Effect of Acupuncture on Menopausal Memory Changes in Women with Breast Cancer

Elizabeth Cole Collins

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EFFECT OF ACUPUNCTURE ON MENOPAUSAL MEMORY CHANGES IN
WOMEN WITH BREAST CANCER

A Dissertation
Submitted to the School of Nursing

Duquesne University

In partial fulfillment of the requirements for
the degree of Doctor of Philosophy

By
Elizabeth Cole Collins

May 2013
EFFECT OF ACUPUNCTURE ON MENOPAUSAL MEMORY CHANGES IN WOMEN WITH BREAST CANCER

By

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Approved March 19, 2013

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ABSTRACT

EFFECT OF ACUPUNCTURE ON MENOPAUSAL MEMORY CHANGES IN WOMEN WITH BREAST CANCER

By

Elizabeth Cole Collins

May 2013

Dissertation supervised by L. Kathleen Sekula, PhD, APRN, FAAN

Menopausal symptoms are a concern for peri- and postmenopausal women, and for women who have been treated for breast cancer. Changes in memory are a commonly reported menopausal symptom which can interfere with daily activities, occurring in women who experience natural menopause as well as in women who have an abrupt onset of menopause following treatment for breast cancer. Menopause hormone therapy may be contraindicated or unacceptable for many women, reinforcing the need for well-tolerated, non-hormonal treatments for menopausal symptoms. The purpose of this study was to examine the efficacy of acupuncture to improve the menopausal symptom of memory changes in breast cancer survivors, and was a secondary analysis of a placebo-controlled, randomized clinical trial. The Framework for Interactions between the Individual and the Environment was the conceptual framework that guided the study.
Subjects in the parent study were randomized to either the experimental group (symptom-specific acupuncture), control group (non-symptom-specific acupuncture), or enhanced usual care group (instruction on health-related topics). Each group received twelve intervention sessions over an 8-week period. Sixty subjects indicating a positive response to memory items on instruments at baseline were selected for this secondary analysis. The Daily Symptom Diary, Kupperman Index, and Menopause-Specific Quality of Life Questionnaire (MENQOL) measured frequency or severity of perceived memory changes at baseline, midpoint, and end of treatment.

Frequency distributions were used to summarize the data. There were no statistically significant results from the Daily Symptom Diary. Improvement in the enhanced usual care group compared to the acupuncture groups was seen on the Kupperman Index, and validity concerns for this instrument were reviewed. Analysis of the MENQOL data revealed more positive change in the acupuncture groups in improvement of memory than in the enhanced usual care group. These findings support the need for further exploration of targeted interventions such as acupuncture to improve memory difficulties for menopausal women and breast cancer survivors, particularly as advances are made in the understanding of the mechanisms of cognitive change. Acupuncture remains promising as a non-hormonal treatment for menopausal symptoms and merits further investigation.
DEDICATION

This is dedicated to my parents who afforded me the privilege of a wonderful education and a lifetime of learning.
ACKNOWLEDGEMENT

I would like to acknowledge and sincerely thank my dissertation committee: Dr. Kathleen Sekula, advisor and committee chair, for her guidance and insight, and for her support, sensitivity, and humanity; Dr. Linda Goodfellow, committee member, for her attention to detail and many suggestions which enriched this work; and Dr. Susan Cohen, committee member and principal investigator of the parent study, for her guidance and encouragement to “keep writing.”

I would also like to thank my husband for his wisdom, patience, and technical support; and my sister for paving the way.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
</tr>
<tr>
<td>Dedication</td>
</tr>
<tr>
<td>Acknowledgement</td>
</tr>
<tr>
<td>List of Tables</td>
</tr>
<tr>
<td><strong>Chapter 1  Introduction</strong></td>
</tr>
<tr>
<td>Background of the Study</td>
</tr>
<tr>
<td>Purpose of the Study</td>
</tr>
<tr>
<td>Research Questions</td>
</tr>
<tr>
<td>Assumptions</td>
</tr>
<tr>
<td>Limitations</td>
</tr>
<tr>
<td>Definition of Terms</td>
</tr>
<tr>
<td>Significance of the Study</td>
</tr>
<tr>
<td><strong>Chapter 2  Review of the Literature</strong></td>
</tr>
<tr>
<td>Introduction</td>
</tr>
<tr>
<td>Menopausal Memory Changes</td>
</tr>
<tr>
<td>Menopausal Memory Changes in Breast Cancer Survivors</td>
</tr>
<tr>
<td>Menopausal Symptoms and Memory</td>
</tr>
<tr>
<td>Memory in Breast Cancer Survivors</td>
</tr>
<tr>
<td>Acupuncture</td>
</tr>
<tr>
<td>Acupuncture and Menopausal Symptoms</td>
</tr>
<tr>
<td>Acupuncture in Breast Cancer Survivors</td>
</tr>
</tbody>
</table>
Conceptual Framework................................................................. 56

Chapter 3 Methods

Introduction................................................................................... 59

Study Design ................................................................................. 59

Overview of the Parent Study ..................................................... 59

Research Design .......................................................................... 59

Power Analysis ........................................................................... 60

Variables ..................................................................................... 60

Setting ......................................................................................... 60

Sample ......................................................................................... 61

Subject Enrollment ....................................................................... 62

Measures ...................................................................................... 62

Intervention .................................................................................. 66

Data Collection and Management .............................................. 67

Current Study .............................................................................. 68

Protection of Human Subjects .................................................... 68

Data Analysis ............................................................................... 69

Chapter 4 Data Analysis

Introduction................................................................................... 71

Description of the Sample........................................................... 71

Research Questions ..................................................................... 72

Research Question 1 ................................................................. 72

Research Question 2 ................................................................. 90
Chapter 5 Discussion

Introduction ............................................................................................................. 93

Discussion of Results .......................................................................................... 95

Demographic Findings ......................................................................................... 95

Research Questions ............................................................................................. 96

Research Question 1 ......................................................................................... 96

Research Question 2 .......................................................................................... 101

Summary ............................................................................................................. 102

Limitations of the Study ...................................................................................... 103

Implications for Practice ..................................................................................... 104

Suggestions for Future Research ....................................................................... 105

Conclusion ........................................................................................................... 107

References .......................................................................................................... 108

Appendices .......................................................................................................... 134

Appendix A Demographic Data Form ................................................................. 135

Appendix B Daily Symptom Diary .................................................................... 137

Appendix C Kupperman Index .......................................................................... 138

Appendix D Menopause-Specific Quality of Life Questionnaire .................... 139
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Page</th>
<th>Table Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Timeline of Measurements</td>
</tr>
<tr>
<td>4.1</td>
<td>Sample Characteristics</td>
</tr>
<tr>
<td>4.2</td>
<td>Overall Symptom Frequency from Daily Symptom Diary at Baseline Regardless of Group</td>
</tr>
<tr>
<td>4.3</td>
<td>Group Differences in Symptom Frequency from Daily Symptom Diary at Baseline</td>
</tr>
<tr>
<td>4.4</td>
<td>Overall Symptom Severity Rating from Kupperman Index at Baseline Regardless of Group</td>
</tr>
<tr>
<td>4.5</td>
<td>Group Differences in Symptom Severity Rating from Kupperman Index at Baseline</td>
</tr>
<tr>
<td>4.6</td>
<td>Overall Symptom Severity Rating from MENQOL at Baseline Regardless of Group</td>
</tr>
<tr>
<td>4.7</td>
<td>Group Differences in Symptom Severity Rating from MENQOL at Baseline</td>
</tr>
<tr>
<td>4.8</td>
<td>Overall Change in Loss of Concentration Frequency Ratings Regardless of Group (Daily Symptom Diary)</td>
</tr>
<tr>
<td>4.9</td>
<td>Change in Loss of Concentration Frequency Ratings Between Groups (Daily Symptom Diary): Baseline to Week 5, Baseline to Week 9, Week 5 to Week 9</td>
</tr>
<tr>
<td>4.10</td>
<td>Pairwise Comparisons – Change in Loss of Concentration Severity Ratings (Kupperman): Baseline to Week 5</td>
</tr>
<tr>
<td>4.11</td>
<td>Pairwise Comparisons – Change in Loss of Concentration Severity Ratings (Kupperman): Baseline to Week 9</td>
</tr>
</tbody>
</table>
4.12 Pairwise Comparisons – Change in Loss of Concentration Severity Ratings

(Kupperman): Week 5 to Week 9................................................................. 83

4.13 Pairwise Comparisons – Change in Severity Ratings for Experiencing Poor Memory (MENQOL): Baseline to Week 5......................................................... 86

4.14 Pairwise Comparisons – Change in Severity Ratings for Experiencing Poor Memory (MENQOL): Baseline to Week 9......................................................... 87

4.15 Pairwise Comparisons – Change in Severity Ratings for Experiencing Poor Memory (MENQOL): Week 5 to Week 9 ......................................................... 87
Chapter 1

Introduction

Background of the Study

Menopausal symptoms are a concern for peri- and postmenopausal women, and for women who have been treated for breast cancer. Vasomotor symptoms (hot flashes and night sweats) affect approximately 65% of breast cancer survivors (Carpenter et al., 1998; Couzi, Helzlouer, & Fetting, 1995; Mom, Buijs, Willemse, Mourits, & de Vries, 2006), with many women rating them as severe (Carpenter et al., 1998; Couzi et al., 1995).

Changes in memory are another common menopausal symptom reported by women that can affect quality of life. More than half of midlife women identify memory problems, with many indicating interference with day-to-day functioning (Betti et al., 2001; Gold et al., 2000; Mitchell & Woods, 2001, 2011; Simon & Reape, 2009; Weber, Mapstone, Staskiewicz, & Maki, 2012; Woods & Mitchell, 2011). Memory changes occur both in women who experience natural menopause as well as in women who have an abrupt onset of menopause following treatment for breast cancer (Knobf, 2001).

Menopausal symptoms have been attributed to decreasing levels of circulating estrogen, though the mechanism behind these symptoms is not completely understood (Fritz & Speroff, 2011; Pachman, Jones, & Loprinzi, 2010). Estrogen produces a variety of actions on non-reproductive functions in the human brain, including those important for memory (Dumas, Hancur-Bucci, Naylor, Sites, & Newhouse, 2008; McEwen, 2002; McEwen, Gould, Orchinick, Weiland, & Woolley, 1995). Clinical studies of the
influence of estrogen on cognition suggest that estrogen is a factor in maintaining aspects of memory in women (Sherwin, 2003). While a number of studies have shown that menopausal hormone therapy may have specific positive cognitive effects in symptomatic menopausal women (Kampen & Sherwin, 1994; LeBlanc, Janowsky, Chan, & Nelson, 2001; Phillips & Sherwin, 1992; Sherwin, 1988), the safety of menopausal hormone therapy in women following a diagnosis of breast cancer is of concern (Holmberg et al., 2008; Mom et al., 2006). However, study findings are inconsistent regarding risk for breast cancer recurrence associated with menopausal hormone therapy (Col, Kim, & Chlebowski, 2005; DiSaia, Brewster, Ziogas, & Anton-Culver, 2000; Figueiredo et al., 2008).

Complementary and alternative medicine (CAM) therapies have been broadly used by women in the management of menopausal symptoms (Bair et al., 2008; Kessel & Kronenberg, 2004) as well as by women with breast cancer (Boon, Olatunde, & Zick, 2007; Burstein, Gelber, Guadagnoli, & Weeks, 1999; Fenlon & Rogers, 2007; Ganz et al., 2002; Hunter et al., 2004; Lengacher et al., 2006). In a study of 222 women treated for early stage breast cancer, nearly 57% used at least one CAM therapy, including acupuncture (Wyatt, Sikorskii, Wills, & Su, 2010). Breast cancer survivors with treatment-induced menopause may avoid pharmacologic interventions for symptom management after experiencing chemotherapy (Knobf, 2002). A widely practiced therapeutic intervention in the United States, acupuncture has been proposed as a non-hormonal treatment alternative for menopausal symptoms (Borud et al., 2009; Wyon, Wijma, Nedstrand, & Hammar, 2004).
It is estimated that there will be 232,340 newly diagnosed cases of breast cancer in women in the United States in 2013 (Siegel, Naishadham, & Jemal, 2013). The majority of these women are diagnosed at an early stage and 90% can expect to live 5 years or more. Scientific testing of alternative and complementary therapies for management of menopausal symptoms is needed, particularly for women who experience menopause following treatment for breast cancer and others for whom menopausal hormone therapy may not be appropriate or acceptable (NIH State-of-the-Science Panel, 2005).

**Purpose of the Study**

A secondary analysis of an existing data set from a randomized controlled trial was conducted. The purpose of this study was to examine the efficacy of acupuncture to improve memory in breast cancer survivors with menopausal symptoms.

The specific aims of this study were:

1. Examine the treatment effect of acupuncture for menopausal symptom relief using changes in memory as an outcome measure.

2. Examine the effect of acupuncture on memory changes in relationship to improvements in hot flashes and night sweats.

The conceptual framework that guided this study is the Framework for Interactions between the Individual and the Environment (Elliott & Eisdorfer, 1982). It will be described in the review of the literature.
Research Questions

Question 1. What are the effects of menopausal symptom-specific acupuncture on memory in breast cancer survivors with menopausal symptoms?

Hypothesis 1a. Menopausal symptom-specific acupuncture will improve perceived memory changes as measured by self-reports compared to enhanced usual care (education).

Hypothesis 1b. Non-symptom-specific acupuncture will improve perceived memory changes as measured by self-reports compared to enhanced usual care (education).

Question 2. Is there a relationship between improvements in hot flashes/night sweats and perceived memory changes in breast cancer survivors with menopausal symptoms?

Assumptions

The following are the assumptions upon which this study was based.

1. Data collection instruments were completed accurately by the subjects who participated in the parent study.
2. Information provided by the participants in the parent study was truthful.
3. Instruments used in the parent study were valid and reliable in this population.

Limitations

The following are limitations of this study.

1. Participants were self-selected.
2. Data were self-reported.

3. The sample may not be representative of all breast cancer survivors with menopausal symptoms.

4. There was potential for recall bias in the parent study.

**Definition of Terms**

The following are terms used in this study.

**Menopause.** Menopause is the permanent cessation of menses resulting from reduced levels of ovarian hormone secretion. This can occur naturally or be induced by surgery, chemotherapy, or radiation. Natural menopause is defined as 12 months of amenorrhea not associated with a physiologic or pathologic cause (Nelson et al., 2005).

**Menopausal transition.** In an effort to improve comparability of studies of midlife women, a standardized staging system for reproductive aging and the menopause transition has been developed for use in research and clinical settings (Harlow et al., 2012; Soules et al., 2001). The menopausal transition follows a predictable pattern spanning several years’ time, and begins with variations in menstrual cycle length in response to variations in the level of follicle stimulating hormone. The stages of the menopausal transition can be described by the following terms. *Premenopause* is the time up to the beginning of perimenopause, but may also be used to define the time up to the final menstrual period. *Perimenopause* is the time around menopause when menstrual cycle and endocrine changes are taking place, but 12 months of amenorrhea has not yet occurred. This includes *early menopausal transition* and *late menopausal transition* stages, each defined by specific menstrual and endocrine characteristics. *Postmenopause*
actually begins at the time of the final menstrual period, but is not recognized until after 12 months of amenorrhea (Harlow et al., 2012; Nelson et al., 2005; Soules et al., 2001).

**Cognition.** Cognition is a comprehensive term comprising the following mental processes by which knowledge is acquired, stored, and used: attention, perception, working memory, executive function, spatial ability, language, learning, memory - figural and verbal (Loring, 1999).

**Memory.** There are various forms of memory which implicate different parts of the brain and different neurophysiologic processes. Episodic memory differs from other major memory systems, which include semantic memory, procedural memory, and working (short-term) memory (Tulving, 2003).

**Episodic memory.** This form of memory involves exposure to new information during a discrete event (or episode), followed by conscious recollection of the information at a later time. The interval between exposure and recall can be minutes, days, or years. Episodic memory for information that is encoded through words or retrieved through verbal maneuvers is described as episodic verbal memory (Henderson, 2009, 2011).

**Semantic memory.** Learned memory of facts and concepts, such as the capital of a country, describes semantic memory which is strongly language-based. In contrast to episodic memory, details of time, place and context are not crucial to semantic memory (Craik, 2003).

**Procedural memory.** This form of memory allows for the performance of activities or skills, such as riding a bicycle, and does not require explicit recollection of the past (Balota, Dolan, & Duchek, 2000).
**Working memory.** Working memory refers to information held and manipulated in the mind for a short period of time, and incorporates executive functions such as attention and sequencing (Baddeley, 1996; Craik, 2003).

**Memory testing.** Different measures of memory tap different aspects of the memory systems (Lockhart, 2003). Several types of memory tests frequently used in research studies on memory changes in menopause are included here. Memory testing may also be referred to as neurocognitive or neuropsychological testing.

**Recall tests.** The recall of a list of words or a paragraph with or without cues or reminders is often used to study episodic verbal memory. Techniques for measuring episodic verbal memory include word-list learning, paragraph or story recall, and immediate and delayed recall (Craik, 2003).

**Verbal fluency.** Verbal fluency is the speed and ease of verbal production, and is typically measured by the quantity of words generated within a time limit in response to a stimulus or within a restricted category (e.g., animals or groceries). A test of verbal fluency calls on semantic memory, and reveals organization of thinking (Lezak, Howieson, & Loring, 2004).

**Memory span.** Tests of memory span require a person to repeat back accurately a list of digits or words over several trials. Solving a verbal problem, doing mental arithmetic, or completing a test of memory span involve working memory (Craik, 2003).

**Perceptual speed.** This test examines aspects of visual recognition and attention. It is a picture matching test in which visuoperceptual accuracy and speed in making perceptual judgments influence performance (Lezak et al., 2004; Strauss, Sherman, & Spreen, 2006). Perceptual speed can also be referred to as processing speed.
Memory changes.

Terminology. Various terms were used to describe women’s experiences with memory during the menopausal transition. Examples included here are from several research instruments, research reports, and other publications noted in this study: undesirable changes in memory; types of memory changes such as: can’t recall words or phone numbers, forgot purpose of behavior, concentration problems, need memory aids, forgot events (Mitchell & Woods, 2001); cognitive disturbances (Nelson et al., 2005); from the Daily Symptom Diary and Kupperman Index, both used in this study: loss of concentration (Kupperman, Blatt, Wiesbader, & Filler, 1953; Kupperman, Wetchler, & Blatt, 1959); from the Menopause-Specific Quality of Life Questionnaire used in this study: experiencing poor memory (Hilditch et al., 1996); from the Study of Women’s Health Across the Nation (SWAN) symptom inventory: forgetfulness (Gold et al., 2000); from the Cancer Rehabilitation Evaluation System questionnaire: difficulty remembering, difficulty concentrating, difficulty thinking clearly (Ganz et al., 1996); from the Breast Cancer Prevention Trial Symptom Checklist: forgetfulness, difficulty concentrating, easily distracted (Ganz et al., 2002).

Measurement. In this study, memory changes were self-reported. On the Kupperman Index, loss of concentration is rated by severity on a scale of 0 – 3, as not present, mild, moderate or severe. On the Daily Symptom Diary, loss of concentration is noted by frequency defined as the number of times per day it occurs. On the Menopause-Specific Quality of Life Questionnaire, experiencing poor memory is rated on a scale of 0 – 6, from not at all bothered to extremely bothered.
Hot flashes. A hot flash (or flush) is a spontaneous sensation of warmth, sometimes associated with perspiration, resulting from a vasomotor response to declining estrogen levels (Nelson et al., 2005). Hot flashes are defined as recurrent, transient periods of flushing, sweating and a sensation of heat, which may be accompanied by palpitations, a feeling of anxiety, and occasionally followed by chills. The severity, duration and frequency of hot flashes can vary both within and between individuals. Hot flashes are a phenomenon of women who are in transition to menopause, or who have become postmenopausal, either naturally or because of a medical or surgical intervention (Kronenberg, 1990).

Vasomotor symptoms of hot flashes and night sweats are sudden sensations of intense heat with sweating and flushing typically lasting 5 to 10 minutes. Hot flashes occur with a greater frequency and severity in premenopausal women who experience a sudden onset of menopause due to oophorectomy, or medical conditions or treatments that result in diminished ovarian hormone production (NIH State-of-the-Science Panel, 2005).

Measurement. In this study, hot flashes were self-reported. On the Kupperman Index, hot flashes are rated by severity on a scale of 0 – 3, as either not present, mild, moderate or severe. On the Daily Symptom Diary, hot flashes are rated by frequency or the number of times per day they occur. On the Menopause-Specific Quality of Life Questionnaire, hot flashes are rated on a scale of 0 – 6, from not at all bothered to extremely bothered.
**Night sweats.** Night sweats are hot flashes which occur at night, often while sleeping (Nelson et al., 2005). Night sweats have been referred to as hot flashes during sleep or during sleeping hours, or as nighttime hot flashes (Maki et al., 2008).

**Measurement.** Night sweats were self-reported in this study. They are rated as described under hot flashes on the Daily Symptom Diary and the Menopause-Specific Quality of Life Questionnaire. Night sweats are not reported on the Kupperman Index.

**Hormone therapy.**

**Menopausal hormone therapy.** Hormone therapy for treatment of menopausal vasomotor symptoms consists of either estrogen in combination with a progestin, or estrogen alone.

**Adjuvant hormone therapy.** Hormonal therapy, also called endocrine therapy, used in the treatment of breast cancer refers to treatment with a selective estrogen receptor modulator, usually tamoxifen, or an aromatase inhibitor, such as anastrozole.

**Complementary and alternative medicine.** Complementary and alternative medicine (CAM) includes a range of diverse medical and health care systems, practices, and products that are not usually considered part of conventional medicine. The National Center for Complementary and Alternative Medicine divides CAM practices into the following categories: mind and body medicine, natural products, energy medicine, manipulative and body-based practices, movement therapies, and whole medical systems. Acupuncture is considered to be a practice of mind and body medicine, but also plays a role in manipulative and body-based practices and energy medicine. Traditional Chinese medicine, an example of a whole system developed in a non-Western culture, includes
the practice of acupuncture as one of its key components (NCCAM, 2011; Nedrow et al., 2006).

**Acupuncture.** Acupuncture can be defined as the insertion of one or more needles into specific sites on the body surface for therapeutic purposes. These sites, called acupuncture points, can also be stimulated with heat, electrical currents, pressure, or laser light (Ernst, 2006). Acupuncture points are thought to stimulate the central nervous system to release chemicals that change the experience of pain, or that cause the release of other chemicals. Possible mechanisms for these biochemical changes are conduction of electromagnetic signals, activation of opioids, and changes in the brain, such as release of neurotransmitters (Ma, 2004; Nestler & Dovey, 2001).

**Symptom-specific acupuncture.** Symptom- or site-specific needling occurs at classical acupuncture points specific for a dysfunction or disease. These points have usually been derived from traditional Chinese ideas about illness. Most clinical trials use this approach (C. Vincent & Richardson, 1986). Menopausal symptom-specific acupuncture was used in this study.

**Placebo control acupuncture.** Various types of acupuncture may be used as a placebo control. Used in this study, non-symptom-specific acupuncture (nonspecific acupuncture) consists of needling valid acupuncture points that do not address the target symptoms. Sham acupuncture is needling at sites off any acupuncture channels, also called meridians. Use of placebo needles simulates the sensation of acupuncture without skin penetration. Placebo needles may be used at valid or sham points (Nir, Huang, Schnyer, Chen, & Manber, 2007).
Significance of the Study

Adjuvant chemotherapy and/or hormonal therapy are commonly prescribed as treatment for women with breast cancer, and may precipitate suppression of ovarian function and the onset of menopausal symptoms (Pérez-Fidalgo et al., 2010). Women who are premenopausal at the time of breast cancer diagnosis may experience consequences of attention, learning, and memory deficits at the same time they may be developing careers, maintaining relationships, and raising children (Bender, Paraska, Sereika, Ryan, & Berga, 2001). These women may be at greater long-term risk of cognitive impairment due to an extended lifetime exposure to a reduced estrogen environment (Nappi et al., 1999; Shuster, Rhodes, Gostout, Grossardt, & Rocca, 2010), as well as more severe vasomotor symptoms due to an abrupt decline in estrogen (Carpenter, Johnson, Wagner, & Andrykowski, 2002; Fenlon & Rogers, 2007; Knobf, 2006).

Several well-controlled studies have shown that estrogen treatment maintains verbal memory in healthy women, although the size of the effect is modest (Sherwin, 1997). Women with spontaneous complaints of memory deficits give credence to the significance of these symptoms in everyday life, notwithstanding their magnitude as measured with neuropsychological testing. Clinical experience suggests that women are more reluctant to endure the classic menopausal symptoms that often influence daily functioning such as hot flashes, insomnia, and disturbances in memory. Memory takes on more importance in light of the increase in female life expectancy (Sherwin, 1998), and in the number of long-term breast cancer survivors who experience cognitive changes.
secondary to cancer diagnosis and treatment (Ganz, 1998; Ganz, Greendale, Petersen, Kahn, & Bower, 2003; Wefel, Witgert, & Meyers, 2008).

Alternative interventions for the management or attenuation of changes in memory in women following breast cancer treatment have not been sufficiently tested. At a consensus development conference, the National Institutes of Health encouraged further studies of the clinical value of acupuncture for various health conditions (NIH Consensus Development Panel on Acupuncture, 1998). The results of this study may provide breast cancer survivors with a nonhormonal treatment option for menopausal symptom management.
Chapter 2
Review of the Literature

Introduction

The purpose of this study is to examine the efficacy of acupuncture in improving memory in breast cancer survivors who are experiencing menopausal symptoms. This chapter reviews the literature pertinent to the menopausal symptom of memory changes as it affects women in the menopausal transition, women who are breast cancer survivors, and women whose menopause has been induced by breast cancer treatment, as well as how the symptoms of hot flashes and memory changes interact during the menopausal transition. Literature on acupuncture used as a therapy for menopausal symptoms in healthy women and breast cancer survivors is reviewed. Lastly, the theoretical framework that underpins this study is presented.

Menopausal Memory Changes

Change in memory is one of a constellation of symptoms experienced by menopausal women. Little research has been done about the natural history of development of cognitive changes as perceived by women as they approach menopause. In an effort to describe these types of changes, Mitchell and Woods (2001) interviewed 230 women enrolled in the Seattle Midlife Women’s Health Study. Participants had a mean age of 46.7 years and were identified as being in early, middle, or late menopausal transition stages. Sixty-two percent reported memory changes, which were categorized as problems recalling words and numbers, forgetting everyday behaviors, need for memory
aids, forgetting events, and concentration problems. These changes were most frequently attributed to role burden and stress, getting older (though not associated with an actual age or menopausal status), and health problems. The women did not directly link memory changes to hormones or menstrual cycle changes. Woods, Mitchell and Adams (2000) studied participants in the Seattle Midlife Women’s Health Study (n = 205) who completed the Memory Functioning Questionnaire. Perceived memory functioning was more closely related to perceived health status, depressed mood, and perceived stress than to perimenopausal classification or age.

In the Study of Women’s Health Across the Nation (SWAN), a cross-sectional survey of menopausal and other symptoms was completed in a multiracial, multiethnic sample of 12,425 women aged 40-55 years (Gold et al., 2000). Crude prevalence odds ratios were calculated for associations between symptoms and selected characteristics, including age, education, race/ethnicity, menstrual status, and physical activity. Most women were pre- or early perimenopausal, with the prevalence of symptoms varying more by menstrual status than by age. All symptoms were more frequent in women who were not premenopausal, with more than 40% of early peri-, late peri-, and postmenopausal women reporting forgetfulness compared with 31.2% of premenopausal women. The prevalence of forgetfulness was higher in women who were not employed full time, had less than a high school education, and those reporting less physical activity.

In midlife women, many studies measuring cognitive performance using neurocognitive testing include assessment of episodic verbal memory (also referred to as verbal memory) because of evidence that estrogen may play a particular role in maintaining or enhancing verbal memory in surgically menopausal women (Phillips &
Sherwin, 1992; Sherwin, 1988; Sherwin & Tulandi, 1996), as well as its relevance to dementia risk (Maki et al., 2010). Episodic verbal memory involves exposure to new information during an event (or episode), followed by conscious recollection of the information at a later time. Effort is required on the part of the rememberer for encoding and retrieval of the information. The interval between exposure and recall can be minutes, days, or years (Henderson, 2009). Episodic verbal memory is mediated by the hippocampus and prefrontal cortex (O'Reilly & Rudy, 2001; Wheeler, Stuss, & Tulving, 1997), regions of the brain rich in estrogen receptors and potentially susceptible to decreases in estrogen (Morrison, Brinton, Schmidt, & Gore, 2006). Structural changes in the hippocampus concomitant with increased verbal memory performance have been seen during the menstrual cycle when estrogen levels are high (Protopopescu et al., 2008), and postmenopausal estrogen administration has been associated with greater hippocampal size (Eberling et al., 2003). The types and patterns of cognitive improvement seen in clinical studies using estrogen therapy suggest that estrogen’s effect may be specific to the frontally mediated cognitive processes involved in verbal recall and learning (Keenan, Ezzat, Ginsburg, & Moore, 2001).

Several studies have examined cognitive performance as women transition to menopause. Some of these include women who have experienced natural menopause as well as those with surgically-induced menopause, and/or women taking menopausal hormone therapy.

In a cross-sectional analysis of 326 women (\(\bar{x} \text{ age} = 56.7\)) in the Melbourne Women’s Midlife Health Project, menopausal status was categorized as early or late menopausal transition, and early or late postmenopause (Henderson, Guthrie, Dudley,
Burger, & Dennerstein, 2003). Forty-six percent of women were in the early postmenopause group. Current users of menopausal hormone therapy (MHT) comprised 23% of the women in the study. An episodic verbal memory task using a word list with immediate and delayed recall was administered. Memory did not vary significantly with menopausal status, and was not associated with current or prior use of MHT, or with MHT duration. In the 139 postmenopausal women in the study who were never-users of MHT, memory scores were unrelated to years since the final menstrual period.

A group of 108 healthy, naturally postmenopausal women enrolled in the longitudinal, population-based Betula study on memory, health and aging in Sweden were examined based on their use of MHT (Yonker et al., 2006). There were 43 MHT users (x̄ age = 58), and 65 non-MHT users (x̄ age = 59.9). Five different hormone preparations were being used: estriol alone, two estriol preparations each with a different progestin, and two estradiol preparations each with a different progestin. Women completed cognitive tasks including episodic verbal memory, verbal fluency, semantic memory, and spatial visualization. There was a significant effect of MHT on episodic verbal memory ($F = 10.15, p < .002$) and verbal fluency tasks ($F = 3.82, p < .05$), with MHT users performing better than non-users. The correlation between serum estradiol levels and episodic verbal memory was also significant ($r = 0.22, p < .02$). The effect of MHT on other memory tasks did not reach significance, nor did estradiol levels correlate with other types of cognitive performance.

A cross-sectional study of 1657 women (x̄ age = 49.7) in the SWAN study was conducted to examine cognitive function in the menopause transition (Luetters et al., 2007). Menopausal status categories were pre-, early peri-, late peri-, and
postmenopausal. Women completed measures of verbal episodic memory, working memory, and processing speed, and a symptom checklist and interview. After adjustment for variables including age, education, and menopausal symptoms, no relationship was found between cognitive test performance and menopausal stage. Serum hormone levels were not related to cognitive performance in any menopausal stage.

Herlitz and colleagues (2007) looked at cognitive performance across the menopause transition in a group of 242 women in the Swedish Betula study. Premenopausal (n = 129, \(\bar{x}\) age = 46.6), perimenopausal (n = 58, \(\bar{x}\) age = 51.6), and postmenopausal (n = 55, \(\bar{x}\) age = 53.8) women were tested on cognitive measures of episodic verbal and semantic memory, verbal fluency, spatial visualization, and face recognition. MHT users were excluded, and 15 women in the postmenopausal group had experienced surgical menopause. There were no differences among the groups on any areas of cognitive performance, nor was there a relationship between serum estradiol levels and cognitive performance.

A large British cohort of women (n = 1261) followed regularly since their birth in 1946 underwent cognitive testing using three different measures at age 53 (Kok et al., 2006). Most of those in natural menopausal transition were postmenopausal (n = 405) or perimenopausal (n = 206), with 73 still premenopausal. The remaining women had undergone hysterectomy and/or oophorectomy (n = 264) or were taking MHT (n = 313). Perimenopausal women had higher scores than postmenopausal women on all measures. No detrimental effect of surgery or MHT was seen. There was no effect of menopause status found on verbal memory, which was assessed using a word list with immediate and delayed recall.
Weber and Mapstone (2009) studied 24 perimenopausal women (\(\bar{x}\) age = 49.7) to determine a relationship between subjective reports of memory problems and performance on objective cognitive tests. Participants completed a cognitive test battery, and self-report questionnaires on depression, memory, quality of life, and overall health. Seventy-nine percent reported some degree of memory loss, with 46% reporting this as moderately severe. Overall, normal memory function was seen on objective testing. Women with more memory complaints did not differ in vasomotor symptoms or hormone levels from those with fewer complaints. However, reported memory complaints were associated with poorer performance on tests of immediate verbal memory (encoding) \((r = 0.48, p = .02)\) and working memory \((r = -0.44, p = .03)\), and greater depressive symptoms \((r = -0.71, p = .00)\), but not with delayed verbal recall (retention), suggesting disruption of attentionally mediated memory processes. The investigators (Weber et al., 2012) replicated this study with a larger sample of perimenopausal women \((n = 75, \bar{x}\) age = 49.3). Of these women, 67% reported some memory loss, with 41% reporting at least moderately severe memory loss. Subjective memory complaints were associated with greater depressive symptoms and worse performance on measures of working memory and complex attention/vigilance, but not on tests of verbal memory. Memory complaints and test performance were not related to hormone levels.

In a rural, community-based study, 495 premenopausal Taiwanese women were followed for 18 months, with neuropsychological testing at baseline and study end (Fuh, Wang, Lee, Lu, & Juang, 2006). Of these women, 114 who progressed to perimenopause (\(\bar{x}\) age = 47.1) were compared with the remaining 381 premenopausal women (\(\bar{x}\) age = 44.7). At follow-up, performance on all tests improved in both groups. Multiple linear
regression was used to compare mean change in cognitive function between groups. Menopausal transition was significantly associated with less improvement on a verbal fluency task \( (p < .001) \), but no significant differences were found on any other measures, including a verbal memory test of word-list learning with immediate and delayed recall, visual recognition, visuomotor tracking, and working memory.

A cohort of 803 women, aged 42 to 52 years, in the Chicago site of the SWAN study who were pre- or early perimenopausal at baseline, and not current users of hormone preparations, completed brief measures of working memory and perceptual speed annually over a two year period (Meyer et al., 2003). Verbal memory measures were not included. Menopausal status endpoint categories were pre-, early peri-, late peri-, and postmenopausal. During the time of observation, 59% had changed menopausal stage, including 15% who became postmenopausal, with 16% changing menopausal status more than once. Linear mixed effects models were used to examine changes over time, and whether rate of change differed by menopausal status. A small but significant improvement in working memory \( (p < .0001) \) and perceptual speed \( (p = .002) \) was seen with aging, but there was no significant incremental change as women progressed from one menopausal stage to another. In pre- and early perimenopausal women, working memory \( (p = .02; p = .0001, \text{ respectively}) \) and perceptual speed \( (p = .03; p = .046, \text{ respectively}) \) improved slightly but significantly over time, with late perimenopausal women also improving in perceptual speed \( (p = .01) \). Postmenopausal women showed significant decrease over time only in perceptual speed \( (p = .02) \). The researchers concluded that transition through natural menopause is not associated with a significant decline in either working memory or perceptual speed.
Greendale et al. (2009) studied 2362 women from the SWAN study over four years (\(\bar{x} \) age = 50 at final testing) looking at longitudinal performance on annual tests of episodic verbal memory, working memory, and processing speed. Menopausal status categories were pre-, early peri-, late peri-, postmenopausal not taking MHT, and postmenopausal currently taking MHT (initiated after final menstrual period). Pre-, early peri-, and postmenopausal women scored higher with repeated testing of processing speed, but scores of late perimenopausal women did not improve over time. Verbal memory scores on delayed recall improved with repetition for pre- and postmenopausal women, but scores of early and late perimenopausal women did not improve. Former hormone users (prior to final menstrual period) had better processing speed and verbal memory, in contrast to current postmenopausal hormone users whose processing speed and verbal memory performance were worse over time compared to premenopausal performance. The performance of postmenopausal women not taking MHT was similar to that of premenopausal women. There were no menopausal transition effects on working memory. The disturbance in cognitive performance during perimenopause was subtle, and viewed as lack of improvement over time rather than overt decline. Return to premenopausal levels of performance in the postmenopause period suggests that cognitive difficulties during the menopause transition are transient. This is the first large, longitudinal study where objective verbal memory test findings are consistent with women’s perceived memory problems during the menopausal transition. In contrast to the results from the Chicago cohort of the SWAN study reported above (Meyer et al., 2003), this study showed effects of the menopausal transition and hormone use on objective cognitive testing (Greendale et al.). These newer results may differ because of the larger
sample size, longer follow-up period and use of additional testing measures, as well as documentation of previous and current hormone use.

Three longitudinal studies measuring women’s memory performance during the menopausal transition were examined (Fuh et al., 2006; Greendale et al., 2009; Meyer et al., 2003), with others being cross-sectional. Findings in cross-sectional studies do not differentiate between the possibility of a lower cognitive baseline rather than cognitive decline. Studies measured different aspects of memory, or may have assessed similar memory functions with different tests. With the exception of one prospective study (Greendale et al., 2009), objective findings from neurocognitive testing do not provide strong evidence for midlife cognitive changes during the menopausal transition with respect to episodic verbal memory. Repeated neuropsychological testing required in prospective studies results in significant practice effects on these tests, particularly in midlife women, decreasing the likelihood of observing change in cognition and requiring large sample sizes to have adequate power (Maki, 2004; Maki et al., 2010). Three cross-sectional studies found associations between memory complaints and tests of attention (Schaafsma, Homewood, & Taylor, 2010; Weber & Mapstone, 2009; Weber et al., 2012) which suggests that aspects of cognition aside from episodic verbal memory may play a role in reduced performance in midlife women.

**Menopausal Symptoms in Breast Cancer Survivors**

Ganz and colleagues (1996) surveyed breast cancer survivors (𝑥 age = 58) at 2 years (𝑛 = 69) and 3 years (𝑛 = 70) after initial surgery who had been assessed at four time points during the first year following treatment. Overall, outcomes on general
measures of health and well being suggested that these women were functioning at a high level compared to patients with other chronic diseases. In spite of these findings, women identified a number of physical and psychosocial problems that persisted or worsened over time. Although not rated as severe in intensity, approximately 50% of each group self reported difficulty remembering, and one-third of the 2-year group and one quarter of the 3-year group self reported that they had difficulty concentrating and thinking clearly.

In a longitudinal study of quality of life (QOL) in long-term, disease-free breast cancer survivors, 763 women (\( \bar{x} \) age = 55.6) were surveyed between 5 and 10 years (\( \bar{x} \) years = 6.3) after diagnosis (Ganz et al., 2002). Considerable stability in health-related QOL was observed since the time of a previous survey (mean time since diagnosis at initial evaluation = 3.4 years) with modest declines in physical functioning that reflected expected age-related changes. A significant increase from baseline was seen in self-reported forgetfulness (\( p = .001 \)), difficulty concentrating (\( p = .047 \)), and being easily distracted (\( p = .014 \)), with a significant decline reported in the frequency of hot flashes (HF) (\( p = .001 \)) and night sweats (\( p = .001 \)). Women without past systemic adjuvant therapy (chemotherapy, tamoxifen, or both) had a better global QOL than those who had received systemic adjuvant therapy (\( p = .005 \)).

Using the Breast Cancer Prevention Trial Symptom Checklist, Crandall and associates (2004) surveyed 476 women (\( \bar{x} \) age = 50) enrolled in a cohort study of breast cancer survivors diagnosed before age 50. An average of six years had elapsed since diagnosis. Menopausal status was classified as premenopausal (13%), perimenopausal (16%), and postmenopausal (71%). Forgetfulness and difficulty concentrating did not differ in prevalence or severity with menopausal status. After adjusting for a number of
core variables in logistic and linear regression models including age, years since diagnosis, type of breast cancer treatment and whether a menopause transition was experienced in relation to breast cancer treatment, peri- and postmenopausal women were no more likely to report these memory symptoms than were premenopausal women, nor were the memory symptoms more severe. Having experienced a menopausal transition after breast cancer therapy did not significantly increase the prevalence or severity of memory outcomes in peri- and postmenopausal women. A statistically significant difference was shown in the prevalence \( (p < .0001) \) and severity \( (p < .0001) \) of HF across menopausal status categories, with an increasing trend with advancing stages of the transition. Perimenopausal \( (\text{OR} \ 4.40, \ 95\% \ CI \ 1.83-10.56) \) and postmenopausal women \( (\text{OR} \ 9.09, \ 95\% \ CI \ 3.73-22.14) \) were significantly more likely to report HF compared with premenopausal women, with the HF also being more severe \( (p = .02; \ p = .0001, \ \text{respectively}) \). Peri- and postmenopausal women with a treatment-related menopausal transition had a greater severity of current HF than those in the same menopausal status groups without a treatment-related transition \( (p = .03) \). Controlling for the additional variable of current tamoxifen therapy, in addition to the core variables, did not change the relationship between menopause status and severity of HF.

Carpenter and Andrykowski (1999) conducted telephone interviews of 114 postmenopausal breast cancer survivors (\( \bar{x} \) age = 58.8) about their menopausal symptoms and QOL. These women had a mean time from last menstrual period of 12 years, and 34.9 months from completion of treatment. Forty-nine percent of the women were pre- or perimenopausal at diagnosis. Overall, the most commonly reported menopausal symptoms (joint pain, feeling tired, trouble sleeping, HF/night sweats) were also the most
severe. The total number and severity of symptoms were significantly related to years postmenopause \( (r = -0.30, \ p = .001) \), with more symptoms and higher severity reported by women with fewer years since last menstrual period. The total number and severity of symptoms were not related to time since diagnosis. Memory changes were not addressed in this study.

In a cross-sectional study of 132 women, Carpenter and colleagues (2002) compared the experience of HF in 69 breast cancer survivors \( (\bar{x} \text{ age} = 57.2) \) to 63 age-matched healthy volunteers \( (\bar{x} \text{ age} = 55.7) \). Breast cancer survivors were at least three months post completion of surgery, radiation, or chemotherapy, and a mean of 39 months post diagnosis. Significantly more survivors reported daily HF (65%) compared to healthy women (16%). HF severity \( (p = .001) \) and bother \( (p = .001) \) were significantly higher among breast cancer survivors in comparison to healthy women. Survivors also reported more frequent and severe HF with greater duration compared to healthy women. The quality of the HF, determined by descriptive phrases from the HF questionnaire (e.g., perspiring, anxious, embarrassed), was similar between groups. Differences in HF were also analyzed using a subset of women who were naturally menopausal, with 22 breast cancer survivors versus 35 healthy women. For naturally postmenopausal breast cancer survivors, HF were significantly more severe \( (p = .027) \), bothersome \( (p = .031) \), and of greater duration \( (p = .003) \) in comparison to naturally postmenopausal healthy women. Survivors reporting HF had a significantly greater interference with daily activities and overall QOL \( (p < .01) \), and those with daily HF reported moderate to severe interference with concentration. The mean number of treatments used to alleviate HF by breast cancer survivors was not significantly different from healthy women. Use of two types of HF
treatments differed significantly between groups; MHT was used by fewer breast cancer survivors, and more survivors had tried nonhormonal prescription medications. Despite similarities in types and numbers of treatments used, breast cancer survivors reported their current HF treatments to be significantly less effective ($p < .05$) than did healthy women.

A pooled analysis combining baseline symptom data from three independent studies of women with breast cancer was done to describe symptom prevalence attributable to breast cancer, and clusters of symptoms across three phases of the disease (Bender, Ergun, Rosenzweig, Cohen, & Sereika, 2005). The three studies included (a) women with early-stage breast cancer post surgery but prior to adjuvant therapy, (b) women with early-stage disease following adjuvant therapy, and (c) women with metastatic disease receiving palliative treatment. A panel of oncology nursing experts determined 13 measured items that were common to all three studies for analysis. Each identified cluster was comprised of symptoms of fatigue, perceived cognitive impairment, and mood problems, with descriptors of each symptom included for the specific study group. This unique symptom cluster may exist across these three phases of the breast cancer disease sequence.

Young mid-life women with breast cancer ($n = 27, \bar{x} \text{ age} = 40.8$) who experienced chemically-induced premature menopause participated in a qualitative study exploring their responses to menopausal symptoms (Knobf, 2001). Mean time since diagnosis was 4.5 years. Changes in menstrual cycle function, HF, and cognition were among those felt to be associated with chemotherapy-induced menopause. Cognitive complaints were commonly described as difficulty concentrating and forgetfulness. Distress associated
with these complaints varied according to their effect on daily functioning at home or at work. HF were common and persistent symptoms, lasting for years following therapy, and became a more dominant concern after chemotherapy was completed. The severity of HF was not quantified, but distress varied considerably from mild to very bothersome. In another analysis of this group of women, Knobf (2002) reported those who experienced more severe physical symptom distress actively searched for symptom relief measures.

Many of these studies assessed menopausal symptoms at a single point in time, and demonstrate that breast cancer survivors who are several years post diagnosis experience a variety of symptoms, including HF and memory changes. Survivors described HF as severe compared to healthy women. HF varied in prevalence and severity with menopausal status and the occurrence of a menopausal transition related to treatment.

**Menopausal Symptoms and Memory**

It has been suggested that HF may be linked to other menopausal symptoms in a cascade of events where HF disturb sleep, leading to irritability, fatigue and memory disturbances (Kronenberg, 1990). Studies examining the relationship between menopausal symptoms and cognition have not found a significant association between subjective reports of HF and verbal memory measures. However, a recent study found that objectively measured HF, compared to self-reported HF, were a significant predictor of poorer verbal memory performance (Maki et al., 2008). Interestingly, several studies of women with HF have found that self-reported HF counts greatly underestimate the
number of objectively recorded HF (Carpenter, Monahan, & Azzouz, 2004; Freedman & Wasson, 2007; Maki et al., 2008; Sievert et al., 2002).

A multicenter pilot study enrolled 180 healthy, naturally postmenopausal women with subjective cognitive complaints aged 45 to 55 years, whose last menses had been completed ≥ 12 and ≤ 36 months prior to study screening (Maki, Gast, Vieweg, Burriss, & Yaffi, 2007). The women were randomly assigned to receive either placebo or conjugated equine estrogen with medroxyprogesterone acetate (MHT group) for four months. Memory (specifically verbal memory and learning) and self-perception of memory function were measured at baseline and at month four. Vasomotor symptoms (hot flashes) were self reported. Analysis of covariance was used to assess changes from baseline. MHT use was associated with improvement in both frequency and severity of hot flashes compared with baseline and placebo. Total scores on the verbal learning test were decreased in both MHT and placebo groups, with no difference between groups. Short- and long-delay free recall subscores decreased in the MHT group which approached significance ($p = .054; p = .066$, respectively). This finding of near-significant, modest negative effects of combined estrogen and progestin therapy, specifically the commonly prescribed hormone preparation used in this study (Maki & Sundermann, 2009), contrasts with findings of earlier studies using estrogen alone (Phillips & Sherwin, 1992; Shaywitz et al., 2003; Sherwin, 1988). Scores on the Memory Functioning Questionnaire showed significant improvement from baseline in self-reported seriousness of forgetting in the MHT group ($p = .028$), but no difference was seen between groups in any measure of the questionnaire at month four. Post hoc analyses were conducted according to presence or absence of HF at baseline. No
differences that had not been seen previously in tests of attention, memory or cognition were detected. In this study, MHT was not associated with improved cognitive function vs. placebo.

In a two-part study, LeBlanc and associates (2007) examined the effects of menopausal symptoms and symptom relief with estrogen therapy (ET) on cognition in early menopause. In the cross-sectional component, 37 women (\(\bar{x}\) age = 53) completed symptom questionnaires, HF diaries and sleep journals for one week prior to cognitive testing. They were then divided into high symptom (n = 17) and low symptom (n = 20) groups. Cognitive measures included assessment of verbal memory using immediate and delayed paragraph recall. In this part of the study, menopausal symptom status was not related to cognition, with women in both groups performing similarly on all measures of cognitive performance. Thirty-two of the women then completed the treatment study with either ET or placebo for eight weeks, with repeat cognitive testing at four and eight weeks. According to self reports, the ET group had significant symptom relief \((p = .03)\), significantly fewer HF \((p = .02)\), and significant improvement in sleep quality \((p = .05)\) than those taking placebo. Women taking ET did not perform better on any of the cognitive measures than those on placebo. Symptom status did not interact with effects of ET on cognition. Because of short test-retest periods of cognitive function (three times in an 8-week period), practice effects may lessen the possibility of measuring a significant hormone effect in this small sample.

Fifty peri- and recently postmenopausal women were randomly assigned to ET (n = 26, \(\bar{x}\) age = 50.8) or placebo (n = 24, \(\bar{x}\) age = 51.3) groups in a study examining estrogen’s influence on specific cognitive processes, and whether its effect is moderated
by HF and sleep (Joffe et al., 2006). A neurocognitive test battery, including measures of verbal memory, was administered at baseline and at the end of 12 weeks of treatment, along with subjective measures of HF and sleep. Prior to treatment, HF were reported by 57.7% and 66.7% of women randomized to ET and placebo respectively. At study end, HF improved in both groups, with a significant improvement in HF from baseline in estrogen-treated women compared with the placebo group ($p = .01$). Comparison of groups using linear regression showed that while there were few differences between groups in performance on cognitive tasks, women in the ET group had significantly fewer perseverative errors during verbal recall ($p = .03$), and a trend toward less interference during verbal recall ($p = .07$). These are measures of executive function rather than verbal memory itself; executive functions are processes mediated by the prefrontal cortex that assist in encoding and retrieval in memory tasks (Maki & Sundermann, 2009). Sleep quality improved in both groups, with no group differences seen. Sleep quality at baseline and at study end did not correlate with change in verbal recall errors or cognitive performance in the women as a whole, or between ET and placebo groups. In this study, improvement in measures of cognitive function (specifically that of attention) in the ET group correlated with improvement in HF but not with sleep quality.

Maki and colleagues (2008) investigated the relationship between objectively measured HF and the primary cognitive outcome measure of verbal episodic memory in a sample of 29 women ($\bar{x}$ age = 53.1) with moderate to severe HF. An ambulatory sternal skin conductance monitor was used to measure HF. Tests of immediate and delayed paragraph recall measured verbal memory. There was an underreporting of objective HF by 43% in a 24-hour period; daytime HF were underreported by 40%, and nighttime HF
by 60%. The total number of objective HF over a 24-hour period showed a significant negative correlation with delayed paragraph recall (\( r = -0.40, p < .05 \)) and showed a negative trend for immediate paragraph recall (i.e., the greater the number of objective HF measured in a 24-hour period, the poorer the performance on the paragraph recall test). The number of objective HF while awake did not correlate with immediate or delayed paragraph recall. Total number of objective HF during sleep had a significant negative relationship with both immediate paragraph recall (\( r = -0.43, p < .05 \)) and delayed paragraph recall (\( r = -0.48, p < .01 \)), even when controlling for sleep duration. Shorter sleep duration had a significant negative relationship with immediate paragraph recall (\( r = -0.41, p < .05 \)). Sleep duration and nighttime HF contributed independently to impaired verbal memory; this suggested to the researchers that the influence of HF on other menopausal symptoms may not be related to sleep disruption. Subjective HF did not correlate significantly with verbal memory performance, which is consistent with previous studies (Joffe et al., 2006; LeBlanc et al., 2007; Maki et al., 2007).

In these studies, the inconsistency seen in the relationship of menopausal HF to memory changes may be attributed to a number of methodological issues that should be considered when interpreting the findings. The studies differed in their design and methodology, including sample size, age of subjects, cross-sectional vs. longitudinal design, use of different hormone preparations and neurocognitive tests, and subjective vs. objective reporting of memory and vasomotor symptoms. In addition, practice effects occurring with repeated neuropsychological testing may have obscured treatment effects.
Memory in Breast Cancer Survivors

Chemically induced menopause is the permanent, premature suppression of ovarian function in response to chemotherapeutic agents. The incidence of menopause varies with different types and doses of chemotherapy, with risk increasing with age (Anders, Johnson, Litton, Phillips, & Bleyer, 2009). The risk of menopause with multi-agent adjuvant chemotherapy for breast cancer can range from 21-71% in younger premenopausal women, to 49-100% in women older than 40 years (Bines, Oleske, & Cobleigh, 1996; Fornier, Modi, Panageas, Norton, & Hudis, 2005; Pérez-Fidalgo et al., 2010; Petrek et al., 2006). For women with breast cancer, adjuvant hormone (or endocrine) therapy refers to treatment with a selective estrogen receptor modulator, usually tamoxifen, or an aromatase inhibitor, such as anastrozole.

In a cross-sectional study, van Dam and colleagues (1998) investigated the effect of high-dose vs. standard-dose chemotherapy on cognitive functioning in breast cancer survivors who had previously undergone surgery. The sample consisted of 34 women treated with high-dose chemotherapy plus tamoxifen (Group 1, $\bar{x}$ age = 45.5), 36 women treated with standard-dose chemotherapy plus tamoxifen (Group 2, $\bar{x}$ age = 48.1), and 34 women as controls with stage I breast cancer who had received no adjuvant therapy (Group 3, $\bar{x}$ age = 46.1). The women in the chemotherapy groups had stage II and III breast cancer, and had finished chemotherapy an average of 2 years earlier. Thirteen of these women had already completed tamoxifen therapy. All women in Group 1 were postmenopausal due to chemotherapy. Two women in Group 2 and 21 women in Group 3 were premenopausal, with the remainder of women in those groups postmenopausal. Women were interviewed about their cognitive problems in daily life, and a
neuropsychological test battery was administered. The two chemotherapy groups expressed significantly more problems with concentration ($p = .006$), memory ($p = .006$), and thinking ($p = .022$) than those in Group 3, with no significant difference between Groups 1 and 2. The scores on neuropsychologic tests were not significantly different between Groups 1 and 2. Group 1 scored significantly lower than Group 3 on seven of the 21 test indices ($p < .05$). Subjects were classified as cognitively impaired when scoring two standard deviations (SD) below the mean of the controls on three or more neuropsychologic tests (32% high dose; 17% standard dose; 9% no chemotherapy). Risk of cognitive impairment was calculated using a logistic regression model, and was high for Group 1 compared with Group 3 ($p = .006$), with a trend toward significance when compared with Group 2 ($p = .056$). The risk of cognitive impairment for Group 2 was elevated in comparison with Group 3, but was not significant. Test results of the pre- and postmenopausal women in Group 3 did not differ. The researchers concluded that high-dose chemotherapy seems to impair cognitive function more than standard dose chemotherapy.

Thirty-nine women with breast cancer who had completed CMF chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) at least six months earlier, and a control group with breast cancer not treated with chemotherapy (n = 34) were examined for cognitive deficits related to treatment (Schagen et al., 1999). The groups were matched for age and time since treatment. Twenty of the women in the first group had their chemotherapy followed with tamoxifen. Subjects were given a neuropsychologic test battery and interviewed for perceived cognitive functioning, similar to an earlier study (van Dam et al., 1998). Three women in the chemotherapy group were
postmenopausal prior to diagnosis, and all other women in that group experienced a menopausal transition related to treatment. In the control group, 13 were postmenopausal and 21 were premenopausal. Results were compared for the pre- and postmenopausal controls with no differences observed. There were no differences between women treated with chemotherapy with tamoxifen and those treated with chemotherapy alone on any outcome measure, so these women were analyzed together as one group. Women in the chemotherapy group identified problems with concentration (31 % vs. 6%, $p = .007$) and memory (21% vs. 3%, $p = .022$) at significantly higher rates than the control group. The chemotherapy group had significant differences on 12 of 21 neuropsychologic test indices ($p < .05$), with worse performance than the control group on visual memory, verbal and motor function, delayed recall (verbal memory), reaction time (speed of information processing), and some measures of mental flexibility and attention. Cognitive impairment was determined using the same method as an earlier study (van Dam et al., 1998). Classification of cognitive impairment was 28% in the chemotherapy group and 12% in the control group. The risk of cognitive impairment was highly increased for women treated with chemotherapy compared with the control group ($p = .013$).

Schagen and colleagues (2002) reevaluated the cognitive status of all patients remaining disease free who had participated in two previous neuropsychological studies (Schagen et al., 1999; van Dam et al., 1998). In the initial cross-sectional studies ($T_1$), testing was conducted two years post-therapy on average. In this study ($T_2$), approximately four years following therapy, the same assessment measures were used. At $T_2$, there were 22 of 34 original participants in the high-dose chemotherapy group, 23 of 36 in the standard-dose group, 31 of 39 in the CMF group, and 27 of 34 in the non-
systemically treated control group. Improvement in performance was seen in all chemotherapy groups, with a slight, though not significant, deterioration on testing in the control group. No differences in test outcomes were found in the chemotherapy groups between women who had completed, were still taking, or who had never used tamoxifen. None of the previously observed differences in cognitive functioning between chemotherapy and control groups was demonstrated at T₂. Interpretation of these findings is limited by differential attrition among the groups due to factors related to disease progression, particularly of women who were classified as cognitively impaired at T₁.

Wieneke and Dienst (1995) administered a battery of neuropsychological tests to 28 women (\(\bar{x}\) age = 42) with stage I or II breast cancer who had completed standard-dose chemotherapy an average of 6.6 ± 4 months earlier (range 0.5-12 months). Eleven women were taking tamoxifen at the time of testing. Menopausal status was not noted. Scores were compared with published test norms of healthy matched controls. Multivariate analyses of variance showed significant decreases in the areas of visual and verbal memory, mental flexibility and processing speed, attention and concentration, visuospatial ability, and motor function. Seventy-five percent of women scored in the range of moderate impairment, which was defined as scoring more than 2 SD below the mean score on at least one neuropsychological measure. Treatment duration, but not type of treatment, time since treatment or tamoxifen therapy, was significantly related to impairment (\(r = 0.39, p < .01\)).

Donovan and colleagues (2005) recruited women diagnosed with stage 0 – II breast cancer who had received chemotherapy and radiotherapy (n = 60, \(\bar{x}\) age = 52.3) or who had received radiotherapy but not chemotherapy (n = 83, \(\bar{x}\) age = 57.6). The
radiotherapy only group was significantly older, had more postmenopausal women, and more women were taking hormone therapy. Menopausal status was assessed only prior to treatment. A neuropsychological test battery and self-report measure of cognitive problems were administered 6 months following completion of treatment. There were no significant group differences on neuropsychologic test scores, prevalence of cognitive impairment (which was low), or scores of cognitive complaints, though both groups reported that they frequently experienced cognitive problems.

Breast cancer survivors (n = 53) with stage 0 – II breast cancer who were 2 to 5 years from diagnosis and a group of healthy controls without cancer (n = 19, x̄ age = 49.2) were enrolled in a study to evaluate the impact of chemotherapy on cognitive function (Castellon et al., 2004). The survivors were divided into treatment groups of chemotherapy (n = 36, x̄ age = 46.8), and no chemotherapy (n = 17, x̄ age = 48.3). Half of the women in the chemotherapy group also received tamoxifen. Menopausal status was not noted. A neurocognitive test battery and self-report questionnaire of cognitive function were administered. Multivariate analysis of variance of cognitive test scores showed that women exposed to chemotherapy scored significantly lower than cancer survivors with no chemotherapy in visuospatial (p = .005), visual memory (p = .01), and verbal learning (p = .03) domains. In an exploratory analysis, women who received both chemotherapy and tamoxifen showed a greater risk of cognitive compromise, having the lowest group means on five of eight cognitive domains. Breast cancer survivors without chemotherapy performed similarly to the healthy controls. The authors noted that overall cognitive compromise in the chemotherapy group was fairly mild in nature.
A prospective, longitudinal study incorporating neuropsychologic testing prior to treatment was designed to evaluate cognitive sequelae in women with breast cancer treated with chemotherapy (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Women diagnosed with stage I – III breast cancer (n = 18, x̄ age = 45.4) were evaluated with a cognitive test battery following surgery, and before the start of chemotherapy (T₁, baseline); approximately six months after baseline, and at least 3 weeks after cessation of drug treatment (T₂); and one year post-chemotherapy, about 18 months after baseline (T₃). Menopausal status was noted only at baseline: premenopausal (n = 9), perimenopausal (n = 1), postmenopausal (n = 8). At baseline, 33% of the women were classified as having cognitive impairment. At T₂, 61% of the group exhibited decline from baseline in one or more cognitive domains, most commonly those related to attention, learning, and processing speed. At T₃, 45% who had experienced decline from T₁ to T₂ showed improvement, 45% remained stable, and 10% had improved on some measures and remained stable on others. The patient cohort as a whole did not show a statistically significant decline in cognitive function from baseline to T₂, or from T₂ to T₃, though a subset of women did demonstrate a decline following chemotherapy. Declines seen were subtle, and performance results often fell within the average range when compared with results of similar healthy control individuals.

Ahles and colleagues (2008) examined neuropsychological functioning of women following surgery for breast cancer prior to starting chemotherapy, radiation, or hormonal therapy. Women (Group 1) with stage I – III breast cancer (n = 110, x̄ age = 54.1), women (Group 2) diagnosed with stage 0 breast cancer (n = 22, x̄ age = 55.8), and healthy controls (n = 45, x̄ age = 52.9) completed a neuropsychological test battery. All
groups’ scores on neuropsychological tests were within the normal range. Using chi-square tests to examine group differences, the researchers found Group 1 was significantly more likely ($p = .002$) to be classified as having lower than expected rate of overall cognitive performance (22%) as compared to Group 2 (0%) and healthy controls (4%). The areas contributing to this classification were verbal fluency, mental flexibility, and visual, verbal and working memory.

In a prospective study, Bender and associates (2006) examined three groups of pre- and perimenopausal women with breast cancer for cognitive changes related to therapy over time. Two groups consisted of women with stage I or II breast cancer: Group 1 ($n = 19, \bar{x} \text{ age } = 40.1$) received chemotherapy alone, and Group 2 ($n = 15, \bar{x} \text{ age } = 44.1$) received chemotherapy and tamoxifen. Group 3 ($n = 12, \bar{x} \text{ age } = 44.5$) consisted of women with breast cancer who received no chemotherapy or tamoxifen.

Measurements included a neuropsychological test battery and self-report of cognitive function. These were administered after surgery and before treatment, if applicable ($T_1$); one week following completion of chemotherapy, and at a comparable time for Group 3 ($T_2$); and at Time 3 ($T_3$), one year following $T_2$. No significant differences were seen between groups on any memory measure at baseline ($T_1$). Women receiving chemotherapy and tamoxifen showed poorer performance on measures of visual and verbal working memory, while women receiving chemotherapy alone exhibited poorer performance in verbal working memory. Most of these changes were seen at $T_3$, when women in Group 2 were still receiving tamoxifen. Scores for women with no treatment showed improvement from $T_2$ to $T_3$, which may be indicative of practice effects. The
researchers suggest that cognitive problems experienced by breast cancer survivors treated with adjuvant therapy are subtle and domain specific.

A cross-sectional study was conducted to compare cognitive abilities of tamoxifen users with healthy controls (Palmer, Trotter, Joy, & Carlson, 2008). The tamoxifen group consisted of women treated for breast cancer with surgery and/or radiation without chemotherapy (n = 23, \( \bar{x} \) age = 45.8) who had been taking tamoxifen for an average of 2.3 years. The healthy control group (n = 23, \( \bar{x} \) age = 45.3) had no cancer history. All women were premenopausal. On a neuropsychological test battery, scores were compared using t tests, with the tamoxifen group having significantly worse scores than the control group on visual memory, word fluency, processing speed, visuospatial ability, and immediate verbal memory tasks. Taking into consideration the study design and small sample size, the authors suggest that tamoxifen use in premenopausal women with breast cancer may be associated with cognitive difficulties.

A number of studies examining cognition in women treated for breast cancer have included women taking hormone therapy, with several studies combining users of tamoxifen and aromatase inhibitors in the same group (Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009a; Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004; Stewart et al., 2008). Women receiving hormone therapy in these studies had never been treated with chemotherapy.

In a cross-sectional study (Jenkins et al., 2004), postmenopausal women with breast cancer taking hormone therapy for an average of 36 months (n = 94, \( \bar{x} \) age = 63.1) were compared to a control group of healthy postmenopausal women (n = 35, \( \bar{x} \) age = 60.9) on a battery of neuropsychological measures. Univariate analysis of variance
showed a significant group difference on the tasks of processing speed ($F = 3.966, p = .049$) and immediate verbal memory ($F = 4.578, p = .034$), with the hormone therapy group demonstrating poorer performance.

Stewart et al. (2008) compared performance on cognitive tests in postmenopausal women with breast cancer who were scheduled to receive chemotherapy ($n = 61$) or hormone therapy ($n = 51$) at baseline ($T_1$) prior to any treatment, and at completion of chemotherapy ($T_2$) with a comparable assessment time for the hormone group. Cognitive change was calculated using a standardized regression-based score involving prediction of retest scores using the baseline scores for each neuropsychological test. A subject showed cognitive decline if scoring 2 or more SD below the predicted score on two or more tests. At $T_2$, the chemotherapy group showed a significantly higher rate of cognitive decline ($\chi^2 = 6.02, p = .014$) than the hormone group (31% and 12%, respectively), with a significant decrease in the working memory domain ($t = -2.0, p = .05$). However, mean scores of both groups were within the normal range of published scores at both time points.

A longitudinal study (Collins et al., 2009a) compared hormone therapy users ($n = 40$) to a chemotherapy group ($n = 53$) at baseline prior to therapy ($T_1$); one month after completion of chemotherapy, approximately 6 months from baseline ($T_2$); and one year after the second assessment ($T_3$). All women were postmenopausal at baseline. In the chemotherapy group, 17% and 72% were taking hormone therapy at $T_2$ and $T_3$ respectively. Calculation of cognitive decline was conducted in the same manner as in an earlier study (Stewart et al., 2008). At $T_2$, the chemotherapy group showed a significantly higher rate of cognitive decline ($\chi^2 = 5.64, p = .02$) than the hormone group (34% and
12% respectively), with working and visual memory most affected. At T3, the chemotherapy and hormone groups did not differ in rate of cognitive decline, but the chemotherapy group scored significantly better in the area of executive function ($t = 2.94$, $p = .004$). The women in the chemotherapy group taking hormonal therapy at T3 had significantly lower scores on processing speed ($t = 2.89$, $p = .01$) and verbal memory ($t = 2.71$, $p = .01$) than women in the chemotherapy group not taking hormonal therapy. The results of this study are in keeping with other longitudinal studies which indicate that cognitive changes emerge during or shortly after chemotherapy and suggest that they may resolve over time (Schagen et al., 2002; Wefel et al., 2004).

Other studies have evaluated the cognitive effects of hormonal therapy in women with breast cancer, comparing tamoxifen to aromatase inhibitors (Bender et al., 2007; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009b; Schilder et al., 2009). In a cross-sectional study, Bender and colleagues (2007) examined cognitive function in postmenopausal women with early stage breast cancer receiving tamoxifen ($n = 16$, $\bar{x}$ age $= 48.2$) and those receiving the aromatase inhibitor anastrozole ($n = 15$, $\bar{x}$ age $= 57.4$). Women in the anastrozole group were significantly older, and women taking tamoxifen had been receiving that therapy for a significantly longer period of time. There was no difference between groups in the number of women who had been treated with chemotherapy prior to hormone therapy. Women receiving anastrozole had significantly worse performance on visual and verbal learning and memory measures than women receiving tamoxifen. After controlling for the covariates of age, therapy duration, years of education, fatigue, anxiety, and depression, impairments in visual and verbal learning and memory domains remained significant for women receiving anastrozole.
Schilder et al. (2009) compared two groups of women with breast cancer taking hormone therapy two years following completion of chemotherapy with a group of healthy postmenopausal controls (Group 3; n = 48). Group 1 (n = 30) was taking tamoxifen, and Group 2 (n = 50) received exemestane, an aromatase inhibitor. Using multivariate analysis of variance, the researchers found no significant difference between Groups 1 and 2 on overall cognitive functioning. Worse overall cognitive functioning was seen between Groups 1 and 2 combined and Group 3 ($F = 2.8, p = .001$). Both hormone therapy groups performed significantly worse than Group 3 on verbal fluency and processing speed measures. Groups 1 and 2 combined reported significantly more hot flashes and night sweats ($p = .001$) than Group 3.

Two groups of postmenopausal women with breast cancer who had never received chemotherapy were treated with tamoxifen (n = 31) or anastrozole (n = 14) (Collins et al., 2009b). A group of healthy postmenopausal women (n = 28) served as controls. Neuropsychological testing was done at baseline ($T_1$) close to initiation of hormone therapy, and repeated 5-6 months later ($T_2$). Measurement of cognitive decline was performed as in earlier studies by the authors (Collins et al., 2009a; Stewart et al., 2008). Cognitive decline from $T_1$ to $T_2$ was seen in all groups (tamoxifen 39%, anastrozole 64%, and controls 7%). The decline in the tamoxifen ($\chi^2 = 8.10, p = .00$) and anastrozole ($\chi^2 = 15.77, p = .00$) groups was significantly different compared to the healthy controls, but did not differ between treatment groups. With covariates of age and education, analysis of covariance showed processing speed ($p = .02$), verbal memory ($p = .03$), and overall cognitive summary scores ($p = .02$) were significantly different between the anastrozole and healthy groups, with the anastrozole group scoring lower. Processing
speed was also significantly lower in the tamoxifen group \( (p = .02) \) compared with healthy controls. The researchers concluded that cognitive changes were subtle in this study, as mean raw scores on cognitive measures in the hormonal groups fell within the range of published norms at both \( T_1 \) and \( T_2 \).

A group of studies on cognitive functioning in breast cancer survivors who received adjuvant therapy demonstrate that a subset of these women show deficits on neurocognitive testing. However, many studies looking at cognition in breast cancer survivors differ in their findings, and have considerable variability in subjects studied (e.g., age, type and dose of chemotherapeutic regimens, use and type of hormonal treatment, time since treatment), as well as in study design and methodology which limit comparability of results. Most studies are cross-sectional, and use different time points of assessment, small sample sizes, varying or no control groups, and different measures of cognitive function. Criteria used to classify cognitive decline or impairment vary. The cognitive domains affected by adjuvant therapy exposure are not consistent across studies, but deficits are frequently seen in memory, learning, attention, processing speed and executive function. Most studies do not address the possible interaction of adjuvant therapy and menopausal status, or change in menopausal status, during treatment on memory. Cognitive impairment may predate adjuvant therapy in some women, and not all studies include pre-treatment evaluation of cognitive function. Cognitive effects of chemotherapy and hormonal therapy may be subtle and difficult to detect. Several studies found that women’s self-reported cognitive complaints are not reflected on objective testing (Bender et al., 2006; Castellon et al., 2004; Donovan et al., 2005). This phenomenon, also seen in studies of healthy midlife women, may be attributed to the lack
of sensitivity of neuropsychological measures used, cross-sectional study design, or lack of consideration of other contributing factors that may influence cognition, such as menopausal status.

**Acupuncture**

Acupuncture is a widely used therapeutic modality which has been proposed as a treatment for menopausal symptoms. Several randomized controlled trials have examined the effectiveness of acupuncture (AP) as a treatment option for menopausal symptoms, in both naturally menopausal women and breast cancer survivors.

**Acupuncture and menopausal symptoms.** Vincent and colleagues (2007) recruited 103 peri- and postmenopausal women aged 45-59 with ≥ five HF per day who were randomized to medical or sham AP groups. Sham AP was defined as needling in nonacupuncture, nonmeridian areas. Ten AP treatments were administered twice weekly for five weeks. Mean daily HF scores (frequency x severity) were calculated for each participant from HF diaries. HF scores decreased from baseline in both groups at end of treatment and at follow-up in seven weeks. There was no significant difference between the two groups. Results did not show that the medical AP was more effective than the sham AP therapy used in this study.

Nir et al. (2007) studied 29 postmenopausal women (x̄ age = 55) with ≥ 7 moderate to severe HF per day who were randomly assigned to active or placebo AP groups. Following treatment principles of traditional Chinese medicine (TCM), active AP was tailored to individual clinical presentations according to a standardized algorithm. Placebo AP was at nonvalid points off AP channels with no needle penetration. Nine AP
treatments were administered: twice weekly for two weeks, then once a week for five weeks with a one month follow-up period. HF scores were derived from daily logs. Improvement in quality of life was measured by the Menopause-Specific Quality of Life Questionnaire (MENQOL). Group differences in percent of change in severity and frequency of HF were assessed using Mann-Whitney tests. Repeated measures analysis of variance was used to calculate HF changes within groups. Both groups had significantly decreased HF frequency from baseline ($p \leq .001$), with no difference between groups. There was a significant decrease in HF severity in the active AP group ($p = .003$), but not for the placebo group, with a significant difference in HF severity between groups ($p = .042$). HF severity and frequency remained lower in the active AP group than the placebo group at the end of the follow-up period. No significant group differences were seen in the four subscales of the MENQOL at any time point. Repeated measures analysis of variance within groups showed a significant improvement in the vasomotor subscale for both groups ($p \leq .001$), but no significant improvement in the other subscales (one of which contains a memory measure). These results show that standardized, individualized AP was associated with a significantly greater decrease in severity, but not frequency, of HF compared to placebo AP treatment of the same duration.

In a secondary analysis of the same group of 29 postmenopausal women and the same treatment protocol used by Nir and colleagues (2007), Huang et al. (2006) assessed the effectiveness of AP on nocturnal HF with similar results. Both groups demonstrated a significant decrease in HF frequency (for both groups, $p = .001$), with no difference seen between groups. A significant reduction from baseline in severity of nocturnal HF was
seen with active AP ($p = .002$), with a significant difference between groups ($p = .017$) in decreased severity of nocturnal HF with active AP.

Wyon and associates (1995) randomized 24 postmenopausal women with vasomotor symptoms aged 47-62 to AP or control groups. The AP group received a combination of electro-acupuncture and classical AP. The control group received superficial needle insertion at the same points. Ten AP treatments were administered: twice weekly for two weeks, then once a week for six weeks with a follow-up period of three months. HF scores were based on daily HF logs. Symptoms were assessed using the modified Kupperman Index. The symptoms on the Index not specified, but most likely did not include a measure of memory. The Wilcoxon signed rank test was used for pairwise comparisons within each group. HF frequency decreased significantly in both groups from baseline through the treatment period (AP, $p = .013$; control, $p = .0033$) and at three months after treatment (AP, $p = .0033$; control, $p = .0069$), with a trend toward greater and longer lasting improvement seen in the AP group. A significant decrease on the Kupperman Index was seen in both groups ($p < .05$), attributed mainly to scores for vasomotor symptoms. No significant differences were seen between groups on any measure at any time. Results did not show that active AP was more effective than the control AP (superficial needling) used in this study.

Borud et al. (2009) recruited 267 postmenopausal women ($\bar{x}$ age = 54) with $\geq 7$ HF per 24 hours on 7 consecutive days with randomization to treatment or control groups. The treatment group received advice on self care for menopausal symptoms in the form of a one-page leaflet, as well as TCM acupuncture with point selection and individualized treatment determined by the acupuncturist. Ten AP treatments were
administered over 12 weeks. The control group received the self care advice leaflet. HF scores were based on daily HF diaries. Health-related quality of life was measured by the Women’s Health Questionnaire (WHQ). Differences between groups were determined with two-sample t tests. HF frequency (\( p < .001 \)) and intensity (\( p < .001 \)) decreased significantly from baseline to 12 weeks in the AP group compared with the control group. In this study, AP plus self care advice was more effective in reducing HF than self care advice alone. Scores on the WHQ memory/concentration domain showed no statistically significant difference in mean change from baseline to week 12 between the AP and control groups. Significant difference was seen with improvement in the AP group in the following WHQ domains: vasomotor (\( p < .001 \)), sleep (\( p = .002 \)), and somatic symptoms (\( p = .01 \)). Follow-up results at 6 and 12 months (Borud, Alraek, White, & Grimsgaard, 2010) showed that statistically significant differences between groups found at 12 weeks were no longer evident.

Cohen and colleagues (2003) recruited 18 peri- and postmenopausal women (\( \bar{x} \) age = 47.3) with self-identified menopausal HF who were randomized to experimental AP or control AP groups. Experimental AP consisted of needling specific points related to menopausal symptoms. The control group received AP treatment described as a general tonic to benefit the flow of qi or vital energy. Six AP treatments were administered: once weekly for three weeks, then once every other week for 3 weeks, followed by a three week nontreatment period. HF data were gathered with daily symptom diaries. Mean monthly HF severity decreased significantly in the experimental AP group from baseline to month two (\( p = .05 \)), baseline to month three (\( p = .005 \)), and baseline to month four (\( p = .019 \)). No change was seen in the control group from baseline
through the treatment phase. Between group comparisons were not done because of the small sample size. Results suggest that menopause symptom-specific AP was effective in reducing severity of HF during the treatment and follow-up periods.

Wyon et al. (2004) randomized 45 postmenopausal women with vasomotor symptoms aged 48-63 to one of three groups. The AP group received electro-acupuncture (EA). The control AP group received superficial needle insertion at different points from EA group. Fourteen AP treatments were administered: twice weekly for two weeks, then once a week for ten weeks. The estrogen group received 2 mg of oral estradiol daily for 12 weeks. All groups had a follow-up period of six months. HF scores were based on daily HF logs. The modified Kupperman Index was used to assess symptom severity, with no mention of a memory item on this version. HF frequency and severity decreased significantly in all groups from baseline by 4 weeks ($F(2,40) = 69.6, p < .001$) and remained unchanged through the follow-up period, though the effect of estrogen was greater than that of EA. No significant difference was found between the acupuncture groups over time. Findings were similar in the Kupperman Index scores, but the more pronounced effect in the estrogen group was not seen at 24 weeks. Though estrogen was more effective than AP, all three treatments were effective in decreasing HF frequency and severity in this study.

Avis and associates (2008) recruited 56 peri- and postmenopausal women aged 44-55 with $\geq$ four moderate to severe HF per day who were randomized to one of three groups. The AP group ($n = 19$) received TCM acupuncture using standardized treatment plus additional needling based on individual diagnostic categories determined by the acupuncturist. The sham AP group ($n = 18$) received superficial needling in
nontherapeutic sites believed to have a minimal effect on HF. Sixteen AP treatments were administered twice weekly for eight weeks. The usual care group (n = 19) had a scheduled clinic visit at four weeks and was instructed not to initiate any new HF treatments. HF scores were calculated from daily HF diaries. A significant decrease was seen in mean frequency of HF between treatment weeks one and eight across all groups ($p = .01$). No significant differences in frequency were found between groups. When combined, the two AP groups had a significantly greater decrease compared with the usual care group ($p < .05$), but did not differ from each other. There was a significant decrease ($p = .02$) over time in the HF index (a calculation involving frequency and severity of HF) in both of the AP groups compared with the usual care group, with no difference between the AP groups. Additional instruments were used to assess secondary study outcomes of hot flash interference, sleep, mood, symptom bother, and health-related quality of life. These included the MENQOL and the Hot Flash Related Daily Interference Scale, both of which contain a measure of memory. No significant results were found for these outcomes other than the two AP groups reporting significantly less vasomotor symptom bother ($p < .02$) than the usual care group. Results of this study show that both standardized AP and sham AP were more effective than usual care in reducing HF.

Zaborowska et al. (2007) recruited 102 postmenopausal women who requested therapy for HF to two parallel studies. For Study I, 60 women were randomly assigned to one of four groups, receiving either electro-acupuncture (EA), AP with superficial needle insertion at different points from the EA group, applied relaxation, or oral estrogen therapy (2 mg estradiol daily) for 12 weeks of treatment. Fourteen AP or EA treatments
were administered: twice weekly for two weeks, then once a week for ten weeks. The applied relaxation group met weekly for 12 weeks. For Study II, 42 women were randomized to receive either a transdermal estrogen patch, or a placebo patch containing no hormone. HF scores were based on daily HF logs for all women. A modified version of the Kupperman Index assessed menopausal symptoms; it is not clear if a measure of cognitive change was included. Statistics were calculated for all six groups. As the EA and superficial AP groups did not differ from each other, they were analyzed together as one AP group. The oral and transdermal estrogen groups also did not differ, and were analyzed as one estrogen group. Changes in HF numbers were calculated using analysis of variance and post-hoc Mann-Whitney tests. Daily HF frequency decreased from baseline in all groups except placebo patch after 4 and 12 weeks. At 4 and 12 weeks, HF were decreased significantly in the estrogen group ($p < .01$) compared with relaxation and placebo patch, but not significantly more than AP. At 4 and 12 weeks, a significant decrease in HF ($p < .05$; $p < .01$, respectively) was seen in the AP group compared with placebo patch, and at 12 weeks ($p < .05$) in the relaxation group compared with placebo patch. The Kupperman Index score did not change in the placebo group from baseline to 12 weeks. A decrease in scores differed significantly in all treatment groups from the placebo group ($p < .01$), with no significant difference seen between the treatment groups. Results indicate that AP and applied relaxation both reduced HF significantly better than placebo. The researchers recommended further evaluation of AP and applied relaxation as alternatives to MHT for menopausal vasomotor symptom relief.

Painovich and colleagues (2012) randomized 33 peri- and postmenopausal women older that age 40 with at least 7 HF per day to traditional AP ($n = 12$), sham AP
(n = 12), or waiting control (n = 9) groups. Sham AP consisted of AP without skin penetration on non-active points. Three AP treatments per week were administered for 12 weeks. Frequency and severity of HF were recorded using a diary, and the MENQOL was completed at study entry and exit to examine symptom impact on quality of life. At the end of treatment, both AP groups showed reduction in HF frequency (≥ 86%) and severity (≥ 78%) compared with the waiting control group, but were not statistically different from each other. Comparison of means from the MENQOL using the Wilcoxon rank sum test demonstrated significant improvement for both AP groups compared with waiting control in the vasomotor domain (p = .01) and in the overall MENQOL score (p = .03). In this study both traditional AP and sham AP were more effective than waiting control in reducing HF.

**Acupuncture in breast cancer survivors.** Nedstrand and colleagues (2005) evaluated the effectiveness of AP and applied relaxation on HF in women treated for breast cancer. Thirty-eight women treated for breast cancer (x̄ age = 53) with moderate to severe HF and either treatment-induced or spontaneous menopause were randomized to groups receiving electro-acupuncture (EA) or applied relaxation. Fourteen EA treatments were administered: twice weekly for two weeks, then once a week for ten weeks. The applied relaxation group met weekly for 12 weeks, with a six month follow-up period for both groups. HF frequency was derived from daily HF logs, and a modified Kupperman Index provided menopausal symptom severity ratings. Memory was not assessed on this version of the Kupperman Index. In the applied relaxation group, HF frequency and symptom severity were significantly reduced from baseline starting at four weeks (p < .001; p < .001, respectively) through the six month follow-up period (p < .0001; p < .001,
respectively). HF frequency and severity of symptoms were also significantly reduced in the EA group from baseline starting at four weeks ($p < .001; p < .001$, respectively) through the six month follow-up period ($p < .0001; p < .001$, respectively). Between group comparisons were not examined due to insufficient power.

Deng et al. (2007) recruited 72 women with breast cancer aged 48-59 with $\geq 3$ HF per day who were randomly assigned to true AP or sham AP groups. The true AP group received needling using a 19-point prescription. Sham AP was without skin penetration at points a few centimeters away from those used in the true AP group. Eight treatments were administered twice a week for four weeks with follow-up at six weeks and six months. Participants in the sham AP group were crossed over to eight sessions of true AP starting at week 7. HF scores were based on diaries. Mean daily HF frequency decreased from baseline in both groups at six weeks. HF reduction was greater in the true AP group, but difference between groups was not significant. A further decrease in HF frequency was seen in the sham AP group after cross-over to true AP at week 7. Reduction in HF frequency was maintained at six month follow-up in both groups but was not significantly different between groups.

Frisk and associates (2008) studied 45 women treated for breast cancer who desired treatment for severe vasomotor symptoms, and randomized them to an electroacupuncture group (EA) or a menopausal hormone therapy (MHT) group ($\bar{x}$ ages = 56.5 and 53.4 respectively). Fourteen EA treatments were administered: twice weekly for two weeks, then once a week for ten weeks. The MHT group received a sequential or continuous estrogen and progestin combination, or estrogen alone. The follow-up period was 24 months. HF scores were derived from daily HF logs, with distress recorded on a
range from 0 = no distress, to 10 = worst possible distress. A modified Kupperman Index assessed menopausal symptoms, but did not include a memory measure. In both the EA (n = 27) and MHT (n = 18) groups, frequency and degree of distress of HF were significantly reduced at all measuring points over 24 months. In the EA group, HF frequency and distress decreased significantly from start of treatment to 12 weeks (for both frequency and distress, \( p < .001 \)), start of treatment to 12 months (\( p = .003; p = .026 \), respectively), and start of treatment to 24 months (\( p = .003; p = .018 \), respectively). A significant difference was seen between groups favoring decrease in frequency and distress of HF in the MHT group at 12 months after start of treatment. Repeated measures ANOVA analysis of the Kupperman Index symptom scores showed a significant treatment effect over time for both groups, with a greater effect in the MHT group at 12 and 24 months (\( p = .002; p = .039 \), respectively). Further analysis of data from this study (Frisk, Källström, Wall, Fredrikson, & Hammar, 2012) examined health-related quality of life using the Women’s Health Questionnaire (WHQ), which includes a memory/concentration domain. The total WHQ score showed a significant decrease at all time points in both groups, indicating improvement in symptoms, but no significant difference in change was evident between groups. At least half of the EA group had a clinically significant change of total WHQ after 12 weeks (the total length of EA treatment) and at 12 months (58% and 50% of the group, respectively). In the MHT group, 39% at 12 weeks, and 59% at 12 months experienced a clinically significant change (MHT therapy was continuous). Anxiety, vasomotor symptom and sleep domain scores on the WHQ, but not memory/concentration scores, improved significantly in the EA group during the 24 month follow-up. In the MHT group, only vasomotor symptom
scores improved. [In 2003, subsequent to this Swedish substudy, the larger, international, multicenter HABITS trial (Hormonal replacement therapy after breast cancer – is it safe?) was halted. Women allocated to receive MHT experienced a high rate of breast cancer recurrence compared with women in non-hormonal treatment groups. All women on MHT were recommended to stop treatment (Frisk et al., 2008; Frisk et al., 2012; Holmberg & Anderson, 2004; Holmberg et al., 2008).]

A prospective, single-arm observational study was conducted to examine the effect of traditional AP on vasomotor symptoms in women treated for early stage breast cancer (n = 50, \( \bar{x} \) age = 54.3) and taking tamoxifen for at least 6 months (de Valois, Young, Robinson, McCourt, & Maher, 2010). In addition to HF diaries, women completed a measure of vasomotor symptom bother, and the Women’s Health Questionnaire (WHQ) which measures health-related quality of life. Traditional AP was administered once weekly for eight weeks. Based on log transformed HF frequency data, a mean HF reduction of 49.8% was seen at end of treatment (\( p < .0001 \)). A significant improvement was also seen in the vasomotor symptom bother score (\( p < .0001 \)), which was considered clinically significant. Paired samples t test results from the WHQ showed a significant change in all domains except attractiveness, including improvement in the memory/concentration domain (\( p = .0001 \)). In addition, clinically meaningful improvements were seen in 7 of the 9 WHQ domains, the exceptions being depressed mood and attractiveness.

Kern and Cohen (2005) constructed a negative binomial, piecewise linear regression model to determine treatment effectiveness of AP in a group of women treated for breast cancer with menopausal symptoms. Women were assigned to one of three
groups for a baseline monitoring week and 12 subsequent treatment weeks: an AP
treatment group, a non-symptom-specific placebo AP group, and an education group. The
AP groups received weekly treatments and the education group had weekly sessions on
healthy living. Only the AP treatment group (n = 16) and the education group (n = 6)
were considered in this analysis of self-reported daytime HF frequency data over 13
weeks; the placebo group was omitted as it did not further inform the model. When the
model was applied to the data, average daily HF frequency for the AP group dropped by
three over 13 weeks, with no noticeable increase or decrease seen in the education group.

Acupuncture studies for menopausal hot flashes vary in sample size and treatment
length, as well as in the types of acupuncture and acupuncture controls used. Most studies
having an acupuncture control arm found no significant difference in effect between
active and control acupuncture groups, with the exception of two studies that analyzed
results of the same trial (Huang et al., 2006; Nir et al., 2007) where a significant decrease
in HF frequency was seen in both AP groups, with significantly decreased HF severity in
the active AP group only. Given that the mechanism of acupuncture is not precisely
understood, this suggests that control procedures meant to be inert may have physiologic
effects (Lund & Lundeberg, 2006). In all studies examined here, acupuncture resulted in
decreased frequency of hot flashes, often reaching statistical significance. Menopausal
hormone therapy is more effective than AP in reducing vasomotor symptoms, but is not a
viable option for many women, especially those with breast cancer. These studies suggest
that acupuncture is a safe alternative that may help women with menopausal symptoms,
and that it merits further investigation.
No AP studies were found that investigated menopause-related memory difficulties as the primary outcome. Memory is frequently examined as a secondary outcome using quality of life scales. Several studies measured memory as a specific memory domain on the WHQ (Borud et al., 2009; de Valois et al., 2010; Frisk et al., 2012), or part of a psychological domain on the MENQOL (Avis et al., 2008; Nir et al., 2007; Painovich et al., 2012). In only one AP and HF study was a significant improvement seen in a specific memory measure (WHQ) in response to AP treatment (de Valois et al., 2010).

**Conceptual Framework**

The Framework for Interactions Between the Individual and the Environment (Elliott & Eis dorfer, 1982) was developed in an effort to view stress research and other work systematically and within a broader context of how the environment can affect the individual. This model, used for the parent study, was chosen to guide this study. It is consistent with the purpose of the study in providing a structure for examining the effect of acupuncture on menopausal symptom of memory changes induced by natural menopause or breast cancer treatment. It has been used as the framework for a study exploring environmental uncertainty and nurse burnout (Garrett & McDaniel, 2001).

Activators are internal or external environmental conditions that change a person’s present state. Reactions are biological or psychosocial responses to an activator. Consequences are sequelae of reactions, and may be biological, psychological, or sociological, and desirable or undesirable. Activators, reactions and consequences can occur at all levels of structural complexity, ranging from molecular to social. Mediators
are modifiers that act on the sequence of activators, reactions and consequences. They help to explain why some individuals experience a different number or severity of consequences in response to the same activators or reactions (Elliott & Eisdorfer, 1982).

In this study, decreased ovarian activity during the menopausal transition or secondary to cancer treatment becomes an *Activator*. The body responds to the *Activator* which has the effect of decreasing serum estrogen levels leading to *Reactions* - the menopausal symptoms of hot flashes and memory changes, among others. These symptoms in turn may influence the ensuing *Consequences* of interference with daily activities, symptom distress and decreased quality of life. Acupuncture is the *Mediator* acting directly on the *Reactions* (a reduction in symptoms), and acting directly (solid line) or indirectly (broken line) on *Consequences* (improvement in symptom distress) (see Figure 2.1).
Figure 2.1. Framework for Interactions Between the Individual and the Environment in women treated for breast cancer receiving acupuncture for menopausal symptoms. Adapted from *Stress and human health: Analysis and implications of research* (p. 19), by G.R. Elliott and C. Eisdorfer (Eds.), 1982, New York: Springer Publishing Company. Adapted with permission.
Chapter 3

Methods

Introduction

This chapter presents the methods used to answer the research questions of the study. The parent study is presented first, followed by the current study. The discussion addresses the design, subject recruitment, instruments, intervention, procedures for data collection, protection of human subjects, and planned data analysis.

Study Design

Study aims were accomplished through secondary analysis of an existing data set compiled for the randomized trial of Menopausal Symptom Relief for Women with Breast Cancer (R01CA80625). Permission for the use of the database was obtained from the principal investigator, Susan M. Cohen, DSN.

Overview of the Parent Study

Research design. The original study design was a placebo-controlled, randomized clinical trial to explore the effect of acupuncture (AP) on menopausal symptoms in breast cancer survivors. The study was single blind, with the researcher and participants blinded on acupuncture group assignment (C. Vincent & Lewith, 1995). A three-group design (site-specific AP, non-symptom specific AP, and enhanced usual care) was used to explore the specific aims. Acupuncture treatment took the form of either menopausal symptom-specific acupuncture (experimental group) or non-symptom
specific needling at classical acupuncture point locations identified in the literature as not relevant to the symptoms associated with menopause (AP control group). The enhanced usual care group received education and materials on menopause symptom management and healthy life activities provided by an educational interventionist.

**Power analysis.** A power analysis was performed for a three-group repeated measures design. HF severity was used as the variable, and HF severity ratings from Kronenberg (1990) were used in the calculation. A moderate effect size of .40 was used based on findings of two studies on acupuncture treatment for menopausal symptoms (Cohen et al., 2003; Wyon et al., 1995). For a power of .80 and $\alpha = 0.05$, the number of subjects needed in each group would be 9, or 27 total subjects. The sample size of the parent study was expanded to 81 to compensate for a smaller effect size of other menopausal symptoms, and to compensate for study attrition due to time commitment or change in health status.

**Variables.**

**Dependent variables.** The dependent variables were:

1. Menopausal symptoms with hot flashes as the primary marker, mood changes, sleep disturbances, and loss of concentration as measured by the Daily Symptom Diary and modified Kupperman Index.

2. Quality of life as measured by the Menopause-Specific Quality of Life Questionnaire.

**Independent variable.** The independent variable was:

1. Acupuncture, site-specific for menopause.

**Setting.** The study was conducted through the Duquesne University and University of Pittsburgh Schools of Nursing. Data were collected at an academic medical
center in southwestern Pennsylvania. Interviews, educational sessions and acupuncture treatments for all study participants took place at the medical center. This facility has four acupuncture rooms available as well as private interview rooms.

**Sample.** A convenience sample was recruited from the general population of women who experienced menopausal symptoms following diagnosis and completion of treatment for breast cancer. A total of 254 women were screened, and 74 were randomized to one of the three groups. Five women dropped out at randomization prior to any intervention; 69 women were consented and completed baseline measurements.

Subjects were selected based on their self-identification of menopausal symptoms that included hot flashes. Inclusion criteria included native English speaking, self-identification of the menopausal symptom of hot flashes following treatment for breast cancer (stage I or II) with subsequent verification of hot flashes on the one week baseline Daily Symptom Diary, willingness to undergo acupuncture treatments for two months, and willingness to record menopausal symptom frequency and severity on a daily basis. Vitamins or other non-hormonal nutritional supplementation such as soy could be taken.

Exclusion criteria included concurrent treatment of menopausal symptoms with hormonal supplementation, herbal remedies or acupuncture (including acupressure), non-hormonal pharmacologic agents prescribed for hot flash relief, or any drugs or conditions known to affect cognitive function. Previous treatment of menopausal symptoms with hormones, herbs or acupuncture must have ceased at least three months prior to enrollment in the study to allow for a sufficient wash out period. Women with lymphedema following surgery for breast cancer were excluded due to the possibility of infection secondary to acupuncture treatments. Women who were presently in
chemotherapy treatment for breast cancer were excluded due to the potential confounding effect of needle acupuncture on chemotherapy side effects (NIH Consensus Development Panel on Acupuncture, 1998). Women with diagnosed clinical depression were excluded due to the effect of depression on cognitive function and quality of life.

Participants were recruited by flyers in oncology offices and clinics. Advertisements were placed in local newspapers and on public transportation.

**Subject enrollment.** Recruitment materials included a phone number for prospective participants to call for information. Initial screening of subjects took place via telephone to verify inclusion/exclusion criteria. Subjects who met inclusion criteria were given a full explanation of the study and invited to participate. A research assistant met with the potential participant, explained the study, and gave the potential participant an informed consent packet. After signing the informed consent form, study subjects were oriented to the Daily Symptom Diary, and randomized into one of the three groups using a table of random numbers.

Following enrollment, all subjects were interviewed in order to obtain demographic information including information on breast cancer history and current treatment. Quality of life measurement was obtained using the Menopause-Specific Quality of Life Questionnaire. The Kupperman Index was used to screen for menopausal symptoms, and the Center for Epidemiologic Studies Depression Scale was administered to screen for depression at the enrollment session.

**Measures.**

**Demographic data form.** A demographic data form (Appendix A) was used to gather basic information including menstrual history, breast cancer diagnosis, stage and
treatments, as well as information on diet (including caffeine), exercise, medication (including vitamins and nutritional supplements), and other self healing practices.

**Center for Epidemiologic Studies Depression Scale.** A screening test for depression was administered using the Center for Epidemiologic Studies Depression Scale (CES-D). Screening was done upon entry into the study. The CES-D is a 20 item scale to determine clinical depression of recent origin (Radloff, 1977). It has high levels of reliability and validity to detect both clinical and non-clinical symptoms of depression (Andresen, Malmgren, Carter, & Patrick, 1994). Concurrent validity was established by correlations with the Hamilton ($r = 0.49 - 0.85$) and Raskin ($r = 0.28 - 0.79$) Depression Scales and the self report Symptom Checklist ($r = 0.72 - 0.87$) (Roberts & Vernon, 1983). Women with clinical depression level scores ($\geq 16$) were excluded from the study and were referred to their primary provider for assessment.

**Daily Symptom Diary.** A Daily Symptom Diary (Appendix B) was used to gather data on the frequency of five menopausal symptoms (hot flashes, night sweats, mood changes, sleep disturbances, and loss of concentration), as well as severity of hot flashes and night sweats on a scale ranging from 0 (not present) to 3 (severe). The study design included a one week baseline recording of menopausal symptoms, and eight weeks of daily symptom recording during the treatment phase. Recording in the Daily Symptom Diary is the usual format for collecting data in menstrual cycle research studies such as menopausal symptom investigations (Sloan et al., 2001). Daily recordings are an intensive method for collecting symptom data. However, women in previous studies conducted by Cohen and associates (2003) have not perceived the daily recordings to be a burden.
**Kupperman Index.** A second measure for the menopausal symptom experience was the modified Kupperman Index (Appendix C) which was administered by the research assistant two additional times over the course of the study. It is a self-report measure *for that day* of the severity of 10 menopausal symptoms, each rated on a scale of 0 (not present) to 3 (severe). Kupperman developed the Index to quantitatively record symptoms associated with the menopausal transition. The Index assigns a higher number to typical menopausal symptoms (e.g., hot flashes) by using a multiplication constant. The items designated as symptoms are similar to those in the Daily Symptom Diary. After multiplication by the constant, a summed total score indicated severity of menopausal symptoms. A score of 15 or less indicated favorable therapeutic response (Kupperman et al., 1953; Kupperman et al., 1959). The Index provides a check for any missing data as well as a comparison for the Daily Symptom Diary recordings.

Reliability and validity evidence for the Daily Symptom Diary was addressed by Bender and colleagues (2005). The relationship between the Daily Symptom Diary and the Kupperman Index was analyzed. A nonparametric correlational analysis of hot flash severity data from the Daily Symptom Diary and the Kupperman Index revealed a correlation of 0.58 (*p* = .000), as well as a statistically significant correlation of 0.61 (*p* = .000) between the Daily Symptom Diary and the Menopause-Specific Quality of Life Questionnaire.

**Menopause-Specific Quality of Life Questionnaire.** Quality of life was measured using the Menopause-Specific Quality of Life Questionnaire (MENQOL), a 29-item questionnaire (Appendix D). The MENQOL has four domains of menopausal symptoms: vasomotor, physical, psychosocial and sexual. Subjects indicated if they had experienced
the symptoms and the extent of symptom bother in the past month. The MENQOL was administered at baseline upon entry into the study, at the end of week five, and at the end of the treatment phase (see Table 3.1). In their original work, Hilditch and associates (1996) determined high face and content validity for the instrument. Test-retest reliability (intraclass correlation coefficients) was vasomotor (0.37), physical (0.81), psychosocial (0.79), and sexual (0.70). In a subsequent analysis, the vasomotor domain intraclass correlation coefficient was 0.78 (Lewis, Hilditch, & Wong, 2005). Radtke and colleagues (2011) examined the psychometric properties of the MENQOL in a sample of postmenopausal breast cancer survivors, finding comparability to earlier psychometric work done with this instrument, and concluding that the MENQOL appears to be a reliable and valid tool for use in this population. A recent evaluation of the MENQOL using factor analysis in a large sample (n = 2703) of healthy postmenopausal women (Van Dole et al., 2012) determined reliability coefficients (Cronbach’s α) for the four original domains as follows: vasomotor (0.87), physical (0.88), psychosocial (0.85), and sexual (0.77).

Table 3.1
Timeline of Measurements

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Week One)</th>
<th>End of 4th Treatment Week (Week Five)</th>
<th>End of 8th Treatment Week (Week Nine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D</td>
<td>Daily Symptom Diary</td>
<td>Daily Symptom Diary</td>
<td>Daily Symptom Diary</td>
</tr>
<tr>
<td>Kupperman Index</td>
<td>Kupperman Index</td>
<td>Kupperman Index</td>
<td>Kupperman Index</td>
</tr>
<tr>
<td>MENQOL</td>
<td>MENQOL</td>
<td>MENQOL</td>
<td>MENQOL</td>
</tr>
<tr>
<td>Demographic Data Form</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. CES-D = Center for Epidemiologic Studies Depression Scale; MENQOL = Menopause-Specific Quality of Life Questionnaire
**Intervention.**

*Experimental group – Menopausal symptom-specific acupuncture.* The experimental acupuncture treatment consisted of specific acupuncture body points related to menopausal symptoms, such as hot flashes, mood changes, sleep disturbances, and loss of concentration. There were 12 acupuncture treatments over 8 weeks. The treatments occurred twice per week for 4 weeks, and then once a week for 4 weeks. The treatments lasted between 20 and 30 minutes. Acupuncture treatments were delivered by a single acupuncturist licensed by the Commonwealth of Pennsylvania with extensive records kept of each session. Needles were manually inserted and rotated to elicit the sensation of de qi. The specific acupuncture points for the experimental group (site specific) were taken from the traditional Chinese literature for women’s complaints. Educational materials were given to subjects following each acupuncture session (see Enhanced usual care group).

*Control group – Non-symptom-specific acupuncture.* Non-symptom-specific needling uses the technique of shallow acupuncture needle insertion at classical acupuncture point locations thought to be irrelevant to the condition being treated. The control acupuncture treatment consisted of needling at valid acupuncture points identified in the literature as not associated with the symptoms of menopause. There were 12 acupuncture treatments over 8 weeks. The treatments occurred twice a week for 4 weeks and then once a week for 4 weeks. The pattern was the same as in the experimental group. The treatments lasted between 20 and 30 minutes. Acupuncture treatments were delivered by a single acupuncturist licensed by the Commonwealth of Pennsylvania with extensive records kept of each session. Needles were manually inserted. Educational
materials were given to subjects following each acupuncture session (see Enhanced usual care group).

**Enhanced usual care group.** The enhanced usual care group received educational materials related to menopausal symptom management and healthy life activities at each intervention point. There were 12 individual visits over 8 weeks. The 12 individual visits occurred twice a week for 4 weeks and then once a week for 4 weeks. At each of the 12 individual visits, the participants received information on one of the following subjects: healthy living, vitamins and minerals, exercise, relaxation, spirituality, herbal supplements, sexuality, and self healing. Materials were prepared from published sources concerning menopause symptom management. Records were kept of each session. The educational sessions were standardized and taught by trained members of the research team, all of whom had worked with menopausal women.

**Data collection and management.** The participants recorded their daily menopausal symptoms using the Daily Symptom Diary for 9 weeks (one week at baseline and every day during the eight treatment weeks). The symptom list of the diary contains five possible menopausal symptoms as well as a space for subjects to include a self-identified symptom. Subjects recorded the daily frequency and severity of the specific symptom. The Symptom Diary is used to evaluate the changes in symptom pattern as a result of the acupuncture treatment. Once a day at bedtime, subjects recorded the frequency and severity of each menopausal symptom during the baseline and treatment phases (total of 9 weeks) of the study. If a change in symptom frequency or severity was attributed to a life event, each subject was asked to note the event in the area on the Daily Symptom Diary called “Events affecting Symptoms.”
At entry into the study, and every four weeks during the treatment phase, subjects were interviewed about the severity of their symptoms using the modified Kupperman Index. The MENQOL was administered upon entry into the study to establish baseline values, at the end of four weeks of treatment, and at the end of the last treatment. All three groups received the same number of subject contacts. The contacts included an initial interview, and twelve intervention sessions.

Each of the participants in the study contributed a significant amount of data. The data instruments gathered information on menopausal symptom experience and quality of life. Upon entry into the study, each participant received a unique study number. With the exception of the consent form and address/phone information, all study instruments carry only the assigned study number.

Once data forms were completed, data were entered into a computerized data base for statistical analysis. The original data forms are kept in a locked file in the principal investigator’s research office. The electronic data are kept in a password protected section of the Center for Research and Evaluation server in the University of Pittsburgh School of Nursing. Only the principal investigator, the statistician and the data manager have access to the electronic data set.

**Current Study**

**Protection of Human Subjects.** Prior to data analysis, approval was obtained from the Duquesne University Institutional Review Board. No new or additional data were collected, and no additional subjects were enrolled for this secondary analysis. The
data were de-identified by a certified person at the University of Pittsburgh School of Nursing. Data were obtained in person from the principal investigator.

**Data analysis.** IBM® SPSS® Statistics 20 Premium GradPack and SAS® 8.2 were used to analyze the data. Frequency distributions and descriptive statistics were used to summarize the data. Frequency distributions are presented in both tabular and graphic form. Categorical variables were compared using the Cochran-Mantel-Haenszel, Fisher’s exact, and chi-square tests as appropriate. Continuous data were compared using analysis of variance (ANOVA), repeated measures ANOVA, or equivalent non-parametric tests as appropriate. A two-tailed significance level of .05 was used. Missing data were assessed for extent and pattern of missingness. Missing data were deemed to be missing completely at random. Overall, approximately 3.7% of all observations were missing, which is considered to be negligible in a study of this type (F. Mandel, personal communication, February 28, 2013). After discussion with the consulting statistician and dissertation committee chair, it was determined that no imputation should be done.

**Research questions.**

*Question 1.* What are the effects of menopausal symptom-specific acupuncture on memory in breast cancer survivors with menopausal symptoms?

*Hypothesis 1a.* Menopausal symptom-specific acupuncture will improve perceived memory changes as measured by self-reports compared to enhanced usual care (education).

*Hypothesis 1b.* Non-symptom-specific acupuncture will improve perceived memory changes as measured by self-reports compared to the enhanced usual care (education) group.
**Question 2.** Is there a relationship between improvements in hot flashes/night sweats and perceived memory changes in breast cancer survivors with menopausal symptoms?

Each subject contributed seven days of daily frequency counts of HF, NS and loss of concentration at three time points: at week 1 (baseline), week 5, and week 9. Symptom ratings from the two other instruments were examined at the same time points. The Kupperman Index measured subjects’ self-reports of symptom severity for that particular day on a scale of 0-3. On the MENQOL, symptom severity experienced over the past month, if present, was rated on a scale of 0-6.

To analyze the effect of acupuncture on memory, a repeated measures ANOVA was used to compare the three treatment groups on the data from the Daily Symptom Diary. Change from baseline was examined on the Daily Symptom Diary, Kupperman Index, and MENQOL using frequency distributions to compare changes in memory reports at baseline to week 5, baseline to week 9, and week 5 to week 9. Pairwise comparisons were performed as necessary.

Although planned, regression analysis to examine if improvement in HF/NS was a predictor of improvement in memory was not pursued. Due to non-significant findings on data from the Daily Symptom Diary, and considerable stability in the proportions of change seen in data from the Kupperman Index and MENQOL, further analyses were not conducted.
Chapter 4  
Data Analysis

Introduction

This chapter describes the results of the data analysis. A description of the sample is presented, followed by the results as they relate to the research questions of the study.

Description of the Sample

In the parent study, a convenience sample of women who were experiencing menopausal symptoms following diagnosis and treatment for breast cancer was recruited. Subjects were selected based on their self-identification of menopausal symptoms, and completion of cancer treatment. Two hundred fifty-four women were screened, and 74 were randomized to one of three groups: non-symptom-specific acupuncture (AP control), menopausal symptom-specific acupuncture (AP specific), and enhanced usual care (EUC). Five women dropped out at randomization; 69 women were consented and completed baseline measurements.

The sample of women for this study (n = 60) was derived from the parent study. All subjects in the parent study who indicated loss of concentration and/or experiencing poor memory at baseline on any one of the three instruments measuring menopausal symptoms were included in this study. Participant characteristics from the Demographic Data Form are described in Table 4.1. One-way analysis of variance (ANOVA) and chi-square tests were conducted to examine between-group differences. The three groups
were not significantly different in age, age at menopause, or in chemotherapy and adjuvant hormone therapies received as treatment for breast cancer.

Table 4.1
Sample Characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total n = 60</th>
<th>AP control n = 20</th>
<th>AP specific n = 22</th>
<th>EUC n = 18</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\bar{x}) (SD)</td>
<td>53 (5.6)</td>
<td>54.4 (5.3)</td>
<td>52.6 (5.2)</td>
<td>51.8 (6.3)</td>
<td>1.12</td>
<td>.33</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>31 (37, 68)</td>
<td>22 (46, 68)</td>
<td>17 (47, 64)</td>
<td>26 (37, 63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menopause*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\bar{x}) (SD)</td>
<td>47.2 (4.5)</td>
<td>48.7 (4.8)</td>
<td>46.3 (4.2)</td>
<td>46.8 (4.5)</td>
<td>1.55</td>
<td>.22</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>22 (34, 56)</td>
<td>22 (34, 56)</td>
<td>19 (34, 53)</td>
<td>17 (37, 54)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total n (%)</th>
<th>AP control n (%)</th>
<th>AP specific n (%)</th>
<th>EUC n (%)</th>
<th>(\chi^2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous chemotherapy</td>
<td>33 (61.1)</td>
<td>9 (50)</td>
<td>15 (78.9)</td>
<td>9 (52.9)</td>
<td>3.96</td>
<td>.14</td>
</tr>
<tr>
<td>Current tamoxifen</td>
<td>25 (43.9)</td>
<td>7 (38.9)</td>
<td>9 (42.9)</td>
<td>9 (50)</td>
<td>0.47</td>
<td>.79</td>
</tr>
<tr>
<td>Current aromatase inhibitor</td>
<td>5 (9.1)</td>
<td>2 (11.1)</td>
<td>2 (9.5)</td>
<td>1 (6.3)</td>
<td>0.25</td>
<td>.88</td>
</tr>
</tbody>
</table>

Note. AP, acupuncture; EUC, enhanced usual care.
* n = 56: four missing values (two AP control, one AP specific, one enhanced usual care).

Research Questions

**Research Question 1.** What are the effects of menopausal symptom-specific acupuncture on memory in breast cancer survivors?

**Instruments.** Three instruments were used to gather data on the menopausal symptom of memory changes. The Daily Symptom Diary will be addressed first, followed by the Kupperman Index and the Menopause-Specific Quality of Life Questionnaire (MENQOL).
Daily Symptom Diary. The data examined in this study generated by the Daily Symptom Diary are frequencies of menopausal symptoms. Memory changes are termed ‘loss of concentration’ in this instrument. At the time points of week one (baseline), week five and week nine, memory data included in this analysis were the total number of episodes of loss of concentration reported by the subjects over the 7 days of that particular week. Though loss of concentration is the main variable of interest, hot flash and night sweat data from the Daily Symptom Diary are also presented as they are important aspects of the menopausal symptom experience, and may further inform the loss of concentration data. Table 4.2 presents the symptom frequencies of the total sample from the Daily Symptom Diary at baseline.

<table>
<thead>
<tr>
<th>Symptom Category</th>
<th>Frequency</th>
<th>Median (Q1, Q3)</th>
<th>Range (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flashes n = 60</td>
<td>47.4 (25.8)</td>
<td>40 (25, 65.5)</td>
<td>116 (6, 122)</td>
</tr>
<tr>
<td>Night Sweats n = 60</td>
<td>16.3 (14.2)</td>
<td>13 (8.5, 21.5)</td>
<td>88 (0, 88)</td>
</tr>
<tr>
<td>Loss of Concentration n = 60</td>
<td>9 (14.0)</td>
<td>5 (0, 9.5)</td>
<td>72 (0, 72)</td>
</tr>
</tbody>
</table>

Note. Q1 = 25th percentile, Q3 = 75th percentile [interquartile range]. Symptom frequency is per week in all symptom categories.

One-way ANOVA testing on these baseline symptom frequencies suggests there are no significant differences between the two AP groups and the enhanced usual care group, as seen in Table 4.3.
Table 4.3
Group Differences in Symptom Frequency from Daily Symptom Diary at Baseline

<table>
<thead>
<tr>
<th></th>
<th>AP control n = 20</th>
<th>AP specific n = 22</th>
<th>EUC n = 18</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hot flashes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x (SD) range (min, max)</td>
<td>53.0 (23.1)</td>
<td>40.1 (23.1)</td>
<td>50.2 (30.7)</td>
<td>1.46</td>
<td>.24</td>
</tr>
<tr>
<td><strong>Night sweats</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x (SD) range (min, max)</td>
<td>19.5 (17.7)</td>
<td>11.6 (8.5)</td>
<td>18.4 (14.8)</td>
<td>1.95</td>
<td>.15</td>
</tr>
<tr>
<td><strong>Loss of concentration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x (SD) range (min, max)</td>
<td>14.0 (21.4)</td>
<td>8.4 (8.7)</td>
<td>4.3 (4.7)</td>
<td>2.4</td>
<td>.10</td>
</tr>
</tbody>
</table>

*Note.* AP, acupuncture; EUC, enhanced usual care. Symptom frequency is per week in all symptom categories.

**Kupperman Index.** This instrument is a self-report of the perceived *severity* of 10 menopausal symptoms, including loss of concentration and hot flashes. The severity rating for each symptom ranges from 0 to 3: not present = 0, mild = 1, moderate = 2, and severe = 3. The Kupperman Index was administered once at each of the three time points. The total sample baseline severity ratings for loss of concentration and hot flashes are described in Table 4.4.

Table 4.4
Overall Symptom Severity Rating from Kupperman Index at Baseline Regardless of Group

<table>
<thead>
<tr>
<th></th>
<th>Hot Flashes n = 60</th>
<th>Loss of Concentration n = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>x (SD)</td>
<td>2.5 (0.62)</td>
<td>1.48 (0.79)</td>
</tr>
<tr>
<td>median (Q1, Q3)</td>
<td>3 (2,3)</td>
<td>1 (1,2)</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>2 (1,3)</td>
<td>3 (0,3)</td>
</tr>
</tbody>
</table>

*Note.* Severity rating: 0 = not present; 1 = mild; 2 = moderate; 3 = severe. Q1 = 25th percentile, Q3 = 75th percentile [interquartile range].
Analysis of differences between groups at baseline with one-way ANOVA tests did not reach significance on loss of concentration ratings, $F(2, 57) = 1.21, p = .31$, or on ratings of hot flashes, $F(2, 57) = 0.85, p = .43$ (see Table 4.5).

Table 4.5
Group Differences in Symptom Severity Rating from Kupperman Index at Baseline

<table>
<thead>
<tr>
<th></th>
<th>AP control $n = 20$</th>
<th>AP specific $n = 22$</th>
<th>EUC $n = 18$</th>
<th>$F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\bar{x}$ (SD)</td>
<td>2.6 (0.6)</td>
<td>2.4 (0.7)</td>
<td>2.6 (0.6)</td>
<td>0.85</td>
<td>.43</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>2 (1, 3)</td>
<td>2 (1, 3)</td>
<td>2 (1, 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\bar{x}$ (SD)</td>
<td>1.4 (0.8)</td>
<td>1.4 (0.9)</td>
<td>1.7 (0.8)</td>
<td>1.21</td>
<td>.31</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>3 (0, 3)</td>
<td>3 (0, 3)</td>
<td>3 (0, 3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. AP, acupuncture; EUC, enhanced usual care.

Menopause-Specific Quality of Life Questionnaire. The MENQOL was administered once at each of the three time points. It is a self-report instrument where subjects rate the perceived severity of a symptom, only if they are experiencing that symptom. The 0 to 6 severity rating for each symptom ranges from “not at all bothered” to “extremely bothered.” For this study, bother is interpreted as an indication of symptom severity. The memory item in this instrument is ‘experiencing poor memory,’ with hot flashes and night sweats also rated. The baseline severity ratings for these three variables by the total sample are shown in Table 4.6.
Table 4.6
Overall Symptom Severity Rating from MENQOL at Baseline Regardless of Group

<table>
<thead>
<tr>
<th></th>
<th>Hot Flashes n = 60</th>
<th>Night Sweats n = 54a</th>
<th>Experiencing Poor Memory n = 55b</th>
</tr>
</thead>
<tbody>
<tr>
<td>x (SD)</td>
<td>4.72 (1.33)</td>
<td>4.13 (1.67)</td>
<td>3.11 (1.49)</td>
</tr>
<tr>
<td>median (Q1, Q3)</td>
<td>5 (4, 6)</td>
<td>4 (3, 6)</td>
<td>3 (2, 4)</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>5 (1, 6)</td>
<td>5 (1, 6)</td>
<td>6 (0, 6)</td>
</tr>
</tbody>
</table>

Note. MENQOL, Menopause-Specific Quality of Life Questionnaire. Severity rating scale from 0 to 6 (not at all bothered to extremely bothered). Q1 = 25th percentile, Q3 = 75th percentile [interquartile range].

Six subjects reported having no night sweats. Five subjects reported not experiencing poor memory.

Analysis of differences between groups at baseline with one-way ANOVA tests did not reach significance on poor memory ratings, $F(2,52) = 0.18, p = .84$; hot flash ratings, $F(2,57) = 0.93, p = .40$; or night sweat ratings, $F(2,51) = 1.11, p = .34$ (see Table 4.7).

Table 4.7
Group Differences in Symptom Severity Rating from MENQOL at Baseline

<table>
<thead>
<tr>
<th></th>
<th>AP control n = 20</th>
<th>AP specific n = 22</th>
<th>EUC n = 15</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x (SD)</td>
<td>4.9 (1.3)</td>
<td>4.4 (1.4)</td>
<td>4.9 (1.3)</td>
<td>0.93</td>
<td>.40</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>4 (2, 6)</td>
<td>5 (1, 6)</td>
<td>5 (1, 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night sweats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x (SD)</td>
<td>4.0 (1.8)</td>
<td>3.9 (1.7)</td>
<td>4.7 (1.5)</td>
<td>1.11</td>
<td>.34</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>5 (1, 6)</td>
<td>5 (1, 6)</td>
<td>5 (1, 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experiencing poor memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x (SD)</td>
<td>2.9 (1.6)</td>
<td>3.2 (1.7)</td>
<td>3.1 (1.0)</td>
<td>0.18</td>
<td>.84</td>
</tr>
<tr>
<td>range (min, max)</td>
<td>6 (0, 6)</td>
<td>6 (0, 6)</td>
<td>3 (2, 5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. AP, acupuncture; EUC, enhanced usual care

**Hypothesis testing.** There are two hypotheses that address the first research question. **Hypothesis 1a.** Menopausal symptom-specific acupuncture will improve
perceived memory changes as measured by self-reports compared to enhanced usual care (education). Hypothesis 1b. Non-symptom-specific acupuncture will improve perceived memory changes as measured by self-reports compared to enhanced usual care (education). These hypotheses will be addressed in this section.

Daily Symptom Diary. The data considered to best answer this research question were frequency data from the Daily Symptom Diary, as more data were collected from each subject using this method. The proposed statistical test for this question was repeated measures ANOVA. The assumptions of parametric tests are: normally distributed data, homogeneity of variance, data measured at least at the interval level, and independence. In repeated measures, the assumption of independence is automatically violated, and the additional assumption of sphericity is included (Field, 2009).

For memory data from the Daily Symptom Diary, normality of the data was examined by construction of histograms and P-P plots, evaluation of skewness and kurtosis, and Kolmogorov-Smirnov tests. These showed that the distribution of the data was not normal. Levene’s test for homogeneity of variance showed that the variances were significantly different at baseline week, $F(2,53) = 7.19, p = .002$, indicating a violation of the assumption. As the data are not normally distributed and variances are significantly different, the conclusions of the repeated measures ANOVA may not be replicable.

Repeated measures ANOVA results for loss of concentration frequencies from the Daily Symptom Diary are as follows. Mauchly’s test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 57.81, p < .001$, therefore degrees of freedom were corrected using the Greenhouse-Geisser estimates of sphericity ($\varepsilon = .59$). No significant
main effects or interactions were found. The group x time interaction ($F(2.39, 63.44) = 1.92, p = .15$), the main effect for time ($F(1.20, 63.44) = 2.77, p = .10$), and the main effect for group ($F(2, 53) = 1.73, p = .19$) were not significant. Frequency of loss of concentration was not influenced by either time or treatment group.

As the assumptions for repeated measures ANOVA were not met, additional analyses based on frequency distributions were used to further investigate the data. The loss of concentration data from the Daily Symptom Diary were analyzed to examine change in symptoms of all subjects regardless of group from baseline to week 5, baseline to week 9, and week 5 to week 9. Frequencies of loss of concentration episodes at week 5 and at week 9 were subtracted from those at baseline, and frequencies at week 9 were subtracted from those at week 5. The data were categorized as follows: negative numbers indicated an increase in symptom frequency (worsening), a zero indicated no change, and positive numbers indicated a decrease in symptom frequency (improvement). The range of frequency counts from baseline to week 5 was -21 to +72, range from baseline to week 9 was -14 to +72, and -11 to +18 from week 5 to week 9. In order to analyze this data, changes in frequency ratings were categorized as worse (-21 to -1), stayed the same (zero), or improved (+1 to +72) during the time period examined. Results are shown in Table 4.8.
To further examine frequency of change in loss of concentration and treatment group, frequency counts from baseline to week 5, baseline to week 9, and week 5 to week 9 were collapsed. The categories were as follows: lowest negative number to -5 = worse, scores of -4 to +4 = stayed the same, and +5 to the highest number = improved. To eliminate small changes that were unimportant, ‘stayed the same’ was defined using the range -4 to +4, which is approximately one-half an episode of loss of concentration per day. Using these categories, 3x3 tables were constructed using treatment group and frequency ratings. Group changes in symptom frequency were compared from baseline to week 5, baseline to week 9, and week 5 to week 9. Because of low expected frequencies in some cells, the assumptions of the chi-square test were not met, and Fisher’s exact test was used (Field, 2009). No significant difference was seen between groups in the change of symptom frequency of loss of concentration from baseline to week 5, from baseline to week 9, or from week 5 to week 9 (see Table 4.9).
Table 4.9  
Change in Loss of Concentration Frequency Ratings Between Groups (Daily Symptom Diary): Baseline to Week 5, Baseline to Week 9, Week 5 to Week 9

<table>
<thead>
<tr>
<th></th>
<th>Baseline to Week 5</th>
<th>Baseline to Week 9</th>
<th>Week 5 to Week 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worse n (%)</td>
<td>Same a n (%)</td>
<td>Improved n (%)</td>
</tr>
</tbody>
</table>
| AP control (n = 19)    | 2 (10.5)           | 12 (63.2)          | 5 (26.3)         | .09  
| AP specific (n = 21)   | 3 (14.2)           | 9 (42.9)           | 9 (42.9)         |  
| Enhanced usual care (n = 18) | 3 (16.7)       | 14 (77.8)          | 1 (5.5)          |  
|                         | 2 (10.5)           | 11 (57.9)          | 6 (31.6)         | .19  
|                         | 2 (10.0)           | 9 (45.0)           | 9 (45.0)         |  
|                         | 5 (29.4)           | 10 (58.8)          | 2 (11.8)         |  
|                         | 1 (5.3)            | 15 (78.9)          | 3 (15.8)         | .15  
|                         | 0 (0)              | 16 (80.0)          | 4 (20.0)         |  
| Enhanced usual care (n = 17) | 4 (23.5)       | 12 (70.6)          | 1 (5.9)          |  

Note: AP, acupuncture. *Same = difference between -4 and +4.

**Kupperman Index.** An analysis of severity of loss of concentration from the Kupperman Index was added to further explore this symptom in this population. This instrument was administered once at baseline, at week 5, and at week 9. Subjects were asked to rate the severity of the symptom of loss of concentration for that day. Symptom severity ratings were 0 = not present, 1 = mild, 2 = moderate, and 3 = severe. Using the actual rating scores, 3-group by 4 x 4 frequency tables were constructed in order to
compare group change in symptom scores from baseline to week 5, baseline to week 9, and week 5 to week 9. Changes in severity ratings were categorized as worse, stayed the same, or improved during the time period examined. Analysis of frequencies was chosen over the Friedman test as the latter examines data only at a particular observation point and does not show change. The Cochran-Mantel-Haenszel statistic was used to test whether proportions of change were the same in all groups. Change in severity ratings on the Kupperman Index for loss of concentration was significantly different between groups from baseline to week 5, $\chi^2(1) = 8.37, p = .004$, from baseline to week 9, $\chi^2(1) = 4.71, p = .03$, and from week 5 to week 9, $\chi^2(1) = 16.52, p < .0001$.

Post hoc testing was conducted to examine pairwise differences among the three groups. Because of multiple comparisons within the same analysis, a Bonferroni correction was used to determine significance at $p < .0167$. As shown in Table 4.10, comparisons of change in severity ratings from baseline to week 5 were significantly different between the AP control and enhanced usual care groups, $\chi^2(1) = 7.72, p = .006$, and between the AP specific and enhanced usual care groups, $\chi^2(1) = 7.21, p = .007$. No significant difference was seen in comparison of the AP specific and AP control groups.
Table 4.10
Pairwise Comparisons – Change in Loss of Concentration Severity Ratings (Kupperman): Baseline to Week 5

<table>
<thead>
<tr>
<th>Baseline to Week 5</th>
<th>Worse n (%)</th>
<th>Same n (%)</th>
<th>Improved n (%)</th>
<th>Total change n (%)</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP control (n = 20)</td>
<td>3 (15)</td>
<td>9 (45)</td>
<td>8 (40)</td>
<td>11 (55)</td>
<td>7.72</td>
<td>.006</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>0 (0)</td>
<td>9 (50)</td>
<td>9 (50)</td>
<td>9 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP specific (n = 21)</td>
<td>5 (24)</td>
<td>5 (24)</td>
<td>11 (52)</td>
<td>16 (76)</td>
<td>7.21</td>
<td>.007</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>0 (0)</td>
<td>9 (50)</td>
<td>9 (50)</td>
<td>9 (50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. AP, acupuncture; EUC, enhanced usual care. Total change is subjects who either worsened or improved.

For the period of baseline to week 9, the AP control and enhanced usual care groups were significantly different, $\chi^2(1) = 6.54, p = .011$ (see Table 4.11). The comparisons of change in the AP specific and enhanced usual care groups, and AP specific and AP control groups did not reach significance.

Table 4.11
Pairwise Comparisons – Change in Loss of Concentration Severity Ratings (Kupperman): Baseline to Week 9

<table>
<thead>
<tr>
<th>Baseline to Week 9</th>
<th>Worse n (%)</th>
<th>Same n (%)</th>
<th>Improved n (%)</th>
<th>Total change n (%)</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP control (n = 18)</td>
<td>4 (22)</td>
<td>7 (39)</td>
<td>7 (39)</td>
<td>11 (61)</td>
<td>6.54</td>
<td>.011</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>0 (0)</td>
<td>6 (33)</td>
<td>12 (67)</td>
<td>12 (67)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. AP, acupuncture; EUC, enhanced usual care. Total change is subjects who either worsened or improved.

For the period of week 5 to week 9 shown in Table 4.12, the change in severity of loss of concentration ratings was significantly different for the AP control and enhanced
usual care groups, $\chi^2(1) = 18.36, p < .0001$, and for the AP specific and AP control
groups, $\chi^2(1) = 11.04, p = .0009$. No significant difference was seen in comparing the AP
specific and enhanced usual care groups.

Table 4.12
Pairwise Comparisons – Change in Loss of Concentration Severity Ratings (Kupperman): Week 5 to Week 9

<table>
<thead>
<tr>
<th>Week 5 to Week 9</th>
<th>Worse n (%)</th>
<th>Same n (%)</th>
<th>Improved n (%)</th>
<th>Total change n (%)</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP control (n = 18)</td>
<td>2 (11)</td>
<td>14 (78)</td>
<td>2 (11)</td>
<td>4 (22)</td>
<td>18.36</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>3 (17)</td>
<td>8 (44)</td>
<td>7 (39)</td>
<td>10 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP control (n = 18)</td>
<td>2 (11)</td>
<td>14 (78)</td>
<td>2 (11)</td>
<td>4 (22)</td>
<td>11.04</td>
<td>.0009</td>
</tr>
<tr>
<td>AP specific (n = 21)</td>
<td>4 (19)</td>
<td>12 (57)</td>
<td>5 (24)</td>
<td>9 (43)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. AP, acupuncture; EUC, enhanced usual care. Total change is subjects who either worsened or improved.

As seen above, the two AP groups from week 5 to week 9 differed significantly from each other, but not at any other time point. The AP specific group showed more change than did the AP control group. Fewer severity scores stayed the same, and change was seen in both the improved and worse directions.

From baseline to week 5, both AP groups showed significant change from the enhanced usual care group, with severity ratings having a greater trend toward worsening than those of the enhanced usual care group. From baseline to week 9, and from week 5 to week 9, there was more change toward improvement in the enhanced usual care group than in the AP control group, indicating that improvement in the enhanced usual care
group ratings occurred after the midpoint of the treatment phase. These results are illustrated in Figure 4.1.

![Figure 4.1](image)

*Figure 4.1. Comparisons of change in severity ratings of loss of concentration between groups using pairwise comparisons (Kupperman Index). AP, acupuncture; EUC, enhanced usual care; APC, acupuncture control; APS, acupuncture specific.*
**Menopause-Specific Quality of Life Questionnaire.** An analysis of experience of poor memory from the MENQOL was undertaken to further explore this symptom. This instrument was administered once at baseline, at week 5, and at week 9. Subjects were asked whether or not they experienced poor memory *in the past month.* If yes, subjects then rated the symptom on a scale of 0 to 6 from “not at all bothered” to “extremely bothered” (interpreted in this study as perceived severity of the symptom).

Frequencies of actual severity scores were examined by treatment group at baseline, week 5, and week 9. A category was included to capture women who indicated they did not experience poor memory at a particular time point, and thus did not rate severity at that time, but may have rated severity at another of the time points. Fisher’s exact test was used. There were no differences seen between groups in actual severity scores at baseline \( (p = .54) \), at week 5 \( (p = .72) \), or at week 9 \( (p = .35) \).

The change in severity for experiencing poor memory was analyzed using frequency tables to compare the AP control, AP specific and enhanced usual care groups from baseline to week 5, baseline to week 9, and week 5 to week 9. Changes in severity ratings were categorized as worse, stayed the same, or improved during the time period examined. The Cochran-Mantel-Haenszel statistic was used to determine if proportions of change were the same in all groups. Change in severity ratings on the MENQOL for experiencing poor memory was significantly different between groups from baseline to week 5, \( \chi^2(1) = 11.3, p = .0008 \); from baseline to week 9, \( \chi^2(1) = 17.9, p < .0001 \); and from week 5 to week 9, \( \chi^2(1) = 28.7, p < .0001 \).

Post hoc testing was done to evaluate pairwise differences among the three groups, with a Bonferroni correction used to determine significance at \( p < .0167 \).
Comparisons of change in severity ratings from baseline to week 5 (see Table 4.13), baseline to week 9 (see Table 4.14), and week 5 to week 9 (see Table 4.15) showed a significant difference for the AP specific and AP control groups, AP specific and enhanced usual care groups, and AP control and enhanced usual care groups at every time point. All three groups were significantly different from each other in the proportion of subjects that remained the same, worsened, and showed improvement.

Table 4.13
Pairwise Comparisons – Change in Severity Ratings for Experiencing Poor Memory (MENQOL): Baseline to Week 5

<table>
<thead>
<tr>
<th>Baseline to Week 5</th>
<th>Worse n (%)</th>
<th>Same n (%)</th>
<th>Improved n (%)</th>
<th>Total change n (%)</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP control (n = 18)</td>
<td>9 (50)</td>
<td>1 (6)</td>
<td>8 (44)</td>
<td>17 (94)</td>
<td>6.49</td>
<td>.011</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>5 (28)</td>
<td>4 (22)</td>
<td>9 (50)</td>
<td>14 (78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP specific (n = 17)</td>
<td>4 (23)</td>
<td>3 (18)</td>
<td>10 (59)</td>
<td>14 (82)</td>
<td>8.25</td>
<td>.004</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>5 (28)</td>
<td>4 (22)</td>
<td>9 (50)</td>
<td>14 (78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP control (n = 18)</td>
<td>9 (50)</td>
<td>1 (6)</td>
<td>8 (44)</td>
<td>17 (94)</td>
<td>8.05</td>
<td>.005</td>
</tr>
<tr>
<td>AP specific (n = 17)</td>
<td>4 (23)</td>
<td>3 (18)</td>
<td>10 (59)</td>
<td>14 (82)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. AP, acupuncture; EUC, enhanced usual care. Total change is subjects who either worsened or improved.*
### Table 4.14
Pairwise Comparisons – Change in Severity Ratings for Experiencing Poor Memory (MENQOL): Baseline to Week 9

<table>
<thead>
<tr>
<th>Baseline to Week 9</th>
<th>Worse n (%)</th>
<th>Same n (%)</th>
<th>Improved n (%)</th>
<th>Total change n (%)</th>
<th>( \chi^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP control (n = 18)</td>
<td>4 (22)</td>
<td>1 (6)</td>
<td>13 (72)</td>
<td>17 (94)</td>
<td>11.38</td>
<td>.0007</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>6 (33)</td>
<td>3 (17)</td>
<td>9 (50)</td>
<td>15 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP specific (n = 21)</td>
<td>2 (10)</td>
<td>3 (14)</td>
<td>16 (76)</td>
<td>18 (86)</td>
<td>13.04</td>
<td>.0003</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>6 (33)</td>
<td>3 (17)</td>
<td>9 (50)</td>
<td>15 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP control (n = 18)</td>
<td>4 (22)</td>
<td>1 (6)</td>
<td>13 (72)</td>
<td>17 (94)</td>
<td>11.40</td>
<td>.0007</td>
</tr>
<tr>
<td>AP specific (n = 21)</td>
<td>2 (10)</td>
<td>3 (14)</td>
<td>16 (76)</td>
<td>18 (86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* AP, acupuncture; EUC, enhanced usual care. Total change is subjects who either worsened or improved.

### Table 4.15
Pairwise Comparisons – Change in Severity Ratings for Experiencing Poor Memory (MENQOL): Week 5 to Week 9

<table>
<thead>
<tr>
<th>Week 5 to Week 9</th>
<th>Worse n (%)</th>
<th>Same n (%)</th>
<th>Improved n (%)</th>
<th>Total change n (%)</th>
<th>( \chi^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP control (n = 16)</td>
<td>4 (25)</td>
<td>7 (44)</td>
<td>5 (31)</td>
<td>9 (56)</td>
<td>19.01</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>6 (33)</td>
<td>9 (50)</td>
<td>3 (17)</td>
<td>9 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP specific (n = 17)</td>
<td>1 (6)</td>
<td>5 (29)</td>
<td>11 (65)</td>
<td>12 (71)</td>
<td>20.08</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>EUC (n = 18)</td>
<td>6 (33)</td>
<td>9 (50)</td>
<td>3 (17)</td>
<td>9 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP control (n = 16)</td>
<td>4 (25)</td>
<td>7 (44)</td>
<td>5 (31)</td>
<td>9 (56)</td>
<td>18.87</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>AP specific (n = 17)</td>
<td>1 (6)</td>
<td>5 (29)</td>
<td>11 (65)</td>
<td>12 (71)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* AP, acupuncture; EUC, enhanced usual care. Total change is subjects who either worsened or improved.
From baseline to week 5 and baseline to week 9, the severity ratings in the AP control group appeared to worsen more than did ratings in the AP specific group, with the AP specific group scores showing improvement from week 5 to 9. This suggests a positive trend for scores in the AP specific group compared to those in the AP control group, with more improvement seen in the AP specific group in the latter half of the treatment phase. In comparison to ratings of the enhanced usual care group, the AP control group scores showed more change at all time points, with initial worsening seen from baseline to week 5, and improvement from baseline to week 9, and weeks 5 to 9. At all time points, the scores of the AP specific group showed greater change and a trend toward improvement compared with scores in the enhanced usual care group. Symptom severity scores in both AP groups appeared to show greater improvement over time than those in the enhanced usual care group (see Figure 4.2).
Figure 4.2. Comparisons of change in severity ratings for experiencing poor memory between groups using pairwise comparisons (MENQOL). AP, acupuncture; EUC, enhanced usual care; APC, acupuncture control; APS, acupuncture specific; MENQOL, Menopause-Specific Quality of Life Questionnaire.
**Hypothesis 1a.** The null hypothesis assumes that menopausal-symptom specific acupuncture will not improve perceived memory changes as measured by self-reports compared to enhanced usual care. No significant difference was seen over time on frequency of loss of concentration episodes from the Daily Symptom Diary. The null hypothesis was not rejected.

**Hypothesis 1b.** The null hypothesis assumes that non-symptom-specific acupuncture will not improve perceived memory changes as measured by self-reports compared to enhanced usual care. No significant difference was seen over time on frequency of loss of concentration episodes from the Daily Symptom Diary. The null hypothesis was not rejected.

**Research Question 2.** *Is there a relationship between improvements in hot flashes/night sweats and perceived memory changes in breast cancer survivors with menopausal symptoms?* No significant differences were seen over time between treatment groups on frequency of loss of concentration episodes from the Daily Symptom Diary. Further examination of the diary data using frequency distributions showed no significant differences when comparing group change in loss of concentration from baseline to week 5, week 5 to week 9, and baseline to week 9.

Results from the MENQOL showed significant differences in the proportion of change in *experiencing poor memory* between all groups at all time points. The proposed analysis utilizing correlation and multiple regression was considered to examine the relationship of improvement in hot flashes/night sweats and memory using the MENQOL data. However, a large proportion of subjects “stayed the same” from baseline to week 5,
week 5 to week 9, and baseline to week 9, and would therefore be eliminated from the analysis. An insufficient number of subjects would remain to obtain an informative result. Based on these characteristics of the data, no further analysis was attempted.

Summary

This study examined the effectiveness of acupuncture on menopause-related memory complaints of women with breast cancer. The women in the AP control, AP specific, and enhanced usual care groups were not significantly different in age, age at menopause, or breast cancer treatments of chemotherapy and adjuvant hormone therapies. Mean frequency or severity of menopausal symptoms was not different between groups at baseline on any of the three instruments used.

Data on frequency of loss of concentration from the Daily Symptom Diary were identified as the best data available to explore the research questions. Repeated measures ANOVA on daily diary data showed that frequency of loss of concentration was not influenced by either time or treatment group. Further analysis using frequency tables to determine change in symptom frequency between groups did not reach significance at any time point.

The Kupperman Index was administered three times, and measured subjects’ self-reports of symptom severity for that particular day. Frequencies using data from the Kupperman Index were analyzed to examine the proportion of change between groups in severity ratings of loss of concentration, which reached significance at all time points. Post hoc testing showed significant differences between some groups with an overall trend toward improvement in the enhanced usual care group compared to the AP groups.
Subjects completed the MENQOL three times, and reported severity of their symptoms, if present, on a scale of 0-6. Examination of frequencies to determine the proportion of change between groups in severity ratings of experiencing poor memory reached significance. In post hoc testing, all three groups were significantly different from each other at every time point. Overall, the AP specific group showed more improvement than the AP control and enhanced usual care groups, with the AP control group showing more improvement than the enhanced usual care group in the second half of the treatment phase.
Chapter 5

Discussion

Introduction

The impetus for this secondary data analysis was the prevalence of memory complaints by postmenopausal women and by breast cancer survivors, and the lack of research on the menopausal symptom of memory changes in response to acupuncture treatment. The need for non-pharmacologic interventions for relief of menopausal symptoms, particularly in women with breast cancer, has been well documented (Knobf, 2011; Woods & Mitchell, 2011).

The Framework for Interactions Between the Individual and the Environment, introduced in Chapter 2, guided the study (Elliott & Eisdorfer, 1982). The internal environmental change of natural or treatment-induced menopause, and subsequent decline in estrogen (Activator), may lead to the experience of a number of symptoms attributed to menopause (Reactions). Consequences such as symptom bother and decreased quality of life are the individual’s response to prolonged or cumulative effects of reactions. The elements of the model are not static, and continually interact with and are modified by each other. Reactions to an activator may be transient and produce no remarkable consequences, or may be sufficiently intense as to result in considerable consequences. For example, vasomotor symptoms reported by breast cancer survivors are more severe than those described by healthy women (Carpenter et al., 2002; Mar Fan et al., 2010). Acupuncture, the Mediator in the model for this study, was examined for its effect on the Reactions, specifically on the symptom of perceived memory changes.
An aspect of the model pertinent to this particular analysis is that *activators* can be *potential activators* under some circumstances. This acknowledges that the internal environment, or *activator*, of reduced estrogen may not be the actual or sole *activator*, or the *activator* in all women. As new data emerges, the model keeps the door open for *potential activators* such as genetic susceptibility, stress of a cancer diagnosis, cancer treatment, or the biology of the disease itself (Ahles, Root, & Ryan, 2012; Cimprich et al., 2010). Inherent in the model is that *reactions* to an *activator* may vary in intensity from one individual to another and within the same individual at different times, which was seen in the measurements of symptom frequency and severity in this study at three time points. This model acknowledges that *reactions* that produce *consequences* may not be completely understood, thus tolerating the current lack of understanding of the etiology of cognitive changes in menopausal women and breast cancer survivors (Ahles & Saykin, 2007). *Mediators* may be biological and psychological, supporting the inclusion of acupuncture in the model despite its unknown mechanism of action. *Mediators* can vary in their effect on individuals, which was observed in the outcomes of this study.

The primary purpose of this study was to examine the efficacy of acupuncture to improve the menopausal symptom of memory changes in breast cancer survivors. A discussion of the findings is presented here in relation to the research questions and pertinent literature. Limitations of the study, suggestions for future research and implications for nursing practice are included.
Discussion of Results

Demographic Findings. A convenience sample of breast cancer survivors who were experiencing menopausal symptoms was recruited for the parent study. Subjects were selected based on their self-identification of menopausal symptoms, and completion of cancer treatment. These women were randomized to one of three groups: non-symptom-specific acupuncture (AP control), menopausal symptom-specific acupuncture (AP specific), and enhanced usual care.

The sample of women in this secondary analysis are those in the parent study who indicated loss of concentration or experiencing poor memory at baseline on any one of the three instruments measuring menopausal symptoms. The frequency and severity of memory symptoms indicated on the three instruments did not differ between groups at baseline. As might be anticipated in a randomized trial, there were no differences between groups at baseline in age, age at menopause, previously having received chemotherapy, or currently taking adjuvant hormonal therapy. The age range of 37 to 68 years in this sample is similar to that in other studies examining the effect of acupuncture on the menopausal symptom experience of breast cancer survivors (de Valois et al., 2010; Frisk et al., 2008; Nedstrand et al., 2005; Walker et al., 2010). Breast cancer treatment history is important to this study, as chemotherapy and hormone treatment can have an impact on memory in women with breast cancer, and a subset of women may be susceptible to cognitive impairment following these treatments (Ahles et al., 2012; Ahles & Saykin, 2007; Ahles et al., 2008; Bender et al., 2006; Castellon et al., 2004; Wefel et al., 2004).
**Research Questions.** The research questions and hypotheses in this study were generated from the literature on acupuncture treatment for menopausal symptoms. The primary outcome in these studies is usually reduction of vasomotor symptoms. Studies where subjects received acupuncture resulted in an improvement in vasomotor symptoms, often reaching a statistically significant decrease in severity and frequency. Additionally, with the exception of a small randomized trial (Cohen et al., 2003), studies that included control groups receiving control or sham needling not only found a significant decrease in vasomotor symptoms in these groups, but were not able to show a statistical difference between the symptom-specific and control acupuncture arms (Avis et al., 2008; Deng et al., 2007; A. Vincent et al., 2007; Wyon et al., 1995; Wyon et al., 2004; Zaborowska et al., 2007).

Frequency data from symptom diaries are typically used to evaluate change in vasomotor symptoms in intervention studies. In this study, frequencies of loss of concentration as a measure of memory were extracted from the Daily Symptom Diary for a total of 21 days over a period of nine weeks. The diary was considered the best source of data, as the two other instruments would each provide only 3 ratings of a single memory measure.

**Research Question 1.** *What are the effects of menopausal symptom-specific acupuncture on memory in breast cancer survivors with menopausal symptoms?*

**Instruments.** The three instruments that were used in the parent study to gather symptom data included a measure of memory. The results of each are examined here.

*Daily Symptom Diary.* The Daily Symptom Diary did not yield significant results from the analysis of loss of concentration frequencies. It is possible that examining
frequency is not an adequate way to measure memory issues. Subjects’ interpretation of the term loss of concentration may not be sufficiently comprehensive to capture memory changes that women experience in their daily activities such as difficulty recalling words, forgetfulness, or difficulty thinking clearly. Or the term could be construed to mean something more serious. This may have affected accuracy of reporting, as no definition of the term was provided on the diary.

At the same time they were recording loss of concentration, women were also recording frequency of mood changes and sleep disruption, as well as frequency and severity of HF and night sweats on the diary. Making a number of entries in the diary involving different symptom categories may interfere with accurate recall or recording. The diary format is commonly used in menopause symptom studies for recording frequency and severity of vasomotor symptoms alone (Guttuso Jr., DiGrazio, & Reddy, 2012; Sloan et al., 2001), with additional instruments employed for other symptom assessments. No menopause studies have been found that include a memory measure as part of a daily diary.

Kupperman Index. The results from the Kupperman Index were different from the Daily Symptom Diary. As in the Daily Symptom Diary, the terminology for the memory measure in the Kupperman Index is loss of concentration. But in this instrument, severity rather than frequency is assessed with an immediate time frame for that day. Symptoms are rated by the subjects on a scale from 0 to 3, yielding one report of loss of concentration at each of the three time points. In this study, subjects responded verbally to items on this instrument upon interview by the research assistant.
Frequency distribution analysis of the ratings showed the proportion of change in symptom scores to be significantly different between groups at all three time points. On examination of pairwise comparisons, symptom severity scores in the enhanced usual care group appeared to show greater improvement over time than those in the AP groups, which is an unexpected finding.

The Kupperman Index is often included in studies to measure severity of menopause symptoms. Psychometric evaluation of reliability and validity of the index is sparse, but it may have face validity in that it appears to measure the symptoms (Alder, 1998). A “modified” version of the index is typically used, though the origin of the modified version is difficult to trace. The exact modifications of the original index are not clear and may vary from study to study. In studies that incorporate the modified index, specific items on the instrument are not always identified. Nedstrand and associates (2005) provide a description of 11 items on a modified Kupperman Index, with no memory measure included. The list of symptoms on a “validated” Kupperman Index used in another AP study was slightly different, but also did not include memory (Hervik & Mjåland, 2009). Four of the 11 symptoms on the modified Kupperman Index are assigned a weight used in calculation of a final sum score. Menopause symptom severity is determined by the total score, and ratings of each individual symptom are not analyzed, which is the approach typically used in the reporting of index results (Frisk et al., 2008; Wyon et al., 1995; Wyon et al., 2004; Zaborowska et al., 2007). According to Alder (1998), summing scores of diverse symptoms is not statistically valid as the Kupperman Index has not been subjected to factor analysis.
Our study examined the rating of loss of concentration alone, an unweighted single item on the index which has been found on one modified version of the index. The aforementioned version was developed for a trial of a new formulation of menopause hormone therapy vs. placebo, and only total scores were reported (Gelfand et al., 2003). Alder (1998) noted that the Kupperman Index does not meet current psychometric standards, and that conclusions drawn from research based on this invalid instrument may be unsound. Therefore, the usefulness of these results from the Kupperman Index may be limited. Concerns about subjects’ interpretation of the term loss of concentration are described above.

Menopause-Specific Quality of Life Questionnaire. On this instrument, subjects were asked if they have experienced poor memory. If so, the subject then rated the bother, or severity, of the symptom in the past month on a scale of 0 to 6, producing one report of symptom severity at each of the three time points. Subjects’ verbal responses to the MENQOL items were recorded by the research assistant.

The results from the MENQOL differed from those of the Daily Symptom Diary and the Kupperman Index. Analysis of frequencies of the ratings showed a significant difference in the proportion of change in symptom scores between groups, with significant differences seen between all groups at all three time points in pairwise comparisons. Symptom severity scores in both AP groups appeared to show greater improvement over time than those in the enhanced usual care group. This is consistent with the literature where both control acupuncture and symptom-specific acupuncture are more effective than a non-acupuncture control in reducing frequency and severity of hot flashes (Avis et al., 2008; Painovich et al., 2012; Wyon et al., 2004; Zaborowska et al.,
The positive trend toward improvement in the AP specific group compared to the AP control group is not a typical finding in acupuncture and hot flash studies. With rare exception (Hervik & Mjåland, 2009; Huang et al., 2006; Nir et al., 2007), control acupuncture has not been found to be different in effect from symptom-specific acupuncture in menopausal symptom studies.

There is ongoing discourse about the challenge of selecting an appropriate acupuncture control (or sham) condition in acupuncture research. Most forms of sham acupuncture have biophysical effects, and are not considered to be inert. A range of non-specific mechanisms may be activated regardless of what needling techniques are used or where needling occurs. Even if the effect of the acupuncture control is small, it may be harder to discern a difference between true (verum) acupuncture and control acupuncture (Birch, 2006; Langevin et al., 2006; C. Vincent & Lewith, 1995).

In the MENQOL, the time frame of symptom severity being reported is one month, as opposed to one day, which could lead to more careful consideration of the character of the symptom by the subject. The term experiencing poor memory is different from that in the other instruments, and may be interpreted by the subjects as more inclusive of the memory challenges women experience in daily functioning. This term may prompt subjects to recall difficulties that originate from a different memory function than that of loss of concentration. Recent studies of menopausal cognitive complaints demonstrated a relationship between perceived symptoms and objective findings on cognitive testing, with results suggesting that subjective memory difficulties during the menopausal transition are associated with working memory and complex attention.
(Weber et al., 2012) as well as with verbal memory (Schaafsma et al., 2010; Weber & Mapstone, 2009).

The measure of *experiencing poor memory* on the MENQOL is one of seven items in the psychosocial domain, which includes self reported feelings of anxiety, depression, dissatisfaction with life and wanting to be alone. It has not been assessed as an individual item separate from the psychosocial domain in studies of acupuncture and menopausal symptoms. In acupuncture studies that have included the MENQOL as a measure, a significant decrease in symptom bother was found in the vasomotor domain, but not in any other domain (Avis et al., 2008; Nir et al., 2007; Painovich et al., 2012). In a factor-analytic evaluation of the MENQOL, poor memory was one of a few items found that cross-loaded across more than one domain, and thus did not add statistical value to the scoring of the psychosocial domain (Van Dole et al., 2012). An analysis of this single memory measure, apart from the psychosocial domain, may be more informative about treatment effects of acupuncture on cognitive change. However, the results from the MENQOL in this study, while intriguing, may not be as sound as findings obtained with a reliable and valid instrument that measures perception of everyday memory functioning, such as the Memory Functioning Questionnaire (Gilewski, Zelinski, & Schaie, 1990), or with objective neurocognitive testing.

**Research Question 2. Is there a relationship between improvements in hot flashes/night sweats and perceived memory changes in breast cancer survivors with menopausal symptoms?** No significant differences were seen over time between treatment groups on frequency of loss of concentration episodes from the Daily Symptom Diary. Further examination of the diary data using frequency distributions showed no
significant differences when comparing group change in loss of concentration at any time point. The proposed analysis for this question was considered in order to examine the relationship of improvement in hot flashes/night sweats and memory using the MENQOL data. A large proportion of subjects showed no change at each of the time points and would be eliminated from the analysis, resulting in an insufficient number of subjects to draw a meaningful conclusion. Based on these characteristics of the data, no further analysis was undertaken.

**Summary.** Not all AP and menopause symptom studies include a measure of memory. In addition to the instruments used to assess memory change in this study, there are other quality of life scales seen in AP studies that include memory. The Menopause Rating Scale (MRS) measures severity of aging symptoms and their impact on health-related quality of life. It is comprised of three dimensions: psychological, somatic and urogenital. The psychological dimension includes a question on impaired memory (Berlin Center for Epidemiology and Health Research, 2008; Heinemann et al., 2004). The MRS was included in a study on the effects of AP on hot flashes in peri- and postmenopausal women (Kim et al., 2010).

Another instrument used in AP studies is the Women’s Health Questionnaire (WHQ) which is a health-related quality of life measure for mid-life women and consists of nine subscales, one of which is memory/concentration (Hunter, 1992, 2000). The WHQ was used in the ACUFLASH study, a randomized trial comparing the effect of AP and self-care on hot flashes in postmenopausal women (Borud et al., 2009; Borud et al., 2010). Two studies on AP and vasomotor symptoms in breast cancer survivors used the WHQ (de Valois et al., 2010; Frisk et al., 2012). After 8 weeks of AP in a single-arm,
observational study, significant improvement from baseline was seen in the memory/concentration subscale of the WHQ (de Valois et al., 2010). This is the only acupuncture study found to date that shows specific improvement in the menopausal symptom of memory changes using a quality of life scale.

While there were no statistically significant results from the Daily Symptom Diary, some interesting trends were seen in the analysis of memory data from the MENQOL in favor of AP over enhanced usual care, and an indication that more positive change was seen in the AP specific group than in the AP control group. Though there are inconsistencies in the literature, AP remains promising as a non-hormonal treatment for menopausal symptoms, including memory difficulties, and merits further investigation.

**Limitations of the Study**

There are some recognized limitations to this study. The data on the variables being measured were obtained by self-report, including medical and treatment history. Self-report bias can lead to inaccurate responses, and over- or under-reporting of symptoms. Self-reports may be influenced by misunderstanding of instructions by the participants. However, self-report is a common and valid method used in studies of this type, and objective measurements are not always possible to obtain. It is possible that the results of this study are not representative of the larger population of breast cancer survivors who are experiencing menopausal symptoms, though the demographic findings appear to be comparable to similar studies in the literature.

This study is also limited because it is a secondary data analysis, and instruments were selected to address other primary research questions. This may have limited further
exploration and examination of the variable of memory. For example, there were no data available on education and time since menopause, both of which may have some influence on performance on cognitive measures. Additionally, a more detailed examination of perceived memory functions with an instrument specific to this menopausal symptom may have offered important information about the symptom experience.

Implications for Practice

There are a large number of women affected by menopausal symptoms because of natural or surgical menopause, or as a result of cancer treatment. As the number of breast cancer survivors has increased, management of symptoms and their impact on quality of life has become imperative for healthcare providers to address.

Following treatment for breast cancer, subtle cognitive impairment may exist in a variety of cognitive domains. The menopausal symptom of cognitive difficulties can have a negative impact on work, social and family relationships, and everyday activities (Woods & Mitchell, 2011). Psychological distress and negative emotions can increase women’s’ subjective evaluation of the severity of their symptoms (Thurston et al., 2008). Recognition and acknowledgement of cognitive changes should be part of ongoing care. Assessment tools to evaluate symptom distress should be used. Symptom clusters, which include cognitive difficulty, have been identified for the breast cancer experience and menopause transition that could be helpful in guiding interventions for multiple symptoms often experienced concurrently (Bender et al., 2005; Cray, Woods, Herting, & Mitchell, 2012). Interventions that support or improve memory function, including
alternative therapies, cognitive behavioral therapy (Ferguson et al., 2012), and cognitive training (Von Ah et al., 2012), may have a positive impact on quality of life.

There is ongoing research into the potential underlying mechanisms of cognitive impairment following a diagnosis of and treatment for breast cancer, as well as research on pharmacologic and nonpharmacologic interventions. Healthcare providers need to stay informed about advances and evolving evidence related to these areas (Von Ah, Jansen, Allen, Schiavone, & Wulff, 2011).

Providers should be knowledgeable about complementary and alternative therapy resources, and make informed and appropriate referrals to qualified practitioners (Smith & Bauer-Wu, 2012). Women who have experienced a treatment-induced menopause, and are taking a selective estrogen receptor modulator or an aromatase inhibitor, may not want to take additional medication to manage menopausal symptoms. Pharmacologic therapy with drugs such as antidepressants for menopausal vasomotor symptoms may interact with adjunct hormonal therapy to reduce its effectiveness (Kelly et al., 2010).

**Suggestions for Future Research**

There is a need for effective, well-tolerated nonhormonal treatments for menopausal symptoms, especially in women with breast cancer, yet there are few studies designed to evaluate the effectiveness of interventions to treat cognitive changes. The results of this study helped to identify areas of consideration for future research.

The results reinforce the need for cognitive measures that are more specific than the questions and instruments used in this study. Objective, neuropsychological testing should be included, which would allow analysis and comparison of objective and
subjective memory data. A tool should be selected that measures self-perception of everyday memory issues rather than single items or subscales of larger survey instruments not specific to memory. This could avoid misinterpretation of the meaning of broader questions. An example of a reliable and valid instrument is the Memory Functioning Questionnaire (MFQ) (Gilewski et al., 1990). The MFQ is used in several large studies, such as the Study of Women’s Health Across the Nation, and the Seattle Women’s Health Study, as well as in studies on menopausal transition (Maki et al., 2007; Weber & Mapstone, 2009; Weber et al., 2012). The MENQOL-Intervention scale could be used in an acupuncture intervention trial (Lewis et al., 2005). Three items were added to the physical subscale of the MENQOL, and the valid recall period for symptoms is one week rather than one month. Results could then be more reliably compared to a Daily Symptom Diary. Demographic data should include level of education. This is strongly associated with cognitive performance, and can reveal increased risk for cognitive impairment (Lezak, Howieson, Bigler, & Tranel, 2012). Memory should continue to be examined in relationship to other menopausal symptoms and their response to acupuncture with a goal to build evidence for a multisymptom intervention that could address multiple symptoms without adverse effects.

In an acupuncture study, it would be interesting to include the Outcome Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000). This would provide a measure of subjects’ expectations of treatment benefit and treatment credibility, and assess whether the treatment and control interventions were adequately matched and comparable in their psychological impact (Deng et al., 2007; Kim et al., 2010; Otte, Carpenter, Zhong, & Johnstone, 2011; C. Vincent & Lewith, 1995). This is especially
relevant considering the ongoing debate about a satisfactory acupuncture placebo (Birch, 2006; Lund & Lundeberg, 2006; C. Vincent & Lewith, 1995).

**Conclusion**

The primary purpose of this study was to examine the efficacy of acupuncture to improve the menopausal symptom of memory changes in breast cancer survivors. Analysis of the MENQOL data revealed more positive change in the acupuncture groups in improvement of memory than in the enhanced usual care group. These findings support the need for further exploration of targeted interventions such as acupuncture to improve memory difficulties for menopausal women and breast cancer survivors, particularly as advances are made in the understanding of the mechanisms of cognitive change in these women.
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114


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Appendices
Appendix A
Demographic Data Form

Demographic Data Form

Menopause Symptom Relief for Women with Breast Cancer

Date_________ Participant #_________ Age_________ DOB_________

Marital status________ Educational level________ Household income________

Employment (FT/PT; type)______________________________________________

Children (gender & age)_________________________________________________

LMP _________   PMP________ Date of/Age at Menopause___________________

Menstrual Cycle Changes:  No Change______Cycles Longer______Cycles Shorter_____

Menopause: Natural ____ Related to Breast Cancer Treatment ____ Not Menopausal____

HRT History:
1) Estrogen____ Progestin____ Dates:
2) Estrogen____ Progestin____ Dates:
3) Estrogen____ Progestin____ Dates:

Other Hormones__________ Dates:

Current Medications:

Breast Cancer Diagnosis ________________________________ Stage______________

Date of Breast Cancer Diagnosis___________ Lymph Node Involvement: Yes____ No____

Surgery:
1) __________________________ Date_______
2) __________________________ Date_______

Hormone Therapy_______________________ Date Begun______ Date Ended_____

Chemotherapy _____________________ Date Begun______ Date Ended_____

Radiation _________________________ Date Begun______ Date Ended_____

Other ___________________________ Date Begun______ Date Ended_____

135
Demographic Data Form

Hot Flash Remedies

Date:

Participant #

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<th>Comments</th>
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Appendix B
Daily Symptom Diary

**Daily Symptom Calendar**

**Daily Legend**

**Frequency (Freq):**
Number of times per day symptom occurs

**Severity (Sev):**
0 = NOT PRESENT
1 = MILD
2 = MODERATE
3 = SEVERE

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</table>

*MILD -a warm sensation without sweating that leaves you able to continue your daily activity
MODERATE -a warm sensation associated with sweating that leaves you able to continue your daily activity
SEVERE -a hot sensation associated with sweating so intense that you have to stop your activity
Appendix C
Modified Kupperman Index

Menopausal Index according to Kupperman

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Constant Factor</th>
<th>Variable factor of the degree of severity</th>
<th>Week 1</th>
<th>Week 5</th>
<th>Week 9</th>
<th>Week 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flashes</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profuse Perspiration</td>
<td>2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sleep Disturbances</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>2</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Depressive Moods</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling of Vertigo</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of Concentration</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Joint Pain</td>
<td>1</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Palpitation</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Participant # ____________
Date ________________
Appendix D
Menopause-Specific Quality of Life Questionnaire (MENQOL)

Participant #

J. R. Hilditch et al. / Maturities 24 (1996) 161-175

THE MENOPAUSE-SPECIFIC
QUALITY OF LIFE QUESTIONNAIRE

Primary Care Research Unit
Department of Family and Community Medicine
Sunnybrook Health Science Centre
University of Toronto

Copyright: John R. Hilditch, Jacqueline Lewis 1992

The development of this questionnaire was funded by CIBA-Geigy Canada Ltd., Mississauga, Canada

This Questionnaire may be used freely for research purposes. The authors request acknowledgement in any research publications in which the questionnaire is used.
INSTRUCTIONS

Each of the items in the questionnaire is in the form of the examples below:

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bothered</td>
<td>bothered</td>
</tr>
<tr>
<td>0 1 2 3 4 5 6</td>
<td>0 1 2 3 4 5 6</td>
</tr>
</tbody>
</table>

NIGHT SWEATS □ □ -- 0 1 2 3 4 5 6
No Yes

Indicate whether or not you have experienced this problem in the last month.

IF YOU HAVE NOT EXPERIENCED THE PROBLEM:

Mark “No” □

NIGHT SWEATS □ □ -- 0 1 2 3 4 5 6
No Yes

Go to the next item.

IF YOU HAVE EXPERIENCED THE PROBLEM:

Mark “Yes” then circle how bothered you were by the problem.

NIGHT SWEATS □ □ -- 0 1 2 3 4 5 6
No Yes

Go to the next item.

This questionnaire is completely confidential. Your name will not be associated with your responses. However, if for any reason you do not wish to complete an item, please leave it and go on to the next one.
The Menopause-Specific Quality of Life Questionnaire

For each of the following items, indicate whether you have experienced the problem in the PAST MONTH. If you have, rate how much you have been bothered by the problem.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all Bothered</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HOT FLUSHES OR FLASHES</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>2. NIGHT SWEATS</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>3. SWEATING</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>4. BEING DISSATISFIED WITH MY PERSONAL LIFE</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>5. FEELING ANXIOUS OR NERVOUS</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>6. EXPERIENCING POOR MEMORY</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>7. ACCOMPLISHING LESS THAN I USED TO</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>8. FEELING DEPRESSED, DOWN OR BLUE</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
### The Menopause-Specific Quality of Life Questionnaire

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all Bothered</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. BEING IMPATIENT WITH OTHER PEOPLE</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>10. FEELINGS OF WANTING TO BE ALONE</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>11. FLATULENCE (WIND) OR GAS PAINS</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>12. ACHING IN MUSCLES AND JOINTS</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>13. FEELING TIRED OR WORN OUT</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>14. DIFFICULTY SLEEPING</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>15. ACHESS IN BACK OF NECK OR HEAD</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>16. DECREASE IN PHYSICAL STRENGTH</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>17. DECREASE IN STAMINA</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>18. FEELING A LACK OF ENERGY</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>19. DRYING SKIN</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
### The Menopause-Specific Quality of Life Questionnaire

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all Bothered</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. WEIGHT GAIN</td>
<td>□ □</td>
<td>□ □</td>
</tr>
<tr>
<td></td>
<td>No  Yes</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>21. INCREASED FACIAL HAIR</td>
<td>□ □</td>
<td>□ □</td>
</tr>
<tr>
<td></td>
<td>No  Yes</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>22. CHANGES IN APPEARANCE, TEXTURE, OR TONE OF YOUR SKIN</td>
<td>□ □</td>
<td>□ □</td>
</tr>
<tr>
<td></td>
<td>No  Yes</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>23. FEELING BLOATED</td>
<td>□ □</td>
<td>□ □</td>
</tr>
<tr>
<td></td>
<td>No  Yes</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>24. LOW BACKACHE</td>
<td>□ □</td>
<td>□ □</td>
</tr>
<tr>
<td></td>
<td>No  Yes</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>25. FREQUENT URINATION</td>
<td>□ □</td>
<td>□ □</td>
</tr>
<tr>
<td></td>
<td>No  Yes</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>26. INVOLUNTARY URINATION WHEN LAUGHING OR COUGHING</td>
<td>□ □</td>
<td>□ □</td>
</tr>
<tr>
<td></td>
<td>No  Yes</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>27. CHANGE IN YOUR SEXUAL DESIRE</td>
<td>□ □</td>
<td>□ □</td>
</tr>
<tr>
<td></td>
<td>No  Yes</td>
<td>0 1 2 3 4 5 6</td>
</tr>
</tbody>
</table>

---

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Primary Care Research Unit
Department of Family and community Medicine
Sunnybrook Health Science Centre
University of Toronto
<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all bothered</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. VAGINAL DRYNESS DURING INTERCOURSE</td>
<td>No</td>
<td>Yes</td>
<td>→ 0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>29. AVOIDING INTIMACY</td>
<td>No</td>
<td>Yes</td>
<td>→ 0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>