
The effect of massage for women with breast cancer

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*“The massage is a little luxury
in the middle of disaster...it makes me relax
and it is not only frightening to come here
and that has been important to me”*

(Patient from study 2)

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Abstract

THE EFFECT OF MASSAGE FOR WOMEN WITH BREAST CANCER

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Breast cancer is the most common type of cancer in females. The effect of massage in the field of oncology has been investigated to some extent. The present thesis explored the effect of light pressure effleurage massage in women with breast cancer in six main domains; nausea, anxiety, depression, quality of life, stress and cellular immunity. It also described the experience of massage during chemotherapy.

The effect of light pressure effleurage was investigated on nausea, anxiety and depression in women with breast cancer undergoing chemotherapy. Five part-body massage treatments were given during chemotherapy infusion. Massage significantly lowered nausea ($p=0.025$) compared with control treatment. No significant differences were shown between study groups on anxiety and depression.

The experience of light pressure effleurage during chemotherapy treatment was studied using phenomenology as theoretical framework. The essential meaning of receiving massage during chemotherapy was described as a retreat from the feeling of uneasiness toward chemotherapy. Results revealed five themes: a distraction from the frightening experience, a turn from negative to positive, a sense of relaxation, a confirmation of caring and finally they just felt good.

The effect of light pressure effleurage on immunity was investigated in women with breast cancer undergoing radiation. Ten massage treatments, 20 minutes duration, was administered to hands or feet during three weeks. Main variables were NK (Natural Killer) and T cells. The effect of massage on cortisol, oxytocin, anxiety, depression and quality of life was also studied. We were not able to demonstrate any significant differences between study groups on any of the variables in this study. Possible explanation to the lack of response was that the patients were included during radiation treatment and that this therapy, even when given tangentially only to the breast, has some direct immunosuppressive effect. Another explanation was that ongoing radiation therapy is a strong psychological stressor that indirectly affects the immune and neuroendocrine systems.

The immediate effect of light pressure massage on immunity was also investigated. Patients received one full-body massage, 45 minutes duration. Main variable was NK cells, secondary variables cortisol, blood-pressure and heart rate. Massage treatment had significant effect on NK cell function compared with the control group ($p=0.03$). Furthermore, massage significantly lowered systolic blood-pressure ($p=0.03$) and heart rate ($p=0.04$) compared with the control group. No significant effects were demonstrated on cortisol or diastolic blood-pressure.

Keywords: breast neoplasm, massage, effleurage, experience, nausea, anxiety, depression, stress, immunity, quality of life.

List of publications

The thesis is based on the following papers, which will be referred to by their Roman numerals (I-IV).

- I. Billhult A, Bergbom I, Stener-Victorin E. 2007. Massage relieves nausea in women with breast cancer who are undergoing chemotherapy. *J Altern Complement Med.* Jan-Feb;13(1):53-7.
- II. Billhult A, Stener-Victorin E, Bergbom I. 2007. The experience of massage during chemotherapy treatment in breast cancer patients. *Clin Nurs Res.* May;16(2):85-99.
- III. Billhult A, Lindholm C, Gunnarsson R, Stener-Victorin E. The effect of massage on cellular immunity, endocrine and psychological factors in women with breast cancer – a randomized controlled clinical trial. Submitted *J Altern Complement Med.*
- IV. Billhult A, Lindholm C, Gunnarsson R, Stener-Victorin E. The effect of effleurage massage on natural killer cells, cortisol, heart rate and blood pressure in women with breast cancer – a randomized controlled trial. Submitted *BMC Complementary and Alternative Med.*

Abbreviations

ANS	Autonomic nervous system
HAD	Hospital anxiety and depression scale
VAS	Visual analogue scale
FEC	Fluorouacile, epirubicine, cyclophosphamide
BRT	Breast radiation treatment; radiotherapy only to the breast area
NKCC	Natural killer cytotoxicity
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
TNM	Tumour-nodes-metastasis (global standard in cancer staging)

Definitions

Adjuvant therapy:	Treatment given after the primary treatment to increase the chances of cure.
Alternative therapies:	Other than conventional treatment
Complementary Therapies:	In addition to conventional treatments.
Complementary and Alternative Medicine:	“A group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. Complementary medicine is used together with conventional medicine, and alternative medicine is used in place of conventional medicine.” NCCAM (National Center for Complementary and Alternative Medicine, Publication No. D156, 2002)
Effleurage:	Gentle stroking along the length of a muscle
Friction:	Deep massage applied by circular motions of the thumbs or fingertips
Hacking:	Light slaps or karate chops
Kneading:	Squeezing across the width of a muscle
Lumpectomy:	Surgical procedure to remove a tumor and a small amount of tissue around it.
Massage:	“Manual soft tissue manipulation, and includes holding, causing movement, and/or applying pressure to the body” AMTA (American Massage Therapy Association) (Source: http://www.amtamassage.org/about/definition.html)
Mastectomy:	Surgical procedure to remove the whole breast
Petrissage:	Pressure applied across the width of a muscle
Tapotement:	Rapid percussive movements
Vibration:	Oscillating or trembling motion quickly and repeatedly

Introduction

Massage has been used since the ancient Greeks. Traditionally, massage is not offered by mainstream medical care, resulting in patients often turning to the private sector. Only in recent years have the effects of massage been scientifically studied. Collected research on massage is clouded by the many factors influencing the possible effects. For instance, massage is a manual technique that often involves person-to-person contact, meaning gender and interpersonal relationships become important factors. It encompasses many different massage techniques including various amounts of pressure and thereby, various target organs. It can be administered to a small or large part of the body. Interval and length of massage sessions can vary. All of these factors influence the effect of massage and make comparisons and additive effects difficult and inconclusive. Lack of evidence of effect contributes to massage not being a natural part of traditional western medicine. This thesis attempts to make a small contribution to the research on effects of massage with hope to illuminate at least some of the benefits of one form of massage; light pressure effleurage, for women with breast cancer.

Breast cancer

Incidence

Breast cancer is the most common type of cancer in females accounting for 29.5% of all cancer types (Socialstyrelsen [National Board of Health and Welfare]., 2006, January 26). It has increased in women, since the start of the regional register in 1960, by more than two-fold (Onkologiskt Centrum., 2003). It affects about 6900 women yearly in Sweden increasing with age, peaking after menopause (Socialstyrelsen [National Board of Health and Welfare]., 2006, January 26).

Treatment and side-effects

Treatment options available for breast cancer are surgery, chemotherapy, radiation and endocrine therapy.

Surgery is either breast conserving i.e. lumpectomy or more radical i.e. mastectomy (Jönsson., 2004). As part of the diagnostic procedure, the surgeon also removes the axillary lymph nodes to examine whether these are also cancerous. In recent years a new technique called sentinel-node biopsy, allows the clinician to determine whether cancer has spread to the axillary nodes by extracting only one node called the sentinel node. This is the first lymph node the cancer is likely to reach from the tumor, resulting in decreased morbidity (Bergkvist., 2004).

Chemotherapy is a comprehensive term for a drug treatment aimed at stopping the growth of cancer cells. It is often given systemically injected into the blood stream. This treatment is an adjunct to surgery to prevent relapse of cancer (Bergh., 2004).

Radiation and sometimes chemotherapy follows surgery to eliminate any microscopic cancer cells in the remaining breast tissue. Radiation is a type of x-ray that can destroy the

cancer cells and careful treatment planning allows the surrounding normal tissue to be spared (Fornander., 2004).

Endocrine therapy is used if the tumor is hormone receptor positive. This therapy decreases the degree of growing tumor cells and is an effective anti-tumoral treatment (Rutqvist., 2004).

These treatments often entail numerous troublesome side effects such as pain, nausea, weakness and fatigue (Foltz, Gaines & Gullatte., 1996; Hickok, Roscoe, Morrow et al., 1999). Patients continue to experience discomfort despite pharmacological treatment. In addition, many patients with breast cancer experience post-operative stress (Luecken, Dausch, Gulla et al., 2004; Millar, Purushotham, McLatchie et al., 2005), and as many as 50% of all patients with breast cancer experience depression and anxiety during the year following diagnosis (Burgess, Cornelius, Love et al., 2005). In turn, patients quality of life is compromised (Avis, Crawford & Manuel., 2005). Treatment for breast cancer also affects immune function. Chemotherapy targets fast-dividing cells such as cancer cells in the body. However, other cells are also affected, including cells of the immune system. This can lead to one of the most serious side-effects of chemotherapy, a low count of infection-fighting white blood cells, putting the patient at risk of infections.

Massage

History

The history of massage reveals that it is a global and ancient practice starting before recorded history. Through time it has evolved from ancient civilizations to modern with declines and revivals during the 20th century. During the 1990s and early 2000s research on the effects of massage has increased as a result of heightened interest. Per Henrik Ling (1776-1839) introduced Swedish massage aiming to maintain and restore health and balance in the human organism. It includes five massage techniques; effleurage, petrissage, friction, tapotement and vibration. Later, touch without movement and joint movements were added forming the basis for the Western massage tradition (Benjamin & Tappan., 2005).

Massage techniques

Although there are many massage techniques such as petrissage, effleurage, hacking, friction and kneading (Vickers & Zollman., 1999), many cancer patients experience petrissage, kneading etc. as uncomfortable and heavy-handed. It was therefore of interest to investigate the effect of a lighter type of massage, effleurage, since it seemed to be the method best suited to cancer patients. It is a method that has been practiced in Sweden in recent years. Various terms such as effleurage, light effleurage, effleurage massage, light pressure massage, light pressure effleurage, massage, skin massage and stroking have been used throughout the articles included in this thesis. All of these illuminate the same technique used i.e. strokes with light pressure to the skin. In the effort to decide on which term would be the best, a Medline search of research articles using the above terms concluded “effleurage” to be the most commonly used term. Since this thesis investigated the effect of light pressure effleurage, “light pressure effleurage” is therefore used in this

thesis together with massage, which is used as a generic name for all types of massage techniques when citing earlier research and possible explanations for the effects of massage.

Effects of massage

Earlier studies

Massage effects have been studied in several contexts. However, there are difficulties in comparing studies due to the different techniques used, duration and interval of massage, and area of body massaged. Nevertheless, previous studies point out several areas of positive effects of massage.

The effect of massage has been studied on depression and anxiety in children and it was found that urinary cortisol and nor epinephrine levels decreased in the massage group (Field, Morrow, Valdeon et al., 1992). The effect of massage has also been evaluated on anxiety in adults. Healthy subjects were allocated to either massage or rest in a chair. EEG was monitored before, during and after the sessions. In addition, before and after the sessions, the subjects performed mathematical computations, completed POMS Depression and State Anxiety Scales and provided a saliva sample for cortisol. Findings showed that massage therapy offered benefits in not just alleviating the physiological effects of anxiety, but also in improving mental alertness (Field, Ironson, Scafidi et al., 1996). Another study demonstrated positive effects of massage on anxiety in institutionalized patients (Fraser & Kerr., 1993).

Furthermore, the effect of massage on immune function has been studied. Ironson et al. (Ironson, Field, Scafidi et al., 1996) investigated the effect of massage on immune function in 29 men (20 HIV+, 9 HIV-). Results showed that daily massages for 20 days increased the number and function of circulating natural killer (NK) cells. In addition, cortisol as well as anxiety levels decreased and relaxation increased in the massage group. Diego et al. (Diego, Field, Hernandez-Reif et al., 2001) studied 24 young patients infected with HIV. Patients were allocated to either massage or progressive relaxation. Improved immune function measured by NK cell number, was seen after massage twice weekly for 12 weeks. Positive effects of massage on anxiety and depression were also seen in this study. In addition, the effect of a single massage treatment on NK cells and anxiety has been investigated. Nine healthy adults with anxiety prior to an exam were massaged for one hour. Positive effects were seen on NK cell function as well as State Trait Anxiety Inventory (STAI) and VAS measuring stress (Zeitlin, Keller, Shiflett et al., 2000). This study however, was not randomized or controlled.

Massage and cancer

Massage has previously been shown to relieve pain in men with cancer (Weinrich & Weinrich., 1990), reduce depression in women with breast cancer (Hernandez-Reif, Field, Ironson et al., 2005) and patients with advanced cancer (Soden, Vincent, Craske et al., 2004) as well as patients with cancer (Cassileth & Vickers., 2004). Massage can also decrease anxiety in patients with advanced cancer (Ferrell-Torry & Glick., 1993), and breast cancer (Hernandez-Reif, Ironson, Field et al., 2004), and relieve nausea in cancer

patients (Ahles, Tope, Pinkson et al., 1999; Grealish, Lomasney & Whiteman., 2000). In addition, one study examined the effect of massage on immune function in breast cancer patients. Fifty-eight women were allocated either to massage (n=22), relaxation (n=20) or to a control (n=16) consisting solely of standard medical care. Results revealed an increase in NK cell numbers and lymphocytes in the massage group (Hernandez-Reif, Field, Ironson et al., 2005).

Only a few studies of patient experience of massage have been carried out. Billhult et al. (Billhult & Dahlberg., 2001) investigated patient experience of effleurage integrated into daily care at an oncology unit. Results showed that the essential meaning of receiving effleurage was to get a meaningful relief from suffering. Five themes were identified; an experience of being special, a positively developed relationship with the personnel, a sense of feeling strong, a balance between autonomy and dependence, and just feeling good. Corner, Cawley, & Hildebrand (Corner, Cawley & Hildebrand., 1995) reported positive effects of massage such as increased relaxation, release of tension and stiffness, and pain relief in a quasi-experimental study of fifty-two patients with cancer.

Possible explanations for the effects of massage

The exact physiological mechanism of the effect of massage is unknown. However, previous research has led to theories forming hypotheses to serve as possible explanations to the effects of massage.

Gate-control theory

The gate control theory offers an explanation of the pain-relieving effect of massage (Melzack & Wall., 1965). This theory is based on the idea that there are gates in the dorsal horn of the spinal cord that inhibits pain transmission aiming to the brain. If the gate is open, pain reaches the brain. If the gate is closed, pain is reduced. Pain from the periphery is transmitted by means of A-delta and C-fibers. When entering the dorsal horn, they activate the excitatory synapses, which then transmit pain to the brain. Touch, pressure and vibration activate thicker afferent nerve fibers, the so-called A-beta fibers. When they enter the dorsal horn, they activate inhibiting interneurons that release GABA which in turn inhibits the transmission in A-delta and C-fibers both pre- and postsynaptic. This results in activation of so-called gate control and the pain is reduced.

Oxytocin

Central neuroendocrine effects such as increased release of oxytocin can also account for the positive effects of massage, although these studies were performed on rats (Uvnäs-Moberg, Bruzelius, Alster et al., 1993; Lund, Lundeberg, Kurosawa et al., 1999; Lund, Ge, Yu et al., 2002). Studies on oxytocin in humans are complicated by confounding factors influencing the secretion of oxytocin. However, oxytocin seems to have an anxiolytic effect (Uvnäs-Moberg., 2000), resulting in relaxation which in turn can decrease nausea, lower blood pressure and heart-rate. Thus, relaxation may explain the effect of massage on nausea, blood pressure and heart-rate. Benson et al. (Benson, Beary & Carol., 1974) described this phenomenon as a decrease in activity of the sympathetic nervous system in relaxed states.

Cortisol

Cortisol is a corticosteroid hormone, released by the adrenal cortex, which increases the available resources of glucose via the liver. It is in a sense, a survival hormone in extreme circumstances such as starvation and stress. Stress increases the release of adrenocorticotrophic hormone (ACTH) via the pituitary gland and hypothalamus and stimulates the adrenal cortex to produce and release cortisol. Increased levels of cortisol in the blood, in turn regulate the release of ACTH. This is the so called hypothalamus-pituitary-adrenal (HPA) axis. Circadian cortisol cycle vary with the highest levels in the morning and lowest around midnight (Holt-Lunstad & Steffen., 2007). Illnesses such as burnout (Pruessner, Hellhammer & Kirschbaum., 1999) and chronic fatigue syndrome (MacHale, Cavanagh, Bennie et al., 1998) can occur when the circadian cortisol cycle is disturbed. Cortisol is involved in the stress response by increasing blood pressure and suppressing the immune system.

Immune system

The exact molecular mechanisms behind the effects of massage treatment on immune cells are unknown. A possible mechanism could be that massage leads to release of neuropeptides, which in turn may exert immunomodulatory effects on leukocytes. It is shown that massage leads to increase in oxytocin levels in rats which in turn might affect immune function (Lund, Ge, Yu et al., 2002). However, these neuropeptides may also be affected by stress.

Another possible mechanism behind the effects of massage on immune function is the secretion of histamine. An earlier study showed release of histamine after manual lymphdrainage massage (Kurz, Kurz, Litmanovitch et al., 1981). Histamine has been shown to stimulate NKCC in rats (Hellstrand, Asea & Hermodsson., 1990). The effect of massage on NKCC could therefore be explained by secretion of histamine. Histamine, in turn can also be affected by stress.

Furthermore, the effect of massage on cellular immunity might be explained by decreased cortisol levels. Prolonged increased levels of cortisol may result in prolonged immunosuppression (O'Leary., 1990). Inversely, normal circadian cortisol rhythm may allow for increased oxytocin and histamine secretion and thereby, improved immune function.

Serotonin

Serotonin is a neurotransmitter involved in regulating the HPA axis. Furthermore, higher serotonin concentrations may also explain the pain-relieving effect of massage (Ironson, Field, Scafidi et al., 1996; Hernandez-Reif, Ironson, Field et al., 2004).

Autonomic Nervous System

The effect of massage may be due to a shift in activity in the autonomic nervous system (ANS) from a state of sympathetic to parasympathetic response. This theory, however, has been debated and no general consensus exists (Moyer, Rounds & Hannum., 2004).

The limbic structures

Massage stimulates A-beta fibers. These signals reach the hypothalamus via the spinal cord. The hypothalamus is thought to interact with the limbic system which is involved in emotion and memory (Lännergren, Ulfendal, Lundeberg et al., 2005). It is possible that the positive experience of massage is caused by the limbic structures. Ouchi et al. (Ouchi, Kanno, Okada et al., 2006) conclude that the forebrain-amygdala system is involved in mediating activities in the autonomic system in the presence of comfortable sensation such as light massage on the back.

Theoretical framework

Massage and nausea

Nausea is one of the most common side-effects of chemotherapy, despite pharmacological treatment options (Foltz, Gaines, Gullatte et al., 1996; Hickok, Roscoe, Morrow et al., 1999). Furthermore, a study showed that younger patients (< 65 years of age) experienced nausea and emesis more intensely than older patients (Dodd, Onishi, Dibble et al., 1996). Massage has been shown to relieve nausea in cancer patients (Grealish, Lomasney, Whiteman et al., 2000). This study used massage techniques such as stroking, lifting and squeezing. Study I was designed to investigate the effect of effleurage alone, on nausea in women with breast cancer undergoing chemotherapy. The theoretical basis for investigating the effect of effleurage on nausea was the possible explanation that massage triggers the release of oxytocin (Uvnäs-Moberg, Bruzelius, Alster et al., 1993; Lund, Lundeberg, Kurosawa et al., 1999; Lund, Ge, Yu et al., 2002), which has an anxiolytic effect. This induces relaxation which in turn reduces nausea.

Massage and anxiety and depression

As many as 50% experience anxiety and depression during the year after diagnosis (Burgess, Cornelius, Love et al., 2005). Massage has in previous studies been shown to reduce anxiety in cancer patients (Ferrell-Torry & Glick., 1993; Corner, Cawley, Hildebrand et al., 1995) and adults (Field, Ironson, Scafidi et al., 1996) and depression in patients with cancer (Cassileth & Vickers., 2004) and in adolescents with HIV (Diego, Field, Hernandez-Reif et al., 2001). Again, these studies used massage techniques such as rocking, compression, kneading and pulling. Study I and III illuminated the effect of effleurage on anxiety and depression with the underlying theoretical framework that massage decreases tension by modulating ANS and the HPA-axis.

Massage and stress

Many women with breast cancer experience post-operative stress (Luecken, Dausch, Gulla et al., 2004; Millar, Purushotham, McLatchie et al., 2005). Earlier research of massage has shown decreased distress in cancer patients (Ahles, Tope, Pinkson et al., 1999) and decreased stress in adults as measured by cortisol (Field, Ironson, Scafidi et al., 1996). Study III and IV therefore investigated the effect of massage on cortisol hypothesizing that massage decreases stress via the HPA-system.

Massage and immunity

The basis for investigating the effect of effleurage on immunity is that the cells of the human immune system have the capability of providing surveillance against not only virus cells, but also cancer cells (Okvat, Oz, Ting et al., 2002). The cells of interest were NK cells (paper III and IV), T helper cells and cytotoxic T cells (paper III). NK cells and cytotoxic T cells (assisted by T helper cells) can kill cancer cells (Sompayrac., 1999).

Aims of the thesis

General

The general aim of this thesis was to study the effect of light pressure effleurage massage on nausea, anxiety, depression, cellular immunity, stress and quality of life. Furthermore, the aim was to describe the experience of massage during chemotherapy.

Specific

- *To study the effect of massage on nausea, anxiety and depression in breast cancer patients undergoing chemotherapy (I).*
- *To study the experience of massage in patients with breast cancer during chemotherapy treatment (II).*
- *To study the effect of repeated massage on cellular immunity by studying the number and activity of circulating NK cells, CD4+ and CD8+ T cells as well as cortisol, anxiety, depression and quality of life in patients with breast cancer (III).*
- *To study the immediate effect of a single massage on cellular immunity and stress by studying NK cells, cortisol, pulse and blood pressure in patients with breast cancer (IV).*

Material and methods

Ethics

All studies (I-IV) were approved by the Regional Ethical Review Board. The ethical issues discussed were:

- *The possibility that patients could react emotionally during massage treatment as tension was released. If this occurred, participants were offered support by staffers.*
- *Pain induced by a quick needle prick when drawing blood.*

Patients

The patients in studies I (N = 39) and II (N = 10) were undergoing chemotherapy and therefore recruited at the chemotherapy ward. These patients had undergone surgery and were scheduled for adjuvant chemotherapy treatment. The chemotherapy treatment was FEC (Fluorouracil 600 mg/m² (Mayne Pharma Plc, Warwickshire, Great Britain), Epirubicin 75 mg/m² (Pharmalink AB, Upplands Väsby, Sweden) and Cyclophosphamide 600 mg/m² (Baxter Medical AB, Kista, Sweden)), given every third week for a total of seven treatment cycles. Side-effects of this treatment are nausea, hair-loss, increased risk of infection (due to temporary effect of the bone-marrow), loss of appetite, fatigue and diarrhoea (obtained at <http://www.cancerhelp.org.uk>).

The patients in studies III (N = 22) and IV (N = 30) were undergoing radiation therapy and were therefore recruited from the radiation department. These patients had undergone surgery but not chemotherapy, and were scheduled for 5 weeks of radiation therapy to the breast (BRT). This treatment is given once daily for 25 days at 2 Gy/day totalling 50 Gy. Side-effects of redness and itching are limited to the radiation area. The reaction develops two or three weeks after initiation of treatment and healing may take four to six weeks. Demographic data for all patients are shown in Table 1.

Table 1. Demographic data for study participants paper I-IV.

	PAPER I (N=39)		PAPER II (N=10)	PAPER III (N=22)		PAPER IV (N=30)	
	Massage (N=19)	Control (N=20)	Massage (N=10)	Massage (N=11)	Control (N=11)	Massage (N=15)	Control (N=15)
Age (years)	50.5	53.1	50	61.2	63.5	61.1	60.8
Mean (SD)	(10.1)	(8.4)	(8.5)	(4.9)	(9.1)	(7.1)	(6.9)
Type of surgery							
(no):							
Lumpectomy/sentinel node:	4	2	1	10	11	14	15
Lumpectomy/axillary node dissection:	11	9	8	1	0	1	0
Mastectomy/axillary node dissection:	4	9	1	0	0	0	0
Stage (TNM):							
I	4	1	0	10	11	13	14
II A	9	12	4	0	0	2	1
II B	5	7	3	0	0	0	0
III	1	0	3	1	0	0	0
Mean time since diagnosis (months)	2.5	3	5	4.8	4.8	3.1	3.1

Measurements

Visual analogue scale (paper I)

A Visual Analogue Scale (VAS) was used to evaluate nausea and anxiety. The VAS was chosen because it is designed to provide information about internal, subjective feelings such as nausea and anxiety (Lee & Kieckhefer., 1989). Earlier studies on massage have used VAS to measure nausea (Ahles, Tope, Pinkson et al., 1999; Grealish, Lomasney, Whiteman et al., 2000). The patients reported nausea and anxiety on a 100-mm scale with the verbal anchors: “no nausea/anxiety at all”, 0, and “worst possible nausea/anxiety”, 100. The changes in the VAS ratings before and after each intervention were classified as positive if the rating indicated improvement and negative if it did not. Furthermore, the proportion of an individual’s total positive VAS-changes was calculated. Thus, if a patient improved in three out of five interventions, the patient received a score of 60%. Results were analyzed using the Mann Whitney’s test.

Validity and reliability of VAS should be evaluated for each particular situation assessed (Lee & Kieckhefer., 1989). Criterion-related validity was determined in paper I, by exploring how VAS anxiety correlated with HAD anxiety. VAS anxiety was positively correlated with HAD anxiety and consequently found to be valid ($p = 0.003$, $r^2 = 0.24$, non-parametric rank correlation). VAS nausea was not tested for validity because no other

instrument was used to measure nausea. It has, however, been used in previous studies to measure nausea. Reliability was not tested in this study. However, test-retest reliability and interrater reliability has been established for VAS measuring altitude sickness (Wagner, Tatsugawa, Parker et al., 2007).

Hospital anxiety depression scale (paper I and III)

We used the Hospital anxiety depression (HAD) scale to measure mood as it is a scale designed for outpatients. HAD measures the level of anxiety and depression in two 7-item separate subscales. Each item has four response alternatives (0-3), reflecting a continuum of increasing level of anxiety/depression. Scale scores range from 0 (no symptoms) to 21 (maximum distress) for each subscale (Appendix 1). HAD is a reliable self-assessment scale that can detect level of anxiety/depression. The subscales are valid measures of the severity of emotional disorder, < 7 points = non-case, 8-10 points = possible clinical case and > 10 points = probable clinical case (Zigmond & Snaith., 1983). Results were analyzed with Mann Whitney's test to detect differences between groups.

Validity for the Swedish version of HAD is satisfactory with Mood Adjective Check List. Internal consistency reliability is satisfactory (Chronbach's alpha>0.80).

Phenomenology (paper II)

A phenomenological approach was chosen because the experience of massage was the focus of the study. The aim of phenomenology is to understand the essential structure of a phenomenon under investigation. It is a method where human experience as it is lived is in focus, along with meaning and intersubjectivity (Merleau-Ponty., 1964). Husserl created the basis for this scientific method that unites science and everyday life, and Giorgi has developed a method suitable for caring science research (Giorgi., 1985).

To increase the possibility of illuminating the phenomenon, the researcher must have an open mind. This openness is characterized by a will to understand, see, and hear. The researcher's openness is optimized by nearness and immediacy, but must be paired with an ability to be distant. If nearness is too dominating, the researcher loses openness in the encounter with the phenomenon. The researcher must thus be flexible and able to change from nearness to distance, that is, the life-world researcher must have an ability to stay at a comfortable level of involvement.

In order to focus on the phenomena under investigation, one needs to put aside prejudices of the world, or pre-understanding. This is also called bracketing or phenomenological reduction and is central to phenomenological work (Giorgi., 2005). By being aware of the foundation of phenomenology, data was collected by interviews. Patients were interviewed using one opening question: "Please tell me about your experience of the massage". Follow-up questions such as: "Can you tell me more about that" were then asked to get a deeper understanding of patient experience. Interviews were audiotaped, transcribed into text and analyzed for meaning.

The phenomenological analysis entailed three concrete phases, whole-parts-whole. Phase one consisted of reading data as a whole to get a global sense of data. In phase two, the researcher divided data into parts forming relevant meaning units expressed in everyday language. These were then transformed from raw data into disciplinary language. Phase three went back to the whole phase to search for the scientific essence by using free

imaginative variation. The essence is the single structure, that within the variations that does not vary (Giorgi., 1997).

Central to phenomenology is openness, bracketing and free imaginative variation. By adhering to the described research method, validity can be achieved, and is achieved, if the description truly captures the intuited essence. No reality claims are being made in phenomenological research (Beck., 1994).

Life satisfaction questionnaire (paper III)

The Life satisfaction questionnaire (LSQ) was used because it is an instrument developed specifically for Swedish women with breast cancer. LSQ is a 37 item instrument designed to measure quality of life (Carlsson & Hamrin., 2002). Each item has 7 response alternatives and a high score indicates high quality of life (Appendix 2). Results were analyzed with Mann Whitney's test to detect differences between groups.

LSQ has been tested for validity by a principal component analysis and reliability by Chronbach alpha-coefficients. It was found to have acceptable validity and reliability (Carlsson, Hamrin & Lindqvist., 1999).

State-trait anxiety inventory (paper III)

State and trait anxiety was evaluated using State Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene et al., 1983). It is a 40 item instrument divided in two subscales measuring state and trait anxiety respectively. The scale consists of four response alternatives (1-4) and a high score indicates a high level of anxiety (Appendix 3). Results were analyzed with Mann Whitney's test to detect differences between groups.

STAI has been tested and shown both validity and reliability (Spielberger, Gorsuch, Lushene et al., 1983).

Heart rate and blood-pressure (paper IV)

We wanted to record heart rate (HR) and blood pressure (BP), based on the notion that massage can shift the ANS from a state of sympathetic to parasympathetic response. The patient was in a supine position for 5 minutes prior to recording HR and BP. HR and BP were recorded twice before massage/control visit and twice afterwards to avoid measurement error. HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded manually by a nurse. A second observer not involved in the study recorded HR and BP for a subset of the patients to avoid bias. Results were analyzed with Student's T-test to detect differences between groups.

Immunological measures (paper III and IV (NK cells only))

NK and T cells

Venous blood was collected (20 ml) into heparin-containing (60 USP units of sodium heparin/tube) Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) after radiation but within 15 minutes before and after massage/visit and processed within 3 hours.

Further analysis was performed in two steps:

1. Peripheral Blood Mononuclear Cell (PBMC) Isolation:

Peripheral blood mononuclear cells were isolated by density centrifugation using Lymphoprep (Fresenius Kabi, Norge AS). Whole blood was diluted 1:1 with sterile phosphate buffered saline without Ca or Mg (PBS) (Dulbeccos PBS, PAA Laboratories GmbH, Pasching, Germany), carefully layered on top of Lymphoprep, centrifuged at $400\times g$ for 20 min at 20°C . The mononuclear cells were removed using a pipette and then washed 3 times with 50 ml PBS (centrifuged at $200\times g$ for 10 min at 4°C). PBMCs were then suspended in 2 ml culture medium (RPMI 1640) supplemented with 5% fetal calf serum and 1% L-glutamine and counted. Absolute cell numbers were determined by Automatic cell counter (Sysmex KX-21, Sysmex Deutschland, GmbH).

2a. Phenotypic Characterization of Peripheral Blood NK cells,

T helper and cytotoxic T cells:

Frequency, absolute numbers, and expression of activation markers of NK cells and T cells in peripheral blood were analysed by four-colour, flow cytometry. Peripheral blood mononuclear cells were diluted in a solution containing phosphate-buffered saline (PBS), 1% FCS, 0.1% sodium azide, and 0.5 mM EDTA (FACS-buffer). 0.5×10^6 cells/well were placed in 96-well V-bottom plates and pelleted (3 min, $300 \times g$, 4°C). Thirty μl of an optimal concentration of FACS and the following antibodies (Ab) was added: fluorescein isothiocyanate (FITC)-conjugated anti-CD69 (3 μl), phycoerythrin (PE)-conjugated anti-CD56 (3 μl), allophycocyanin (APC)-conjugated anti-CD25 (6 μl), peridinin-chlorophyll-protein complex (PerCP)-conjugated anti-CD3 (1 μl), PerCP-conjugated anti-CD4 (6 μl) (paper III), FITC-conjugated anti-CD8 (3 μl) (paper III) (all Ab's were from Becton Dickinson Bioscience, San Jose, CA). Isotyped-matched controls were included in each experiment. Plates were incubated in the dark for 30 min, followed by two washing steps ($300 g$ for 3 min at 4°C) and a final re-suspension step in FACS-buffer before analysis. Frequency, absolute numbers, and expression of activation markers of NK cells and T cells in peripheral blood were analyzed by four-colour flow-cytometry using FACS Calibur (Becton Dickinson). 10.000 cells in the lymphocyte gate were collected for each sample. Analysis was by Flow-Jo (Treestar Inc).

2b. NK cell cytotoxicity:

PBMCs were isolated as for the flow-cytometry, counted and 500 000 cells per well were put in triplicate in U-shaped 96 well plates. Cells were then diluted to obtain 4 different effector-to-target cell ratios (50:1, 25:1, 12.5:1, 6.25:1). The lytic activity of NK cells was determined by ^{51}Cr -release cytotoxic assay¹⁶ within 3 hours of the blood draw. A constant number of ^{51}Cr -labeled leukaemia target cells (K562) were put into the wells and mixed with the PBMCs. Tumour cell lysis was quantified in a Gamma counter (Cobra-Auto Gamma, Packard) by measuring the amount of ^{51}Cr released following 16 hours of incubation. Sixteen instead of the standard four hours of incubation was chosen for practical reasons after concluding that the relative differences of ^{51}Cr release between samples were not affected by the prolonged

incubation time. Percent lytic activity was then calculated using the formula: $(ER-SR)/(MR-SR) \times 100$, ER being experimental release, SR spontaneous release and MR maximal release of chromium. NKCC was calculated as the area under curve:

$$\left(area = \int_a^b f(x).dx \right)$$

Cortisol (paper III and IV)

Cortisol is a neuroendocrine stress hormone which was analyzed wherefore cortisol levels are positively correlated with stress and blood pressure. Saliva was collected in saliva collection tubes (Salivette, Sarstedt, Nümbrecht, Germany) after radiation treatment, within 15 minutes before and after massage/control visit. Samples were frozen for approximately 6 months at -20° and analyzed by radioimmunoassay (RIA), (Spectria Cortisol RIA, Orion Diagnostica, Espoo, Finland) (Hansen, Garde, Christensen et al., 2003). Analyses of cortisol were carried out in the Department of Clinical Chemistry, Sahlgrenska University Hospital.

Oxytocin (paper III)

Measure for neuroendocrine function was oxytocin. Oxytocin was analyzed because it seems to have an anxiolytic effect in rodents (Uvnäs-Moberg., 2000). Venous blood (6 ml) was collected into K2 EDTA tubes (Greiner Bio-one GmbH, Kremsmunster, Austria) in the morning and centrifuged at 3000 rpm for 10 minutes within 3 hours and stored at -80° C. Oxytocin was analyzed in plasma using Enzyme Immunoassay (EIA), (Assay Designs Inc, Ann Arbor, Michigan, USA). 600 μ L plasma were extracted with 1200 μ L 96 % ethanol, incubated, centrifuged, evaporated and resolved in 300 μ L assay buffer (containing proteins). After centrifugation, samples and calibrators of 100 μ L were analysed in duplicates in a goat anti-rabbit IgG microtiter plate. After addition of 50 μ L conjugate (alkaline phosphatase conjugated with oxytocin) and 50 μ L antibody (rabbit polyclonal antibody to Oxytocin), the samples were incubated at 4° C for 18-24 hours. The excess reagents were washed away with buffer (Tris buffered saline containing detergents, 5 times 350 μ L) and 200 μ L substrate (p-nitrophenylphosphate) was added. After 1 hour incubation at room temperature the enzyme reaction was stopped by adding 50 μ L trisodium phosphate in water and the yellow color generated, was read on a microplate reader at 405 nm. The intensity of the colour is inversely proportional to the concentration of oxytocin. The measured optical density of the standards was used to calculate the concentrations of oxytocin in the sample. Analyses were carried out in the Department of Neurochemistry, Sahlgrenska University Hospital, Mölndal.

Massage treatment

The massage consisted of light pressure effleurage and included strokes using palms and fingers of both hands. The estimated pressure was calculated by letting the nurse that performed the majority of the massage treatments in paper I-IV, administer massage to an individual not participating in the studies and thereafter place both hands on a scale using the same pressure. This procedure was repeated three times to produce a mean pressure. The surface area of both hands was then estimated and finally the pressure used could be

calculated to 0,0090 kg/cm². This pressure was used in all four studies. No instructions were given regarding conversation during massage in any of the studies. However, the duration, interval, area of body being massaged and exact location of the massage differed between studies.

Paper I

The massage took place at the chemotherapy ward during chemotherapy infusion with patients sitting in a comfortable chair. In total, five massage treatment sessions were given in three week intervals.

The massage followed a standardized massage protocol and lasted for 20 minutes. The patients were able to choose between either both feet/lower legs or both hands/lower arms massage. The duration was the same for the two massage options (Table 2). The massage was given by five hospital staffers (nurses and nurse's aids) trained in the massage technique. A cold-pressed vegetable oil was used to reduce friction, and the limb was wrapped in a towel immediately after the massage.

Paper II

Ten patients from study I were recruited to study II. The massage treatment was therefore the same for paper II as for paper I. The patients were interviewed after the massage sitting in the same chair in the chemotherapy ward.

Paper III

The patients received 10 effleurage massage treatments during 3 to 4 weeks. Every massage session took place directly after the scheduled radiation with patients sitting in a comfortable chair at the oncology clinic. The patients could choose between massage either on both feet/lower legs or both hands/lower arms, both following a standardized massage protocol lasting 20 minutes (Table 2). A cold-pressed vegetable oil was used, and the limb was wrapped in a towel after the massage. The massage was given by a registered nurse trained in the massage technique.

Table 2. Massage protocol study I-III.

Foot/lower leg:

- *Strokes from the ventral side of the foot up around the knee and back to the foot.*
- *Small circular movements on the side of the calf from the foot to the knee.*
- *Circular stroking around the sides of the knee and the ankle.*
- *Stroking on the ventral side of the foot.*
- *Circular movements on the sides of each toe.*
- *Strokes on the dorsal side of the foot.*
- *Strokes from the ventral side of the foot up around the knee and back to the foot.*

Hand/lower arm:

- *Strokes from the hand up to the elbow and back to the hand.*
- *Small circular movements on the side of the arm from the hand to the elbow.*
- *Circular stroking around the elbow and the wrist.*
- *Stroking on the dorsal side of the hand.*
- *Circular movements on the sides of each finger.*
- *Strokes on the ventral side of the hand.*
- *Strokes from the hand up to the elbow and back to the hand.*

Paper IV

The patients received one full-body light pressure effleurage treatment by the same registered nurse involved in paper III. Patients were placed on a massage table in a room in the radiation department and the massage, following a standardized protocol, lasted about 45 minutes (Table 3).

Table 3. Massage protocol study IV.

Patient lies in supine position on the massage table draped with a blanket:

- *Beginning at the foot, effleurage on ventral side of the leg and back to the foot. Circular movements around the knee joint as well as around the ankle. Small circular movements bilateral on the leg starting at the foot, conclude with long strokes back to the foot. Drape the leg with blanket. Same procedure on the other leg and foot (10 minutes total).*
- *Beginning at the hand, effleurage on ventral side of the arm and back to the hand. Circular movements around the shoulder joint, elbow and wrist. Small circular movements bilateral on the arm starting at the hand, conclude with long strokes back to the hand. Effleurage on the dorsal side of the hand. Circular movements bilateral of each finger. Strokes on the ventral side of the hand. Drape the arm with blanket. Same procedure on the other arm and hand (10 minutes total).*
- *Effleurage from middle of forehead towards the temple (2 minutes).*

Patient moves to prone position:

- *Effleurage of the scalp (3 minutes).*
- *Effleurage from the sacral area to the neck fanning out on the shoulders and back to the sacral area. Circular movements starting at the sacral area towards the neck. Effleurage from the spine moving lateral on both sides. Stroking from neck to sacral area using both hands intermittent (10 minutes).*
- *Beginning at the foot, effleurage on dorsal side of the leg and back to the foot. Circular movements around the knee joint as well as around the ankle. Small circular movements bilateral on the leg starting at the foot, conclude with long strokes back to the foot. Drape the leg with blanket. Same procedure on the other leg and foot (10 minutes total).*

Control visit

The control visit had identical conditions as massage treatment regarding time frame, exact location, chair (paper I, II and III) and massage table (paper IV). It consisted primarily of unstructured conversation. No instructions were given to the visit person as to limits of conversation topics.

Statistical analysis

All statistical tests were two-sided and a *p*-value of less than 0.05 was considered significant in all studies.

In Paper I no calculation of sample size was made. The values obtained from the VAS ratings were transformed so that the changes in ratings before and after each intervention were classified as positive if the rating indicated improvement and negative if not. Furthermore, the proportion of an individual's total positive VAS-changes was calculated. Thus, if a patient improved in three out of five interventions, the patient received a score of 60%. This percentage was then used to calculate difference in change between groups with Mann Whitney's test. The changes in the HAD score were calculated for anxiety and depression. Epi-Info version 3.3.2 (Center for Disease Control, Atlanta, USA) was used for all analyses.

Paper II contained no statistical analyses.

In Paper III calculation of sample size was done. Previous studies of massage available at the time of planning Paper III were used for sample size calculations. Based on a power of 0.80, alpha level 0.05 and assuming a two-tailed test, a sample size analysis for the primary outcome measures change in NK cell number, change in NK cell function and change in T-cell number, resulted in a need for 14, 22, and 14. Thus 22 were chosen. Change in other variables was secondary outcome measures.

Differences in change between groups were analyzed with Student's *t*-test for continuous, normally distributed data with equal variances between groups. Kolmogorov-Smirnov's test was used to determine distribution of data. Bartlett's test for inequality of population variances was used to determine if variances differed between groups. In case of statistically significant baseline differences between groups, covariance analysis was used instead of Student's *t*-test or Mann-Whitney's test. Kolmogorov-Smirnov's test was analyzed using SPSS version 13 and Epi-Info version 3.3.2 (Center for Disease Control, Atlanta, USA) was used for all other analyses.

In study IV, sample size calculation was made for the primary outcome measure based on previous studies of massage available at the time of planning this study. Based on a power of 0.80, alpha level 0.05 and assuming a two-tailed test, a sample size analysis resulted in a need for 22 patients for NKCC and 14 patients for NK cell number. These studies, however, did not include results of immediate effects of massage. Consequently, a sample size of 15 per group (30 totally for the study) was decided. Changes in cortisol, blood pressure and heart rate were secondary outcome measures. Differences between groups were analyzed with Student's *t*-test as data were normally distributed. SPSS version 13 was used for all analyses.

Results

Paper I. The effect on nausea, anxiety and depression

The aim of the present study was to examine the effect of light pressure effleurage on nausea, anxiety and depression in women with breast cancer undergoing chemotherapy.

Results

Effleurage significantly reduced nausea compared with the control treatment ($p = 0.025$, Mann Whitney's test) when measured as percentage improved occasions. Mean improvement was 73.2% (SD 32.3) in the massage group (median/interquartile range 80%/40-100), compared to mean 49.5% (SD 32.2) (median/interquartile range 45%/20-77.5) in the control group (Figure 1). Differences in anxiety between the two treatment regimes were not statistically significant.

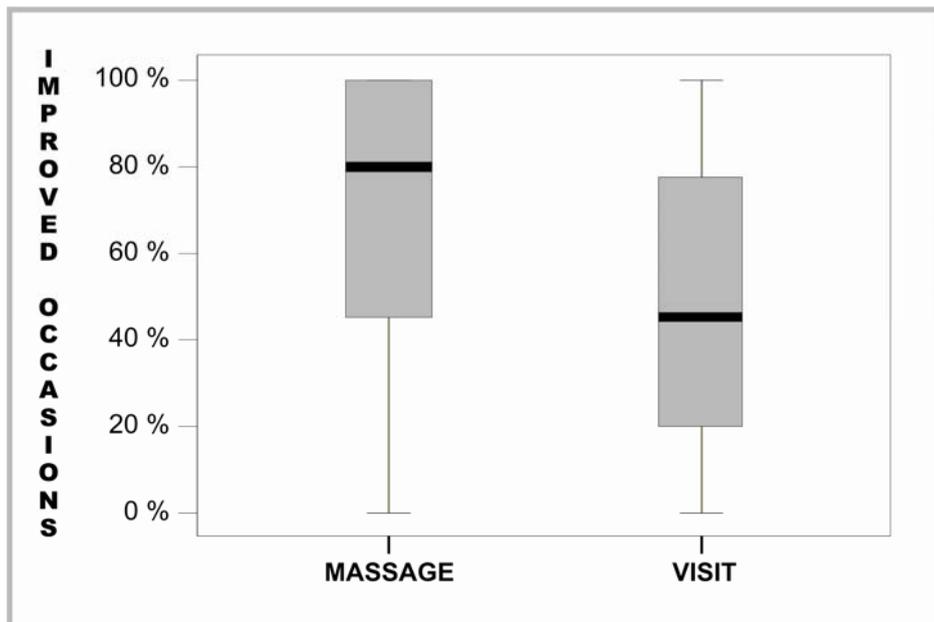


Figure 1. Median change scores in nausea for the massage and visit groups.

Mean change for HAD anxiety was -0.1 sum score (SD 2.9) in the effleurage group (median/interquartile range $\pm 0/-1-2$), compared to mean 1.3 sum score (SD 2.6) (median/interquartile range $1/0-3$) in the control group. Mean change for HAD depression was -0.7 sum score (SD 2.8) in the effleurage group (median/interquartile range $\pm 0/-3-1$), compared to mean 0.6 sum score (SD 1.22) (median/interquartile range $\pm 0/0-1$) in the control group. There were no differences between groups in changed sum scores for HAD anxiety or HAD depression. The HAD anxiety and the VAS anxiety were positively correlated ($p = 0.003$, $r^2 = 0.24$, non parametric rank correlation).

Conclusion

Effleurage is an interesting alternative that may be administered by family members, thus enabling treatment at home. Although this study indicates that effleurage can be useful by reducing nausea in breast cancer patients undergoing chemotherapy, it needs to be confirmed in studies with larger samples.

Paper II. The experience of massage during chemotherapy

The objective of this study was to describe the experience of effleurage in patients with breast cancer during chemotherapy treatment.

Results

Results revealed five themes: the patients experienced distraction from the frightening experience, a turn from negative to positive, a sense of relaxation, a confirmation of caring and finally they just felt good. In conclusion, the findings of this study show that effleurage offered a retreat from uneasy, unwanted, negative feelings connected with chemotherapy treatment.

Conclusion

It is clear that chemotherapy is distressful for patients. It causes fear and tension in addition to the physical side effects of breast cancer treatment. We wanted to illuminate the experience of effleurage when given in conjunction to a troublesome treatment such as chemotherapy. This study showed that effleurage offered a retreat from these uneasy, unwanted, negative feelings of cancer treatment. Light pressure effleurage is a treatment that can be added to the arsenal of treatment choices available to the oncological staff.

It is important to note that effleurage can be offered to those patients benefiting from it, within a short time. Based on the descriptions of the patients, their experience of effleurage could counteract the uneasy feeling toward chemotherapy treatment. It is possible that the findings of this study could be generalized to similar situations concerning unwanted treatment other than chemotherapy treatment. However, we cannot be certain that the results can be applied to all caring situations.

Paper III. The effect on cellular immunity, endocrine and psychological factors

The primary aim of the present study was to study the effect of repeated light pressure effleurage massage on cellular immunity in patients with breast cancer. Furthermore, a secondary aim was to evaluate the effect of massage on cortisol, oxytocin, anxiety, depression and quality of life in patients with breast cancer.

Results

Twenty-two women, aged 51 to 83 (mean=62 $sd=7.2$) were enrolled (Table 1). Ten patients had right side and twelve left side breast cancer. All but one patient had stage I

cancer according to the TNM classification. The remaining patient had stage 3. Furthermore, 21 patients had lumpectomy/sentinel node dissection and 1 patient lumpectomy/axillary node dissection. Mean time since diagnosis was 4.8 months for both groups.

Mean age in the effleurage group was 61 (SD 4.9) and in the control group 64 (SD 9.1). Four women chose hand/lower arm massage, and the rest foot/lower leg massage. The massage group had at baseline, a higher NK cell cytotoxicity (NKCC) compared to the control group ($p=0.025$). No other baseline differences between groups were found. Thus, comparison of changes in NKCC between groups was made with covariance analysis using NKCC at baseline and treatment allocation as independent variables, the latter being a class variable.

There were no statistically significant differences in change of outcome measures between groups. Thus, in this study effleurage could not be demonstrated to have effect on NK cells, T cells, hormones or psychological measures. Covariance analysis did not alter this for NKCC.

Conclusion

We were not able to demonstrate any significant differences between treatment groups on cellular immunity, cortisol, oxytocin, anxiety, depression or quality of life. There are several possible explanations. One is that radiation therapy, even when given tangentially only to the breast, has some direct immunosuppressive effect. Another explanation might be that ongoing radiation therapy is a strong psychological stressor that indirectly affects the immune and endocrine systems. Furthermore, the light pressure effleurage administered to part-body may not be intense enough to affect outcome variables.

Paper IV. The effect on natural killer cells, cortisol, heart rate and blood pressure

The primary aim of the present study was to investigate the immediate effect of a single, full-body, light pressure effleurage on cellular immunity in women with breast cancer. The secondary aim was to measure the immediate effect of a single effleurage on cortisol concentrations in saliva, heart rate and blood pressure.

Results

Thirty women, aged 50 to 75 years (mean=61 sd=7.2) with breast cancer undergoing 5 weeks of adjuvant radiation therapy at an oncology clinic in southwestern Sweden were enrolled in the study (Table 1). Fifteen patients had right sided and 15 left sided breast cancer. Twenty-nine women had a lumpectomy/sentinel node dissection and 1 had a lumpectomy/axillary node dissection. Twenty-seven women had stage 1, and 3 women stage 2, according to the tumor, nodes, metastasis (TNM) classification. Mean age was 61.1 ($sd=7.6$) years for the massage group and 60.8 ($sd=6.9$) years for the control group. Mean time from diagnosis was 3.1 months for both groups.

To evaluate the effect of a full-body effleurage on NK cells, the frequency and total number of circulating NK cells were compared in women receiving massage and subjected to control visits. Full-body effleurage did not influence the frequency or total number of

peripheral blood NK cells. We also studied the effect of effleurage on cytotoxic activity of NK cells by the Cr-release assay. NK cellular cytotoxicity expressed as mean area under the curve, obtained from 4 serial dilutions of effector-to-target cells was, before intervention, similar in both groups. The control group decreased more than the massage group in NKCC ($p = 0.03$). Finally, we compared the frequencies of NK cells expressing the surface activation markers CD69 and the α -chain of the interleukin-2 receptor (CD25). No significant effects of massage treatment were seen for these variables.

We investigated the effect of effleurage on the HPA-axis by measuring salivary cortisol. No significant differences were seen between groups in cortisol levels.

The effect of effleurage on heart rate and blood pressure was recorded to measure the relaxation level and as an indication of modulation of the ANS. Effleurage decreased heart rate significantly compared with a control visit ($p = 0.04$). Effleurage also decreased systolic blood pressure significantly compared with visit controls ($p = 0.03$). Furthermore, the diastolic blood pressure decreased in the effleurage group compared with control visit, but this difference did not reach statistical significance ($p = 0.07$).

Conclusion

A single full-body light pressure effleurage massage has a short term effect on NK cell function, heart rate and systolic blood pressure in patients with breast cancer. However, it is not known for how long this effect remains and if it is of clinical relevance. Thus, future studies should focus on elucidating how long the effect on the immune system remains and if clinical parameters such as quality of life and recurrence of cancer are affected.

Discussion

Complementary therapies

Many patients seek non-pharmacological treatments to complement the regular medical care. The literature shows that up to 66% of patients with breast cancer are users of complementary treatments (Henderson & Donatelle., 2004). In Sweden, up to 50% are users of complementary treatments (Jensen, Lekander, Nord et al., 2007). Complementary therapies are defined as “Therapies used in addition to conventional treatments” (NCCAM, 2002). It is important to note that massage is a form of complementary therapy and not an alternative therapy which would imply that it substitutes for a traditional treatment. Complementary therapies, as the term suggests, are to be given in addition to traditional therapies, and may enhance the effect of the traditional treatment.

Cancer patients are common users of complementary therapies (Vickers & Cassileth., 2001), probably because they experience side-effects not always easily treated by traditional therapies. Complementary therapies may also maintain and improve wellness and quality of life (Deng & Cassileth., 2005).

It is important to note that complementary medicine may be complementary in one culture and traditional in another. Reflexology is an example that has the status of being traditional in China but is considered alternative or complementary in the Western traditional medicine. A central concept of many types of complementary medicine is to give thought and care to the whole person (holistic) rather than providing treatment for a specific disease or symptom. This holistic view and the emphasis on maintaining good health may be appealing for those with chronic illness or for those who want to improve their quality of life.

Study I and II

Study I aimed to investigate the effect of effleurage specifically on nausea and anxiety. The results showed that effleurage could decrease nausea compared with a control visit. With this in mind, it would be of interest to find out what was predominant in the patients' experiences of effleurage during chemotherapy. Therefore, study II was planned using a subset (10) of the participants in study I.

Surprisingly, the results from study II did not encompass nausea, anxiety or depression. Instead, the patients talked about distraction from a frightening experience, a turn from negative to positive, a sense of relaxation, a confirmation of caring and just feeling good. The findings of study II showed that effleurage offered a retreat from uneasy, unwanted, negative feelings connected with chemotherapy treatment. Thus, study II did not validate study I, but rather study II generated new areas of investigation for the future such as the effect of massage on symptom distress.

Anticipatory nausea/chemotherapy induced nausea

Study I investigated the effect of effleurage on nausea, anxiety and depression in patients with breast cancer undergoing chemotherapy. They were massaged during chemotherapy infusion which meant that chemotherapy-induced nausea may have been present. Anticipatory nausea however, is a common problem among patients undergoing

chemotherapy. The distinction between the two was impossible to make since the patients were massaged in the chemotherapy ward and the anticipatory nausea, if present, had already started. The effect of massage specifically on anticipatory nausea was therefore not investigated in this study. Such a study would have to take place prior to going to the chemotherapy ward.

History of motion sickness was not noted in Study I. It is known that a previous history of motion sickness predisposes the patient to chemotherapy-induced nausea (Morrow., 1984). It would therefore have been valuable to record the history of motion sickness in relation to the results of massage in this study.

We did not document the use of any other complementary treatment other than massage in this study. It is possible that some of the patients had used other treatments such as herbal remedies during the study period, whereby it would have been valuable to document these.

Study III and IV

Study III was planned hypothesising that effleurage could positively influence cellular immunity. Patients were offered the same type of part-body light pressure effleurage in study III, as in study I and II to obtain consistency between studies in the thesis. Previous studies of massage had shown increases in cellular immunity in patients with breast cancer and HIV (Ironson, Field, Scafidi et al., 1996; Hernandez-Reif, Field, Ironson et al., 2005). These studies used other massage techniques such as traction, pressing, stretching and compressing. The results from study III can therefore not be compared to the results of these studies since light pressure effleurage was used.

No significant differences were seen between study groups on any of the studied variables. Possible explanation was that patients were undergoing radiation treatment, which directly or indirectly could affect patients. Secondly, stimulation intensity by either area of body being massaged, duration, interval or pressure used could be a contributing and confounding factor to the results. Study IV was therefore planned to encompass a full-body light pressure effleurage at one occasion, measuring direct effect of massage on cellular immunity. Surprisingly, NK cell cytotoxicity (NKCC) mean measure was markedly lower in the visit control group at the second measure while mean measure of NKCC was relatively stable in the effleurage group. Light pressure effleurage therefore, seemed to counteract the decrease, as indicated by the significantly smaller decrease in the NKCC mean measurement for the effleurage group.

Methodological issues

Handling of data

Study I evaluated the effect of massage on nausea, anxiety and depression. This study examined whether VAS anxiety and HAD anxiety measured similar phenomenon since two instruments were used to measure anxiety. This was not, however, done for nausea since VAS was the only instrument used. Another instrument measuring nausea could

have been added, in order to be able to establish criterion-related validity and further strengthen the results of the study.

The question of how to handle changes in VAS measures is debated. To avoid numerical interpretation of the scale, data from VAS were dichotomized to increased or decreased, in paper I. Any change, small or large, in measure from baseline (before measure) was therefore considered as increased or decreased. The magnitude of change required for clinical relevance can be discussed, however it was not possible to estimate the “least amount of millimeters” necessary to satisfy clinical relevance.

Three instruments; HAD (paper I and III), LSQ (paper III) and STAI (paper III) were used. Data from these instruments were handled using ordered structure but not equality between scale steps. One could argue that sum score could not be used to calculate data because this would imply numerical interpretation. Another approach would have been to refrain from sum score and analyze each item separately. However, to be able to compare results with other published studies, the manual of these instruments were followed meaning addition of responses from several items to a total sum score.

Another aspect in this situation is if change between baseline and follow up can be calculated using subtraction or if the proper method is to recode change to increased or decreased. This issue is basically the same as the issue of calculating sum score. Using subtraction requires equidistant scale steps which an ordinal scale does not have.

In this situation, after careful consideration of advantages and disadvantages, the approach of calculating sum score and using simple subtraction to estimate change for HAD, LSQ and STAI was used. These estimates of changes were then compared between groups using Mann-Whitney’s U -test for ordinal data.

Sample size calculation

Sample size calculation was done when planning study III and IV. One factor to consider in calculating sample size is clinical relevance. It was however, not possible to estimate clinical relevance of massage in relation to immune function since these studies were not evaluating survival or recurrence of cancer. We then based the sample size analysis on previous studies investigating the same variables as we did. These studies had not reported standard deviations based on mean changes as we intended to do. Sample size calculation was hence done on data available from pre-post measures for the massage group. Based on a power of 0.80, alpha level 0.05 and assuming a two-tailed test, a sample size analysis was done for change in NK cell number, change in NK cell marker and change in T-cell number. Change in NK cell number was calculated based on the studies by Hernandez-Reif et al (Hernandez-Reif, Ironson, Field et al., 2004) and Ironson et al (Ironson, Field, Scafidi et al., 1996), resulting in a need for 7 patients per group (Table 2). Sample size analysis for change in NK cell marker was calculated based on the studies by Diego et al (Diego, Field, Hernandez-Reif et al., 2001) and Ironson et al (Ironson, Field, Scafidi et al., 1996), resulting in a need for 11 patients per group (Table 2). Sample size analysis for change in T cell number was calculated based on the studies by Diego et al (Diego, Field, Hernandez-Reif et al., 2001) and Ironson et al (Ironson, Field, Scafidi et al., 1996), resulting in a need for 7 patients per group (Table 2).

As mentioned above mean change measure for all of the above variables was estimated based on available pre-post measures. Since all mean change measures were based on two different studies, two values were obtained and the estimated change determined was

between these two values. SD for change was estimated as a percentage of mean change measure. The percentage was calculated in the upper proportion level of SD for the pre and post measures. Based on this analysis of sample size, we included 11 subjects per group in study III. Sample size in study IV was based on the same previous data as study III but only on NK cells. To compensate for possible drop-outs, we included 15 subjects per group in study IV.

Table 2. Calculation of sample size paper III and IV.

Cell type	Pre-measure	Post-measure	Estimated change	Sample size no
NK cell number ¹ (SD)	214-235 (129-161)	252-263 (95-142)	30 (20)	7
NK cell marker ² (SD)	93-101 (54-66)	112-157 (65-110)	25 (20)	11
Cytotoxic T cell number ³ (SD)	751-765 (328-360)	812-821 (394-583)	60 (40)	7

¹ Mean number /mm³ in the lymphocyte gate and monocyte gate

² Mean number /mm³ in the lymphocyte gate

³ Mean number /mm³

General applicability of results

Patients in study I, III and IV were consecutively included. It would be presumed that all of these patients liked to get massage, should they have been allocated to massage treatment. This may induce bias, as all the patients were favorably disposed to massage. However, there were very few patients that did not want to participate (paper I = 2 patients, paper III = 1 patient and paper IV = 1 patient). Therefore, it would have been very difficult to recruit patients that did not appreciate massage. Consequently, the patients that served as study populations in study I, III and IV were in all probability, representative of breast cancer patients in Sweden undergoing chemotherapy treatment (paper I) and radiation treatment (paper III and IV).

The results from paper II are not universal in the sense that they apply to all patients in all situations. Giorgi wrote: "In other words, to force clarity on a phenomenon that does not have that attribute does not necessarily result in clarity. Rather, the relationship to the nature of the phenomenon being investigated also has to be taken into account." (Giorgi., 2005). So phenomenological analyses of lived experiences depend on context and content, therefore universality can only be attained if a very high degree of abstraction is used. What can then the result in paper II be used for? Qualitative methodology has its strengths in validity. When asking patients to unbiased, tell about their experience of receiving

massage, no predisposed meaning of the result is formed. The result therefore illuminates the experience of the patients in the given situation. This new knowledge may be applicable to similar caring situations, but one cannot say that they are for sure. Rather, the result can be used to get a greater understanding of the various dimensions of receiving massage during chemotherapy treatment and form new areas of investigation.

Confounding factors

There are many confounding factors that can cloud the results of a massage study. When planning a study evaluating the effect of massage, one needs to illuminate as many of these factors as possible, while trying to minimize the effect of remaining confounding factors. One factor to consider is the interpersonal meeting between the massager and the patient. Study I and II used several different massage/visit persons, due to practical reasons, as opposed to study III and IV that had the same massage/visit person. When asking the patients in study II about the consequence of having different massage persons, they responded that it did not matter, although they recognized that there were different massage persons from time to time.

Another confounding factor to consider is instructions regarding conversation with the massage/visit person. One possibility is to restrict conversation during massage/visit. However, we estimated this restriction to bear negative consequences for the study.

Furthermore, the environment in which the massage/visit takes place is important. All study participants (massage/visit) were subjected to the same room in the separate studies. Study I and II took place in the chemotherapy ward, which was a rational location since the aim was to find out effects and experiences of massage during chemotherapy treatment. Study III and IV however, took place at the oncology clinic directly after radiation treatment. This location might have influenced the patients in a negative way concealing possible effects of massage. Study III and IV was set up to include women during ongoing radiation therapy. In replicating these studies it would be advisable to wait at least 3 months after radiation treatment to avoid possible immunosuppressive or psychological effects associated with radiation treatment. Inclusion during radiation therapy was not judged as a problem however, when planning these studies. In addition, treatment at another location would be beneficial to avoid possible negative psychological effects associated with the oncology clinic.

The control group was subjected to visits only to control for the non-specific effects of attention. One possibility was to give the control group a sham massage or very light touch. The studies included in this thesis however, evaluated light pressure effleurage which would have made a control of very light touch too similar to the intervention.

Other factors that can influence results in a massage study are massage technique used, practitioner qualifications, interval, duration and area of body being massaged (dose), as well as statistical methods used to analyze data.

Conclusion

The conclusions to be drawn from the results of this thesis are that light pressure effleurage does not affect cellular immunity when investigating T cells. Nor does light pressure effleurage affect anxiety, depression, cortisol, oxytocin, quality of life or diastolic blood pressure.

In contrast, light pressure effleurage appears to decrease nausea during chemotherapy treatment. Full-body effleurage also appears to affect NK cell cytotoxicity, modulate ANS with a decrease of systolic blood pressure and heart rate. Nausea, NK cells, blood pressure and heart rate however, have only been studied directly after effleurage which means that the results apply to acute effects only.

Considering that many breast cancer patients experience post-operative stress (Luecken, Dausch, Gulla et al., 2004) and that chemotherapy-induced nausea is a common side-effect (Johansson, Steineck, Hursti et al., 1992; Foltz, Gaines, Gullatte et al., 1996; Sitzia, North, Stanley et al., 1997; Hickok, Roscoe, Morrow et al., 1999) it is of importance to decrease these symptoms. Light pressure effleurage can be offered to breast cancer patients as a complement to traditional care to directly decrease symptoms associated with stress and nausea.

In addition, the patients receiving chemotherapy experienced the effleurage as a retreat from the feeling of uneasiness toward chemotherapy. Since chemotherapy treatment is not, in praxis, optional to patients, the mere 20 minutes of effleurage could balance the uneasy feeling associated with chemotherapy with something good and of their own choice.

In conclusion, light pressure effleurage is a treatment that can be added to the arsenal of treatment choices available to the oncological staff.

Future considerations

Future studies evaluating massage in the field of oncology using qualitative method are needed. The seriousness of a cancer and treatment, places the patient in a troublesome position where specific variables to investigate may be difficult to foresee. Adopting an open mind when interviewing patients, contributes to understandings that may go undetected without a qualitative approach. This new knowledge can then be evaluated using quantitative methods to lay a strong foundation for lasting implementation in health care.

Furthermore, studies on the effect of massage should set out to minimize the consequences of confounding factors as previously described. Future studies should also include long term follow-up measures to evaluate the persistence of effects of massage as well as interval, duration and dose. Finally, the clinical relevance of effects of massage needs to be investigated. Future studies could include the effect on survival, recurrence of disease and quality of life.

Appendix

1. HAD

Detta formulär innehåller frågor om hur du har känt dig under den senaste veckan.

Besvara frågorna genom att markera det svarsalternativ du tycker stämmer bäst.

Obs fyll i hela cirkeln, så här: ○⇒●. Om du är osäker, markera det alternativ som känns riktigast.

1. Jag känner mig spänd eller "uppskruvad"

- För det mesta
- Ofta
- Då och då
- Inte alls

2. Jag uppskattar samma saker som förut

- Precis lika mycket
- Inte lika mycket
- Bara lite
- Knappast alls

3. Jag får en slags känsla av rädsla som om någonting förfärligt håller på att hända

- Alldeles bestämt och rätt illa
- Ja, men inte så illa
- Lite med det oroar mig inte
- Inte alls

4. Jag kan skratta och se saker från den humoristiska sidan

- Lika mycket som jag alltid kunnat
- Inte riktigt lika mycket nu
- Absolut inte så mycket nu
- Inte alls

5. Oroande tankar kommer för mig

- Mycket ofta
- Ofta
- Då och då men inte så ofta
- Bara någon enstaka gång

6. Jag känner mig glad

- Inte alls
- Inte ofta
- Ibland
- För det mesta

7. Jag kan sitta i lugn och ro och känna mig avslappnad

- Absolut
- Oftast
- Inte ofta
- Inte alls

8. Jag känner mig som om jag gick på "lågt varv"

- Nästan jämt
- Mycket ofta
- Ibland
- Inte alls

9. Jag har en slags känsla av rädsla som om jag hade "fjärilar i magen"

- Inte alls
- Någon gång
- Rätt ofta
- Mycket ofta

10. Jag har tappat intresse för mitt utseende

- Absolut
- Jag bryr mig inte så mycket om det som jag borde
- Jag kanske inte bryr mig om det riktigt så mycket
- Jag bryr mig precis lika mycket om det som förut

11. Jag känner mig rastlös som om jag måste vara på språng

- Verkligen mycket
- En hel del
- Inte så mycket
- Inte alls

12. Jag ser framemot saker och ting med glädje

- Lika mycket som förut
- Något mindre än jag brukade
- Klart mindre än jag brukade
- Nästan inte alls

13. Jag får plötsliga panikkänslor

- Verkligen ofta
- Rätt ofta
- Inte så ofta
- Inte alls

14. Jag kan njuta av en bra bok, ett bra radio eller TV-program

- Ofta
- Ibland
- Inte så ofta
- Mycket sällan

HAD: Zigmund & Snaith, 1983. Acta Psychiatr Scand, 67: 361-70;

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2. LSQ

Ref. Carlsson M & Hamrin E. 2002. Evaluation of the life satisfaction questionnaire (LSQ) using structural equation modelling (SEM). *Quality of Life Research*, 11:415-425

LSQ (Life Satisfaction questionnaire) EXPERIENCE OF LIFE SITUATION

The questions below deal with your health and life situation. The information you give will be treated confidentially. Please answer all the questions.

Which of the symptoms or problems below have caused you difficulties during the past week? Put an X in the box that best corresponds to your experience.

1. Tiredness

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

2. Lack of fitness

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

3. Sleep disturbances

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

4. Loss of appetite

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

5. Diarrhoea

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

6. Constipation

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

7. Dizziness

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

8. Palpitation of the heart

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

9. Breathing difficulties

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

10. Muscular weakness

To a very high degree

To a high degree

To a fairly high degree

To some degree

To a low degree

Almost not at all

Not at all

11. Pain

- To a very high degree ()
- To a high degree ()
- To a fairly high degree ()
- To some degree ()
- To a low degree ()
- Almost not at all ()
- Not at all ()

12. Nausea

- To a very high degree ()
- To a high degree ()
- To a fairly high degree ()
- To some degree ()
- To a low degree ()
- Almost not at all ()
- Not at all ()

13. How do you perceive your health overall?

- My health is very poor ()
- My health is poor ()
- My health is fairly poor ()
- My health is neither poor nor good ()
- My health is fairly good ()
- My health is good ()
- My health is very good ()

I Describe your work situation. (Put an X in the box that corresponds best to your situation during the past week)

- I work full-time ()
- I work part-time ()
- I am not gainfully employed ()

14a. If you are gainfully employed, how happy are you with your work situation?

- I am very unhappy with my work situation ()
- I am unhappy with my work situation ()
- I am fairly unhappy with my work situation ()
- I am neither unhappy nor happy with my work situation ()
- I am fairly happy with my work situation ()
- I am happy with my work situation ()
- I am very happy with my work situation ()

II If you are not gainfully employed, explain why?

- I am unemployed ()
- I am a housewife ()
- I am sick-listed ()
- I am on sickpension ()
- I am an old-age pensioner ()
- I am unable to work ()
- I do not want to work because I want to do other things ()
- Other reasons () _____

14b. If you are not gainfully employed, how happy are you with your life situation?

- I am very unhappy with my life situation ()
- I am unhappy with my life situation ()
- I am fairly unhappy with my life situation ()
- I am neither unhappy nor happy with my life situation ()
- I am fairly happy with my life situation ()
- I am happy with my life situation ()
- I am very happy with my life situation ()

III Has your financial situation changed during the past year?

- Yes ()
 No ()

15. Describe your financial situation

- My finances are very unsatisfactory ()
 My finances are unsatisfactory ()
 My finances are fairly unsatisfactory ()
 My finances are neither unsatisfactory nor satisfactory ()
 My finances are fairly satisfactory ()
 My finances are satisfactory ()
 My finances are very satisfactory ()

16. Are you happy with where you live?

- I am very unhappy with where I live ()
 I am unhappy with where I live ()
 I am fairly unhappy with where I live ()
 I am neither unhappy nor happy with where I live ()
 I am fairly happy with where I live ()
 I am happy with where I live ()
 I am very happy with where I live ()

17. How active have you been during the past week?

- I have been very passive ()
 I have been passive ()
 I have been fairly passive ()
 I have been neither passive nor active ()
 I have been fairly active ()
 I have been active ()
 I have been very active ()

**How do you feel about your activities (i.e. what you have done) during the past week?
 To what extent have your activities been:**

18. Fun/stimulating

- Not at all ()
 Almost not at all ()
 To a low degree ()
 To some degree ()
 To a fairly high degree ()
 To a high degree ()
 To a very high degree ()

19. Interesting

- Not at all ()
 Almost not at all ()
 To a low degree ()
 To some degree ()
 To a fairly high degree ()
 To a high degree ()
 To a very high degree ()

20. Creative

- Not at all ()
 Almost not at all ()
 To a low degree ()
 To some degree ()
 To a fairly high degree ()
 To a high degree ()
 To a very high degree ()

21. Independent

- Not at all ()
 Almost not at all ()
 To a low degree ()
 To some degree ()
 To a fairly high degree ()
 To a high degree ()
 To a very high degree ()

22. Useful

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

23. Meaningful

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

How do you experience your relationships with other people from the following perspective?

Choose and assess a significant person from your family.

To what extent do you feel the relationship is:

24. Emotionally satisfying

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

25. Fun/stimulating

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

26. Meaningful

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

27. Independent

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

28. Varied

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

Choose and assess a significant person from your friends.

To what extent do you feel the relationship is:

29. Emotionally satisfying

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

30. Fun/stimulating

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

31. Meaningful

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

32. Independent

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

33. Varied

- Not at all ()
- Almost not at all ()
- To a low degree ()
- To some degree ()
- To a fairly high degree ()
- To a high degree ()
- To a very high degree ()

34. How do you perceive your overall quality of life?

- My quality of life is very low ()
- My quality of life is low ()
- My quality of life is fairly low ()
- My quality of life is neither particularly low or particularly high ()
- My quality of life is fairly high ()
- My quality of life is high ()
- My quality of life is very high ()

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3. STAI

FRÅGEFORMULÄR STAI/STATE, form Y-1

INSTRUKTIONER

Nedan följer ett antal påståenden som människor har använt för att beskriva hur de känner sig. Läs varje påstående och ringa in den av siffrorna 1 till 4 som bäst svarar mot hur Du känner Dig just nu, dvs. precis i denna stund. Det finns inga rätta eller felaktiga svar. Fundera inte för mycket på något påstående utan svara som Du först tycker på hur Du känner Dig just nu.

	Inte alls	Något	Ganska	Mycket
1. Jag känner mig lugn	1	2	3	4
2. Jag känner mig trygg	1	2	3	4
3. Jag känner mig spänd	1	2	3	4
4. Jag känner mig ansträngd	1	2	3	4
5. Jag känner mig väl till mods	1	2	3	4
6. Jag känner mig upprörd	1	2	3	4
7. Jag oroar mig just nu över möjliga olyckor	1	2	3	4
8. Jag känner mig tillfreds	1	2	3	4
9. Jag känner mig rädd	1	2	3	4
10. Jag känner mig nöjd och belåten	1	2	3	4
11. Jag har självförtroende	1	2	3	4
12. Jag känner mig nervös	1	2	3	4
13. Jag känner panik	1	2	3	4
14. Jag känner mig obeslutsam	1	2	3	4
15. Jag känner mig avslappnad	1	2	3	4
16. Jag känner mig belåten	1	2	3	4
17. Jag känner mig orolig	1	2	3	4
18. Jag känner mig förvirrad	1	2	3	4
19. Jag känner mig säker	1	2	3	4
20. Jag känner mig glad	1	2	3	4

FRÅGEFORMULÄR STAI/STATE, form Y-2

INSTRUKTIONER

Nedan följer ett antal påståenden som människor har använt för att beskriva hur de känner sig. Läs varje påstående och ringa in den av siffrorna 1 till 4 som bäst svarar mot hur Du känner Dig just i allmänhet. Det finns inga rätta eller felaktiga svar. Fundera inte för mycket på något påstående utan svara som Du först tycker passar in på Dig just nu.

	Nästan aldrig	Ibland	Ofta	Nästan alltid
1. Jag känner mig behaglig till mods	1	2	3	4
2. Jag känner mig nervös och rastlös	1	2	3	4
3. Jag känner mig nöjd med mig själv	1	2	3	4
4. Jag önskar att jag vore lika lycklig som alla andra	1	2	3	4
5. Jag känner mig misslyckad	1	2	3	4
6. Jag känner mig utvilad	1	2	3	4
7. Jag är lugn och samlad	1	2	3	4
8. Jag känner att svårigheter tornar upp sig så att jag inte kan klara av dem	1	2	3	4
9. Jag oroar mig alltför mycket över småsaker	1	2	3	4
10. Jag är lycklig	1	2	3	4
11. Jag har störande tankar	1	2	3	4
12. Jag saknar självförtroende	1	2	3	4
13. Jag känner mig trygg	1	2	3	4
14. Jag har lätt att fatta beslut	1	2	3	4
15. Jag känner mig otillräcklig	1	2	3	4
16. Jag är nöjd och belåten	1	2	3	4
17. Jag kan inte låta bli att grubbla	1	2	3	4
18. Jag tar besvikelser så hårt att jag inte kan släppa tanken på dem	1	2	3	4
19. Jag är jämn i humöret	1	2	3	4
20. Jag blir spänd och ur gängorna när jag tänker på de problem jag har för tillfället	1	2	3	4

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References

- Ahles, T.A., Tope, D.M., Pinkson, B., Walch, S., Hann, D., Whedon, M., Dain, B., Weiss, J.E., Mills, L. & Silberfarb, P.M. (1999) Massage therapy for patients undergoing autologous bone marrow transplantation. *J Pain Symptom Manage* 18, 157-163.
- Avis, N.E., Crawford, S. & Manuel, J. (2005) Quality of life among younger women with breast cancer. *J Clin Oncol* 23, 3322-3330.
- Beck, C.T. (1994) Reliability and validity issues in phenomenological research. *West J Nurs Res* 16, 254-62 discussion 26.
- Benjamin, P. & Tappan, F. (2005) Tappan's handbook of healing massage techniques-4th ed. Prentice Hall, London.
- Benson, H., Beary, J.F. & Carol, M.P. (1974) The relaxation response. *Psychiatry* 37, 37-46.
- Bergh, J. (2004) Cytostatikabehandling. In Bröstcancer. Edited by Jönsson P.-E. Astra Seneca, Södertälje. pp 225-244.
- Bergkvist, L. (2004) Kirurgisk behandling - lymfkörtlar. In Bröstcancer. Edited by Jönsson P.-E. Astra Seneca, Södertälje. pp 165-177.
- Billhult, A. & Dahlberg, K. (2001) A meaningful relief from suffering experiences of massage in cancer care. *Cancer Nurs* 24, 180-184.
- Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M. & Ramirez, A. (2005) Depression and anxiety in women with early breast cancer: five year observational cohort study. *BMJ* 330, 702.
- Carlsson, M. & Hamrin, E. (2002) Evaluation of the life satisfaction questionnaire (LSQ) using structural equation modelling (SEM). *Qual Life Res* 11, 415-425.
- Carlsson, M., Hamrin, E. & Lindqvist, R. (1999) Psychometric assessment of the Life Satisfaction Questionnaire (LSQ) and a comparison of a randomised sample of Swedish women and those suffering from breast cancer. *Quality of Life Research* 8, 245-253.
- Cassileth, B.R. & Vickers, A.J. (2004) Massage therapy for symptom control: outcome study at a major cancer center. *J Pain Symptom Manage* 28, 244-249.
- Corner, J., Cawley, N. & Hildebrand, S. (1995) An evaluation of the use of massage and essential oils on the wellbeing of cancer patients. *Int J Palliat Nurs* 1, 67-73.
- Deng, G. & Cassileth, B.R. (2005) Integrative oncology: complementary therapies for pain, anxiety, and mood disturbance. *CA Cancer J Clin* 55, 109-116.
- Diego, M.A., Field, T., Hernandez-Reif, M., Shaw, K., Friedman, L. & Ironson, G. (2001) HIV adolescents show improved immune function following massage therapy. *Int J Neurosci* 106, 35-45.
- Dodd, M.J., Onishi, K., Dibble, S.L. & Larson, P.J. (1996) Differences in nausea, vomiting, and retching between younger and older outpatients receiving cancer chemotherapy. *Cancer Nurs* 19, 155-161.
- Ferrell-Torry, A.T. & Glick, O.J. (1993) The use of therapeutic massage as a nursing intervention to modify anxiety and the perception of cancer pain. *Cancer Nurs* 16, 93-101.
- Field, T., Ironson, G., Scafidi, F., Nawrocki, T., Goncalves, A., Burman, I., Pickens, J., Fox, N., Schanberg, S. & Kuhn, C. (1996) Massage therapy reduces anxiety and enhances EEG pattern of alertness and math computations. *Int J Neurosci* 86, 197-205.

- Field, T., Morrow, C., Valdeon, C., Larson, S., Kuhn, C. & Schanberg, S. (1992) Massage reduces anxiety in child and adolescent psychiatric patients. *J Am Acad Child Adolesc Psychiatry* 31, 125-131.
- Foltz, A.T., Gaines, G. & Gullatte, M. (1996) Recalled side effects and self-care actions of patients receiving inpatient chemotherapy. *Oncol Nurs Forum* 23, 679-683.
- Fornander, T. (2004) Strålbehandling. In *Bröstcancer*. Edited by Jönsson P.-E. Astra Seneca, Södertälje. pp 193-206.
- Fraser, J. & Kerr, J.R. (1993) Psychophysiological effects of back massage on elderly institutionalized patients. *J Adv Nurs* 18, 238-245.
- Giorgi, A. (1985) Phenomenology and psychological research. Duquesne University Press., Pittsburgh.
- Giorgi, A. (1997) The theory, practise, and evaluation of the phenomenological method as a qualitative research procedure. *J Phenomenol Psychol* 28, 235-260.
- Giorgi, A. (2005) The phenomenological movement and research in the human sciences. *Nurs Sci Q* 18, 75-82.
- Greulich, L., Lomasney, A. & Whiteman, B. (2000) Foot massage. A nursing intervention to modify the distressing symptoms of pain and nausea in patients hospitalized with cancer. *Cancer Nurs* 23, 237-243.
- Hansen, A.M., Garde, A.H., Christensen, J.M., Eller, N.H. & Netterstrøm, B. (2003) Evaluation of a radioimmunoassay and establishment of a reference interval for salivary cortisol in healthy subjects in Denmark. *Scandinavian Journal of Clinical and Laboratory Investigation* 63, 303-310.
- Hellstrand, K., Asea, A. & Hermodsson, S. (1990) Role of histamine in natural killer cell-mediated resistance against tumor cells. *Journal of Immunology* 145, 4365-4370.
- Henderson, J.W. & Donatelle, R.J. (2004) Complementary and alternative medicine use by women after completion of allopathic treatment for breast cancer. *Altern Ther Health Med* 10, 52-57.
- Hernandez-Reif, M., Field, T., Ironson, G., Beutler, J., Vera, Y., Hurley, J., Fletcher, M.A., Schanberg, S., Kuhn, C. & Fraser, M. (2005) Natural killer cells and lymphocytes increase in women with breast cancer following massage therapy. *Int J Neurosci* 115, 495-510.
- Hernandez-Reif, M., Ironson, G., Field, T., Hurley, J., Katz, G., Diego, M., Weiss, S., Fletcher, M.A., Schanberg, S., Kuhn, C. & Burman, I. (2004) Breast cancer patients have improved immune and neuroendocrine functions following massage therapy. *J Psychosom Res* 57, 45-52.
- Hickok, J.T., Roscoe, J.A., Morrow, G.R., Stern, R.M., Yang, B., Flynn, P.J., Hynes, H.E., Kirshner, J.J. & Rosenbluth, R.J. (1999) Use of 5-HT₃ receptor antagonists to prevent nausea and emesis caused by chemotherapy for patients with breast carcinoma in community practice settings. *Cancer* 86, 64-71.
- Holt-Lunstad, J. & Steffen, P.R. (2007) Diurnal Cortisol Variation is Associated With Nocturnal Blood Pressure Dipping. *Psychosomatic Medicine* 69, 339-343.
- Ironson, G., Field, T., Scafidi, F., Hashimoto, M., Kumar, M., Kumar, A., Price, A., Goncalves, A., Burman, I., Tetenman, C., Patarca, R. & Fletcher, M.A. (1996) Massage therapy is associated with enhancement of the immune system's cytotoxic capacity. *Int J Neurosci* 84, 205-217.

- Jensen, I., Lekander, M., Nord, C., Rane, A. & Ekenryd, C. (2007) Complementary and Alternative Medicine (CAM) A Systematic review of Intervention Research in Sweden. Complementary and Alternative Medicine (CAM). Karolinska Institutet. pp 8.
- Johansson, S., Steineck, G., Hursti, T., Fredrikson, M., Fürst, C.J. & Peterson, C. (1992) Aspects of patient care. Interviews with relapse-free testicular cancer patients in Stockholm. *Cancer Nurs* 15, 54-60.
- Jönsson, P.-E. (2004) Kirurgisk behandling - bröst. In *Bröstcancer*. Edited by Jönsson P.-E. Astra Seneca, Södertälje. pp 151.
- Kurz, W., Kurz, R., Litmanovitch, Y.I., Romanoff, H., Pfeifer, Y. & Sulman, F.G. (1981) Effect of manual lymphdrainage massage on blood components and urinary neurohormones in chronic lymphedema. *Angiology* 32, 119-127.
- Lännergren, A., Ulfendal, M., Lundeberg, T. & Westerblad, H. (2005) Nervsystemets högre funktioner. Fysiologi. Studentlitteratur, Lund. pp 161.
- Lee, K.A. & Kieckhefer, G.M. (1989) Measuring human responses using visual analogue scales. *West J Nurs Res* 11, 128-132.
- Luecken, L.J., Dausch, B., Gulla, V., Hong, R. & Compas, B.E. (2004) Alterations in morning cortisol associated with PTSD in women with breast cancer. *J Psychosom Res* 56, 13-15.
- Lund, I., Ge, Y., Yu, L.C., Uvnäs-Moberg, K., Wang, J., Yu, C., Kurosawa, M., Agren, G., Rosén, A., Lekman, M. & Lundeberg, T. (2002) Repeated massage-like stimulation induces long-term effects on nociception: contribution of oxytocinergic mechanisms. *Eur J Neurosci* 16, 330-338.
- Lund, I., Lundeberg, T., Kurosawa, M. & Uvnäs-Moberg, K. (1999) Sensory stimulation (massage) reduces blood pressure in unanaesthetized rats. *J Auton Nerv Syst* 78, 30-37.
- MacHale, S.M., Cavanagh, J.T., Bennie, J., Carroll, S., Goodwin, G.M. & Lawrie, S.M. (1998) Diurnal variation of adrenocortical activity in chronic fatigue syndrome. *Neuropsychobiology* 38, 213-217.
- Melzack, R. & Wall, P.D. (1965) Pain mechanisms: a new theory. *Science* 150, 971-979.
- Merleau-Ponty, M. (1964) *The Primacy of Perception*. North Western University Press, Evanston.
- Millar, K., Purushotham, A.D., McLatchie, E., George, W.D. & Murray, G.D. (2005) A 1-year prospective study of individual variation in distress, and illness perceptions, after treatment for breast cancer. *J Psychosom Res* 58, 335-342.
- Morrow, G.R. (1984) Susceptibility to motion sickness and the development of anticipatory nausea and vomiting in cancer patients undergoing chemotherapy. *Cancer Treatment Reports* 68, 1177-1178.
- Moyer, C.A., Rounds, J. & Hannum, J.W. (2004) A meta-analysis of massage therapy research. *Psychol Bull* 130, 3-18.
- O'Leary, A. (1990) Stress, emotion, and human immune function. *Psychological Bulletin* 108, 363-382.
- Okvat, H.A., Oz, M.C., Ting, W. & Namerow, P.B. (2002) Massage therapy for patients undergoing cardiac catheterization. *Alternative Therapies in Health and Medicine* 8, 68-70 72 74-5.
- Onkologiskt Centrum, V.S. (2003) *Cancerincidens Västra Sjukvårdsregionen 1997-2001. Rapport Regionala Tumörregistret 2003*. pp 1.

- Ouchi, Y., Kanno, T., Okada, H., Yoshikawa, E., Shinke, T., Nagasawa, S., Minoda, K. & Doi, H. (2006) Changes in cerebral blood flow under the prone condition with and without massage. *Neurosci Lett* 407, 131-135.
- Pruessner, J.C., Hellhammer, D.H. & Kirschbaum, C. (1999) Burnout, perceived stress, and cortisol responses to awakening. *Psychosomatic Medicine* 61, 197-204.
- Rutqvist, L.-E. (2004) Endokrin behandling. In *Bröstcancer*. Edited by Jönsson P.-E. Astra Seneca, Södertälje. pp 207-224.
- Sitzia, J., North, C., Stanley, J. & Winterberg, N. (1997) Side effects of CHOP in the treatment of non-hodgkin's lymphoma. *Cancer Nurs* 20, 430-439.
- Socialstyrelsen [National Board of Health and Welfare] (2006, January 26) Cancer Incidence in Sweden, 2004. Statistics - Health and Diseases. Retrieved May 12, 2006 from <http://www.socialstyrelsen.se/Statistik/statistik_amne/Cancer>. Socialstyrelsen, Stockholm. pp 16.
- Soden, K., Vincent, K., Craske, S., Lucas, C. & Ashley, S. (2004) A randomized controlled trial of aromatherapy massage in a hospice setting. *Palliat Med* 18, 87-92.
- Sompayrac, L. (1999) How the immunessystem works. Blackwell Science, Malden, Mass.
- Spielberger, C.D., Gorsuch, R.L., Lushene, R., Vagg, P.R. & Jacobs, G.A. (1983) The state-trait anxiety inventory. Consulting Psychologists Press, Palo Alto, CA.
- Uvnäs-Moberg, K. (2000) Effekter av massage. Lugn och beröring, oxytocinets läkande verkan i kroppen. Bokförlaget Natur och kultur, Stockholm. pp 146.
- Uvnäs-Moberg, K., Bruzelius, G., Alster, P. & Lundeberg, T. (1993) The antinociceptive effect of non-noxious sensory stimulation is mediated partly through oxytocinergic mechanisms. *Acta Physiol Scand* 149, 199-204.
- Vickers, A. & Zollman, C. (1999) ABC of complementary medicine. Massage therapies. *BMJ* 319, 1254-1257.
- Vickers, A.J. & Cassileth, B.R. (2001) Unconventional therapies for cancer and cancer-related symptoms. *Lancet Oncol* 2, 226-232.
- Wagner, D.R., Tatsugawa, K., Parker, D. & Young, T.A. (2007) Reliability and utility of a visual analog scale for the assessment of acute mountain sickness. *High Altitude Medicine & Biology* 8, 27-31.
- Weinrich, S.P. & Weinrich, M.C. (1990) The effect of massage on pain in cancer patients. *Appl Nurs Res* 3, 140-145.
- Zeitlin, D., Keller, S.E., Shiflett, S.C., Schleifer, S.J. & Bartlett, J.A. (2000) Immunological effects of massage therapy during academic stress. *Psychosom Med* 62, 83-84.
- Zigmond, A.S. & Snaith, R.P. (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67, 361-370.