnorna och männen. Vi fann också att effekten kvarstod hos många patienter över ett år, och var därmed både mer långvarig och större än vad tidigare studier visat med placebobehandling i tablettform för vegetativa besvär. Hormonbehandlingen hos kvinnorna var mer effektiv, men den behandlingen fick avbrytas pga att den säkerhetsanalys som gjordes i HABITS, visade att hormonbehandlingen gav fler recidiv i bröstcancer. I studien av vegetativa besvär hos män med prostatacancer fann vi ingen signifikant skillnad i effekt på flusher mellan elektrostimulerad och traditionell akupunktur men en signifikant minskning av antalet flusher per dygn till ungefär hälften i båda grupperna.

I delarbete III och V fann vi att livskvaliteten och sömnen förbättrades hos kvinnorna, där förbättringen var associerad till en minskning i antalet och besvärsgrad av flusherna. Sömn och livskvalitet förbättrades i samma grad hos akupunktur- och hormon-gruppen, trots att hormonbehandlingen hade en större effekt på de vegetativa besvären än akupunktur. Man kan då spekulera i om akupunktur har andra effekter, än att bara minska flusherna. Hos männen skedde ingen markant förbättring i livskvalitet, men viss förbättring i sömn. Däremot uteblev en försämring i livskvalitet hos denna grupp med spridd cancer och som i många fall också hade tecken till cancer progress. Även i denna grupp var förändringen i livskvalitet och sömn associerad med antalet och besvärsgrad av svettningar och vallningar.

Urinanalyserna i delarbete IV visade ingen statistiskt säkerställd förändring i U-CGRP, men en tendens till att minskade flusher sammanföll med minskade U-CGRP mängder, och sambandet mellan flusher och U-CGRP bör studeras vidare.

Sammanfattningsvis finns det få behandlingsalternativ mot värmevallningar och svettningar hos kvinnor med bröstcancer och män med prostatacancer. Akupunktur minskade dessa besvär med mer än hälften, hos de flesta patienter i våra studier. Effekten kvarstod upp till ett år och nio månader efter att behandlingen har avslutats, och behandlingen påverkar livskvalitet och sömn i en positiv riktning, framförallt hos kvinnorna. Akupunktur kan vara ett behandlingsalternativ mot vegetativa besvär när hormonbehandling inte är lämplig, men bör undersökas ytterligare. Mekanismerna bakom akupunkturs effekt är oklara, och bör studeras vidare.

List of publications

This thesis is based on the original publications, which are referred to in the text by their Roman numerals I-V

I. Mats Hammar, Jessica Frisk, Örjan Grimås, Maria Höök, Anna-Clara Spetz, Yvonne Wyon. Acupuncture treatment of vasomotor symptoms in men with prostatic carcinoma: a pilot study. *Journal of Urology* 1999;161(3):853-56.

II. Jessica Frisk, Sara Carlhäll, Ann-Christine Källström, Lotta Lindh-Åstrand, Annika Malmström, Mats Hammar. Long-term follow-up of acupuncture and hormone therapy on hot flushes in women with breast cancer: a prospective, randomized, controlled multicenter trial. *Climacteric* 2008; 11(2):166-74

III. Jessica Frisk, Ann-Christine Källström, Najme Wall, Mats Fredriksson, Mats Hammar. Impact of acupuncture or hormone therapy on Health Related Quality of Life (HRQoL) in women with breast cancer and hot flushes. *Supportive Care in Cancer*. In press. E pub ahead 2011 Apr 6

IV. Jessica Frisk, Anna-Clara Spetz, Hans Hjertberg, Bill Petersson, Mats Hammar. Two modes of acupuncture as a treatment for hot flushes in men with prostate cancer - a prospective multicenter study with long-term follow up. *European Urology* 2009;55(1):156-63.

V. Jessica Frisk, Hans Hjertberg, Bill Petersson, Anna-Clara Spetz, Mats Hammar. The effect of acupuncture on Health Related Quality of life in men with prostate cancer and hot flushes. Submitted

Abbreviations

ADT	Androgen Deprivation Therapy
AI	Aromatase Inhibitor
ANOVA	Analysis Of Variance
BCa	Breast Cancer
BMI	Body Mass Index kg/m ²
CGRP	Calcitonin Gene Related Peptide
EA	Electrostimulated Acupuncture
ER	Estrogen Receptors
GnRH	Gonadotrophin Releasing Hormone
HABITS	Hormones After Breast Cancer – Is It Safe?
HER2	Human Epidermal Growth Factor Receptor 2
HRQoL	Health Related Quality of Life
HT	Hormone Therapy
Hz	Hertz
IQR	Inter Quartile Range
KI	Kupperman’s Index
NKA	Neurokinin A
NPY	Neuropeptide Y
PCa	Prostate Cancer
PgR	Progesterone Receptor
PGWB	Psychological and General Well-Being Index
PSA	Prostate Specific Antigen
RCT	Randomized Controlled Trial
SD	Standard Deviation
SERM	Selective Estrogen Receptor Modulator
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TA	Traditional Acupuncture, without electrostimulation
TCM	Traditional Chinese Medicine
U-	Urine
WHQ	Women’s Health Questionnaire

Preface

Hot flushes and night sweats are common and disturbing symptoms in women around menopause. Women with breast cancer (BCa) experience the same symptoms, often worsened by the cancer treatment. As a medical student in the mid-nineties I took part in some studies with a research group led by professor Mats Hammar at the department of Obstetrics and Gynaecology, Linköping University. The studies concerned menopause, hot flushes, possible mechanisms and treatments. Despite this interest in gynaecological research, my first locum as a physician turned out to be at a department of Surgery, at Ludvika Hospital. There I decided that general surgery was my main interest. Within a few months, I encountered patients with prostate cancer (PCa), treated with castration. Their main complaint was surprisingly the hot flushes from the anti-androgen treatment (ADT), not the cancer in itself and there was no really recommended therapy for the vasomotor symptoms. This gave me the idea to try, by means of a pilot study, one of the treatments we had studied earlier on menopausal women in Linköping, i.e. acupuncture. Thanks to positive colleagues at Ludvika hospital, supportive ideas from Mats Hammar and a physiotherapist with education in acupuncture, it was possible to perform a pilot study, which showed that the men decreased their hot flushes by almost 70 % after 10 weeks of therapy, and still three months after treatment had ended the men had a 50% decrease in number of hot flushes. This study, which is paper I in the present thesis, was the first to investigate acupuncture for hot flushes in men with PCa, and it has been cited frequently. When studying hot flushes, the mechanisms become interesting. It is frustrating to see a phenomenon, try to develop and evaluate treatments for it, and still not in full understand the mechanisms behind it.

That is the reason why CGRP (Calcitonin Gene Related Peptide) became interesting, a neuropeptide that I studied as a medical student in several ways, for an example in my female student colleagues' 24-h urine collections ¹ and in skin biopsies in postmenopausal women, and CGRP has followed me through the hot flush studies, while still leaving me bewildered and yet fascinated.

Introduction

It has been shown that men with PCa, castrationally treated with anti-androgen treatment (ADT), and women with BCa experience hot flushes, which can be very distressing, and long lasting²⁻⁴. Few treatment alternatives have been shown to be effective and safe^{5,6}. The incidence of both BCa and PCa is increasing, but mortality is decreasing, resulting in a growing group of surviving patients with a history of cancer and hot flushes. There is thus a need to find alternative treatments for the hot flushes in these growing patient groups. The encouraging result from the pilot study of acupuncture treatment of hot flushes in men was the main reason for me that led me to continue the work to assess acupuncture as a possible treatment for these groups of cancer patients. The mechanisms behind the flushes are also puzzling, where CGRP, a vasodilating and sweat gland stimulating neuropeptide might be a component.

Definition

Hot flushes

A hot flush is described as a sudden onset of heat in the upper trunk, spreading to the arms and face, often with subsequent sweating and later a chill. The combination of hot flushes and sweating are often denoted as vasomotor symptoms, or vegetative symptoms and may occur at daytime, but also at night ³. Hot flushes are defined in this thesis as the hot flushes that are secondary to a decline in the production of the sex steroids estradiol and testosterone. Hot flushes could also arise from other diseases, or as a paramalignant phenomenon and as side effects from a number of drugs. These kinds of hot flushes are not discussed further in this thesis but should be considered in the clinical situation, and it is probable that these flushes are at least partially caused by other mechanisms.

Health Related Quality of Life (HRQoL)

There is no consensus on the definition of Quality of Life (QoL) or HRQoL, or how to properly measure it. QoL has been defined rather broadly to cover the individual's total perception of QoL, independent of disease or disease specific symptoms. HRQoL seems to be given a narrower definition, usually by investigating and describing how a patient group with a certain disease or condition is affected by, for example, a treatment or a symptom (related to the specific disease or condition). HRQoL is in this thesis defined as "an individual's perceived physical, mental and social health status affected by cancer diagnosis or treatment" ⁷, where, in other studies, the definition could be used, and modified to refer to a disease or condition other than cancer, such as menopause for example.

Sleep

Sleep is an important factor that affects overall HRQoL. There is no consensus on the definition of sleep, just as there is no consensus on the definition of HRQoL. Sleep may be looked on from physiological, behavioural and psychological perspectives, and Kryger et al defined sleep as "a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment or a temporary loss of consciousness" ⁸. In this thesis, the parameters of sleep are defined as the subjectively reported number of times woken up/night and the number of hours slept/night.

Breast cancer and prostate cancer

Incidence of breast cancer

BCa is the most common cancer in women accounting for about $\frac{1}{4}$ of the total new female cancer cases⁹. The BCa incidence in women seems to be increasing worldwide¹⁰, even though during the past few years, reports of a decreased incidence have been published, related in time to a lower use of hormone therapy (HT)¹¹⁻¹³. The age-standardized BCa incidence in Sweden has increased by 0.8 -1.2 %/year in the past 20 years and was 145.2/100 000 in year 2009, compared to 135.1/100 000 in year 2000¹⁴, resulting in 7300 new BCa cases in Swedish women in 2009. The highest incidence rates in the world are reported from Europe, North America, Australia and New Zealand, with lower incidence rates in parts of Asia and Africa⁹.

Factors such as early menarche, pregnancy at older age, decrease in breast feeding, lower number of births, late menopause, use of HT and contraceptive pills, and diet are changing worldwide, with a possible increasing effect on BCa development⁹. Mode of registration, prevention and screening also affect the incidence rate. In addition, improved diagnostic tools, and earlier diagnoses, with effective treatment methods lead to an increasing number of women with a history of BCa⁹.

Incidence of prostate cancer

The PCa incidence has declined in some countries, but increased in most⁹. In Sweden, the age-standardized incidence has increased with 2.7%/year, and was 223.7/100000 during 2009, compared to 197.7/100000 in 2000, with 10300 new PCa cases reported in Sweden in 2009¹⁴.

PCa is the most common male cancer in Europe, North America and parts of Africa, being over 1/3 of male cancers, and this is also where the incidence rates are the highest⁹. These differences may be due to the most common risk factors for PCa: age, ethnic origin and heredity, but also environmental factors, differences in screening activities and registration routines for cancer¹⁵. Since the number of men above 65 years of age is expected to increase four-fold world-wide between 2000 and 2050, with an increased life expectancy from 63.7 to 74.4 years, we can expect a continuous rise in the incidence of PCa¹⁶. The prevalence of patients with a history of PCa will also increase due to more sensitive diagnostic tools and more effective treatment.

Staging of breast and prostate cancer

The most widely used system for staging cancer is the TNM (Tumour, Nodes, Metastasis) system. It describes the extent of the primary *tumour* (T stage), the absence or presence of local lymph *nodes* metastases (N stage) and the absence or presence of distant spread *metastasis* (M stage)¹⁷.

The staging system provides a strategy for grouping patients with respect to prognosis. Therapeutic decisions may be supported by the staging system, when histological and receptor aspects, menopausal status (BCa), general health, age, risk factors, and HRQoL are considered. TNM is also a tool in research, because study populations may be strictly defined. The TNM classification is essentially the same for all cancers, but specific details are included for each type of cancer.

Prostate cancer

Diagnosis of PCa

The main diagnostic tools used for PCa include digital rectal exam, serum concentration of prostate specific antigen (PSA) and transrectal ultrasonography. PSA is produced almost exclusively in the prostate gland, and is normally excreted in the semen. The definite diagnosis is made by histopathological examination of prostate biopsy cores or TUR-P (transurethral resection of the prostate) specimen, which also gives the differentiation grade of the tumour, predicting the prognosis and directing the choice of treatment. The most common type of PCa is adenocarcinoma¹⁸.

The differentiation grade is given as the Gleason Score, which describes the tumour's architecture, graded from 1-5 (1= well differentiated, 5=low differentiated), and is the sum of the two most dominant patterns of growth (the most dominant pattern + the second most dominant pattern = Gleason score)¹⁹.

To evaluate the lymph node status, a dissection of the pelvic lymph nodes is recommended. Metastases are found mainly in the bone, but also in the liver and lungs. The presence of cancer growth in lymph nodes or metastases is highly prognostic and directs the treatment. Together with palpation and biopsy of the primary tumour, these findings decide the TNM status of the PCa.

Screening for PCa with PSA is advocated in some countries but not in others, and the debate is on-going about the benefits of screening for PCa. Finding a small, not clinically significant cancer, may impair the patient's HRQoL, but may save some patients from an advanced disease and mortality in PCa. The European Association of Urology Guidelines conclude that there is not, up to this date, sufficient evidence to recommend a wide-spread screening for PCa with PSA, and a Cochrane analysis suggests that screening is not beneficial for individuals with a shorter life expectancy than 10-15 years^{20 21}.

Despite the increased use of PSA to detect PCa at an early stage, locally advanced or metastatic disease is found in almost 10% of European patients screened in a multi-centre RCT²².

Treatment of PCa

Depending on the TNM status, Gleason Grade, PSA levels, patient's age, concomitant disease, sexual function and the patient's preferences, treatment is chosen and individualized.²⁰ The dilemmas are to treat the cancer and prevent death from PCa, and at the same time avoid treatment side effects and impaired HRQoL. If the cancer is localized only within the prostate gland, then radical prostatectomy, radiation therapy or active surveillance is suggested^{20 23}. To treat a locally advanced PCa, without metastases, radical prostatectomy, radiation therapy, anti-androgens or androgen deprivation therapy (ADT) are the options. Recommended therapy for metastatic, locally advanced PCa, and for biochemical recurrence (i.e. PSA increase only) is ADT by bilateral orchiectomy or administration of Gonadotrophin Releasing Hormone-analogue (GnRH-a) since androgens are essential for growth of cancer in the prostate^{18 24 25}.

ADT results in a lack of testosterone, which induces apoptosis in the prostate gland cells and inactivates the tumour. Orchiectomy is an irreversible, cheap, safe treatment that rapidly decreases testosterone levels by extirpation of the main testosterone producing organ. Orchiectomy may be chosen when there is metastatic growth that for example causes severe pain or spinal cord compression. GnRH-a is a reversible treatment that reduces testicular testosterone production by down regulating the GnRH receptors, with discontinued LH and FSH secretion. Estrogen treatment is sometimes used as a PCa treatment, inhibiting the LH-secretion, but is associated with risks of cardiovascular events²⁶. ADT have side-effects like vasomotor symptoms, loss of libido, erectile dysfunction, anemia, bone loss and even fatigue and depressed mood, which may affect HRQoL negatively²⁷. In 2008, more than 20% of the diagnosed PCa cases in Sweden were locally advanced tumours, and of all the newly diagnosed PCa's 30% received ADT in some form²⁸.

Anti-androgens, competing with androgens at the receptor level in the prostate cell, like bicalutamid and cyproterone acetate may be recommended to patients with a localized or a generalized disease, mainly if impotence is to be avoided.

Not all patients respond to ADT, and some develop a resistance to the treatment with progress of the disease. These patients have a poor prognosis where palliative chemotherapy can be a choice for some patients. Pain control, blood transfusions, antiemetics, hot flush treatment and supportive care should be considered to give a good palliative treatment for this patient group²⁸.

Breast cancer

Diagnose of BCa

For BCa the TNM classification is used as a prognostic tool, along with the tumor biology and histopathology. The most common histopathological type of BCa is invasive

ductal cancer, which represents up to 85% of all invasive BCa, whereas invasive lobular cancer represents 5-15%. Cancer in Situ is also of ductal or lobular origin ^{29 30}.

The BCa diagnose is preferably made with a triple–diagnostic approach, with clinical examination of the breast and axillas, imaging (usually mammography) and needle biopsy. Sentinel node-biopsy and axillary lymph node dissection are not only elements of a treatment, but are also a diagnostic tool that, together with the receptor status, histopathology and TNM class, directs the further treatment to adjuvant endocrine treatment, chemotherapy, monoclonal antibodies and/or radiation therapy ^{29 30}.

The presence of estrogen (ER) and progesterone receptors (PgR) predicts responsiveness to endocrine treatment ³¹, and 70-80% of invasive BCa tumours express hormone receptors. Another receptor, Human Epidermal growth factor Receptor 2 (HER2) is a membrane tyrosine kinase and oncogene, that is amplified and overexpressed in some breast cancers ³²

Treatment of BCa

Primary treatment of BCa is surgery, total mastectomy or breast conserving surgery with partial mastectomy. Some patients are treated preoperatively with chemotherapy, in order to decrease the tumour size. Radiation therapy is offered to patients with partial mastectomy, and some women with total mastectomy ^{29 30}

Adjuvant endocrine treatment is recommended if the tumour is ER or PgR positive. Tamoxifen, a Selective Estrogen Receptor Modulator (SERM), is the oldest, and for many years the most commonly used endocrine treatment, but now other SERMs are also used. Treatment with SERM results in tumour depression, but also anti-estrogenic side effects, like hot flushes and night sweats, vaginal atrophy, arthralgia and sexual dysfunction. There is also a risk for thromboembolic events, stroke and endometrial cancer ³³. SERMs are better tolerated than chemotherapy, and it is recommended that SERMs be used for at least five years after diagnosis ³⁴, if not switched to other treatment. In postmenopausal women, Aromatase inhibitors, AI, should be suggested as adjuvant endocrine treatment³⁵. AI prevent the peripheral metabolism of androgens to estrone and estradiol ³⁰, and are associated with a risk of side effects such as hot flushes, joint aches, osteoporosis and bone fractures.

Monoclonal antibodies, (trastuzumab) could be used in targeting the HER2 receptor at the cancer cell-membrane and decreasing the growth rate of the tumour. In some patients with generalized disease, chemotherapy may be added ³⁰.

In summary, the BCa treatment needs to be individualized, taking into account the TNM stage, the ER and PgR receptors and HER2 status, heredity, age, concomitant diseases, HRQoL and the patients' preferences. A multidisciplinary approach is necessary, since the diagnosis requires combining at least knowledge of surgery, oncology, pathology, radiology and caring science. Several large studies are conducted, and still on-going, on how to optimize the adjuvant endocrine treatment for the differ-

ent patient groups. Length and timing of treatment, alterations between SERM and AI, and combinations with chemotherapy are all being studied, and guidelines, both regional and international, are written to help the clinician treat their patients in an optimal way^{29 30 35 36}.

Hot flushes

The hot flushes we have studied are secondary to a decline in the production of the sex steroids estradiol and testosterone either due to the normal menopausal transition in women, or effects from cancer treatment on gonadal sex steroid production in women and men. The prevalence of hot flushes in premenopausal women is about 15-30%, in perimenopausal women 35-50%, and 30-80 % in postmenopausal women³⁷. The hot flushes persist in median for five years, but may last lifelong^{38 39}. Hot flushes are present in most societies, but vary widely in prevalence, probably due to factors like diet, lifestyle, genetics, ethnicity, socioeconomic factors, BMI, climate and attitude towards aging^{40 41}.

In healthy men, there is an age-dependent lowering of testicular testosterone production. This may explain why about a third of healthy men over 55 years of age experience hot flushes, and half of those men describe them as bothersome⁴². However, these flushes do not occur to the same extent as in menopausal women or men with PCa and ADT.

Hot flushes in BCa and PCa

Hot flushes are more common in BCa- and PCa- patients than in healthy subjects. For these women the symptoms are more frequent, last longer, are more distressing and are also related to breast cancer treatment, such as tamoxifen^{3 4 43}. Breast cancer treatment may impair ovarian function which may thus either cause menopause or make menopausal symptoms worse. Impairment of gonadal function is also the aim of ADT in men with generalised PCa, thus leading to decreasing production of testosterone but increasing the risk of hot flushes.

After three months of treatment with Tamoxifen, almost 40% of the women reported newly emergent vasomotor symptoms⁴⁴, and women who had been on Tamoxifen for less than a year reported hot flushes in 81%, with a majority of those also reporting night sweats. Ten years after menopause, more than 50% of the BCa patients still reported hot flushes, more so if younger age at diagnosis, higher BMI and use of Tamoxifen⁴³. Almost two-thirds of the breast cancer survivors report that hot flushes compromise their QoL, and sleep problems were commonly reported^{45 46}, and the most common request for additional treatment from breast cancer survivors is relief for hot flushes⁴⁷.

In men, the hot flushes were first described by Cabot in 1896⁴⁸, who studied patients who had been surgically castrated as treatment for prostatic enlargement, and described symptoms as “uncomfortable flushes of heat, similar to those experienced by women at the time of menopause”. In 1934, McCullagh and Renshaw concluded that seven of 12 men after orchiectomy, reported hot flushes 4-5 times/day, and that the flushes lasted for many years⁴⁹. When men castrated, medically or surgically for prostate cancer are studied, most studies report hot flushes in 70-80%^{2 50 51}, with up to 27% of the men reporting this as the most troublesome adverse effect⁵². Karling et al reported hot flushes in 68 % of the men during treatment. Five years after start of therapy, 70% of them still suffered from hot flushes, most of them with the same intensity and frequency as when the treatment started², and several men experienced the flushes as being life-long⁵¹. Men with ADT due to PCa have a high cancer-related distress at the start of the treatment, no matter if they experience hot flushes or not. However, if the men have no hot flushes, the distress decreases after three months, but the distress remains at a high level if the men suffer from hot flushes⁵³. This sometimes makes the men discontinue their cancer treatment.

Mechanisms behind the hot flushes

The mechanisms behind hot flushes are thought to be similar in men and women. Hot flushes are probably started centrally in the brain, in the thermoregulatory centre in the hypothalamus. Signals are sent peripherally, through nerves that control sweat gland activity and blood vessel tonus, probably mediated by substances like CGRP that dilates peripheral blood vessels and activate sweat glands, especially on the upper trunk and face. This leads in turn to increased blood flow in mainly the arms and hands and loss of energy from the warm skin, radiating energy to the surroundings and consuming energy when evaporating sweat, all reactions leading to a lowering of the central body temperature. Behavioural reactions, like opening a window, taking off a blanket from the bed or buttoning up also lead to a lower central body temperature. These vasomotor reactions produce a subjective feeling of warmth in the upper part of the body, arms, neck and face, and a blushing feeling. Objective changes can also be measured as increased peripheral blood flow in arms (measured by plethysmography), changing of skin blood flow, measured by laser-doppler flowmetry⁵² augmented skin temperature and improved skin conductance, especially in the sternal region, due to stimulation of sweat glands⁵⁴⁻⁵⁶. If a flush persists for minutes a central lowering of the core body temperature is measurable⁵⁵.

In the healthy individual, it is believed that the thermoregulatory centre has a thermoneutral zone, and a certain set point. Having a thermoneutral zone means that between certain central body-temperature limits, the body does not need to regulate the temperature with changed vasomotion or regulation of sweat gland activity. When the temperature rises, as with physical activity or in a warm surrounding temperature, the

upper limit of the thermoneutral zone is reached or passed, and the hypothalamus sends signals to the periphery, to lower the temperature, by increased peripheral blood flow and sweating. When the production of sex steroids decreases, due to age or medical treatment, the activity of noradrenalin (NA), β -endorphins and serotonin changes, making the thermoneutral zone narrower^{57 58}.

The hypothalamus then seems to react to smaller temperature changes than before, leading to more frequent and sudden increases in peripheral blood flow and activation of sweat glands, which is interpreted as hot flushes. It is not known why the tendency to increase body temperature and then cause reactions in order to decrease the central temperature is more common than the opposite reaction. Chills are sometimes reported after a flush, which is probably the reaction when thermoregulation again tries to increase central temperature to previous levels.

A slightly alternative explanatory theory for hot flushes is that sex steroids, i.e. estradiol and testosterone, have a stabilizing effect on the set point in the thermoregulatory centre, probably by affecting β -endorphins, NA and serotonin.⁵⁹

There is thus no single mechanism that is generally accepted as the mechanism behind hot flushes, but rather a combination of several systems, affecting the thermoregulatory centre in the hypothalamus.

Neurotransmitters involved in the thermoregulation

The peripheral mechanisms behind hot flushes are thus vasodilation and stimulation of sweat gland. Different vasoactive substances such as Vasoactive Intestinal Peptide (VIP), Substance P, Neuropeptide Y (NPY), Nitric Oxide, CGRP, Neurokinin A (NKA) and Adrenomedullin have been speculated as mediators of hot flushes. A Japanese group studied castrated male rats, and injected CGRP, Adrenomedullin or amylin intravenously. An increased skin temperature was shown in the CGRP group, which in turn could be inhibited by a CGRP antagonist or testosterone. Adrenomedullin and amylin, members of the same family as CGRP, did not induce a skin temperature change⁶⁰. Plasma concentrations of VIP, did not increase during a hot flush, whereas CGRP did⁶¹. Substance P is sometimes co-localized with CGRP in nerves⁶², and could hypothetically affect the peripheral thermoregulation, since it is known to produce a vasodilation and edema, partially by releasing nitric oxide. NKA, is related to the sensation of warmth⁶³ and Wyon et al could not confirm an increase of NKA in plasma during a hot flush, but CGRP and NPY increased⁶⁴. In 24 h urine collections, however, only CGRP, but not NKA, NPY or Substance P seemed to change, related to flushes⁵⁹. When studying neuropeptides in plasma as a mechanism of a short hot flush, one needs to take into account the short half-life of neuropeptides in plasma, where the half-life of CGRP is about seven minutes,^{65 66} which makes the timing of the sampling crucial.

Calcitonin Gene Related Peptide (CGRP)

Calcitonin Gene Related Peptide (CGRP) is a 37-amino acid peptide, discovered in 1983⁶⁷. It is produced in nerves, both centrally and peripherally and is widely distributed in the central and peripheral nervous system. Estrogen and progesterone have been shown to stimulate CGRP synthesis in dorsal root ganglia neurons⁶⁸, and sex steroids increase plasma concentrations of CGRP during pregnancy in rats⁶⁹. In female oophorectomized rats, the plasma levels of CGRP were lower than in sham operated rats, with an increased amount of CGRP receptors in the mesenteric arteries, which are involved in vasodilatation. It is therefore hypothesized that a lowering of estrogen actually results in a lower level of plasma CGRP. This could in turn results in an increased amount of CGRP receptors, perhaps even hypersensitive, which, when CGRP is injected, or released from neurons, leads to an elevated skin temperature⁷⁰. The injection of adrenalin in healthy men, resulted in an increase of systolic blood pressure, heart rate and a simultaneous increase of plasma CGRP, suggesting that adrenaline may modulate CGRP release in humans⁷¹.

Peripherally, CGRP is usually colocalized in C-fibers with a range of other peptides⁷². In humans both α -CGRP, and β -CGRP have been described, where the latter is mainly produced in the enteric nerves, and has more than a 90% structural similarity to α -CGRP. CGRP belongs to a family of peptides that include adrenomedullin, mainly produced in non-neural tissues such as vascular tissue and amylin, produced in the β -cells of the pancreas and intermedin. α -CGRP and β -CGRP are most similar in structure and biological activities⁷³.

CGRP has profound effects on the cerebral circulation and also the cerebral as well as peripheral microcirculation and is a very potent vasodilating and sweat gland stimulating neuropeptide. When CGRP is injected intradermally, an increased local blood flow is seen⁶⁷, and when it is distributed intravenously in low doses, it results in facial flushing, and only high doses result in a decreased blood pressure⁷². CGRP appears mainly to act close to the site of its release which may explain why it does not seem to be involved in blood pressure regulation, but rather in micro vascular conditions, such as Raynaud's phenomenon, migraine and possibly hot flushes.

It has been shown that healthy men, who had CGRP injected intravenously, reported warmth on the upper trunk and face, similar to the hot flushes around menopause⁷⁴. The peripheral skin temperature also rise, together with a lowering of the blood pressure and increase of heart rate⁷⁵. Something that also indicates that CGRP is a mediator of the flushes is the fact that our group found that women who decreased their hot flushes decreased their 24 h U-CGRP⁵⁹. Urinary excretion of CGRP over 24 hours is interpreted as proportional to the total release of CGRP during 24 hours, with a potential to catch increases in CGRP, during flushes. Another study showed that menopausal women with flushes had higher U-CGRP levels than both post-, and premenopausal women without hot flushes¹. Both in women with flushes^{64 65 76} and in

men, with castrationally treated PCa and hot flushes⁷⁷, plasma CGRP increased during a hot flush. However, when U-CGRP was measured before and after start of ADT in elderly men with PCa⁷⁷, changes in U-CGRP were not significant, although a majority of the men had developed hot flushes. This leads to questions about problems with consequent collection of urine in the elderly men, and what impact sex differences and a generalized cancer disease have on the metabolism of CGRP before its excretion in the urine.

Monitoring of hot flushes

Numbers of flushes are important, but in the end, the distress the woman experiences by the hot flushes is probably even more important, and should therefore be measured as well, and regarded as an important variable when evaluating treatment effect. Another way of evaluating the numbers of hot flushes, and the distress caused by them together, is the so called “Hot Flush Score”⁷⁸. Numbers (quantitative measure) are multiplied with the distress by flushes (qualitative measure), in a way that numerically amplifies the change induced by the treatment. For example, if the hot flush frequency is reduced by 50%, and the severity or distress by 50% compared to baseline, as from 10x10 to 5x5, the hot flush score decrease is thus from 100 to 25 = 75%, which makes the impression of a larger decrease than that of 50% of frequency or distress in itself.

The number of hot flushes can be measured both objectively, and subjectively. Objective measurements of hot flushes include observation of changing of skin blood flow, measured by laser-doppler flowmetry, skin temperature and conductance measurement, blood flow in arms (plethysmography), and core body temperature measurement^{52 56}. Subjectively, hot flushes can be monitored by means of log-books, with could be manual or electronic. When these methods are compared, some studies have shown high, some low association between subjective and objective monitoring.

It is concluded though, that the hot flush frequency and hot flush severity or distress both have impact on the patients daily life, and should both be evaluated, and that subjective monitoring should be considered as a useful, valid method for measuring numbers of hot flushes. This method is easy to administer, and is a suitable method in clinical studies^{54 79}.

Health Related Quality of Life

In the early 1970's, Quality of Life (QoL) and Health Related Quality of Life (HRQoL) started to interest researchers including and clinicians. HRQoL has become an important aspect to be considered when choosing and evaluating treatments of various diseases. It is no longer only mortality and morbidity that should be considered in deciding on further interventions for a patient, but also HRQoL. HRQoL may be defined as “an individual's perceived physical, mental and social health status affected by

cancer diagnosis or treatment”⁷. Cancer survivors are often adversely affected for many years after treatment by fatigue, depression, pain, sleep problems, sexual dysfunction and physical impairment⁸⁰.

HRQoL in patients with BCa and PCa

The PCa and BCa patients in our studies have many aspects making HRQoL assessment important.

Men with advanced PCa, and mostly age 70 or older, have a chronic disease, with a high risk of progressing further, even if it most often not possible to know, if or when the cancer will progress. There are also multiple symptoms like nausea and pain that may have an impact on daily functions. Social interactions, with worries for family members, or worry about being alone with a severe disease, may impair HRQoL. The knowledge of having a malignant disease that may progress can cause anxiety and sleep problems. Sexual impairment caused by the disease and especially by its treatment may also affect HRQoL⁸⁰.

For women with BCa, the disease often strikes at a younger age, most commonly in mid-life, which is associated with other concerns as well, such as work, family, and menopause. Many women with BCa work at the time of the diagnosis, and sometimes the cancer has an economical impact on the woman’s life as well. Questions about the aesthetics, female identification and sexual impairment are also important, both related to the surgery and the anti-hormonal treatment. Sleep disturbances and fatigue are common⁸⁰ and may be impaired by night sweats, anxiety, nausea and pain.

In both BCa and PCa, hormonal deprivation, due to cancer treatment or menopause, may cause hot flushes and sweating, which often interfere with daily activities, sleep, and HRQoL^{53 79 81-83}, and may make some patients stop their cancer treatment prematurely.

HRQoL in all cancer patients depends on many things, including how long after the diagnosis the HRQoL is assessed, kind of treatment, prognosis, social relations, other life stressors⁸⁴, and also the patient’s age and the culture he/she lives in^{85 86}.

The type of BCa treatment may affect HRQoL, where adjuvant therapy (chemotherapy or endocrine treatment) may impair HRQoL, not only during treatment^{87 88} but also after the treatment has been stopped⁸⁹. The type of negative effects on HRQoL may vary with the type of adjuvant treatment^{87 88} and must be taken in account when choosing the individual patient’s therapy. The type of surgery may matter for the HRQoL, but here, time is also an important factor. In the early post-operative phase, the type of surgery (mastectomy or breast conserving therapy) may not have a large impact on HRQoL, and the advantage of sentinel node biopsy before axillary lymph node dissection at an early stage, seems to decrease with time⁹⁰. However, when a patient has survived the acute phase of the disease, and when post-operative cancer

controls have been performed without signs of recurrence, and chemotherapy or adjuvant treatment may have been stopped, then arm symptoms and body image may become important⁹¹⁻⁹³. For all these reasons, BCa and its treatments cause changes in HRQoL in different phases of the disease⁹⁴.

In women with BCa the HRQoL increases with time from diagnosis^{89 95}, whereas in men with PCa and lymph node metastases, the HRQoL rather decreases with time⁹⁶, possibly because the disease is usually progressing⁹⁷. If there already are skeletal metastasis, the HRQoL is also poor⁹⁸.

The type of treatment chosen for PCa matters for HRQoL, and different domains are affected differently. For example, radical prostatectomy seems to have a greater negative impact on urinary and sexual function than radiation therapy^{99 100}.

Hot flushes decrease the HRQoL in men with ADT and PCa¹⁰¹. Use of ADT in men with asymptomatic PCa and lymph node metastases, impair sexual, emotional, and physical function, and cause hot flushes and a worse overall HRQoL compared to watchful waiting¹⁰². Men with ADT for at least 12 months had worse HRQoL, than men who had undergone a prostatectomy as cancer treatment, but whether it is the ADT in itself or the difference in cancer disease that causes the difference is not clear¹⁰³. The presence of comorbidity, which is common in this usually older patient group, also affects HRQoL negatively¹⁰⁴, independent of the type of treatment chosen. This is probably true, also for women.

Anxiety is increased, both in PCa and BCa patients⁸⁰ and this is known to worsen insomnia.

Sleep

Sleep is an important factor in HRQoL. Sleep has several aspects, like sleep latency, number of wake ups/night, how long the wake ups last before going back to sleep, total length of night sleep, time spent in bed at night, and sleep effectiveness (% of the time spent in bed actually asleep, with more than 85% being the limit for a good sleep)¹⁰⁵. Sleep may be disturbed by nocturia, night sweats, partner, anxiety, pain, gastrointestinal problems, nausea, pruritus, noise, light etc. Other factors affecting sleep may be shift-work, intake of caffeine, alcohol, and sleeping remedies.

In a Dutch community population, 50 years and older, 15-37% report sleep disturbances, and women reported poorer sleep quality, more night time wake ups, less napping and more sedatives/sleeping remedies than the male population, that on the other hand reported more sleepiness during the day¹⁰⁶. Other studies confirm sleep problems in cancer patients^{107 108}, where women with BCa patient commonly report sleeping problems.

Menopausal women, compared to premenopausal were 3.4 times more likely than premenopausal women to report sleeping problems¹⁰⁹ and in 436 healthy women, age

35-49 years, subjective poor sleep was associated with both hot flushes and low estradiol levels¹¹⁰ but also with high anxiety and depression levels. In men with PCa, sleep disturbances are reported, and in an American cohort of 210 PCa patients, HRQoL had the most negative scores if the patients were 65 years old or younger, diagnosed within a year, and with metastatic disease. These fairly young patients reported increased sleep disturbances, and in those patients diagnosed within a year hot flushes were commonly reported as well⁸⁶. Even if the patients have been treated with prostatectomy, a third of the patients report sleep disturbances, where 50% of the sleep problems had occurred after the cancer diagnosis and are related to pain, anxiety, depressed mood and androgen-blockade related problems¹¹¹.

Sleep and sleep disturbances can be studied in laboratories, where objective measurements are done with polysomnography, but also in an ambulatory way, either objectively with devices such as actigraphy, or subjectively with patients recording sleep parameters like number of hours slept/night, sleep latency, sleep effectiveness, daytime sleepiness, fatigue, and how these factors affect different aspects of HRQoL^{106 112 113}.

In this thesis, the hours slept/night, and numbers of and distress caused by hot flushes/night have been quantitative values of sleep. The quality aspect was the WHQ sleep scores. The PGWB subscore for vitality is used as a measurement of the impact of sleep on HRQoL, but this subscore may be affected by other factors.

Correlation between hot flushes, HRQoL, sleepiness and fatigue

In some literature sleepiness and fatigue are presented together, as one unit, whereas in some it is separated. However, sleepiness is rather a subjective perception, related to a need of sleep which follows the circadian rhythm. Fatigue, is rather a great lack of energy and sleep, often perceived in association with a disease, such as cancer. Fatigue results in discontinuation of activities, and does not need to be only sleepiness, but also physical and mental tiredness as well as motivation reduction¹¹⁴. Fatigue is often described as a component of HRQoL and is a common symptom in cancer patients, with incidence rates 25-99%, depending on types of assessment and patient groups¹¹⁵.

Fatigue and depressed mood are often associated in cancer patients, and mechanisms involving dysregulation in serotonin, circadian rhythm disruptions and hypothalamic-pituitary-adrenal axis dysfunction are mechanisms that are discussed by Barsevick et al¹¹⁵

Fatigue, depression and worsened HRQoL are common and distressing side-effects not only of the cancer itself, but also the treatments used¹¹⁵⁻¹¹⁸ but in women with BCa, fatigue seems perhaps more related to menopausal symptoms, sleep and depression^{119 120} than to type of BCa treatment. Women who seek treatment for menopausal symptoms after breast cancer report the reason for seeking help being hot flushes (41%), night sweats (36%), loss of interest in sex (30%), difficulty in sleeping

(25%) and fatigue (22%)¹²¹. In men with ADT, the treatment is associated with fatigue and sleep disturbances¹²². The cancer may contribute in itself, and the treatment has obvious effects that may cause fatigue (lowering of testosterone and hemoglobin), but the hot flushes possibly disturb sleep as well. As Lintz et al have shown⁸⁶, patients with PCa, reported extensive fatigue, hot flushes and sleep disturbances.

Treatment of hot flushes

In women

Many women seek medical advice for their hot flushes, and it is the medical profession's task to find a suitable treatment for the individual woman. It has been suggested that a decrease of hot flush number of 50 % is needed to be of clinical significance and relevance for the woman¹²³. Another study suggests that a decrease of 0.42 wake ups /night makes a meaningful difference for women¹²⁴.

The treatment of choice for hot flushes in otherwise healthy women, is Hormone Therapy (HT), which usually is an estrogen combined with a progestagen to prevent hyperstimulation of the endometrium. HT reduces the hot flushes in women by 90-95%, compared to 10-50 % with placebo treatment¹²⁵⁻¹²⁷, and may improve QoL¹²⁸, but also increases the breast cancer risk^{129 130} and probably the risk of breast cancer recurrence¹³¹.

Prospective randomized controlled studies^{132 133} have shown increased risk of cardiovascular events, especially in women 60 years and older, as well as increased risk of breast cancer¹³³. Long-term use of HT has already been shown in the late 1980's to increase the risk of developing breast cancer, something later confirmed by the Million Women Study¹³⁰, and in a prospective randomized study, Women's Health Initiative (WHI)¹³³. The Million women Study concluded that if the start of HT use was five years or later after menopause, there was little or no risk for developing breast cancer, whereas the risk was significantly increased if the HT used had commenced before, or within five years after menopause¹³⁴, a time that is commonly associated with hot flushes for many women. Due to these findings, (and perhaps due to side-effects like irregular bleeding and mastalgia), the use of HT dramatically decreased after 2002, when the WHI results were published, and many women were thereafter reluctant to use HT¹³⁵. A Cochrane analysis in 2004 also confirmed increased risk of breast cancer after five years of HT, increased risk for venous thromboembolism and coronary events after one year of use, stroke (three years use), and gallbladder disease¹³⁶. In older, otherwise healthy women, the risk of dementia was increased. In women younger than 60, the risk was only elevated for thromboembolic events, with combined, continuous HT¹³⁶. This has led to an increasing demand for alternative treatments for hot flushes.

Tibolone is a synthetic steroid which, including its metabolites, has estrogenic, progestagenic and androgenic properties. It decreases menopausal vasomotor symptoms and it has been suggested that its use does not affect the breast. A prospective placebo controlled study, however, showed higher recurrence rate in women on tibolone than in those who had a placebo, which is why it is not recommended as treatment of flushes in women treated for BCa¹³⁷.

Pharmacological alternatives to HT have been tried with various results^{5 138-140}. Most common are SSRI/SNRI which now, paroxetine in particular, has been speculated to also increase risk of breast cancer recurrence, by inhibiting the Cytochrome p-450 2D6 enzyme, which normally metabolizes tamoxifen to active metabolites and thereby decreasing the preventive effect of Tamoxifen^{141 142}. SSRI are also associated with several side effects, and the decrease of hot flush frequency differs between type of SSRI/SNRI and also between studies⁵. For example, sertraline results in an 11% reduction of hot flush frequency¹⁴³, paroxetine in 45-50 % reduction¹⁴⁴, and venlafaxine 30-58%¹⁴⁵. Suvanto-Luukkonen et al showed that citalopram and fluoxetine had an effect similar to that of a placebo during a 9 month study¹⁴⁶. Gabapentin has recently been tried, with a mild effect on the number of flushes, 20-45%^{147 148}. Clonidine has been tried, but the effect is uncertain, with a reduction of the number of hot flushes by only 20-40%^{5 149}. Belladonna ergotamine is a sedative, that has shown no sustaining decrease of flushes, but is associated with several side effects¹⁵⁰. Herbal remedies and dietary supplements have been tried, and some of them, containing phytoestrogen with estrogenic effects, have been found to have slight effects on the flushes, but the side effects are not well studied and could theoretically affect breast cancer risk^{151 152}. Other non-pharmacological treatments have been suggested, such as paced respiration¹⁵³, relaxation therapies^{154 155}, exercise^{156 157} and acupuncture.

Since women with a history of breast cancer often experience more severe vasomotor symptoms than healthy menopausal women, there is a great need for treatment for these women. Theoretically, HT would not only increase the risk of developing breast cancer, but also increase the risk of breast cancer recurrence. However, epidemiological studies did not confirm this hypothesis, but rather indicated a decreased risk of breast cancer recurrence with HT use¹⁵⁸. The need of treatment for hot flushes in this group of patients, combined with the results of those epidemiological studies, led to the ethical approval and initiation of a number of studies, prospectively testing HT in breast cancer survivors with troublesome vasomotor symptoms^{137 159 160}.

In men

For men with castrationally treated prostate cancer, there are few treatment alternatives available. Randomized, controlled studies have only been eight weeks or shorter, why long-term effects and side-effects are unknown. Hormonal alternatives, i.e. estrogen,

cyproterone acetate and megestrol acetate, decrease the flushes by 75-100%¹⁶¹⁻¹⁶³. They are however associated with risk of severe side effects, like cardiovascular events, and even risk of cancer progress^{6 164 165}.

SSRI/ SNRI are also used, but with moderate effect on the flushes, that has not yet been verified in an RCT⁶. Gabapentin is suggested as a treatment, but has not shown convincing results¹⁶⁶. Neither Clonidine¹⁶⁷ nor herbal remedies⁶ have been proven effective, which leaves the men with few treatment alternatives.

Acupuncture treatment

Acupuncture treatment has been used in Traditional Chinese Medicine (TCM) for thousands of years. It started to seriously interest the medical professionals and others in the Western world, in the 1980s, and has since then grown in use. The clinical use is developing, partially because the method is considered effective and safe, but perhaps also because it can be offered as treatment by acupuncturists outside the official health care system. In 1997, The National Institutes of Health (NIH) Consensus Development Conference on Acupuncture concluded, "There is sufficient evidence of acupuncture's value to expand its use into conventional medicine and to encourage further studies of its physiological and clinical value."¹⁶⁸

There are three possible components of acupuncture that need to be taken into account (figure 1), and may have an impact on the results : 1) the needling component, such as needle size, depth, stimulation and location 2) specific non-needling components, such as TCM diagnosis and palpation 3) non-specific, non-needling components, such as belief and expectancy, therapeutic setting, time and attention¹⁶⁹. For scientific purposes, it is necessary to identify and control as strictly as possible all three of these factors, and then to describe them to enable comparative studies. The needling component is perhaps, but not necessarily, the most important factor for physiological responses.

Traditional acupuncture (TA) uses needles at the specific acupuncture points, defined by TCM. There are several hundred acupuncture points, and there is a variability between acupuncturist in locating the acupuncture points¹⁶⁹. This is believed by some to matter, since a "sham-point" may be stimulated instead of a "true" acupuncture point. However, the sham points are not defined anatomically or physiologically, so there is a lack of proof to show that these points are less active than true acupuncture points, and they are therefore not a suitable placebo control for acupuncture treatment

¹⁷⁰

The needles are inserted at different depths, and with different thickness of needle. Thereafter, the needle may be twirled to evoke the “DeQui” sensation, which is a sensation of distention and numbness¹⁷¹. Electro-stimulation may be added to some of the needles, with either high frequency (e.g. 80-100 Hz) or low frequency (e.g. 2 Hz), for a supposedly additional effect^{172 173}. This stimulation is believed to activate peripheral nerve endings, muscles and also connective tissue. The nerve stimulation causes affer

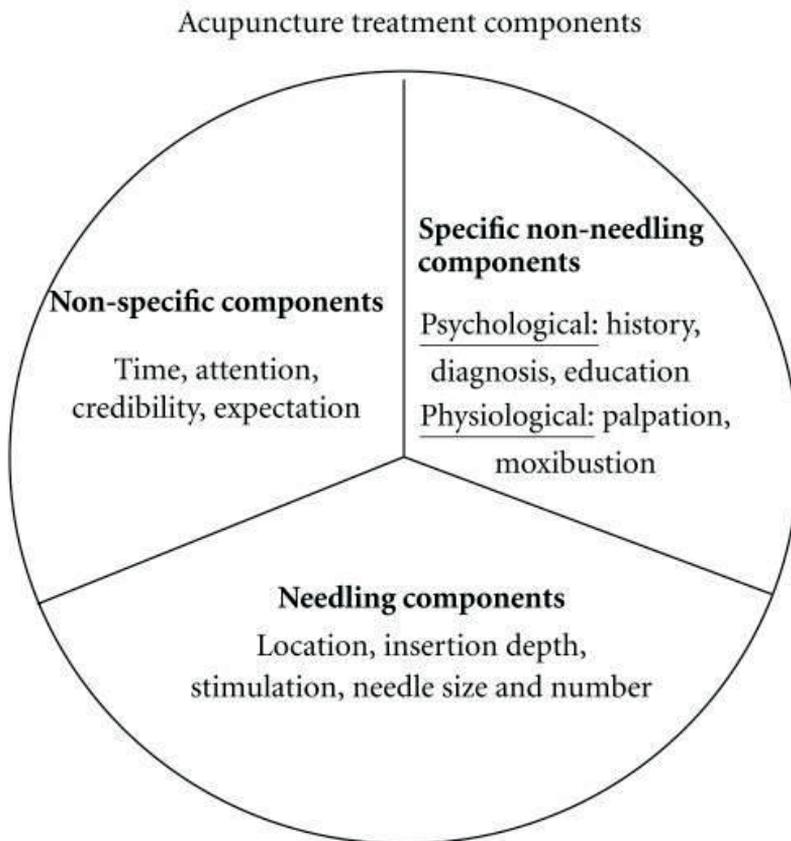


Figure 1

Components of acupuncture treatments broken down into nonspecific versus specific nonneedling versus needling as described by Langevin HM, et al. Evid Based Complement Alternat Med doi: 10.1155/2011/180805¹⁶⁹.

ent signals, which increase for example central β -endorphins, and serotonin, and probably also activate receptors¹⁷⁴⁻¹⁷⁶. Some studies have shown a decreased activity, measured by fMRI, in the amygdala and hypothalamus, when acupuncture is given¹⁷⁷. It may be speculated that during hot flushes there is a high neuronal activity in the hypothalamus, and that acupuncture may reduce this activity, perhaps mediated by increased β -endorphin release, and decreased nor-adrenalin activity.

Acupuncture for hot flushes

Acupuncture is now used, and accepted, for pain relief and nausea¹⁷⁸. In 1987, acupuncture was tried for dysmenorrhea¹⁷⁹. The idea, with hormonal changes/instability causing symptoms, especially from the reproductive system, was then applied by us on hot flushes in menopause, where there are also hormonal changes that cause symptoms (i.e. hot flushes). This idea was also supported by the theory that acupuncture could release β -endorphins, Substance P and serotonin^{180 181} and according to our theory thereby stabilize the thermoregulatory centre in the hypothalamus. This led to a study, evaluating electrostimulated acupuncture (EA) and traditional acupuncture (TA) on menopausal women with hot flushes⁵⁹. Wyon et al could show that EA and TA decreased the number of, and distress caused by hot flushes by at least 50% after eight weeks of treatment, and found also that there was a simultaneous decrease of urinary excretion of CGRP during 24 hours. The effect on the hot flushes remained at the follow up three months after end of treatment.

Theory and hypothesis

Theory: Hot flushes are believed to be induced by sudden resetting of the hypothalamic thermoregulation, which is less stable due to changing levels of neurotransmitters like beta-endorphins, in turn lowered due to decreased sex steroids.

Hypothesis: a treatment that stimulates the opioid activity in the hypothalamus, could make the thermoregulation more stable, and thus decrease the hot flushes. Acupuncture is believed to increase hypothalamic opioid activity and may therefore be a treatment alternative for hot flushes. By decreasing the numbers and distress by hot flushes, the HRQoL and sleep may increase.

Aims of the study

The general aim of the research leading to this thesis was to evaluate the effect of acupuncture on hot flushes and HRQoL in men with prostate cancer and women with breast cancer.

Specific aims

To evaluate whether acupuncture therapy could be used to treat hot flushes in men with PCa treated with castration therapy (paper I).

To evaluate the effect in women with BCa and hot flushes of 12 weeks of acupuncture or two years of hormone therapy on both the number of hot flushes per unit time and the level of distress caused by hot flushes as measured by log books, and climacteric symptoms measured by Kupperman's Index (paper II).

To evaluate the effect in women with BCa and hot flushes of 12 weeks of acupuncture or two years of hormone therapy on HRQoL and sleep measured by log books and validated HRQoL questionnaires (paper III).

To investigate whether HRQoL and sleep are associated with number of hot flushes and distress caused by hot flushes in women with BCa and hot flushes (paper III).

To evaluate the effect in men with PCa and hot flushes of 12 weeks of traditional acupuncture or electrostimulated acupuncture on both the number of hot flushes per unit time and the level of distress caused by hot flushes as measured by log books (paper IV).

To evaluate possible changes in urinary 24 hour excretion of CGRP in men with PCa and hot flushes from baseline to the end of the 12th week of acupuncture treatment and after 6, 9 and 12 months after treatment was started (paper IV).

To evaluate the effect of 12 weeks of traditional acupuncture or electrostimulated acupuncture, in men with PCa and hot flushes on HRQoL and sleep measured by log books and a validated HRQoL questionnaire (paper V).

To investigate whether HRQoL and sleep are associated with hot flushes in men with PCa and hot flushes (paper V).

Materials and methods

Design

The pilot study (paper I) was an open, non-controlled prospective study, where men with prostate cancer and ADT who were seeking help for hot flushes were treated with traditional acupuncture for 10-12 weeks. The group was followed for 24 weeks including the treatment period.

Acu-HABITS (paper II, III) was a clinical, randomized, controlled study, where women with a history of breast cancer who were seeking help for hot flushes were included in the regional part of the international, multicenter HABITS (Hormones After Breast Cancer – is it Safe ?) study¹⁵⁹. The first aim of the HABITS study was to evaluate the risk of breast cancer recurrence with HT, in women with a history of breast cancer. Women were randomized between HT and an alternative, non-hormonal treatment for hot flushes. The HABITS study was designed and launched before our region was included. When the South East region of Sweden was invited to participate in the HABITS study, we decided to suggest acupuncture as the first “alternative, non-hormonal treatment” for all patients included in our region. The women were thus either treated with HT for two years, or acupuncture for 12 weeks. Both groups were followed for two years including the treatment period.

RAMP; “Randomized Acupuncture study of Men with Prostate cancer”, (paper IV,V) was a clinical, randomized controlled study, where men with prostate cancer and ADT who were seeking help for hot flushes, were randomized to traditional acupuncture, or electrostimulated acupuncture, for 12 weeks. The groups were followed for one year including the treatment period.

Study participants

In the pilot study (paper I), seven men with prostate cancer, ADT and hot flushes, age 65-80 years (median 74 years) were recruited from the outpatient clinic at the Department of Surgery, at the County Hospital of Ludvika. They were offered acupuncture for 12 weeks, six men completed at least 10 weeks of treatment, where drop outs were due to medical conditions.

In papers II and III, 45 women from Kalmar (n = 8), Linköping (n = 25) and Norrköping (n = 12), were offered to participate in a research study to which we had given the name “acu-HABITS”. Their demographic data are shown in table 1. Eighteen women were randomized to HT, and 27 to EA. A flowchart (paper II,III) shows the treatment and follow up periods. The international HABITS study was prematurely closed, due to a safety analysis, which showed increased risk of recurrence in the HT arm¹⁵⁹. We aimed to include all the patients in the South-east region that were includ-

ed in the HABITS study, irrespective of number. We had earlier conducted studies on hot flush treatment, and learned that 20 patients were enough to show a treatment effect within a group. Thus, we intended that minimum 20 patients per study arm would be eligible, and we managed to include and randomize 45 due to early closure of which 44 were planned for treatment. Unfortunately, the treatments were unevenly distributed between the groups.

In paper IV-V, 49 men were screened for participating in the RAMP study, and 36 men were found to be eligible. Out of these 36 men measurements of serum testosterone concentrations showed that five of them did not have castration levels, and were therefore excluded. Thereafter 31 men from Jönköping (n = 3), Linköping (n = 13) and Norrköping (n = 15) were randomized and planned for treatment. Their demographic data are shown in table 1. Fifteen men were randomized to EA, and 16 men to TA. A flowchart (paper IV,V) presents the treatment and follow up period.

study	Acu-HABITS(II-III) ♀ n=44	RAMP (IV-V) ♂ n=31
Age at inclusion in study	55(52-59;range 43-69)	73(62-78;range 50-84)
Age at cancer diagnosis	53(46-57;range 33-67) n=41	71(58-76;range 49-81)
Years from cancer diagnosis	2(1-4.8; range 0.5-17)	1(1-3; range 0.5-8) n=30
Years from menopause	5.0(1.3-9.6; range 0.5-24)	x
Smokers yes/no	9/35 (20,5%)	5/31 (16.1%)
BMI kg/m ²	24(22-26; range19-34) n=42	27(26-28;range23-32) n=30

Table 1. Demographic data on 44 women randomized in the acu-HABITS (paper II,III), and the 31 men randomized in the RAMP study (paper IV,V). Data presented as median (IQR 25-75; range)

Monitoring

Hot flushes

The number of hot flushes for each patient was registered daily before bedtime in log books, registering the number from the last night and day separately, for all studies. For paper I, hot flushes were registered one week before treatment and thereafter for one week after 2, 6, and 10 weeks of therapy, and finally three months after end of treatment. For papers II-V, the numbers were registered as in paper I, but also the distress caused by hot flushes was assessed by the patients, graded between 0-10, with 10 being the greatest distress. Flush data were registered daily two weeks before treatment, during week 1-12 of treatment, and then one week at 6, 9, 12 months (paper II-V), 18 and 24 months after start of treatment (paper II,III).

Sleep

The number of hours slept/night, and times woken up/night were registered in the same log books as for the flushes (paper III,V). Subscales related to sleep and fatigue in PGWB and WHQ were analysed in papers at baseline and throughout the studies (paper III and V).

Climacteric symptom

Kuppermans' Index was published in 1959 to assess climacteric symptoms for women during menopause¹⁸². A Swedish version has been developed¹⁸³, with eleven symptoms (vasomotor symptoms, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgia, headache, palpitations, sweating and vaginal dryness).

The patients score the symptoms between 0-3, and vasomotor symptoms are multiplied by four, sweating, nervousness and insomnia by two, and the other symptoms multiplied by one, leaving a total maximum score of 51. The patients filled in the Index themselves (paper II), before treatment, and at 3, 6, 9, 12, 18 and 24 months after start of treatment.

Health Related Quality of Life

Psychological and General Well-Being Index (PGWB)

PGWB is a validated, generic HRQoL instrument, developed to estimate intrapersonal changes in well-being and distress¹⁸⁴ and a Swedish version has been developed¹⁸⁵. It has six subscales; anxiety, depressed mood, positive well-being, self-control, general health, and vitality. PGWB is made of 22 questions, with scores between 0-5, as in a Likert scale, yielding a total possible score of 110, which is considered maximum well-being. A clinically significant change of PGWB was described by Croogs et al¹⁸⁶, where a difference of <0.2 SD was considered to be of no clinical relevance, 0.2-

0.59 as a mild, 0.6-1.0 as a moderate, and >1.0 as a substantial change. PGWB has previously been used to assess treatment effects, and effect of cancer related symptoms in different patient groups, like breast cancer¹⁸⁷⁻¹⁸⁹, androgen deficiency¹⁹⁰ brain cancer survivors with Growth Hormone deficiency¹⁹¹ and menopause^{192 193}.

PGWB was filled in by the patients at baseline, 3, 6, 9, 12 months after start of treatment (paper III,V), and also at 18 and 24 months after start of treatment (paper III).

Women's Health Questionnaire (WHQ)

The Swedish version of WHQ¹⁹⁴, was used to assess disease-specific HRQoL, with menopause symptoms in focus. It is suggested to be used as a part of a HRQoL assessment, although it does not measure the presence or impact of a certain disease (like cancer). It can be used to evaluate treatments, preventions and other interventions. Thirty-six symptoms were subjectively graded into a four-point Likert scale¹⁹⁵. The symptoms are divided into nine subscales: depressed mood, somatic symptoms, anxiety/fear, vasomotor symptoms, sleep problems, sexual behaviour, menstrual symptoms, memory/concentration and attractiveness. One of the four items in the "menstrual symptoms" subscale referred to menstrual bleeding, and this was excluded in the analysis in this mainly postmenopausal population, and the subscale was renamed "hormonal symptoms". Two questions about sexual behaviour were to be answered only if the woman had an active sex life, which excluded nine women. This subscale was therefore excluded due to too many pre-treatment drop-outs. Subscales were analyzed and a total score was made according to Hunter¹⁹⁵, where the two lower grades were merged to "0" and the two higher to "1". Maximum score of wellbeing is zero points. A clinically significant and relevant change has been suggested by Hunter as a difference of 0.1-0.2.

WHQ has been used widely to assess HRQoL in patients with menopausal symptoms with^{155 196 197} and without BCa^{198 199}.

The WHQ was filled in by the women at baseline, and at 3, 6, 9, 12, 18 and 24 months after start of treatment (paper III). In the Swedish version¹⁹⁴, there is a translation of question number 21, where the original statement is "I feel rather lively and excitable" which is a positive statement. It has been translated into Swedish to mean "I feel nervous and easily get upset" ("Jag känner mig nervös och blir lätt uppjagad") which is a negative statement. This will lead to wrong results when the negative statement scores are reversed as explained in the original instructions by Hunter¹⁹⁵, although the effect is minor since only one question is involved. If this incorrect translation of the original WHQ is recognized, it is possible to make a correct calculation.

Log-books for depressed mood and sleepiness/fatigue

In paper V, the men with PCa, had filled in daily log-books, for flush and sleep data. In the same log-book the men also evaluated before bedtime on a Likert scale, (0-10) the degree of depressed mood and sleepiness/fatigue.

CGRP and testosterone

U-CGRP was analysed in the study reported in paper IV in 24 hours collections of urine before, after 12 weeks of treatment and at 6, 9, and 12 months after start of treatment.

At the inclusion visit in paper IV and V blood samples were drawn in order to analyze concentrations of s-testosterone and s-luteinizing hormone (s-LH), to confirm castrational levels of sex steroids. S-testosterone and s- LH levels were checked again after 12 weeks of treatment, to confirm that the subjects' castration status had not changed, which could have affected the results.

Treatment method

Acupuncture therapy (paper I-V):

Treatment was given by a physiotherapist for 30 minutes twice a week during the first two weeks, and then once a week during the following 10 weeks. In the pilot study (paper I), one physiotherapist administered the acupuncture to all the patients at the hospital. In the HABITS study (paper II-III) five acupuncturists provided acupuncture, at hospitals or private practices. In the RAMP study (paper IV-V) five acupuncturists provided acupuncture (EA or TA), at hospitals or private practices. They all had completed a university course in acupuncture equal to at least three months full-time studies and thereafter extensive, usually many years, practical experience of acupuncture therapy. They were instructed both orally and in writing about the acupuncture points and also told not to discuss expected or experienced effects from the treatment with the patients.

Twelve sterile stainless-steel acupuncture needles (Hwato, 0.25mm diameter, 15mm long and 0.30mm diameter, 30mm long) were inserted to a depth of 5-20 mm in the defined points and twirled to evoke needle sensation (De Qi)⁵⁹. De Qi is described as tension, numbness and often as a radiating sensation from the point of insertion, reflecting activation of muscle-nerve afferents (mainly A-delta fibres). In the EA group, acupuncture was given with two Hz in four points and "traditional acupuncture" in eight points as previously described for women with hot flushes⁵⁹ (appendix 1 and 2, STRICTA for RAMP and acu-HABITS).

Hormone Therapy (paper II-III)

In the HABITS study 18 women were randomized to HT for two years. Women less than two years after menopause had sequential estrogen/progestogen combination, whereas women more than two years after menopause were prescribed continuous combined estrogen/progestogen in order to avoid bleedings. Unopposed estrogen was prescribed to women who were hysterectomized. Tibolone was not allowed. According to the protocol HT should be used for 24 months and then be stopped. However, after a safety analysis of the HABITS study showing increased recurrence risk in the HT group, all women were recommended to stop HT. Consequently, two women in our study stopped HT already after one year.

Analysis method

CGRP (Paper IV)

Urine was collected for 24 hours by the men in the RAMP study (paper IV-V). Five 10ml samples were saved from each urine collection, and saved in a -70°C freezer, until transported to, and analyzed at the Department of Clinical and Experimental Medicine/Neurochemistry, University Hospital of Linköping. One 10 ml sample was used for each urine collection, and all samples were analyzed at the same time, to avoid differences in analysis method, such as different binding capacity of the radioligand.

Samples were extracted and concentrated five times using a reverse-phase C18 cartridge (Sep Pak, Waters) and analysed for Calcitonin Gene-Related Peptide-like immunoreactivity (CGRP-LI), using competitive radio immunoassays²⁰⁰. CGRP-LI was analysed using antiserum CGRPR8 raised against conjugated rat CGRP. HPLC-purified (125) I-histadyl rat CGRP was used as radioligand and human CGRP as calibrator. The cross-reactivity of the assay to SP, neurokinin A, neurokinin B, neuropeptide K, gastrin, neurotensin, bombesin, islet amyloid polypeptide, adrenomedullin, neuropeptide Y and calcitonin was less than 0.01%. Cross-reactivity toward human CGRP α and β was 93% and 24%, respectively, and toward rat CGRP α and β 100% and 120%, respectively. Intra- and interassay coefficients of variation were 8 and 14% respectively. The lower limit of detection in the original samples was 0.4 pmol/L for CGRP.

At the inclusion visit in the RAMP study blood samples were drawn for analysis of s-testosterone and s-LH to confirm their castration levels of sex steroids. The analyses were performed according to clinical routines at the department of Clinical Chemistry, University Hospital of Linköping, Sweden.

Statistical methods (Papers I-V)

The statistical methods used in the five papers are shown in table 2. Statistical analyses were performed using Statview for paper I, and SPSS (version 12-19; SPSS Inc., Chicago Il. USA) for papers II-V. A significance level of $p < 0.05$ was used for all variables.

Sample sizes in study I-IV were chosen, based on results from our own earlier studies. Sample size calculations were made in advance, based on earlier studies, evaluating changes in number of hot flushes. Power calculations after the studies were made to identify the power with which we could identify that the flushes had changed significantly from baseline to three months after treatment in the EA groups. Descriptive statistics were used for demographic data, and presented as means and SD. T-test for numerical data and χ^2 for categorical data were used to evaluate if the groups differed in demographic data at baseline.

For comparisons within the groups, over time, non-parametric methods were mostly used, since the data were not normally distributed.

For analyses within the groups, over time, the Wilcoxon signed-rank test was used. It is a non-parametric test for the case of two related samples or repeated measurements on a single sample (e.g. numbers of hot flushes at baseline in the EA group, compared to numbers of hot flushes after three months of treatment in the same group). This test does count all the individuals data that appear at both measuring points.

Non-parametric methods are seen by some statisticians as leaving less room for improper use and misunderstanding, due to their wide applicability and robustness. However, in cases where a parametric test would be appropriate, non-parametric tests may have less power. In other words, a larger sample size can be required to draw conclusions with the same degree of confidence.

For comparison of changes over time, and between groups, Analysis Of VAriances, ANOVA was used. ANOVA provides a statistical test of whether or not the means of several groups are equal. For example, it compares the mean changes of number of hot flushes in the EA group, over time, at several measuring points, and then compares if these mean changes differ from the mean changes over time in the HT group. ANOVA is useful in comparing three or more measuring points. However, even though this method compares means, but it is still the method of choice to compare changes over time between groups, and was therefore used. Also, our groups hot flush data were often normally distributed, which made these test acceptable. It could be argued that we could have used the Kruskal-Wallis test, since this is a non-parametric test. The Kruskal-Wallis test does, however, not permit inclusion of more than one variable in the analysis. The Friedman's test may be used for within group

analysis of non-parametrical data over time at more than two time points, but only one group can be analyzed.

Linear Regression analysis was used in papers III and V, to analyze whether variables were dependent on each other, and to what extent. The analyses were made to determine possible variables that treatment might affect, and to what extent these changes in the independent variables would affect dependent variables. Measurements were made mainly at baseline, for example, to see if, and to what extent “times woken up/night” were associated with “numbers of hot flushes/ night”. A r value was presented, to indicate the extent to which the variables were linearly associated, and a coefficient for the independent variable ($y=a+bx$, where the b-value is the coefficient above) was given, where for example it was possible to see what happened with the “times the patients woke up/night”, if the “number of hot flushes/night” decreased. This method cannot define which variable is actually affecting the other, but to what extent they were aligned.

Statistical methods in paper	I	II	III	IV	V
Descriptive analyses	x	x	x	x	x
t-test	-	x	x	x	x
χ^2	-	x	x	x	x
Wilcoxon Signed Rank Sum test	-	x	x	x	x
Repeated measure, Analysis of variance (ANOVA)	x	x	x	x	x
Friedman's test	x	-	-	-	-
Linear Regression Analysis	-	-	x	-	x

Table 2. Statistical methods used in paper I-V.

Missing data

Missing data were substituted for with the mean of the previous and the following value for the specific individual and variable. In case the missing data were the last data, with no following values, the mean value for the group was used to replace the missing data²⁰¹. The amount of missing data is presented separately in each paper.

Ethical considerations

In all studies, the men and women received oral and written information on the respective study before giving their informed consent, and they were informed that they could leave the study at any time, with no need to explain the reason and with no further consequences on their future care and treatment. The studies were approved by the Regional Ethical Review Board in Linköping and were performed according to the Declaration of Helsinki and Good Clinical Practice. (Ethical permission numbers Paper I: 190/1994 and 155/1955, Paper II and III: 045/1998, Paper IV and V: 03/2000)

For study I, the ethical dilemma was, as in any pilot study, that we did not know if the treatment we offered was a treatment at all, or just a waste of the patient's time. Also, we did not know if it would cause any side effects that would be harmful. However, acupuncture was earlier tried with promising results on menopausal women with hot flushes, and no severe side effects were reported⁵⁹. No reports on acupuncture causing progress of cancer had been found.

For the acu-HABITS study (paper II,III), the ethical dilemma was to give HT to women with a history of BCa, where there had been studies suggesting that HT was associated with an increased risk of BCa²⁰². However, there were other studies suggesting there was not such an association, and concluded "This study was unable to demonstrate a significant increase in risk of breast cancer recurrence for women who used HT and suggests that the time is now appropriate for a randomized prospective trial of hormone therapy after breast cancer"¹⁵⁸.

No randomized controlled trials (RCT) had been previously performed using HT for women with a history of BCa and hot flushes, which left these women in a state of uncertainty on what treatment was suitable or possible for them. Treatment with HT was accepted as treatment for disturbing flushes in women with BCa in some countries, whereas others had a more restrictive approach. This lack of evidence-based knowledge was not fair to any of the women, neither the treated nor untreated, when there was no RCT evaluating risks and benefits of HT in women with a history of BCa.

Since there were no studies that demonstrated that BCa could reoccur due to HT, our patients were to have no sign of recurrence when entering the study. Moreover, every patient had a yearly follow-up with an oncologist or breast surgeon throughout the study. A safety analysis of the main HABITS study was also performed by an external safety board intermittently, and after 5 years the study was stopped due to increased rate of BCa recurrence in the HT group. In contrast to HT, EA is not considered to cause cancer or be a factor in affecting the progression of cancer.

Regarding the RAMP study (papers IV-V), acupuncture is associated with few side effects, the majority of which are considered minor. The ethical dilemma in this study was that we ideally should have had a 12 month waiting list group as a control.

This seemed, however, unethical in a group of patients with a severe cancer disease, seeking help for disturbing hot flushes. The results from our pilot study suggested that acupuncture could ease the symptoms, making us design the study to avoid having to leave any of the groups with a long period of no treatment.

Results

The major findings and some new analyses are presented below in a comparative way, and are briefly commented on. For detailed results please see the respective papers.

The major findings were that the number of hot flushes decreased by more than 50% in a pilot study (paper I) of men with PCa and hot flushes, treated with EA for 10-12 weeks (paper I). The decrease remained at a follow up three months after the treatment had ended. These results were confirmed in two randomized controlled studies in which men (paper IV,V) and women (paper II,III) were treated with acupuncture or HT. In these studies, distress caused by hot flushes was also reported by the patients and decreased as well. In these studies the effect lasted up to at least one year after acupuncture treatment had ended, even if the number of flushes did increase to some extent. In the women treated with HT, the effect on the hot flushes lasted as long as the women used HT, up to two years. HRQoL, measured by WHQ, increased in women treated with EA as well as HT, whereas the PGWB score only increased in the EA group. In the men, HRQoL did not increase during therapy. The number of hot flushes/night decreased in the acu-HABITS and RAMP studies, and the number was in turn associated with number of wake ups/night.

Power calculations were made after the studies were completed and we found that we had >90% power to identify changes in the number of hot flushes after 12 weeks of EA treatment, compared to baseline in study II-III, and >80% in study IV-V, with a significance level of 95% in both studies to identify that the flushes had changed significantly.

Hot flushes

The number of hot flushes decreased significantly in all the treatment groups. The group with the strongest decrease of both number of hot flushes and distress caused by hot flushes consisted of the women in the acu-HABITS study, randomized to HT. This was expected, since HT is the gold standard for treatment of vasomotor symptoms. In the acupuncture groups, the largest decrease of number of hot flushes after 12 weeks of treatment appeared in the pilot study with a 78% decrease of hot flush numbers after 10 weeks of treatment (Figure 2). The women with EA treatment reported a 52% decrease (paper II), and the men with EA a 44% decrease in median number of hot flush-

es/24 hours after 12 weeks of treatment (paper IV). The TA group reported a decrease of 57%, and the summarized results of change in median number of hot flushes/24 hours in the RAMP study are presented in figure 3. The distress caused by flushes was not measured in the pilot study, but was an important measure in the following acu-HABITS and RAMP studies, since it is this variable that most probably affects the patients' daily life, even if the number of flushes does also matter.

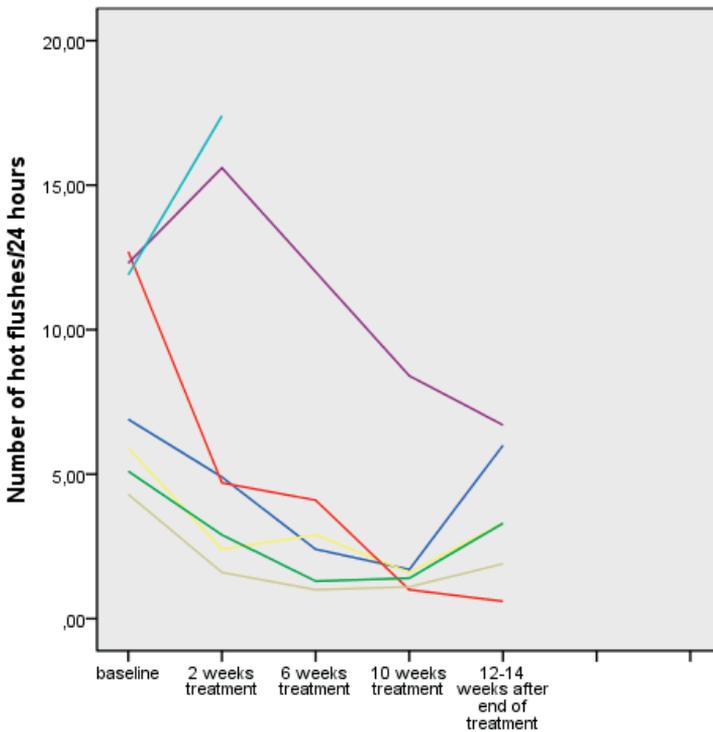


Figure 2. Number of hot flushes/24 hours in seven men in the pilot study (paper I).

In the acu-HABITS study (paper II), the median distress caused by flushes during 24 hours decreased by 66 % after 12 weeks of EA (from 10.3(8.4-14.3 IQR) to 3.5(1.0-8.9 IQR)). In the group consisting of the 63% of the women who had a decrease of distress larger than 50%, the decrease in median distress during 24 h was 79%. In the men in the RAMP study (paper IV) the decrease of distress caused by hot flushes was 60% in the whole group receiving EA (from 8.2(6.5-10.7 IQR) to 3.3(0.3-8.1 IQR)), but of the 50% of the men who had a decrease larger than 50%, the decrease of median distress during 24 h was 93%. The hot flushes tended to return with time, but in some

patients, the decrease persisted throughout the one or two years of the study (paper II,IV; Table 3).

Time	Paper I – ♂ Median no flush/24h (IQR:25-75) ;n:p-value	Paper II- ♀ Median no flush/24h (IQR:25-75) ;n:p-value	Paper IV- ♂ Median no flush/24h (IQR:25-75) ;n:p-value
baseline	6.9(5.1-12.3);7	9.6(6.6-9.9);19	7.4(5.5-12.0);15
12 weeks *	1.5(1,1-3,4);6:0.03	4.3(1.0-7.1);19:<0.01	4.1(2.0-6.5);14:<0.01
6 months ast	3.3(1.6-6.2);6:0.03	3.6(1.6-6.9);18:<0.01	5.5(2.6-7.4);12:0.01
9 months ast	x	3.5(1.4-6.9);16:<0.01	4.7(1.6-6.8);12:0.02
12 months ast	x	4.9(1.8-7.3);14:0.01	6.2(4.2-6.5);11;ns
18 months ast	x	2.1(0.9-4.0);8:0.01	x
24 months ast	x	2.1(1.6-2.8);7:0.02	x

Table 3. Number of hot flushes after 12 weeks of treatment with EA in paper I,II and IV(*denotes the pilot study, where follow up was after 10 weeks).

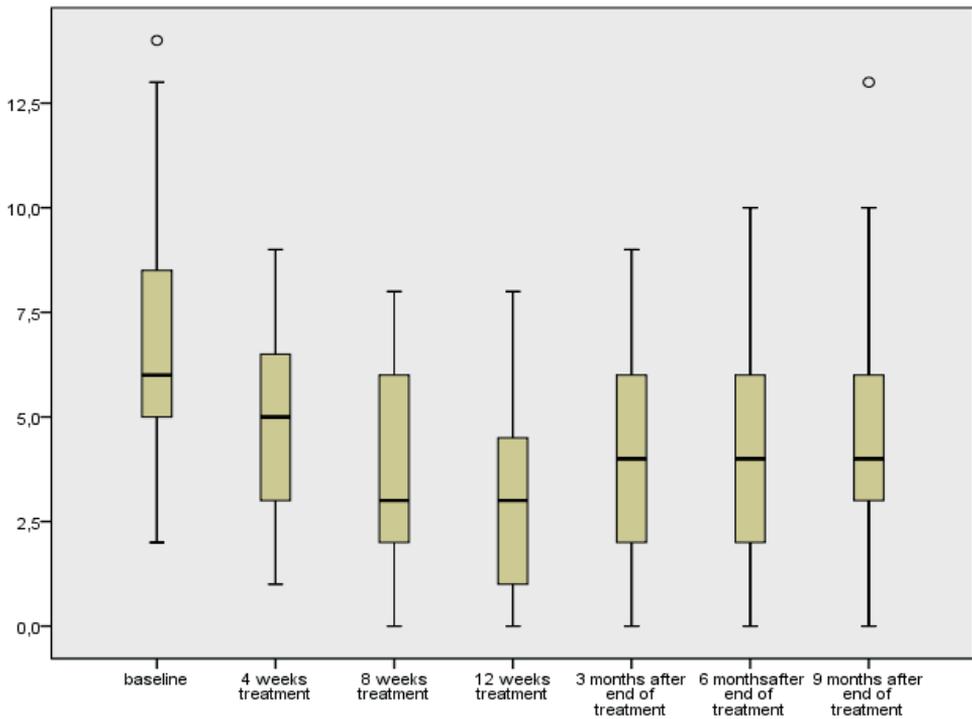


Figure 3. Numbers of hot flushes/24 hours in 24 men with PCa and hot flushes who had EA or TA treatment for 12 weeks and were followed up to 9 months after end of treatment. Box-plots with median, box representing the 25-75 IQR, and the outer lines the minimum and maximum values.

There was no placebo control group, but in the men in the RAMP study (paper IV,V), eight patients waited more than six weeks for their treatment, and filled in log-books during the waiting period. No changes in log book data occurred during these six weeks without treatment, but already after four weeks of acupuncture significant changes in hot flush frequency and distress were reported (table 4 and figure 4).

variable	6w pretreatment	1w pretreatment	4 w treatment	8 w treatment
Sleepiness/fatigue	1.5(1.0-4.5)	1.5(0.3-4.5);p=ns	1.5(0-3.8);p=ns	1.5(0.3-4.5);p=ns
depressed mood	0.5(0.0-1.0)	0.5(0.0-1.8); p=ns	0.0(0.0-2.5); p=ns	0(0.0-2.5); p=ns
Number of flush-es/day	5.0(3.5-6.8)	5.0(3.3-6); p=ns	3.0(1.3-4.8); p=0.01	2.0(0.0-4.8);p=0.03
Distress flush-es/day	4.5(2.0-6.0)	3.5(1.3-5.5); p=ns	2.0(0.3-4); p=0.01	2.0(0.0-3.0); p=0.01
Number of flush-es/night	2.0(1.0-2.8)	2.5(1-3); p=ns	1.0(0.0-1.8); p=0.04	1.0(0.0-1.8); p=0.03
Distress flush-es/night	2.5(1.0-4.0)	3.0(1.5-5.5); p=ns	1.0(0.3-2.5); p=0.04	1.0(0.0-2.5); p=0.03
Times woken up/night	2.0(1.3-3.8)	2.0(1.3-3.8); p=ns	1.5(1.0-2.8); p=0.03	2.0(1.3-2.8); p=ns
Hours slept/night	6.0(5.3-6.8)	6.0(6.0-6.8); p=ns	6.5(6-7); p=0.04	6.0(5.3-6.8); p=ns

Table 4. Log-book data for eight patients, during six weeks on a waiting list before treatment, and after 4 and 8 weeks of treatment. Data are presented as median (IQR: 25-75); p-value for comparison to 6 weeks pretreatment data. P values non significant (ns) if $p \geq 0.05$.

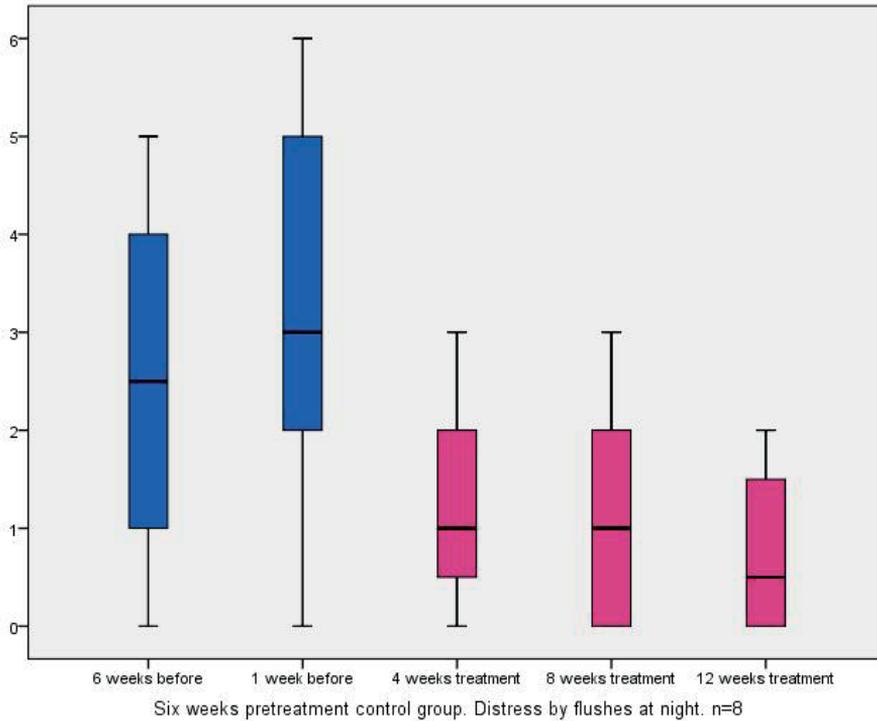


Figure 4. Changes in distress caused by hot flushes/night in eight men with PCa, recording data during six weeks before treatment, and during eight weeks of treatment (blue boxplots= before treatment and purple boxplots= during treatment, with median, the box representing the 25-75 IQR, and the outer lines the minimum and maximum values).

In the acu-HABITS study 19 women completed 12 weeks of EA, and 11 of them needed some kind of treatment during the two-year follow up (flowchart paper II and III) due to low effect on flushes or flushes returning. It was up to the treating doctor and the patient to freely decide on the kind of treatment, and five women had another treatment session of EA, two had HT and four had other non-HT. Of the women randomized to HT, one changed to EA.

Among the men in the RAMP study two men in the TA group, and one in the EA group received another kind of treatment, after 12 weeks of acupuncture (see flowchart in paper IV and V).

Hot flush score

In the acu-HABITS (II,III), the hot flush score decreased in the EA group by 80% after 12 weeks of treatment. In the HT group the hot flush score decreased by almost 100%. In the RAMP study (IV,V), the EA group decreased their hot flush score by 78% and the TA group by 77 % after 12 weeks of treatment.

Health Related Quality of Life

HRQoL was measured by means of log books (paper V), PGWB (paper III,V), and WHQ (paper III). Sleep parameters consisted of data from log books (paper III,V), the vitality subscale of PGWB (paper III,V) and the sleep subscale of WHQ (paper III). A summary of HRQoL and sleep data from baseline to 12 weeks of treatments in the acu-HABITS and RAMP studies (paper III,V) is given in Table 5.

Variable	RAMP baseline EA n=15	RAMP 12 weeks EA n=14	RAMP baseline TA n=16	RAMP 12 weeks TA n=15	Acu- HABITS baseline EA n=26	Acu- HABITS 12 weeks EA n=19	Acu- HABITS Baseline HT n=18	Acu- HABITS 12 weeks HT n=18
Numbers of hot flushes/night	2.0 (1.0-3.0)	0.5 (0-1.0); 0.003	2.5 (2.0-3.0)	1.0 (0-3.0); 0.04	3.7 (2.3-4.5)	0.9 (0.3-3.0); <0.001	2.3 (0.6-3.2)	0 (0-0.2); 0.002
Distress by hot flushes/night	4.0 (2.0-6.0)	0.5 (0-4.0); 0.021	4.0 (2.3-5.0)	1.0 (1.0-3.0); 0.001	5.1 (3.8-7.4)	1. (0-4.6); 0.001	3.4 (0.6-6.6)	0 (0-1.4); 0.002
Times woken up/night	2 (2-3)	1(1-2); 0.005	3 (1-4)	3(2-4); ns	3 (2-4)	2 (1-3); 0.01	2 (1-3)	1 (1-2); 0.01
Hours slept/night	6.0 (5.0-7.0)	6.0 (5.5-7.0); ns	6.0 (5.0-7.0)	6.0 (6.0-7.0); ns	6.4 (6-7.1)	7.3 (5.4-7.6); <0.05	6.3 (5.8-6.8)	6.6 (6.0-7.1); 0.03
Total PGWB	89 (76-93)	88 (82-97); ns	88 (77-96)	91 (76-93); ns	78 (54-89)	79 (68-93); 0.002	75 (59-88)	90 (62-97); ns
PGWB vitality	13 (9-17)	15 (14-16);ns	14 (10-16)	14 (11-16);ns	11 (7-15)	13 (9-17); 0.007	13 (8-17)	13 (9-17); ns
WHQ sleep score	x	X	x	x	0.50 (0-0.75)	0.33 (0-0.67); <0.05	0.33 (0-0.67)	0 (0-0.33); 0.01
Log book sleepiness/fatigue	2.0 (1.0-3.0)	2.0 (0.8-3.3); ns	2.0 (1.0-3.0)	2.0 (0-3.0);ns	x	x	x	x

Table 5. Sleep and HRQoL variables in men with PCa and women with BCa (III,V). Data presented as median (IQR: 25-75); P-value denotes differences comparing 12 weeks data with baseline data with Wilcoxon Signed Rank Sum test. P values non significant (ns) if $p \geq 0.05$.

The sleep data in the six week pretreatment waiting list group did not change in any aspect before treatment, but after four weeks of treatment the number of hot flushes as well as the distress caused by them, as well as the number of times woken up/night and hours slept/night, changed (table 3). The effect on the hot flushes remained after eight weeks of treatment, but not the hours slept/night or times woken up/night.

The total PGWB scores were significantly lower ($p < 0.05$) at baseline for the 44 women (paper III) as a group with a median of 78 (IQR: 59-89), compared to the 31 men (paper V; 89 (IQR: 76-93)). Changes in total PGWB in women with BCa from baseline to 12 weeks are illustrated in figure 5, from baseline to 12 months in figure 6, and in men with PCa from baseline to 12 months in figure 7.

In the women in the acu-HABITS (paper III) the PGWB subscale score vitality increased significantly between baseline and 12 weeks of EA treatment. However, there were 26 patients evaluated at baseline, but only 19 fulfilled the treatment. It may be argued that this is improvement due to the drop outs, but the Wilcoxon test and an ANOVA analysis confirmed that the 19 patients who actually received 12 weeks of EA did improve their subscale score vitality significantly. Furthermore the seven women who never started or completed 12 weeks of EA treatment actually had similar ($p = 0.16$) median subscale vitality score at baseline of 13 (IQR: 11-15) as the 19 women who fulfilled treatment who had 10 (IQR: 5-14). The 14 patients who had no other treatment than 12 weeks of EA during 12 months improved their vitality score significantly (ANOVA, $p = 0.013$) as well. In the HT group there was no significant change in the subscale vitality.

In the whole group of men in the RAMP study, there was no statistically significant improvement of the subscale score vitality. However, in the EA group, the actual change of median vitality score was 2 points. This is, according to Croogs et al ¹⁸⁶ a substantial clinically relevant change, where the limit for substantial clinically relevant change is >1 SD, and this change was 2 SD.

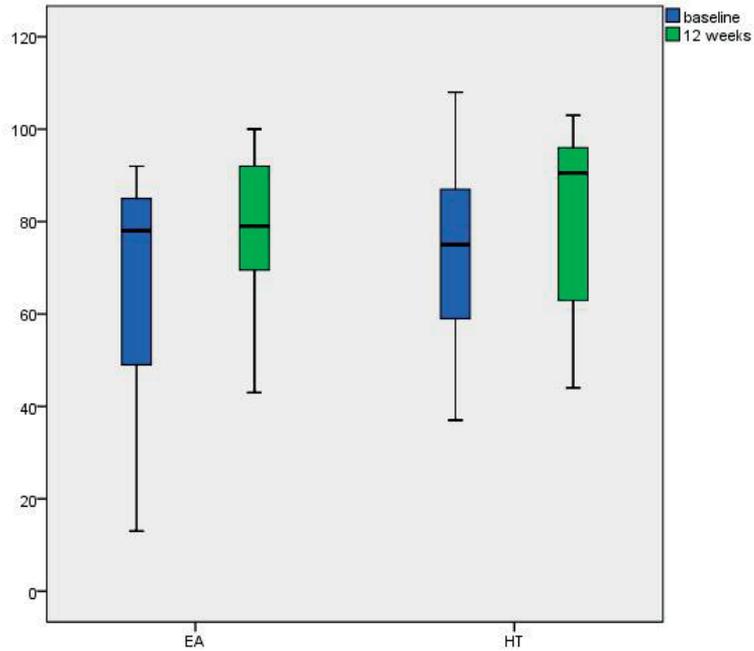


Figure 5. The total PGWB score in the EA (n=19) and HT (n=18) groups (paper III) at baseline and after 12 weeks of treatment. The median in the EA group did not change, but the “low scorers” increased their score to an extent that caused a significant change on a group level. The HT group did not change their scores to a significant level, even though the median increased. Blue boxplots= before treatment and green boxplots= during treatment, with median, the box representing the 25-75 IQR, and the outer lines the minimum and maximum values.

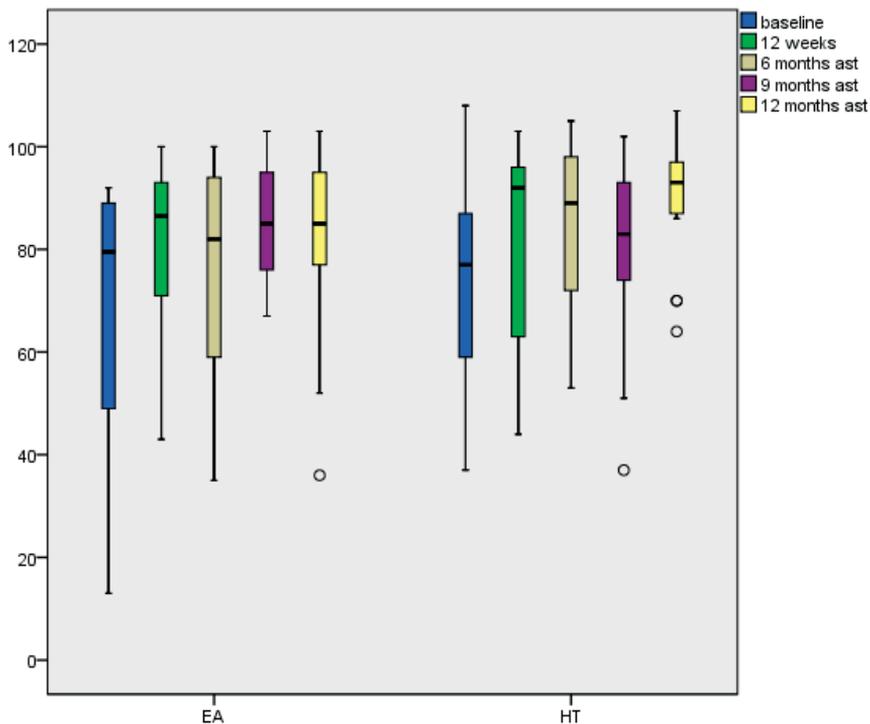


Figure 6. The total PGWB score in women with BCa, with EA (n=14) for 12 weeks and HT (n=17) for two years (paper III) at baseline and followed for 12 months after start of treatment (ast). Boxplots with median, the box representing the 25-75 IQR, and the outer lines the minimum and maximum values.

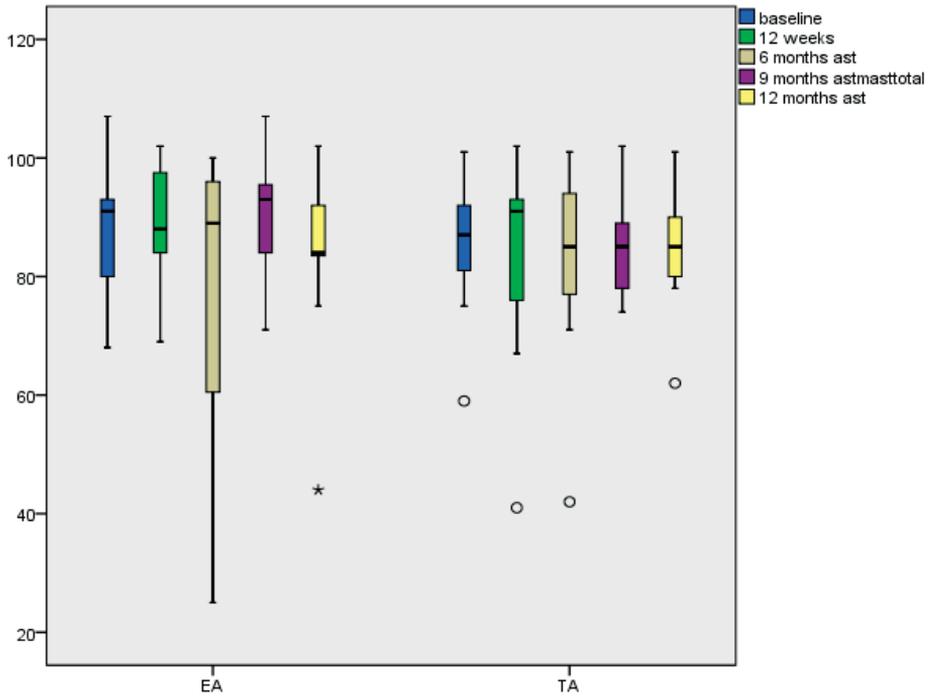


Figure 7. Total PGWB in men with PCa, with EA (n=11) and TA (n=13) for 12 weeks (paper V), at baseline and followed for 12 months after start of treatment (ast). Boxplots with medians, the box representing the 25-75 IQR, and the outer lines the minimum and maximum values.

Linear regression analysis

With linear regression analyses we assessed if hot flushes affected HRQoL in women with BCa and men with PCa.

We chose as independent variables (IV) those that we either thought could be affected by treatment, such as the number of hot flushes, or variables that were independent of treatment, but may affect HRQoL anyway, such as age at diagnosis and years from cancer diagnosis.

By performing a linear regression analysis, it is possible to see what the correlation coefficient is (r), to what extent the independent variables affect the dependent variable (R^2), and numerically how much the independent variable affects the dependent variable (B). A scatter plot diagram is a way to visualize the association between a dependent and an independent variable. Figure 8 illustrates the association at baseline between times woken up/night and number of flushes/night in women with BCa (paper III).

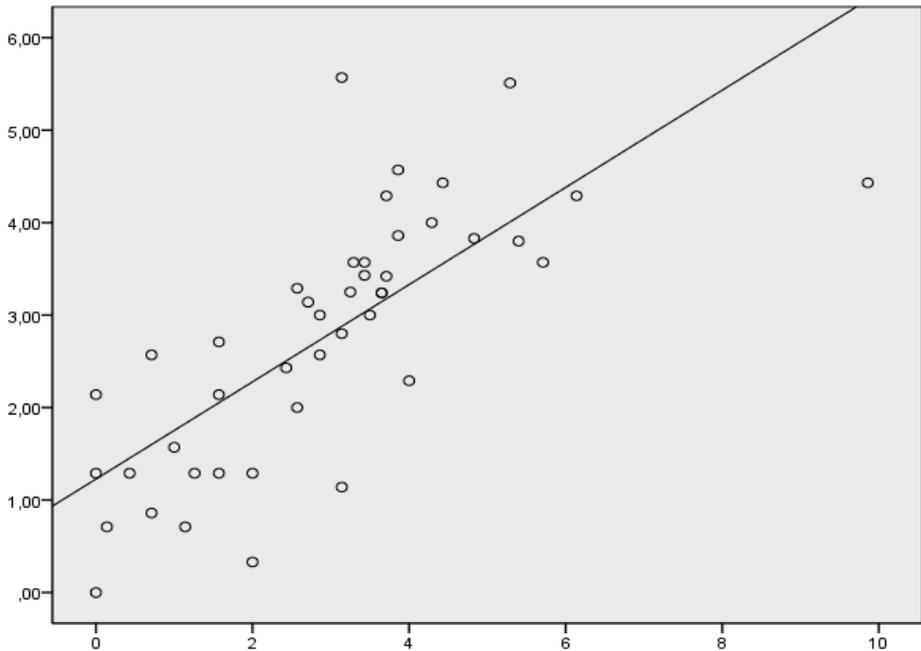


Figure 8. Scatter diagram illustrating the association between times woken up/night (dependent) and number of hot flushes/night (independent) at baseline in women with BCa (n=44). $r = 0.55$

Table 6 illustrates how the independent variable “number of hot flushes/ night” is associated with some of the dependent variables as presented below. It also exemplifies the effect of decreasing or increasing the number of hot flushes/night in the patients in our studies. For example, if a woman has a decrease in the number of hot flushes/night with 2 (this was true in the HT group after 12 weeks of treatment, and the EA group decreased their median number of flushes/night with 3), the total PGWB score would increase by 2.2 points. To achieve a clinically relevant improvement in total PGWB in the acu-HABITS material, the hot flushes/night need to be decreased by 4. For example in the men in the RAMP study, if the number of hot flushes/24 hours is the independent factor and total PGWB the dependent factor, and the flushes would decrease by 3-3.3, as they do in our study after 12 weeks of treatment with EA or TA, the total PGWB score would increase by >2.4 which is a relevant, but mild increase of PGWB in this study.

Another aspect of decreasing the number of hot flushes/night, is the strong association with number of times waking up/night. This variable probably strongly affects sleep

quality, which we did not have one single variable to use, but rather indications such as WHQ sleep score and the log book variable sleepiness/fatigue. These variables are both strongly associated with the number of hot flushes/night and number of times waking up/night.

variables	♀	♀	♀	♀	♀	♀	♀	♂	♂	♂	♂	♂	♂	♂
IV No flushes/night	0	1	2	r	R ²	p	B	0	1	2	r	R ²	p	B
DV total PGWB	81.1	78.5	75.9	0.25	0.06	0.11	-2.6	88.0	86.9	85.8	0.13	0.02	0.48	1.1
DV PGWB vitality	13.4	12.7	12.1	0.27	0.07	0.07	-0.7	15.3	14.5	13.7	0.33	0.11	0.07	0.8
DV wake ups/night	1.1	1.8	2.3	0.74	0.55	<0.001	0.5	0.8	1.5	2.2	0.71	0.49	<0.001	0.7
DV hours slept/night	6.3	6.3	6.3	0.02	0.001	0.88	-0.02	5.8	5.8	5.8	0.01	<0.00	0.96	0.0

Table 6. Linear regression analysis in acu-HABITS (paper III, ♀) and RAMP (paper V, ♂) illustrating how changes in number of hot flushes/night were associated with PGWB and sleep variables. r=correlation coefficient, summarizing the magnitude of the relationship between the dependent variable (DV) and the independent variable (IV), R²= The squared correlation coefficient, indicating the proportion of variance in the DV explained by the IV, B= the numeric change in the IV, with a direction, (+ or -). P-value denotes the probability that the B value is equal to zero, and that there is no association between the IV and the DV.

Calcitonin Gene-Related Peptide

Collections of 24 h urine before treatment, after twelve weeks of treatment, and at 3, 6 and 9 months after treatment had ended, were performed by the patients (paper IV). CGRP did not change significantly after 12 weeks of treatment, or later. In the group of 15 patients who decreased their hot flushes by 50% or more, CGRP was 12.1(IQR 9.4-16.3) at baseline and 8.9(IQR 7.4-14.5) after 12 weeks of treatment ($p=0.37$). A linear regression analysis did not show a significant association between numbers of hot flushes/24h at baseline and u-CGRP. What a clinically significant change is in CGRP is not known, and it is difficult to compare results with other studies, due to different batches of antibodies.

Discussion

This thesis focuses on the effect of acupuncture on hot flushes and sweating, as well as HRQoL and sleep in women with a history of BCa, and men with PCa. The overall findings were that the flushes decreased by more than 50% in both men and women who were treated with acupuncture, and that the distress caused by the flushes decreased even more. It was also shown that the effect lasted up to at least nine months after the treatment had ended, even if the number of flushes did increase to some extent and some patients needed additional treatment.

In women with a history of BCa, HRQoL and sleep improved to a similar extent in the acupuncture group as in the group who had HT. In the men with PCa we could not show significant changes in HRQoL, perhaps due the stage of the disease and its progress. It may be that acupuncture in men with advanced PCa prevented decreased HRQoL that would otherwise have occurred due to deteriorated health in these men with a progressive disease.

Effects of acupuncture on hot flushes

Before our pilot study (paper I) there were no reports on effects of acupuncture in men with hot flushes, whereas there were some, albeit few studies on women with hot flushes. Later some studies have been published with varying design and results.

In women

We caused more pronounced decreases in hot flush frequency with 12 weeks therapy than Deng et al. with substantially shorter therapy. They randomized 72 women with BCa and hot flushes to proper acupuncture or sham acupuncture, twice a week for four weeks and only found a reduction in hot flush frequency with 28% and 24%, respectively.

Hervik 2009²⁰³ randomized 59 women with breast cancer and tamoxifen between TA or sham acupuncture for 10 weeks, twice a week the first five weeks, and once a week for the last five weeks. The TA group decreased their number of and distress caused by flushes by 50-60% after 12 weeks of treatment with a decrease of 30% still 12 weeks after end of TA. In the sham group the number of flushes decreased by 25% after 12 weeks of treatment, and this decrease disappeared 12 weeks later. Also KI improved in the TA group but not in the sham group. These results in their TA group are similar to ours but they seem to have a working placebo control. Their placebo

method was to insert the needles 2-3 mm, at a sham point well away from the acupuncture point.

In a single arm study with individualized acupuncture De Valois ¹⁹⁷ treated 50 women with BCa and tamoxifen in eight treatment sessions. Their results were similar to ours with a 50% reduction of hot flushes and night sweats at the end of treatment, and with still some effect 18 weeks after end of treatment. Also in line with our findings, HRQoL, measured by WHQ showed significant improvements at the end of treatment, and the women reported that the hot flushes and night sweats were less of a problem, which is of great clinical relevance.

Liljegren et al ²⁰⁴ randomized 72 women with BCa and tamoxifen between traditional acupuncture and a non-insertive needling at sham-points for five weeks, twice a week, and evaluated after six weeks. Both groups decreased hot flush frequency and severity (with 42% in the true acupuncture group, and 47% in the control group). They thus had a smaller effect than we found but also a shorter treatment period. As we describe in paper V, a 50% decrease after 12 weeks, is not necessarily shown after only four weeks.

In a study of 50 women with BCa and treatment with tamoxifen or aromatase inhibitors Walker and coworkers randomized the women with hot flushes to either 12 weeks of acupuncture, (twice a week for four weeks, and then once weekly for eight weeks) or venlafaxine, initial dose 37.5 mg, and then 75 mg if tolerated. Before randomization 30 women rejected taking part in the study, because they did not want SSRI treatment, whereas no one rejected because of acupuncture. Acupuncture was as effective as venlafaxine, in reducing the hot flush frequency and severity but with longer lasting effects after treatment had ended. The effect of venlafaxine declined already two weeks after end of treatment. Acupuncture also decreased depressive and menopausal symptoms to the same extent as venlafaxine, and improved sex drive in some women, as well as their energy, and well-being ²⁰⁵. The acupuncture group reported no side effects, whereas the venlafaxine group reported several. This study had a more intensive treatment the first week, and also included the specific, non-needling components of diagnosing the patient by TCM, and choosing optional needling points, according to the results of 30-minute counselling before start of treatment. The 50% decrease in hot flush frequency and severity is similar to our results after 12 weeks of treatment. It is interesting though, that even if they had added a specific non-needling procedure we had the same effects on flushes (paper II), as did venlafaxine.

To put our findings in perspective a great number of studies have focused on effects of pharmacological alternatives like SSRI and SNRI on hot flushes. Some studies of SSRI or SNRI for hot flushes in women with BCa have found between 13% and 58% reduction of number of flushes/24 hours ⁵. Many of these treatments have pro-

nounced side effects, the studies are of short duration and the effect apparently, as shown by Walker and co-workers, disappears rapidly after treatment is stopped. Loprinzi et al concluded that venlafaxin, fluoxetine, paroxetine, sertraline and gabapentin are more effective than placebo in decreasing the hot flush score. The presented mean decrease of the hot flush score was between 3-41%¹⁴⁰, which should be compared to our 70-80 % decrease of the hot flush score in patients receiving acupuncture. It is important to scrutinize if studies of hot flushes report changes in frequency and severity/distress separately, or as the combined Hot Flush Score. The latter is a product of frequency and distress and as long as they are both reduced, the product will be presented as an even larger reduction.

EA has previously been compared with applied relaxation as treatment of hot flushes in women with breast cancer and the two therapies were found to have similar effects on number of flushes/24 hours¹⁵⁴. In a subgroup of women using tamoxifen throughout the study the reduction was similar but with a slower onset. In our study (paper II) the number of women using tamoxifen was the same in both study arms but too low (four in each) to admit a valid statistical analysis.

In men

Acupuncture treatment for hot flushes in men with PCa has been evaluated in a few studies. Filshie et al reported a mixed population of cancer patients with hot flushes including 11 men with prostate cancer. The acupuncture treatment was initially given by an acupuncturist but was later self-administered at home by the patients. For the whole study population they found that 79% of the patients had at least a 50% reduction of hot flush frequency but no results on the group of men were reported.

Auricular TA was tried in 70 men with PCa and hot flushes²⁰⁶. The TA was administered in a group setting once a week for 10 weeks, with a hot flush frequency reduction of 70%. In this kind of group treatment, it cannot be excluded that there may be a positive effect of being together with other patients with the same kind of symptoms, but it may also be a negative effect, by for example not being able to relax in a group.

Two later studies have been conducted. Beer et al evaluated 10 weeks of TA given twice a week for four weeks, and once weekly for six weeks. They reported a decrease in hot flush score just above 50% after end of treatment, but did not follow the patients longer. No severe side effects were reported²⁰⁷.

Ashamalla and coworkers treated 14 men with PCa and hot flushes with EA for four weeks²⁰⁸. They showed a decrease in hot flush score of 68% after two weeks of treatment and 89% after end of treatment, with a remaining effect at 8 months follow

up. These results are somewhat stronger than ours and those by Beer and coworkers. This may be related to the larger numbers of needles, and more needles with EA, which could express a more intensive treatment than ours.

For men with hot flushes and PCa, there are few treatment alternatives available. Hormonal alternatives, such as estrogen, cyproterone acetate and megestrol acetate, decrease the flushes by 75-100%¹⁶¹⁻¹⁶³ but are associated with risk of severe side effects^{6 164 165}. SSRI/ SNRI have been tried with moderate effect on the flushes, and have not yet been verified in an RCT . Neither Clonidine¹⁶⁷ nor herbal remedies have been proven effective, which leaves the men with few treatment alternatives, with acupuncture suggested to be one⁶.

Acupuncture compared with sham or placebo therapy for hot flushes

In order to establish the effects of acupuncture it can be compared with sham needles or acupuncture given at sham points. Nir et al randomized 29 postmenopausal women with hot flushes to an individually tailored acupuncture at true acupuncture points, or selected sham points, with a non-penetrating needle²⁰⁹. The treatment included nine sessions over seven weeks, and showed a significant decrease in severity in the true acupuncture group, but not in the sham treated group, whereas frequency decreased significantly and to a similar extent in both groups. These results have been referred to by others as a proof of no effect of acupuncture, since it was not better than the sham acupuncture, but the absence of evidence is not always evidence of absence. There was still a significant reduction in numbers of hot flushes in both groups which may implicate, as also suggested by the authors, that their sham therapy was not inert.

In an analysis of two randomized controlled studies on menopausal women with hot flushes but without BCa, Zaborowska et al found that EA, TA as well as applied relaxation for 12 weeks caused a greater reduction in hot flushes/24 hours than did treatment with a transdermal placebo patch²¹⁰.

Side effects of acupuncture

There are few adverse events reported in acupuncture studies. In our studies side effects were reported by totally three patients (all in the RAMP study), a cm sized hematoma, fatigue at the day of acupuncture, and disliking the needles. In general, there are few severe side effects related to acupuncture as performed by an established acupuncturist in health care. A German retrospective study concluded that out of 230 000 patients who received a mean of 10 acupuncture sessions for different conditions, 8.6% reported some kind of adverse event, with bleeding and hematoma at the needling site as the most common (58% of the reported adverse events), pain (19% of the reported

adverse events) and interestingly 0.04% of all the patients reported sweating. Two patients developed pneumothorax, and one a nerve damage, of these >2 million needling sessions²¹¹. Rare cases of deaths are also reported, in a review of systematic reviews on acupuncture, where five cases were reported. Four were related to pneumothorax, and one to an aortoduodenal fistula²¹².

It may be argued that acupuncture stimulates ovarian function, e.g. by reducing sympathetic tonus²¹³, and thereby reduces vasomotor symptoms at least in women not too many years after menopause when some ovarian function still remains. However, Dong et al²¹⁴ successfully treated hot flushes in 11 menopausal women for five weeks with acupuncture but did not find any changes in LH, FSH, estradiol, progesterone or prolactin from baseline. This is in line with findings from Wyon et al who did not find any changes in estradiol or FSH concentrations in women treated with acupuncture for 12 weeks⁵⁹, and in the RAMP study (paper IV), we found no changes in s-testosterone or s-LH after 12 weeks of treatment.

The effect of acupuncture on Health Related Quality of Life and sleep in cancer patients

Acupuncture may be used in cancer patients to alleviate pain and nausea. This in turn may affect HRQoL and perhaps sleep. Few studies have been made to evaluate if acupuncture by reducing hot flushes may improve HRQoL and sleep.

TA treatment for 25 men with PCa and hot flushes was tried by Beer et al²⁰⁷. They reported a decrease in hot flush score larger than 50%, after 4 weeks of TA twice weekly and then once weekly for six weeks. They registered HRQoL, related to the hot flushes with the Hot Flash Related Daily Interference Scale, HFDIS, and Short Form 36-item before, during and after treatment. To determine the effect on sleep Quality, the Pittsburgh Sleep Quality Index, PSQI, was administered. The HFDIS showed significant improvements already after four weeks of treatment, which were confirmed after 10 weeks of treatment. However, the generic HRQoL assessment tool, SF-36, did not show any changes. There was no general improvement in sleep in the whole group, but in the group of patients who decreased their hot flush score by at least 50%, there was a significant improvement of sleep quality, measured by the PSQI. Patients, who did not decrease their flushes, also did not decrease their sleeping difficulties. These results are in line with our results in men with PCa, where we could not find a significant change in a broad, general HRQoL instruments score (PGWB). Nevertheless, they used a HRQoL instrument, relating to the symptoms and disturbances of hot flushes, and here they could verify an improvement. This HFDIS was developed for patients

with hot flushes and BCa²¹⁵, but probably, as with the WHQ, there are several questions that matter for both genders, in a situation of hormone dependent cancer.

In the men who were treated by auricular TA for 10 weeks by Harding et al²⁰⁶, a validated cancer related well-being instrument was used, where the patients evaluated their two worst concerns and graded them between 1-6. Before the treatment, the most common primary concern was hot flushes and night sweats, reported by 62% of the patients, sleep disturbances the second most common concern (40% of the men). After 10 weeks of treatment the mean value of concern score, and also of a well-being score in the same instrument, had decreased significantly. In conclusion HRQoL seems to be related to hot flushes in men with PCa when measured with instruments that are disease specific and also take into account the vasomotor symptoms. HRQoL seems to be closely related to sleep quality, in line with the results of the linear regression analysis in the RAMP study (paper V).

De Valois and coworkers conducted a single arm observational study with a similar BCa population and acupuncture method as in the acu-HABITS¹⁹⁷. They recorded hot flushes and WHQ and found a reduced frequency of flushes with about 50% and clinically relevant improvement in seven subscales of WHQ, results that persisted 4 months after end of treatment. A randomized study evaluated applied relaxation and EA in women with BCa and hot flushes with a symptom check list measuring general psychological well-being and with a mood scale. They found a significant improvement in the symptom check list and mood scales in parallel with decreasing hot flushes and the effect lasted up till three months after end of treatment²¹⁶. Apparently also in women with BCa acupuncture may improve HRQoL perhaps through decreasing the hot flushes.

Calcitonin Gene-Related Peptide

In an earlier study, we found that U-CGRP decreased in woman successfully treated with acupuncture for their hot flushes⁵⁹. The 24 hour urinary excretion of CGRP did not change significantly in men with EA or TA even if there was a slight albeit non-significant decrease in the men with decreased hot flushes. This is in line with a previous study by Wyon et al who could not find changed CGRP excretion in urine in 15 men with PCa, studied before and after three months castration treatment, when 11 of the 15 men developed hot flushes⁷⁷. However, in that patient group, as well as in ours the patients were fairly old, with perhaps impaired vision, and they had other difficulties such as collecting urine due to impaired physical health and urge to void. So in contrast to healthy, younger postmenopausal women, these elderly men may not col-

lect 100% of the urine during 24 hours [60]. This could have been controlled and corrected for by also measuring 24 hour urine creatinine excretion, provided there was no change in renal function during the study. CGRP may also be differently metabolized in healthy versus older patients with a serious disease, into some metabolites that avoid identification. If it is the collection difficulties that cause the diverging results between men and women, the solution could be either to have the patient at hospital for 24 hours every follow up, for a more stringent urine collection or use a urinary catheter. Neither of these methods seemed reasonable in our study presented in paper IV and V.

It is possible to measure CGRP in plasma during a hot flush. However, this demands that the patient stay at the hospital, with 24 hours supervision, and readiness for blood sampling. The half-life of CGRP is short, and it is also shown that patients underreport their hot flushes, which could make us miss sampling events, and thus measure CGRP during too few flushes. Beer et al ²⁰⁷ investigated plasma levels of CGRP at baseline and after four weeks, but could not find any significant changes, which is not surprising.

Methodological considerations

Acupuncture as a treatment for hot flushes

In treating women with hot flushes during menopause, Wyon et al used TA and EA, and could show a decrease of number of and distress caused by hot flushes by more than 50% after eight weeks of treatment⁵⁹. These results made us try acupuncture first in the pilot study (paper I) on men with hot flushes due to PCa treatment, and later as a randomized controlled study in men with PCa and hot flushes (paper IV and V). The results also made us suggest acupuncture as the “non-hormonal treatment” for women with a history of BCa and hot flushes in our regional sub-study of the HABITS study (paper II,III). There had been a few earlier studies on acupuncture therapy in women with vasomotor symptoms²¹⁷ but none on men until our pilot study. Also, none of the previous studies had evaluated the long-term effects.

Electrostimulated acupuncture compared to traditional acupuncture

The rationale for using TA as a comparator to EA (paper IV,V), and not a placebo control is that sham needles or sham points are not shown to be totally inert^{218 219}.

TA has thus been suggested as a control to EA if the effect of the electrostimulation is to be studied¹⁶⁹. EA has also, in earlier studies^{172 173}, been shown to have a stronger effect than TA. The effect of TA is probably a sum of possible physiological effects of acupuncture, procedure related effects, patient’s expectations and placebo effects. If the effect of EA would be superior to the effect of TA, it could be concluded that the difference in effect would be the result of the electrostimulation. However, the slight, non-significant differences in effect on hot flushes that may exist, and that are shown in our paper IV, are too small to be proven with sample sizes such as ours. A sample size calculation could give us the number needed to treat to find significant changes, but to do these large scale studies, when there seem to be no superior effect of the TA, is rather useless. Instead, studies should be conducted with acupuncture, compared with a future functional placebo method, a waiting list group, or other treatments as SSRI or HT, when possible. We did not, however, want to use a waiting list control group and thereby exclude this group of patients from treatment, since these are patients with a metastatic cancer disease and troublesome symptoms.

Choice of placebo/ control

In paper II and III, the control was HT, not a placebo. The aim of the HABITS study was to assess the risk of breast cancer recurrence during and after HT treatment. Our sub-study had the opportunity to compare acupuncture with a treatment that we knew would have an almost 100% effect on the flushes, and our aim was never to show that

EA would be any better than or as good as HT. We could have chosen to split our "non-hormonal treatment" arm into two; EA and a third treatment arm, either "no treatment", just observational, or perhaps SSRI. A "no treatment" arm would probably have had large drop-out numbers, since the women sought help for their flushes, but a design with no treatment could show the natural decline of flushes over time that might have occurred. SSRI seems to have a moderate effect on the flushes, but is associated with side effects such as nausea, dry mouth and sometimes weight gain, and many studies report high numbers of drop-outs due to these side effects ⁵.

Evaluation of acupuncture would be easier with a proper placebo model. Placebo needles and sham acupuncture have been developed, but were not in use at the start of this study. Also both methods probably cause tactile, neuronal and cerebral stimuli ²¹⁹⁻²²¹, and are thus not perfect placebo methods. Since depressed mood, anxiety ²²² and vasomotor symptoms ^{223 224} may be related to low hypothalamic β -endorphin activity, and placebo effects are at least partially caused by increased β -endorphin activity ²²⁵, it is not surprising that placebo affects mood and hot flushes. The oral placebo effect in men has caused 20-50% reduction in number of flushes by using placebo tablets, most often for less than 12 weeks ^{161 166 226} and is almost as large as in women ¹²⁵.

To study EA with the most effective treatment as a control group is achievable if the lower limit of effect wanted of the EA is known beforehand. This is because the size of change in hot flushes does not need to be compared with the most effective treatment, but rather with baseline, or other treatment alternatives. This approach leaves no group of patients untreated. However, the decision to compare with the golden standard treatment needs to be taken in account when results are evaluated for examples in a review ²²⁷. It is not possible to draw the conclusion that there is no effect, when it is not compared to placebo or non-treatment, but compared to an excellent treatment.

In papers IV-V, eight patients had to wait for therapy and comprised a six-week waiting list group, with no treatment, and could therefore be considered as a small waiting list control group. Their log-books were analysed at six weeks and one week before treatment, and after four and eight weeks of treatment, with significant changes in number of hot flushes and distress by hot flushes after four and eight weeks of treatment, but no changes before the treatment started (Table 4).

Mechanism of the acupuncture effects

In the acu-HABITS study, EA relieved vasomotor symptoms in most women with BCa, albeit the symptoms tended to come back during the 21 months follow up after the treatment had ended. One question is if this reduction of hot flushes is caused by

the needling treatment as such or by specific non-needling components, or non-specific non-needling components like placebo effects. The specific non-needling component may be omitted as there was no diagnosing by the acupuncturist, and the needle points were set, so palpation to a greater extent was avoided. However, the distinction between specific needling effects and placebo should have been evaluated with a proper placebo model. To develop a proper placebo treatment, it is necessary to know what component to avoid. As long as it is not established which part of the acupuncture procedure that actually causes the physiological response, it is impossible to develop the perfect placebo model. When it comes to the needling, there are questions on what to be avoided in the placebo situation. Is it, for example, the depth, the twirling that cause stretching of nerves and connective tissue (De Qui), the needle size, the number of insertions or the time of needle insertion that causes the physiological effects? There were no placebo needles available when the HABITS study was designed, and they are still not ideal because they probably cause neuronal stimulation^{169 221}. A randomized study, using functional Magnetic Resonance Imaging showed local cerebral activity with an acupuncture needle, stimulating an acupuncture point, but also with the Streitberger needle at sham points activity was shown²²⁸. In women with breast cancer some studies have used sham points or non-insertive devices, and report effect on flushes even with the control methods^{204 229}. There is also the question, if it is only the needling that needs to be controlled for with a placebo, or if we also need to control for the specific non-needling components and the non-specific non-needling components. To evaluate a placebo method that controls for all three suggested components of acupuncture, would be ideal.

A problem, that many studies on acupuncture encounter, is that by controlling these three factors, we also try not only to describe them, but also omit some of them. For example, in our studies, the specific non-needling components were not allowed, and we did not allow individualization of needling (points, depths etc.). Furthermore the acupuncturist should standardize the non-specific components as much as possible, by not talking about expected results and giving the patients the same time attention. This has been suggested to be the explanation why acupuncture is not as effective as expected in some studies¹⁶⁹, when only one or two of the three components are used.

In our study, however, the long lasting and profound effects of 12 weeks of EA or TA on the vasomotor symptoms up to two years contradict placebo effects which do not usually persist for more than three months. However, a study, following the effect on hot flushes after an oral placebo treatment had been stopped has not yet been conducted or published. Furthermore, we have earlier shown physiological effects of acupuncture treatment on vasomotor symptoms, with decreased urinary excretion of the

vasodilating, sweat-gland stimulating peptide CGRP during successful therapy⁵⁹. We have not, in the present studies, explored possible effects of acupuncture on the thermoregulatory system and neurotransmitters like serotonin, β -endorphin and noradrenaline. Such studies are complicated to perform in humans and should better be performed in an animal model. Physiological central effects of acupuncture have been evaluated in animal models^{181 230 231}.

It could be argued that the decrease in flushes after two years is a physiological and expected reduction over time. This cannot be excluded without an untreated control group, which we considered unethical in this group of patients. However, the effect was shown already within the first 12 weeks, which is far faster than the natural vanishing of flushes, and several studies have shown that the flushes usually last for many years^{2 39 38}.

Choice of method for monitoring hot flushes

There are several ways of measuring hot flushes in patients. Our aim was to evaluate the flushes in an everyday environment, and to evaluate if treatment with acupuncture is possible to conduct outside a university environment, and still standardize it, and assess the effect. Therefore, we decided to use ambulatory measurements with the patients at home, performing daily activities and sleeping in the home environment, instead of the validated laboratory measurements of e.g. sternal skin conductance or temperature. The advantage of the ambulatory mode is the fact that it is administrable to several trial centres, and easy to learn for the practitioner and the patients. Logbooks, “flush diaries”, are widely used, and accepted as a validated measurement with reasonable correlation with objective measurements. Rand et al compared self-reported hot flush frequency and severity with skin-conductance measurement of flushes. They found more physiological events than self-reported flushes, but concluded that it is only the self-reported flushes that the patients find disturbing, and interfering with daily life that have clinical relevance in studies evaluating vasomotor symptoms treatment⁷⁹. Diminishing numbers of subjectively reported flushes, and increasing subjective sleep quality were suggested to be the most direct ways to improve HRQoL.

Choice of HRQoL instruments

In the literature, measurements of QoL and HRQoL are sometimes used without a clear statement about whether it is QoL or HRQoL one wants to study. In one respect, this may not matter, since definitions are not clear, but in a scientific study it would be recommended to state the definition in the study, in order to be clinically and scientifically useful. In our studies we have chosen the definition HRQoL, and aimed to study

the effect of therapies on HRQoL, in patients with a history of cancer, and ongoing vasomotor symptoms. We therefore chose instruments that not only assessed QoL, but also symptoms related to the diseases. PGWB is a generic instrument, but used to cover aspects of general health, social interactions, mood and tiredness for example, and to evaluate over time, the effect of a specific disease or its treatment. In this thesis, however, the cancer is one issue, and the vasomotor symptoms another. Both the cancer and the symptoms possibly affect HRQoL, but the cancer is not treated with acupuncture. Therefore, a symptom specific instrument, WHQ was used for the women to evaluate the climacteric symptoms. There is, to my knowledge, no such symptom-related instrument for men, experiencing these, often considered, female climacteric symptoms. The majority of the questions in the WHQ could actually be useful even in a castrated man, with questions about sleeping difficulties, night sweats, lack of libido, weight gain etc. The HFDIS was developed for women with hot flushes and BCa²¹⁵, but probably, like the WHQ, there are several questions that matter for both genders. Since there is no disease specific instrument developed for men with hot flushes yet, we used daily log-books for both the women and men, which at least is a validated measurement for the hot flushes.

The log-book has not previously been validated for sleepiness/fatigue or depressed mood, but in paper V, the log-book data had a high association with the PGWB domains vitality and depressed mood, and could thus be a useful instrument.

Sleep was initially thought of as the numbers of hours slept/night, appreciated by the patients. Sleep disturbances were only specified by number of wake ups/night and numbers of and distress by hot flushes/night. The questions about sleep (number of times woken up/night and hours slept/night) do not seem to be irrelevant, since both variables are associated with HRQoL, at least measured by PGWB, log-books and WHQ. If a qualitative study on men with PCA and hot flushes would had been conducted before the RAMP study, a deeper insight into the sleeping problems that these men encounter would have helped us in making a more relevant sleep log-book. Now, these questions arose during the study, when talking to the men. Improving the log-book questions or using already validated instruments could have been done. The questions could have been widened, with “What is the reason for waking up?”, and “How much do you sleep during the day?”, “How long are you awake in bed before falling asleep?” The log-book item “Hours slept/night” could have been clarified, and the patients could have been instructed that they should subtract the time they were awake from the total numbers of hours between time falling asleep and rising in the morning, to estimate the sleep effectiveness. It may, however, be difficult to evaluate how long one is awake every time one wakes up during a night, for example by hot

flushes, and thus to give a correct answer. We did not see any major differences in the numbers of hours slept/night in these patients groups. It may be because 1) there are few wake ups at baseline, and small changes in hours are thus difficult to identify 2) there are other reasons left for waking up (like need to visit the bathroom), even when the flushes are reduced 3) the time the patients were awake during the night, is not subtracted from the total sleeping hours.

Factors that may affect numbers of hours slept/night may also be related to intake of caffeine, sleeping remedies and alcohol, and a question asking for such intake could have been added to the log-book, as well as a quantifying question about day-time sleep, and a qualitative question about daytime sleepiness/fatigue and subjectively perceived sleep quality. For the men in paper IV-V, the question of specific medications was brought up at every visit, and the patients were allowed to continue with sleeping pills, if they had used them for a long time, and did not change their intake during the study. This can of course give a picture of these men sleeping better than they would otherwise have done without sleeping remedies, but at least it does not give a false impression that we changed sleep with acupuncture. Even if we would have included a question about alcohol, which affects sleep, it might not have added any strength to our study taking into account the fact that many people do not answer such questions honestly. Hopefully, the randomization distributed alcohol use to be similar in both groups.

There are numerous studies on HRQoL in patients with cancer, especially BCa, where the results may at first sight seem divergent. However, interpreting the results demands knowledge of how the studies are performed, with what aims and the timing of the study, related to the time of diagnose. Only 80% of the RCT's on BCa and HRQoL present which instrument was used, trial and HRQoL sample size, the timing of the HRQoL assessment in relation to diagnosis, and which statistical method was used²³². Not until these quality aspects are fulfilled can the results may be compared and understood.

The strengths of the studies

The strength of the pilot study, paper I, was that no one had ever tried acupuncture for hot flushes in men with PCa before. It showed that improvement was still achievable beyond four weeks, that most patients withstood 12 weeks of treatment, and that the effect on the flushes sustained up to 14 weeks after treatment had ended. These data helped us in conducting the RAMP study (paper IV,V).

One of the strengths of the acu-HABITS study was that the EA was compared to the best possible treatment for hot flushes, HT. We did not expect EA to be as good as HT,

but at least no group was without treatment, which was almost a must when including these patients, who actively sought help for their flushes. Another strength was that the study was multi-centered, in the aspect of using different acupuncturists mimicking clinical every day practice, and not a university setting. This decreases the possible positive effect of one therapist. The acupuncturists were also told not to perform the specific non-needling components of acupuncture, like diagnosing, eliminating one third of the thought effect of acupuncture that is not needling specific. The long post-treatment follow up showed us that some women report that their flushes return after some months, but that the effect may last up to two years.

RAMP study was the first prospective controlled study on EA and TA for men with PCa and hot flushes. Some of the strengths of the acu-HABITS study are also true for the RAMP study. There were few drop outs probably due to lack of treatment alternatives. We did not have a placebo control group but used a waiting list group of eight patients. Our previously used log books data for sleepiness/fatigue and depressed mood were validated in relation to PGWB subscales on vitality and depressed mood by showing a high association in a regression analysis.

The weaknesses of the studies

A weakness with all studies is the lack of an inert control treatment. Therefore we cannot conclude that the results are due to specific treatment effects but may be caused by spontaneous resolution of symptoms or by non-specific treatment effects. These weaknesses have been discussed earlier.

Regarding both the RAMP and acu-HABITS studies log books were used frequently. Asking the same question every day, on a sheet where he/she can see the score of the day before may risk leading the patient to give the same answer every day, if there are no major events. This is called response shift and could perhaps have been avoided by only have given them log-books for example every fourth week during the first 12 weeks, when the patients filled in the forms every day. We did think that we would have greater compliance with the patients filling in the log-books every day, instead of separate timings. We did have a good compliance, with few missing data, but perhaps to the cost of too small differences from day to day. Another alternative would have been to use log-books where the previous data become covered in a kind of sheet when you proceed to the next day.

In the RAMP study we should have measured cancer progress by PSA or specific questions in order to relate to changes in HRQoL. In this patient group a deterioration in HRQoL could be expected and counteracting a possible improvement of HRQoL.

Perhaps a cancer specific HRQoL instrument could have been useful in detecting disease progression.

The weakness with the CGRP analyses was that we did not measure creatinine in urine. However creatinine measurements could be affected by the progressive disease and thus not validated the quality of the urine collections.

It could be argued that the RAMP study (paper IV,V) mainly recruited patients positive to acupuncture therapy. Since the trial only included acupuncture therapy, albeit two different modes of acupuncture, some selection bias of patients with mostly positive expectations towards acupuncture cannot be excluded. We could have asked the participants to fill in a questionnaire about treatment expectations to have measured this bias but unfortunately this was not done. On the other hand, women in the acu-HABITS study had to accept both HT and acupuncture and were therefore hardly, on a group level, biased in a special direction. The fact that a number of women randomized to one arm, asked to switch to the other arm during follow up, suggests that many of them did not have any special preference.

Mainly due to the need for further treatment of the hot flushes a large drop out number was encountered in the acu-HABITS study. If we had used an intention to treat analysis and design the drop-out rates would have been lower but could also have given us more uncertain results. The safety analysis of the main HABITS study caused an early closure which made the size of the treatment groups uneven.

Conclusions

In general we found that treatment with acupuncture in women with a history of BCa, and men with PCa was associated with a decrease of number of and distress caused by hot flushes with at least 50%. This led to decreased disturbances at night, and in women HRQoL improved.

The results from the pilot study (paper I) suggest that acupuncture should be further evaluated as a treatment for vasomotor symptoms in men with PCa.

In the prospective study on men with PCa, the number of and distress caused by hot flushes decreased significantly, and with about 50% in both the EA and TA groups up to nine months after end of treatment.

Times woken up/night decreased transiently in the EA group but not in the TA group. This indicates that there are also other factors than the hot flushes that cause sleep disturbance in these men. HRQoL did not change statistically on a group level.

Number of times woken up/night was strongly associated with numbers of hot flushes/night, and these variables were associated with sleepiness/fatigue at baseline but not after therapy suggesting that the negative impact of flushes on sleepiness/fatigue was decreased by therapy.

U-CGRP did not decrease significantly during the study.

In women with a history of BCa, the number and distress caused by hot flushes, and the score of the Kupperman Index decreased by more than 50% after 12 weeks of treatment with EA, and the effect remained up to two years. HT for two years, and acupuncture for 12 weeks improved HRQoL, including sleep. The effect was as strong in the EA group as in the HT group, and lasted up to two years. HT had an expected stronger effect on the hot flushes, but the similar effects on HRQoL suggest that acupuncture cause additional effects on HRQoL than only on the hot flushes.

By analysing associations in both men and women, it seems that by decreasing the number of hot flushes/night and day, HRQoL may improve, probably related to an improved sleep.

Approximately every 5th patient could be regarded as non-responders to the acupuncture treatment.

Clinical implications

The clinical implication of the results of my thesis would be that if a man with PCa or a woman with BCa seeks advice due to hot flushes, the medical profession first needs to recognize these needs, realizing that the flushes may impair HRQoL and sleep. The treatment alternatives that exist should be presented, and those with negative interactions with the cancer treatment or other concomitant diseases should be avoided. Possible side effects of treatments should be presented for the patient, and thereafter the patient and the health care provider should reach a shared decision as to which therapy – or no therapy – to try. Acupuncture should be presented as one of the treatment alternatives. It is safe, and may decrease the hot flushes and the distress caused by hot flushes, even to the extent that it improves HRQoL and sleep. It should be noted, though, that 20 % of our patients did not respond to the acupuncture to such an extent that it is considered clinically relevant. In these patients, an individualisation of the specific needling, and specific non-needling components may be tried, which we have not tried in our studies.

Future research:

When the studies were running, and when I have been writing this thesis, I have recognized that there are some problems with the design of the studies and that there are fields that I feel need to be investigated further. These are examples:

- In men with hot flushes and PCa, it would be valuable for future studies to follow a population of men from the start of ADT, with PGWB, a cancer specific HRQoL questionnaire, log-books on hot flushes and a validated sleep questionnaire, and then compare men with and without hot flushes with respect to HRQoL issues and sleep. This design would demand that questions be posed repeatedly on changes in medication, progress of disease, and that any treatment of hot flushes would be noted.
- In men with hot flushes and PCa, the data above would be useful when treatments for hot flushes were to be evaluated. EA could be compared to SSRI in a RCT with follow up for a year being necessary in order to answer questions on adverse event, drop-out rates and patient compliance with treatment. Treatment with EA would be 12 weeks initially, but “refilled” on demand by the patient, to enable a fairer comparison to be made. A possible control group could be that both groups of patients would record log books and HRQoL instruments daily during three months before treatment, as a waiting list control. However, if a to-

tally inert placebo needle and method were to exist, that would be the favored choice of control method.

- Exercise has earlier been shown effective on hot flushes during menopause. In men with PCa and ADT, there are other side effects of ADT that may improve by regular, low-intensive exercise, like fatigue, loss of bone and muscle mass, weight gain, and depressed mood. A pilot study would have to be conducted to see if it is feasible to exercise this group of patients, and to what extent it might be possible to measure any positive effects. It would also be interesting to evaluate PGWB, log-books for hot flushes and sleep, BMI, blood pressure and perhaps body composition.
- For men with hot flushes and PCa, a laboratory sleep study would be interesting, where polysomnography would measure the physiological sleep events, and skin conductance and skin temperature would measure the hot flushes simultaneously. In this way, it should be possible to see if the hot flushes relate in time to disturbances in sleep, measured by polysomnography.
- For men with ADT; develop a HRQoL questionnaire, being disease specific in the aspect of androgen deprivation symptoms.
- To answer the question why the findings of u-CGRP in men do not change as in women, when flushes are treated successfully, we have started a comparative study of CGRP in 24 hour collections of urine to evaluate if the metabolites of CGRP or the patients' capability to perform exact urine collections are different in men with a metastatic disease than in healthy men, or menopausal women.
- In women with hot flushes and BCa, a RCT of 12 months could be conducted, with EA in one arm, for 12 weeks, and booster treatment on demand to make an intention to treat analysis more proper, and a SSRI with the lowest impact on the tamoxifen metabolism in the other arm, EA combined with SSRI in the third arm. The long-term follow up is necessary, since the long-term compliance in this group of patient with SSRI for hot flushes has not been verified. This study would measure hot flushes by log books, possible effects on sleep by a validated sleep score, and HRQoL by WHQ and a generic HRQoL instrument. A disease specific HRQoL instrument, related to the BCa could be used, but would have to replace one of the others, to not overload the patients with questionnaires, which may lead to missing data. The patients would fill in the forms every third month.
- To evaluate the duration of the period in which the placebo has its effect, it would be interesting to conduct a RCT where women with hot flushes would be randomized to a placebo pill. HT. or EA for three months and then stop the

treatment. Log-books for hot flush data would be collected at baseline, after three months of treatment, and three and six months after the treatment had ended. It could then be established for how long and to what extent the different treatments had an effect on hot flushes. An inert acupuncture treatment model would be a fourth arm in the study, if there was an established method available.

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Appendix 1(2) STRICTA for the acu-HABITS study (paper II,III)

- Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) items that replace CONSORT 2010 item 5 when reporting an acupuncture trial

- (1) Acupuncture rationale
- (1a) Style of acupuncture :Traditional Chinese Medicine, with Electrostimulation at four points
- (1b) The treatment was chosen, based on earlier studies of acupuncture as treatment of hot flushes in menopausal women ^{59 154}
- (1c) The treatment did not vary within the group, but was administered by six different acupuncturists
- (2) Details of needling
- (2a) Twelve needle insertions per subject per session
- (2b) Acupuncture points and the anatomical position used for needle insertion
- Acupuncture points Anatomical position
- Bilaterally at
- BL 15 (urinary bladder) Thoracic part of the back
- BL 23 (urinary bladder*) Lumbar part of the back
- BL 32 (urinary bladder*) Lumbar part of the back
- Unilaterally at
- GV 20 (Governor vessel) Top of the head
- HE 7 (heart) Ulnar side of the wrist
- PC 6 (pericardium) Volar side of the distal forearm
- LR 3 (Liver) Dorsal side of the foot
- SP 6 (spleen) Lower leg, medial side
- SP 9 (spleen) Lower leg, medial side, below the knee
- * Stimulated with 2 Hz.
- (2c) Depth of insertion : 5-20 mm
- (2d) Responses sought: de qi
- (2e) Manual or electrical stimulation (2 Hz)
- (2f) Needle retention time : 30 minutes from last needle insertion to needle withdrawal
- (2g) Needle type: 0.25mm in diameter and 15mm long, or 0.30mm in diameter and 30mm long (Hwato, Suzhou Medical Instruments, China)
- (3) Treatment regimen
- (3a) Number of treatment sessions: 14
- (3b) Treatments were given with needle retention time 30 minutes, twice a week the first two weeks, then once a week for 10 weeks, total treatment period 12 weeks.

(4) Other components of treatment

(4a) No other interventions or treatments were given in the acupuncture group

(4b) Treatment was given by physiotherapist at hospital or private practice, one patient at a time. Acupuncturists were told not to discuss the treatment or possible effects with the patients. Patients were explained that they were given acupuncture, with electrostimulation at back needles.

(5) Practitioner background

(5) Six physiotherapists with education in and many years of experience of acupuncture administered the treatment. Each patient was treated by only one acupuncturist for the complete series of treatment

(6) Control or comparator interventions

(6a) The comparator in this study is Hormone Therapy, the most effective treatment of hot flushes ¹²⁵The rationale for using this as a comparator, and not a placebo needle is that the aim of the HABITS study was to evaluate the risk of recurrence of breast cancer with HT, or alternative treatment of choice for hot flushes. HT was not optional, but we chose to use acupuncture as our alternative treatment. Our intention was not to prove that acupuncture had a better effect than hormone therapy, but rather to evaluate if it had any effect on flushes, HRQoL and sleep.

(6b) The choice of comparator Hormone therapy, was made by the gynaecologist. Women less than 2 years after menopause were given a sequential estrogen/progestagen combination; if they were more than 2 years after menopause, they were given continuous combined estrogen/progestagen. If hysterectomized, the women received unopposed estrogen. Tibolone was not allowed. According to the protocol, HT should be used for 24 months and then be stopped.

Appendix 2(2) STRICTA for the RAMP study (paper IV,V)

- Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) items that replace CONSORT 2010 item 5 when reporting an acupuncture trial

- (1) Acupuncture rationale
- (1a) Style of acupuncture :Traditional Chinese Medicine Acupuncture (TA), or TA with Electrostimulation at four points (EA)
 - (1b) The treatment was chosen, based on earlier studies of acupuncture as treatment of hot flushes in menopausal women ^{59 154}
 - (1c) The treatment did not vary within the group, but was administered by five different acupuncturists
- (2) Details of needling
- (2a) Twelve needle insertions per subject per session, with the patients laying on the side
 - (2b) Acupuncture points and the anatomical position used for needle insertion
Acupuncture points Anatomical position
Bilaterally at
BL 15 (urinary bladder) Thoracic part of the back
BL 23 (urinary bladder*) Lumbar part of the back
BL 32 (urinary bladder*) Lumbar part of the back
* Stimulated with 2 Hz if randomized to EA.

Unilaterally at
GV 20 (Governor vessel) Top of the head
HE 7 (heart) Ulnar side of the wrist
PC 6 (pericardium) Volar side of the distal forearm
LR 3 (Liver) Dorsal side of the foot
SP 6 (spleen) Lower leg, medial side
SP 9 (spleen) Lower leg, medial side, below the knee
 - (2c) Depth of insertion : 5-20 mm
 - (2d) Responses sought: de qi
 - (2e) Manual or electrical stimulation (2 Hz) in the EA group
 - (2f) Needle retention time : 30 minutes from last needle insertion to needle withdrawal
 - (2g) Needle type: 0.25mm in diameter and 15mm long, or 0.30mm in diameter and 30mm long (Hwato, Suzhou Medical Instruments, China)

(3) Treatment regimen

(3a) Number of treatment sessions: 14

(3b) Treatments were given with needle retention time 30 minutes, twice a week the first two weeks, then once a week for 10 weeks, total treatment period 12 weeks.

(4a) No other interventions or treatments were given

(4) Other components of treatment

(4b) Treatment was given by a physiotherapist at a hospital or private practice, one patient at a time. Acupuncturists were instructed not to discuss the treatment or possible effects with the patients. Patients were explained that they were randomized to acupuncture, with or without electrostimulation at back needles, which they could not see.

(5) Practitioner background

(5) Five physiotherapists with education in and many years of experience of acupuncture administered the treatment. All patients but one received all their treatments from one physiotherapist. One patient had to change physiotherapist during his treatment period, due to a move.

(6) Control or comparator interventions

(6a) The comparator in this study is TA to EA. The rationale for using this as a comparator, and not a placebo control is that sham needles or sham points are not shown to be totally inert. TA has thus been suggested as a control to EA if the effect of the electrostimulation is to be studied¹⁶⁹. EA has also in earlier studies^{172 173} been shown to have a stronger effect than TA, which made TA and EA two interesting alternatives. Also, we did not want to exclude this group of patients from treatment, with a metastatic cancer disease and troublesome symptoms. Eight patients comprised, however, a six-week waiting list, with no treatment, and could therefore be considered as a control group.

(6b) The TA was given in exactly the same way as EA, only without electrostimulation at the points described above

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